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

Pulmonary Arterial Hypertension

Protocol AC-065A401

Post-authorisation safety study (PASS): observational cohort study of PAH patients newly treated with either UPTRAVI® (selexipag) or any other PAH-specific therapy, in clinical practice

EXPOSURE[1]

An international, observational, cohort study of PAH patients newly treated with either UPTRAVI (selexipag) or any other PAH-specific therapy, in clinical practice

Document type:	Amended Global Protocol
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[1] **EXP**loratory **O**bservational **S**tudy of **U**PTRAVI in **R**eal-lif**E**

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 7 Version 8	14 July 2025
Amendment 6 Version 7	22 June 2022
Amendment 5 Version 6	11 January 2021
Amendment 4 Version 5	17 December 2019
Amendment 3 Version 4	11 April 2017
Amendment 2 Version 3	24 February 2017
Amendment 1 Version 2	24 November 2016
Original Protocol Version 1	15 July 2016

Amendment 7 Version 8 (14 July 2025)

Overall Rationale for the Amendment: The primary reason for this global amendment was to amend the milestones to reflect the status of the study and to include OPSYNVI®/YUVANCI® (recently approved by Health Authorities) into the list of PAH-specific marketed products from MAH.

Changes made to the protocol are described in the table below. Where applicable, the same changes have also been made to the corresponding sections of the abstract.

Section Number and Name	**Description of Change**	**Brief Rationale**
Title page: PASS INFORMATION, document header	Protocol version identifier, date, and date of last version of protocol were updated.	Protocol amendment template requirement.
Section 6: Milestones	Study milestones (submission of seventh study protocol, seventh and eighth interim report) were added. Planned dates for the data cut-off of the final study report and submission for final report for PRAC agreement were removed.	Milestones were updated to reflect the status of the study. Dates as indicated were removed as these were not required per template and multiple factors may impact prediction.
Section 9.3: Variables; Section 11: Management and reporting of adverse events/adverse reactions	OPSYNVI/YUVANCI were added to the list of PAH-specific marketed products from the MAH (UPTRAVI, VELETRI/CARIPUL, OPSUMIT, TRACLEER/STAYVEER).	List was updated with the most recent information.

Section Number and Name	Description of Change	Brief Rationale
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

PASS INFORMATION

Title	Post-authorisation safety study (PASS): observational cohort study of PAH patients newly treated with either UPTRAVI (selexipag) or any other PAH-specific therapy, in clinical practice
Acronym	EXPOSURE (**EXP**loratory **O**bservational **S**tudy of **U**PTRAVI in **R**eal-lif**E**)
Protocol version identifier	8
Date of last version of protocol	22 June 2022
EU PAS register number	EU PAS19085
Active substance	Selexipag Pharmacotherapeutic group: Antithrombotic agents, platelet aggregation inhibitors excluding heparin, ATC code: B01AC27
Medicinal product	UPTRAVI
Product reference	H0003774
Procedure number	EMEA/H/C/003774/II/0035
Marketing authorisation holder(s)	Janssen-Cilag International NV
Joint PASS	No
Research question and objectives	This prospective observational cohort study is conducted to further characterise the safety profile of UPTRAVI and to describe clinical characteristics and outcomes of patients newly treated with UPTRAVI in the international post-marketing setting. A cohort of patients newly treated with any other PAH-specific therapy who were never treated with UPTRAVI is included in this study for the purpose of comparing the incidence of major adverse cardiovascular events (MACE) and all-cause death to patients newly treated with UPTRAVI. 1. To describe, overall and in the subset of patients over the age of 75 years, demographics, disease characteristics and clinical course in patients with pulmonary arterial hypertension (PAH), either newly treated with UPTRAVI (UPTRAVI exposed patients), or newly treated with any other PAH-specific therapy who were never treated with

	UPTRAVI (patients initiating another PAH-specific therapy). 2. To further characterise the UPTRAVI safety profile and estimate the incidence rates during the UPTRAVI exposure period of all-cause death and the following important identified or potential risks: - Hypotension - Anaemia - Pulmonary oedema associated with pulmonary veno-occlusive disease - Hyperthyroidism - MACE - Acute renal failure and renal function impairment - Bleeding events - Light-dependent non-melanoma skin malignancy - Ophthalmological effects associated with retinal vascular system - Gastrointestinal disturbances denoting intestinal intussusception (manifested as ileus or obstruction) 3. To compare rates of MACE and all-cause death between UPTRAVI exposed patients and patients initiating another PAH-specific therapy, using a propensity score analysis.
Country(-ies) of study	Preliminary list of countries where the study is to be conducted: Germany, France, Austria, Norway, Denmark, Finland, Sweden, the UK, Belgium, Switzerland, Ireland, the Netherlands, Czech Republic, Slovakia, Italy, Spain, Greece, Canada, Russia, and other countries, as needed, as UPTRAVI becomes commercially available.
Author	PPD PhD Senior Director Epidemiology ☎ PPD PPD

MARKETING AUTHORISATION HOLDER(S)

Marketing authorisation holder(s)	Janssen-Cilag International NV Turnhoutseweg 30 B-2340 Beerse Belgium
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2 LIST OF ABBREVIATIONS AND ACRONYMS

6MWD	6-minute walk distance
ADR	Adverse drug reaction
AE	Adverse event
BMI	Body mass index
BNP	Brain natriuretic peptide
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
COMPERA	Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension
CRA	Clinical research associate
DL_{CO}	Diffusion capacity of the lungs for carbon monoxide
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data collection
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EXPOSURE	EXPloratory observational study of UPTRAVI in real-life
FC	Functional class
GPP	Guidelines for Good Pharmacoepidemiology Practices
ICF	Informed consent form
IEC	Independent Ethics Committee
IP receptor	Prostacyclin receptor
IR	Incidence rate
IRR	Incident rate ratio
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
ISWT	Incremental shuttle walking test
MACE	Major adverse cardiovascular event
MAH	Marketing Authorisation Holder

MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
NT-proBNP	N-terminal of the prohormone brain natriuretic peptide
PAH	Pulmonary arterial hypertension
PASS	Post-authorisation safety study
PBRER	Periodic benefit-risk evaluation report
PH	Pulmonary hypertension
PQC	Product quality complaint
PRAC	Pharmacovigilance Risk Assessment Committee
PVOD	Pulmonary veno-occlusive disease
RHC	Right heart catheterisation
RMP	Risk Management Plan
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SPAHR	Svenska PAH-registret
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
WHO	World Health Organization

3 RESPONSIBLE PARTIES

The list of investigators for each country in which the study is to be performed has not yet been finalised.

4 ABSTRACT

Title

Post-authorisation safety study (PASS): observational cohort study of PAH patients newly treated with either UPTRAVI (selexipag) or any other PAH-specific therapy, in clinical practice.

Rationale and background

UPTRAVI (selexipag) is an orally available selective IP receptor agonist approved in the European Union (EU). UPTRAVI is indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients with World Health Organization (WHO) functional class (FC) II-III, either as combination therapy in patients insufficiently controlled with an endothelin receptor antagonist and/or a phosphodiesterase type 5 inhibitor, or as monotherapy in patients who are not candidates for these therapies.

In the past decade, the paradigm of clinical trials in PAH has changed, from short-term studies which evaluated exercise capacity, to both long-term outcome and combination therapy studies. While the benefits of the new agents and new treatment modalities are clearly established in large clinical trials, data are lacking in populations not studied in clinical trials and on the impact of these new treatments and treatment modalities in real-world clinical practice settings. This PASS will provide contemporaneous observational data on the overall PAH population, including the aged patient population, in clinical practice. The prospective observational follow-up of patients newly treated with UPTRAVI (UPTRAVI cohort) allows this study to put the safety profile of UPTRAVI into real-world context, reporting on all-cause death and other important safety risks, including major adverse cardiovascular events (MACE). Additionally, the same cohort will be observed along with a group of patients newly treated with any other PAH-specific therapy who were never treated with UPTRAVI (Other cohort) to describe clinical characteristics and outcomes of patients with PAH and to compare the incidence of MACE and all-cause death between UPTRAVI patients and patients initiating another PAH-specific therapy. This PASS will be one of the largest cohort studies in PAH since the first large long-term outcome clinical trials were conducted (ie, SERAPHIN, AMBITION and GRIPHON). Overall, by providing real-world data of how UPTRAVI is used in the care of patients with PAH in the setting of new treatment modalities and earlier widespread use, and impact of combination therapy on outcomes, the PAH community of health care providers and patients will benefit from a greater understanding of UPTRAVI in this post-marketing treatment paradigm.

Research question and objectives

The purpose of this PASS is to further characterise the safety profile of UPTRAVI when used in clinical practice and to describe clinical characteristics and outcomes of patients newly treated with UPTRAVI compared with patients newly treated with any other PAH-specific therapy who were never treated with UPTRAVI, in the post-marketing setting.

Main objectives are:

1. To describe, overall and in the subset of patients over the age of 75 years, demographics, disease characteristics and clinical course in patients with PAH either newly treated with UPTRAVI (UPTRAVI exposed patients), or newly treated with any other PAH-specific therapy who were never treated with UPTRAVI (patients initiating another PAH-specific therapy).
2. To further characterise the UPTRAVI safety profile and estimate the incidence rates during the UPTRAVI exposure period of all-cause death and the following important identified or potential risks:
   - Hypotension
   - Anaemia
   - Pulmonary oedema associated with pulmonary veno-occlusive disease (PVOD)
   - Hyperthyroidism
   - MACE
   - Acute renal failure and renal function impairment
   - Bleeding events
   - Light-dependent non-melanoma skin malignancy
   - Ophthalmological effects associated with retinal vascular system
   - Gastrointestinal disturbances denoting intestinal intussusception (manifested as ileus or obstruction)
3. To compare rates of MACE and all-cause death between UPTRAVI exposed patients and patients initiating another PAH-specific therapy, using a propensity score analysis.

Study design

This is a multicentre, international, prospective, real-world, observational cohort study in patients with PAH who either initiated treatment with UPTRAVI less than 1 month prior to enrolment, at enrolment, or during observation (UPTRAVI cohort), or initiated any other PAH-specific therapy less than 1 month prior to enrolment or at enrolment and who were never treated with UPTRAVI (Other cohort). Patients may be unexposed to UPTRAVI at enrolment and initiate UPTRAVI for the first time during the observation period (late initiators), therefore data for these patients contribute to the Other cohort and subsequently to the UPTRAVI cohort.

The study protocol will not mandate any specific schedule of visits or investigations. Patients will be followed by their physician according to clinical practice.

Due to the recent approval of UPTRAVI in the market, no long-term real-world post-authorisation data are available to estimate the duration of UPTRAVI treatment in clinical practice. The study AC-065A302/GRIPHON median time of exposure to selexipag (70.7 weeks) was used as a proxy to assess a minimum observation period in real-world settings (Sitbon 2015). Thus, the planned observation period for each patient enrolled in the study will be at least 18 months from study enrolment, or until the earliest of death, withdrawal of consent, loss to follow-up or study end.

Population

The number of patients planned to be enrolled in the study is 1184 UPTRAVI exposed patients with PAH and 1850 patients initiating another PAH-specific therapy from participating centres. It is expected that approximately 20% of the study population will be over the age of 75 years, based on the age distribution of patients with PAH in the population-based UK registry in which 22% of the overall PAH population are older than 70 years.

To minimise selection bias during patient recruitment, participating sites are requested to invite consecutive patients with PAH who meet the eligibility criteria for either cohort. Each site will keep a site log with information on the number of patients eligible, the number of patients approached about the study, the number of patients who refused to participate and the number of screening failures. Reason for refusal to participate or not being eligible will be captured. Additionally, information on sex, age range, new PAH-specific therapy initiated and WHO FC will be collected for patients participating and not participating in the study, depending on local regulations.

Inclusion criteria at enrolment:

- Patients ≥ 18 years old, and
- Signed patient informed consent form (ICF), and
- Group I PAH patients, and
- Newly initiating UPTRAVI or any other PAH-specific therapy:
  - less than 1 month prior to enrolment, or
  - at enrolment

Exclusion criteria:

- Patients previously exposed to UPTRAVI/selexipag treatment,

- Patients newly initiating any other PAH-specific therapy must not have been previously treated with that same drug,
- Patients enrolled in any ongoing interventional clinical trial

Enrolment is defined as time of ICF signature or new PAH-specific therapy initiation, whichever occurs the latest.

After study site initiation, all patients initiating a new PAH-specific therapy, including UPTRAVI, and satisfying eligibility criteria, will be invited to participate in the EXPOSURE study. Patients having already initiated a new PAH-specific therapy will have to sign the ICF within 1 month of initiation of the new PAH-specific therapy. Eligible patients who died within 1 month of treatment and were not able to be consented, will be included in the study database, where permitted by local regulation. Retrospective data collection will be conducted for these deceased patients during the course of the study on a continuous basis.

To avoid the exclusion from the propensity score process of a large proportion of patients initiating a PAH therapy other than UPTRAVI, the distribution of WHO FC in UPTRAVI and Other cohorts will regularly be checked during study recruitment. If the distribution of WHO FC is not balanced between the two cohorts, recruitment of patients initiating a PAH therapy other than UPTRAVI could be restricted to those with the adequate WHO FC.

Patients will be recruited, and data will be collected in this observational prospective study in compliance with local regulations.

Variables

The following data will be collected for each patient at initiation of a new PAH-specific therapy and throughout the observation period from the existing medical chart, if available per clinical practice, and recorded on an electronic case report form (eCRF). The same data will also be collected, in a retrospective setting, for eligible patients who died within 1 month of treatment and were not able to provide consent, where permitted by local regulation.

- Study specifics (visit date, termination of data entry)
- Demographics (age, gender, country)
- Clinical characteristics (PAH classification, aetiology, date of diagnosis and WHO FC at diagnosis, WHO FC, 6-minute walk distance (6MWD), incremental shuttle walking test (ISWT), height, weight, right heart catheterisation haemodynamics, % predicted DL_{CO}, pericardial effusion, vital signs, transplantation list / pre-transplantation visit, renal insufficiency)
- Laboratory data (haemoglobin, thyroid hormones, NT-proBNP, BNP)

- Medical history
  - Cardiovascular/cerebrovascular disease history (history of myocardial ischaemia, myocardial infarction (MI), cardiac arrest, ischemic or haemorrhagic cerebrovascular disorders, coronary artery revascularisation and unstable angina)
  - Cardiovascular risk factors history (cardiac arrhythmia, cardiac right to left shunts, history of valvular heart disease, cardiomyopathy, carotid and/or coronary artery arteriosclerosis, high body mass index (BMI), diabetes mellitus, metabolic syndrome, smoking status, hyperlipidaemia, systemic hypertension, hypercoagulable state, sleep apnoea syndrome, alcoholism, use of illicit drugs)
  - Other relevant medical history (hypotension, anaemia, pulmonary oedema associated with PVOD, hyperthyroidism, renal impairment, bleeding events, light-dependent non-melanoma skin malignancies, ophthalmological effects associated with retinal disorder, intestinal intussusception manifested as intestinal obstruction / ileus, worsening of WHO FC in the last 6 months prior to initiation of a new PAH-specific therapy)
- Medication
  - UPTRAVI or any other PAH-specific therapy (treatment name, start date, reason for start, dosing regimen, reason for dose reduction, discontinuation date and reason)
  - Other concomitant medications (drug name, indication, route of administration, start/stop date, reason for use)
  - Immunosuppressant/immunomodulatory medication (start/stop date)
- Outcomes
  - Incident comorbidities at time of the visit (hypotension, anaemia, acute renal failure and renal function impairment, bleeding event, pulmonary oedema associated with PVOD, hyperthyroidism, light-dependent non-melanoma skin malignancy, ophthalmological effects associated with retinal vascular system, intestinal intussusception manifested as ileus or obstruction)
  - Hospitalisation (PAH-related or not, admission/discharge dates, reason for hospitalisation)
  - MACE, defined as the occurrence of at least one condition falling into any of the below categories[2]:
    i. Death from cardiovascular causes (sudden death, fatal MI, fatal stroke, fatal arrhythmia)
    ii. Non-fatal MI,
    iii. Non-fatal stroke (ischaemic stroke and/or haemorrhagic stroke),
    iv. Coronary artery revascularisation

[2] See definition in Annex 3.

v. Unstable angina,
vi. Non-fatal cardiac arrest,

– All-cause death (date and cause, PAH-related or not[3])
– Other adverse events (AEs)
  - Any other AE on UPTRAVI or another PAH-specific product from the MAH, irrespective of seriousness and causality
  - Any AE leading to dose decrease or discontinuation of a PAH-specific product from the MAH
  - For females only: currently pregnant

Data sources

Identification of participating countries

The study will be conducted predominantly in several European countries based on the timing of UPTRAVI launch balanced against the need for representation of various European health care systems (centralised/reference centre versus decentralised/non-reference centre; specialist versus non-specialist prescription), in order to provide a generalisable cohort of patients in clinical practice. Depending on UPTRAVI launch dates and study regulatory approvals, the participating countries will include Germany, France, Austria, Norway, Denmark, Finland, Sweden, the UK, Belgium, Switzerland, Ireland, the Netherlands, Czech Republic, Slovakia, Italy, Spain, Greece, Canada, Russia, and other countries, as needed, as UPTRAVI becomes commercially available.

Identification of participating study sites

EXPOSURE is collaborating with the COMPERA registry, by connecting with the COMPERA network of sites. COMPERA is one of the largest international pulmonary hypertension (PH) registries. It is an ongoing prospective registry of patients with newly initiated therapies for PH (NCT01347216).

EXPOSURE is collaborating with country-specific PAH networks which are well developed with long standing expertise in the care and management of PAH patients across defined national PAH reference centre networks.

Beyond these networks of sites, the MAH will further invite sites who prescribe UPTRAVI and are not involved with COMPERA or other country-specific PAH networks.

The EXPOSURE study database will be sponsored by Actelion and owned by the MAH and will be independent from COMPERA or other country-specific PAH networks. Sites that participate in both studies will be asked to enter data in EXPOSURE and only after

[3] See definition in Annex 4.

will the applicable data be transferred to COMPERA or other country-specific PAH networks following agreement from the site and the respective patient.

eCRF data collection

The EXPOSURE eCRF is a stand-alone program, however it will be aligned with the COMPERA eCRF and electronic data collection (EDC) system. Data will be collected by the investigator / study coordinator for each patient at initiation of a new PAH-specific therapy and throughout the observation period from the existing medical record at any clinic visit, on the respective EXPOSURE eCRF. As a study site commitment statement and per local data protection regulations: Study sites endeavour to collect information from physicians not participating in EXPOSURE, who may be involved in the care of the study patient, or other relevant sources (eg, family contact for vital status). Study sites will ensure this information is recorded in the eCRF.

Study size

A precision-based approach for the confidence interval (CI) was used to determine the minimum number of UPTRAVI exposed patients needed to estimate the incidence rate of MACE within the PASS.

The true incidence of MACE in PAH is not available from population-based real-world data sources, except the contemporaneous and real-world observed data in EXPOSURE. An incidence of MACE of 3.0 per 100 person-years was observed among the entire study population in EXPOSURE based on the data cutoff on 30 November 2020. This was designated as an estimate of the background rate of MACE in the general PAH population in real-world settings.

Based on the above incidence rate, several permutations of the precision around the point estimate of 3.0 per 100 patient-years were reviewed to clarify the assumptions in determining the required sample size. In the AC-065A302/GRIPHON study, a 20% increase in MACE events [as defined in Section 9.3.1] was observed between the selexipag versus control treatment groups. This imbalance of MACE between the treatment arms, while raising concerns, has been viewed by the CHMP to be within the bounds of a positive benefit-risk balance. Therefore, an assumption in the calculation of the desired sample size is that an observed incidence of MACE of approximately 20% above the background rate could be considered to be within the 95% margin of error and would indicate no difference from the true background incidence of MACE among patients with PAH. One further assumption is that the true incidence of the background rate of MACE in a real-world context, while unknown, could be presumed to be higher (or lower) than what was observed in the AC-065A302/GRIPHON study with strict inclusion/exclusion criteria. The determination of the precision around the point estimate of 3.0 per 100 person-years should reflect the uncertainty inherent in using clinical trial data to approximate real-world risk. A margin of error of approximately 30% is therefore considered appropriate to

accommodate the uncertainty while not obscuring the true incidence of MACE among exposed patients.

For the sample size calculation, to observe a point estimate of 3.0 per 100 person-years with a 95% CI ranging from 2.07 to 3.93, at a minimum observation time of 18 months, approximately 888 UPTRAVI exposed patients are needed. The level of precision of +/– 0.9 per 100 person-years (half the width of the CI) equates to a relative precision of 31% of the point estimate. This provides a reasonable margin of error around the point estimate of the assumed background rate of MACE.

An increased risk for MACE among the UPTRAVI exposed patients within the PASS study would be indicated if the observed incidence exceeds the upper bound of the 95% CI of the observed background rate in the Other cohort.

In order to achieve comparable treatment groups, the application of the propensity score methodology may result in patients being excluded from the analysis. According to the distribution of patients initiating another PAH-specific therapy in EXPOSURE as of 30 November 2020 data cutoff, additional 50-60% of patients initiating another PAH-specific therapy will be required for propensity score methodology. Thus the comparator group will need 1450 patients initiating another PAH-specific therapy followed for at least 18 months.

To achieve at least 888 patients exposed to UPTRAVI and 1450 patients initiating another PAH-specific therapy followed for a minimum of 18 months, the study target of enrolment will be 1184 UPTRAVI patients and 1850 patients initiating another PAH-specific therapy, assuming a patient retention rate of 75%.

It is also important to estimate the rate for other important safety concerns within this study. Given the study size, assuming a Poisson distribution with power of 0.80, will allow for the detection of any event above a rate of 0.1 in 100 person-years within the study population of 888 UPTRAVI exposed patients.

With a European prevalence of PAH ranging from 15 to 22.6 per million inhabitants (as observed in several European registries), the overall number of people with PAH in the 28 EU member states is estimated to be up to 17000 patients. With a maximum study size of 3034 patients with PAH enrolled (ie, 1184 UPTRAVI exposed patients and 1850 patients initiating another PAH-specific therapy), up to 20% of the total PAH population in the EU will be enrolled and observed. Given the voluntary participation in the study and the MAH projection of the estimated UPTRAVI uptake in the European marketplace, it may take at least 3 years to recruit 1184 UPTRAVI exposed patients and 1850 patients initiating another PAH-specific therapy. The total study duration would be at least 4.5 years.

Results of the propensity score analysis will be examined yearly to assess the number of patients excluded from the analysis by the trimming process. Depending on the findings, the sample size of either cohort may be revised.

Data analysis

Analyses will include descriptive statistics of the UPTRAVI exposed patients and patients initiating another PAH-specific therapy, at initiation of a new PAH-specific therapy and during the observation period.

In order to further characterise the UPTRAVI safety profile, the frequency and IRs will be calculated for important identified and potential risks including MACE and all-cause death in UPTRAVI exposed patients.

MACE and all-cause death IRs observed in UPTRAVI exposed patients will be compared with the rates observed in patients initiating a PAH-specific therapy other than UPTRAVI. A propensity score weighting analysis will be performed on a yearly basis and a summary effect measure will be calculated to provide a risk difference between the two cohorts with a 95% CI, as this method is more efficient when the sample size and number of events are limited, especially if the number of observations in each stratum is low. In order to achieve comparable treatment groups, the application of the propensity score methodology may result in patients being excluded from the analysis. As a precautionary measure, all the covariates collected at initiation of a new PAH-specific therapy, such as demographics, clinical characteristics, WHO FC, relevant medical history or current and prior PAH-specific therapies will be used to achieve a balance of patients between treatment groups. These covariates will be reported by treatment group. The number and proportion of patients excluded from the analysis will also be reported and further described in terms of patient/disease characteristics and incident MACE and all-cause death. Sensitivity analyses will examine the influence of various methods of handling missing covariate data on the results, in order to check the robustness of the results and to ensure that missing data have not had an undue influence. The statistical comparison of IRs will be complemented with a qualitative clinical approach.

Descriptive analysis of patient baseline characteristics of the two cohorts will be performed during the recruitment period and may lead to restriction of recruitment of patients initiating a PAH-specific therapy other than UPTRAVI (ie, based on WHO FC), in order to ensure that both cohorts capture similar patient populations. These analyses will enable an assessment of the representativeness of the study population relative to the overall European PAH population. Population-based data will be described from European PAH data observed in several contemporaneous large PAH national cohorts in Europe (COMPERA, UK Audit, French PAH Registry and SPAHR), in order to determine the generalisability of the study population to the European PAH population.

All analyses from this PASS will be reported at an aggregated level. The comparison of MACE and all-cause death rates will also be presented per country, per European and non-European groups, but used for descriptive purposes only due to study size limitations.

Clinical characteristics at initiation of a new PAH-specific therapy, and the UPTRAVI safety profile will be described overall and in the subset of patients over the age of 75 years.

Milestones

- Start of data collection September 2017
- Registration in the EU PAS register (ENCePP) in 2017 (EU PAS19085)
- Yearly reports to EMA
- Submission of final report 12 months after PRAC agreement that commitment is fulfilled

5 AMENDMENTS AND UPDATES

Global Protocol Amendment 7 Version 8.

6 MILESTONES

Milestone	**Planned date**
Final protocol submission	July 2016
Final protocol 2nd submission	November 2016
Final protocol 3rd submission	February 2017
Final protocol 4th submission	April 2017
Final protocol 5th submission	December 2019
Final protocol 6th submission	January 2021
Final protocol 7th submission	June 2022
Start of data collection	September 2017
<Registration in the EU PAS register (ENCePP)>	EU PAS19085; registered in 2017
<Interim report 1 submission>	March 2018
<Interim report 2 submission>	March 2019
<Interim report 3 submission>	March 2020
<Interim report 4 submission>	March 2021
<Interim report 5 submission>	March 2022
<Interim report 6 submission>	March 2023
<Interim report 7 submission>	March 2024
<Interim report 8 submission>	March 2025
End of data collection	at time of PRAC agreement that commitment is fulfilled
Final study report	12 months after PRAC agreement that commitment is fulfilled

7 RATIONALE AND BACKGROUND

7.1 Background

PAH is a rare, severe and progressive disease ultimately leading to right heart failure and death (McLaughlin 2004, Galiè 2016). PAH is characterised by vasculopathy with extensive remodelling of the pulmonary circulation resulting in narrowing of the arterial lumen and impaired flow-mediated vasodilation. The consequent increases in pulmonary artery pressure and pulmonary vascular resistance limit the ability of the right ventricle to pump blood through the lungs. The pathophysiology of PAH is thought to involve abnormal interactions between endothelial and smooth muscle cells, leading to vasoconstriction, vascular smooth muscle cell proliferation, vascular endothelial proliferation, and *in situ* thrombosis. Reduced prostacyclin synthase activity and IP receptor expression, an up-regulated endothelin system, and abnormalities of the nitric oxide pathway are considered important mediators of these pathologic changes, and form the therapeutic targets for currently available PAH-specific therapies (Chin 2008, McGoon 2009).

UPTRAVI (selexipag) is an orally available selective IP receptor agonist approved in the EU. UPTRAVI is indicated for the long-term treatment of PAH in adult patients with WHO FC II-III, either as combination therapy in patients insufficiently controlled with an endothelin receptor antagonist and/or a phosphodiesterase type 5 inhibitor, or as monotherapy in patients who are not candidates for these therapies (UPTRAVI SmPC).

Clinical and safety data for UPTRAVI were mainly obtained from the multicentre, double-blind, placebo-controlled event-driven Phase 3 clinical trial GRIPHON (AC-065A302), conducted in 1156 patients with PAH. UPTRAVI exposure in this trial was up to 4.2 years (217 weeks), with a median treatment duration of about 1.4 years (70.7 weeks). UPTRAVI demonstrated a 39% risk reduction compared with placebo in the occurrence of a first morbidity or mortality event up to end of treatment + 7 days (Sitbon 2015).

7.2 Rationale

In the past decade, the paradigm of clinical trials in PAH has changed, from short-term studies which evaluated exercise capacity, to both long-term outcome and combination therapy studies. While the benefits of the new agents and new treatment modalities are clearly established in large clinical trials, data are lacking on the impact of these new treatments and treatment modalities in the real-world setting. In addition, due to the improvement of survival and availability of new effective treatments, the demographics of PAH are changing, with a more aged population now being treated (UK Audit 2014).

However, this aged population is poorly represented in clinical trials and sparsely documented in clinical practice.

This PASS will provide contemporaneous observational data on the overall PAH population, including the aged patient population, in clinical practice. The prospective observational follow-up of patients newly treated with UPTRAVI (UPTRAVI cohort) allows this study to put the safety profile of UPTRAVI into real-world context, reporting on all-cause death and other important safety risks, including MACE. Additionally, the UPTRAVI cohort will be observed along with a cohort of patients newly treated with any other PAH-specific therapy who were never treated with UPTRAVI (Other cohort). This study aims to describe the clinical characteristics and outcomes of patients with PAH and to compare the incidence of MACE and all-cause death between UPTRAVI exposed patients and patients initiating another PAH-specific therapy. This PASS will be one of the largest cohort studies in PAH since the first large long-term outcome clinical trials were conducted (ie, SERAPHIN, AMBITION and GRIPHON). By providing real-world data of how UPTRAVI is used in the care of patients with PAH in the setting of new treatment modalities and earlier widespread use, and the impact of combination therapy on outcomes, the PAH community of health care providers and patients will benefit from a greater understanding of UPTRAVI in this post-marketing treatment paradigm.

This PASS for UPTRAVI is part of the European Risk Management Plan.

8 RESEARCH QUESTION AND OBJECTIVES

The purpose of this PASS is to further characterise the safety profile of UPTRAVI when used in clinical practice and to describe clinical characteristics and outcomes of patients newly treated with UPTRAVI compared with patients newly treated with any other PAH-specific therapy who were never treated with UPTRAVI, in the post-marketing setting.

8.1 Main objectives

1. To describe, overall and in the subset of patients over the age of 75 years, demographics, disease characteristics and clinical course in patients with PAH either newly treated with UPTRAVI (UPTRAVI exposed patients), or newly treated with any other PAH-specific therapy who were never treated with UPTRAVI (patients initiating another PAH-specific therapy).

2. To further characterise the UPTRAVI safety profile and estimate the incidence rates during the UPTRAVI exposure period of all-cause death and the following important identified or potential risks:
   - Hypotension
   - Anaemia

- Pulmonary oedema associated with PVOD
- Hyperthyroidism
- MACE (see definition in Section 9.3.2)
- Acute renal failure and renal function impairment
- Bleeding events
- Light-dependent non-melanoma skin malignancy
- Ophthalmological effects associated with the retinal vascular system
- Gastrointestinal disturbances denoting intestinal intussusception (manifested as ileus or obstruction)

3. To compare rates of MACE and all-cause death between UPTRAVI exposed patients and patients initiating another PAH-specific therapy, using a propensity score analysis.

9 RESEARCH METHODS

9.1 Study design

This is a multicentre, international, prospective, real-world, observational cohort study in patients with PAH who either initiated treatment with UPTRAVI less than 1 month prior to enrolment, at enrolment or during observation (UPTRAVI exposed patients, "UPTRAVI cohort", see Section 9.7.1 Analysis sets and groups), or initiated any other PAH-specific therapy less than 1 month prior to enrolment or at enrolment and were never treated with UPTRAVI (patients initiating another PAH-specific therapy "Other cohort", see Section 9.7.1 Analysis sets and groups). Patients may be unexposed to UPTRAVI at enrolment and initiate UPTRAVI for the first time during the observation period (late initiators), therefore data for these patients contribute to the Other cohort and subsequently to the UPTRAVI cohort.

The study protocol will not mandate any specific schedule of visits or investigations. Patients will be followed by their physician according to clinical practice.

Due to the recent approval of UPTRAVI in the market, no long-term real-world post-authorisation data are available to estimate the duration of UPTRAVI treatment in clinical practice. The study AC-065A302/GRIPHON median time of exposure to selexipag (70.7 weeks) was used as a proxy to assess a minimum observation period in real-world settings (Sitbon 2015). Thus, the planned observation period for each patient enrolled in the study will be at least 18 months from study enrolment, or until the earliest of death, withdrawal of consent, loss to follow-up, or study end.

9.2 Setting

The number of patients planned to be enrolled in the study is approximately 1184 patients with PAH who initiated UPTRAVI less than 1 month prior to enrolment, at enrolment or during observation (UPTRAVI cohort), and 1850 patients with PAH, who initiated any

other PAH-specific therapy less than 1 month prior to enrolment or at enrolment (Other cohort). Initiation of the new PAH-specific therapy is the starting point of the study observation period in both cohorts. However, as in a prospective observational setting, a time window after initiation of the new therapy should be allowed to give patients and site staff time to discuss study participation (ie, consenting process); thus a time window of less than 1 month from initiation of the new PAH-specific therapy (after study site initiation) to enrolment (ie, ICF signature) into EXPOSURE is allowed.

It is expected that approximately 20% of the study population will be over the age of 75 years, based on the age distribution of patients with PAH in the population-based UK registry (UK Audit 2014) in which 22% of the overall PAH population are older than 70 years.

To minimise selection bias during patient recruitment, participating sites are requested to invite all consecutive PAH patients who newly initiate a PAH-specific therapy and meet the eligibility criteria for either cohort (UPTRAVI patients/patients initiating another PAH-specific therapy, see Sections 9.2.1 and 9.2.2 Inclusion/exclusion criteria). Each site will keep a site log with information on the number of patients eligible, the number of patients approached about the study, and the number of patients who either refused to participate or were screening failures. Reason for refusal to participate or not being eligible will be captured. Additionally, information on sex, age range, new PAH-specific therapy initiated, and WHO FC will be collected in patients participating and not participating in the study (either because of patient refusal or screening failure), depending on local regulation.

9.2.1 Inclusion criteria at enrolment

- Patients ≥ 18 years old, and
- Signed patient ICF[4], and
- Group I PAH patients (Simonneau 2013), and
- Newly initiating UPTRAVI or any other PAH-specific therapy:
  - less than 1 month prior to enrolment, or
  - at enrolment

9.2.2 Exclusion criteria

- Patients previously exposed to UPTRAVI/selexipag treatment

[4] ICF will be offered by the physician and signed by the patient only after the decision is taken by the physician to treat or not the patient with UPTRAVI.

- Patients newly initiating any other PAH-specific therapy must not have been previously treated with that same drug
- Patients enrolled in any ongoing interventional clinical trial

Enrolment is defined as time of ICF signature or new PAH-specific therapy initiation, whichever occurs the latest.

After study site initiation, all eligible patients initiating a new PAH-specific therapy, including UPTRAVI, will be invited to participate in the EXPOSURE study. Patients having already initiated a new PAH-specific therapy, will have to sign the ICF within 1 month of initiation of the new PAH-specific therapy. Eligible patients who died within 1 month of treatment and were not able to be consented, will be included in the study database, where permitted by local regulation. Retrospective data collection will be conducted for these deceased patients during the course of the study on a continuous basis.

Patients initiating a PAH-specific therapy other than UPTRAVI, and who add a second new PAH-specific therapy during the course of the study, remain in the study in the Other cohort.

Patients initiating a PAH-specific therapy other than UPTRAVI, and who initiated UPTRAVI during the course of the study, will be followed in the UPTRAVI cohort from that point forward (see Section 9.3.2).

To avoid the exclusion from the propensity score process of a large proportion of patients initiating a PAH-specific therapy other than UPTRAVI, the distribution of WHO FC in UPTRAVI and Other cohorts will be monitored regularly during study recruitment. If the distribution of WHO FC is not balanced between the cohorts, recruitment of patients initiating a PAH-specific therapy other than UPTRAVI could be restricted to those with the adequate WHO FC.

A patient will be considered enrolled in the study once all eligibility criteria are met.

Patients will be recruited, and data will be collected in this observational prospective study in compliance with local regulations.

9.3 Variables

Information will be collected as available and per clinical practice visit schedule. Data will be entered by the investigator/study coordinator into a standardised eCRF.

Data will be collected for each patient at initiation of a new PAH-specific therapy and throughout the observational period from the existing medical record at any clinic visit on the respective eCRF. If a patient's data collection is terminated, the date and reason for termination of data collection must be recorded on the eCRF. The same data will also be

collected, in a retrospective setting, for eligible patients who died within 1 month of treatment and were not able to be consented, where permitted by local regulation.

Table 1 provides an overview of the variables collected at initiation of a new PAH-specific therapy and/or during the observation period (follow-up visits), if available, per clinical practice.

At initiation of a new PAH-specific therapy, the most recent data available within 3 months prior to/at initiation of a new PAH-specific therapy will be collected for WHO FC, 6MWD, laboratory data; and the most recent data available within 12 months prior to / at initiation of a new PAH-specific therapy will be collected for right heart catheterisation (RHC) haemodynamics. Other PAH-specific and non-PAH-specific therapies will be recorded if prescribed within 12 months prior to/at initiation of a new PAH-specific therapy, immunosuppressant / immunomodulatory medication prescribed any time prior to / at initiation of a new PAH-specific therapy will be collected.

Table 1 eCRF Data Collection (as Available per Clinical Practice From the Existing Medical Record)

Variable	Initiation of a new PAH-Specific Therapy	Follow-up (at any Clinical Practice Visit)
1 - Study specifics		
Visit date	**X**	**X**
Termination of data entry: date, reason		**X**
2 - Demographics		
Age, gender, country	**X**	
3 - Clinical characteristics		
PAH classification, aetiology, diagnosis date, WHO FC at diagnosis	**X**	
WHO FC (for initiation of a new PAH-specific therapy: within 3 months prior or at; and worsening of in the last 6 months prior to initiation of PAH-specific therapy; yes/no)	**X**	**X**
6MWD (for initiation of a new PAH-specific therapy: within 3 months prior or at)	**X**	**X**
Incremental shuttle walking test (for initiation of a new PAH-specific therapy: within 3 months prior or at)	**X**	**X**
Height	**X**	
Weight	**X**	**X**

Variable	Initiation of a new PAH-Specific Therapy	Follow-up (at any Clinical Practice Visit)
RHC haemodynamics: mPAP, mRAP, PAWP, PVR, cardiac index (for initiation of a new PAH-specific therapy: within 12 months prior or at)	**X**	**X**
% predicted DL_{CO}	**X**	
Pericardial effusion	**X**	
Vital signs: heart rate, systolic/diastolic blood pressure	**X**	
Transplantation list / pre-transplantation visit	**X**	**X**
Renal insufficiency (incl. worsening since last visit during follow-up)**	**X**	**X**
For females only:		
- child bearing potential	**X**	**X**
- currently pregnant (Yes***/No/Unknown)	**X**	**X**
4 - Laboratory data (within 3 months prior or at initiation of a new PAH-specific therapy)		
Haemoglobin	**X**	
Thyroid hormones (hs-TSH, free T3, free T4)	**X**	
NT-proBNP, BNP	**X**	**X**
5 - Medical history (any time prior to initiation of a new PAH-specific therapy)		
Cardiovascular/ cerebrovascular disease history (incl. year of occurrence):		
- History of myocardial ischaemia, MI, cardiac arrest, ischaemic cerebrovascular disorders, haemorrhagic cerebrovascular disorders, revascularisation procedure (coronary and/or carotid) and unstable angina	**X**	
- Cardiovascular risk factors history (cardiac arrhythmia, cardiac right to left shunts, history of valvular heart disease, cardiomyopathy, carotid and/or coronary artery arteriosclerosis, high BMI, diabetes mellitus, metabolic syndrome, smoking status, hyperlipidaemia, systemic hypertension, hypercoagulable state, sleep apnoea syndrome, alcoholism, use of illicit drugs)	**X**	
Other relevant medical history (incl. year of occurrence, number of episodes) *apply for any patient initiating UPTRAVI* (Hypotension, anaemia, pulmonary oedema associated with PVOD, hyperthyroidism, renal impairment, bleeding events, light-dependent non-melanoma skin malignancy, ophthalmological	**X**	

Variable	Initiation of a new PAH-Specific Therapy	Follow-up (at any Clinical Practice Visit)
effects associated with retinal disorder, intestinal intussusception manifested as intestinal obstruction / ileus)		
6 - Medication		
UPTRAVI or any other PAH-specific treatment - Drug name of all individual PAH-specific drug substances - Start date - Reason for start - Dosing regimen (date of up/down titration & dose at each step, maintenance dosing change, reason for dose reduction)	**X**	**X**
- Dose decrease or Discontinuation (date, reason, if due to AE for UPTRAVI [*]or for VELETRI/CARIPUL, OPSUMIT, TRACLEER/STAYVEER, OPSYNVI/YUVANCI[***])		**X**
- History of any PAH-specific therapy within the previous 12 months	**X**	
Other concomitant medications: - drug name - indication - route of administration - start /stop date - reason for use	**X**	**X**
- History of non-PAH-specific therapy within the previous 12 months	**X**	
Immunosuppressant/immunomodulatory medication (any time prior initiation of a new PAH-specific therapy) - Start and stop date(s)	**X**	**X**
7 - Outcomes		
Underlying or incident comorbidities[*] at time of the visit (tick box)		
apply for any patient initiating UPTRAVI - hypotension (if yes, blood pressure) - acute renal failure/renal function impairment (if yes, creatinine and creatinine clearance values) - bleeding event - anaemia (if yes, haemoglobin value) - pulmonary oedema associated with PVOD - hyperthyroidism (if yes, thyroid tests values)	**X**	**X**

Variable	Initiation of a new PAH-Specific Therapy	Follow-up (at any Clinical Practice Visit)
- light-dependent non-melanoma skin malignancy - ophthalmological effects associated with retinal vascular system - intestinal intussusception manifested as intestinal obstruction / ileus		
apply for all patients - non-fatal MI, non-fatal stroke (ischaemic stroke, haemorrhagic stroke), non-fatal cardiac arrest (incl. date of occurrence)	**X**	**X**
Hospitalisation *apply for all patients* - Yes*/No - PAH-related (Yes/No/Unknown) - admission/discharge dates - reason for hospitalisation (incl. coronary artery revascularisation and unstable angina)	**X**	**X**
All-cause death* *apply for all patients* - date and cause (incl. sudden death/sudden cardiac arrest, fatal MI, fatal stroke, fatal arrhythmia, fatal heart failure) - PAH-related (Yes/No/Unknown)		**X**
Other adverse events - *apply for patients treated with any PAH-specific product from the MAH* - any other AE on UPTRAVI, VELETRI/CARIPUL, OPSUMIT, TRACLEER/STAYVEER, OPSYNVI/YUVANCI, irrespective of seriousness and causality (if yes*, main event)		**X**

* The EDC system will request completion of an AE/ADR form for patients exposed to UPTRAVI, VELETRI/CARIPUL, OPSUMIT, TRACLEER/STAYVEER, OPSYNVI/YUVANCI regardless of seriousness and causality of the event; the following frequently known adverse reactions associated with the mode of action of selexipag (headache, diarrhoea, jaw pain, nausea, myalgia, vomiting, pain in extremity, flushing, arthralgia) will not be collected nor reported on an AE/ADR form, unless they fulfil any of the following: any seriousness criteria, lead to UPTRAVI discontinuation or dose reduction, introduction of symptomatic treatment or reflect an unusual pattern of severity based on prescriber's/investigator's medical judgment. These events will also be documented in the Safety Database and Medical Dictionary for Regulatory Activities (MedDRA) coded;

** Investigator/study coordinator will be requested to complete an AE/ADR form if based on their medical judgment a clinically relevant treatment emergent abnormality occurred while exposed to UPTRAVI, VELETRI/CARIPUL, OPSUMIT, TRACLEER/STAYVEER, OPSYNVI/YUVANCI during study participation, regardless of seriousness and causality;

*** The EDC system will request completion of an AE/ADR form for any pregnancy occurring in patient treated with PAH-specific product from the MAH (UPTRAVI, VELETRI/CARIPUL, OPSUMIT, TRACLEER/STAYVEER, OPSYNVI/YUVANCI) as well as for any AE leading to discontinuation or dose decrease of any of these products. These events will also be documented in the safety database and MedDRA coded.

6MWD = 6-minute walk distance; AE = adverse event; ADR = adverse drug reaction; BMI = body mass index; BNP = brain natriuretic peptide; CCB = calcium channel blocker; DL_{CO} = diffusion capacity of the lungs for carbon monoxide; EDC = electronic data collection; free T3 = free triiodothyronine; free T4 = free thyroxine; HIV = human immunodeficiency virus; hs-TSH = high-sensitivity thyroid-stimulating hormone; MI = myocardial infarction; mPAP = mean pulmonary artery pressure; mRAP = mean right atrial

pressure; NT-proBNP = N-terminal of the prohormone brain natriuretic peptide; PAH = pulmonary arterial hypertension; PAWP = pulmonary artery wedge pressure; PVOD = pulmonary veno-occlusive disease; PVR = pulmonary vascular resistance; RHC = right heart catheterisation; WHO FC = World Health Organization functional class.

For patients who initiated UPTRAVI during the observation period (late initiators, see definition in Section 9.7.1 Analysis sets and groups), the following variables will be collected at time of initiation of UPTRAVI (Table 1): the clinical characteristics section, NT-proBNP, BNP, the medical history section, the UPTRAVI treatment/other PAH-specific therapy section, the outcomes section and the AEs section. These variables may contribute to the treatment decision by the physician or influence clinical outcomes of interest and therefore be included as potential influential covariates in the propensity score model. The medical history section collected at time of UPTRAVI initiation will also be relevant to further characterise the safety profile of UPTRAVI.

9.3.1 Outcome definition and measures

To describe the PAH clinical course, the following outcomes will be evaluated in all patients with PAH:

1. Occurrence of hospitalisation (PAH-related/not related)
2. WHO FC change (from initiation of a new PAH-specific therapy/from previous visit)
3. Occurrence of all-cause death (PAH-related/not related/unknown)

To further characterise the UPTRAVI safety profile, the following outcomes will be evaluated in UPTRAVI exposed patients:

1. Occurrence of the following important identified or potential risks (Yes/No, according to physician judgment):
   - Hypotension
   - Anaemia
   - Pulmonary oedema associated with PVOD
   - Hyperthyroidism
   - Acute renal failure and renal function impairment
     - by category: acute renal failure or renal function impairment
     - composite outcome (occurrence of any of the above: Yes/No)
   - Bleeding events
   - Light-dependent non-melanoma skin malignancy
   - Ophthalmological effects associated with retinal vascular system
   - Intestinal intussusception manifested as intestinal obstruction/ileus
2. Occurrence of any other AEs
3. Discontinuation of UPTRAVI and reason for stopping

To compare rates of MACE and all-cause death, the following outcomes will be evaluated in UPTRAVI exposed patients and patients initiating another PAH-specific therapy:

1. Occurrence of MACE, defined as the occurrence of at least one condition falling into any of the below categories[5]:
    i. Death from cardiovascular causes (sudden death, fatal MI, fatal stroke, fatal arrhythmia)
    ii. Non-fatal MI
    iii. Non-fatal stroke (ischaemic stroke and/or haemorrhagic stroke)
    iv. Coronary artery revascularisation
    v. Unstable angina
    vi. Non-fatal cardiac arrest
        - by category
        - composite outcome (occurrence of any of the above: Yes/No)
2. Occurrence of all-cause death (PAH-related[6]/not related/unknown)

9.3.2 Exposure definition and measures

Observation period is defined as time from initiation of new PAH-specific therapy to the earliest of death, withdrawal of consent, loss to follow-up, or end of the study.

Exposure period is defined as time from initiation of new PAH-specific therapy to the earliest of discontinuation + 7 days of this therapy, death, withdrawal of consent, loss to follow-up, or end of the study.

Patients in the Other cohort who initiate UPTRAVI for the first time during the observation period (defined as late initiators for analysis purposes in Section 9.7.1) will be followed, from that point forward, as UPTRAVI exposed patients for analysis.

Per the inclusion criteria, patients initiating a PAH-specific therapy other than UPTRAVI should be naïve to UPTRAVI/selexipag; therefore, patients who discontinue UPTRAVI during the observation period are not eligible to enter the Other cohort.

Patients initiating a PAH-specific therapy other than UPTRAVI, and who add a second new PAH-specific therapy during the course of the study, remain in the study in the Other cohort.

9.3.3 Covariate definition and measures

The following covariates will be considered for analysis as well as for exploring their relationship to the safety-related outcomes:

[5] Category definitions in Annex 3.
[6] Definition in Annex 4.

1. Age at enrolment, gender
2. PAH medical history:
   - PAH aetiology, time since diagnosis
   - WHO FC, 6MWD, ISWT, haemodynamics from most recent RHC
3. Medical history of previous and ongoing clinically significant underlying diseases and comorbid conditions (eg, cardiovascular risk factors, renal insufficiency, diabetes mellitus)
4. Reason for new PAH-specific therapy prescription (eg, clinical worsening, other) and its treatment duration, maintenance dose and regimen
5. PAH-specific, non-PAH-specific and other therapies at new PAH-specific therapy initiation and during the observation period (including treatment exposure time)

9.4 Data sources

9.4.1 Identification of participating countries

The study will be conducted predominantly in several European countries based on the timing of UPTRAVI launch balanced against the need for representation of various European health care systems (eg, centralised/reference centre versus decentralised/nonreference centre; specialist versus non-specialist prescription), in order to provide a generalisable cohort of patients in clinical practice. Depending on UPTRAVI launch dates and study regulatory approvals, the participating countries may include Germany, France, Austria, Norway, Denmark, Finland, Sweden, the UK, Belgium, Switzerland, Ireland, the Netherlands, Czech Republic, Slovakia, Italy, Spain, Greece, Canada, Russia, and other countries, as needed, as UPTRAVI becomes commercially available.

9.4.2 Identification of participating study sites

EXPOSURE is collaborating with the COMPERA registry by connecting with the COMPERA network of sites. COMPERA is one of the largest international PH registries, with long standing expertise in the collection of PAH-specific data. It is an ongoing prospective registry of patients with newly initiated therapies for PH (NCT01347216).

EXPOSURE is collaborating with country-specific PAH networks which are well developed with long standing expertise in the care and management of PAH patients across defined national PAH reference centre networks.

Beyond these networks of sites, EXPOSURE will further invite sites who prescribe UPTRAVI and are not involved with COMPERA or other country-specific PAH networks.

The EXPOSURE study database will be sponsored by Actelion and owned by the MAH and will be independent from COMPERA or other country-specific PAH networks. Sites that participate in both studies will be asked to enter data in EXPOSURE and only after will the applicable data be transferred to COMPERA or to other country-specific PAH networks following agreement from the site and the respective patient.

9.4.3 eCRF data collection

The EXPOSURE eCRF is a stand-alone document, however it will be aligned with the COMPERA eCRF and EDC system. Data will be collected by the investigator / study coordinator for each patient at initiation of new PAH-specific therapy and throughout the observation period from the existing medical record at any clinical visit on the respective EXPOSURE eCRF. Retrospective data collection will be done, for those eligible patients who died within the first month of treatment and were not able to provide consent, where permitted by local regulation.

As a study site commitment statement and per local data protection regulations: all study sites (defined as investigator/ study coordinator) endeavour to collect information from physicians not participating in EXPOSURE, who may be involved in the care of the study patient, or other relevant sources (eg, family contact for vital status). Study sites will ensure this information is recorded in the eCRF.

9.5 Study size

A precision-based approach for the CI was used to determine the minimum number of UPTRAVI exposed patients needed to estimate the incidence rate of MACE within the PASS.

The true incidence of MACE in PAH is not available from population-based real-world data sources, except the contemporaneous and real-world observed data in the EXPOSURE database. An incidence of MACE of 3.0 per 100 person-years was observed among the entire study population in EXPOSURE, with a total of 30 patients with events over 992 person-years, based on the data cutoff on 30 November 2020. This was designated as an estimate of the background rate of MACE in the general PAH population in real-world settings.

Based on the above incidence rate, several permutations of the precision around the point estimate of 3.0 per 100 patient-years were reviewed to clarify the assumptions in determining the required sample size. In the AC-065A302/GRIPHON study, a 20% increase in MACE events [as defined in Section 9.3.1] was observed between the selexipag versus control treatment groups. This imbalance of MACE between the treatment arms, while raising concerns, has been viewed by the Committee for Medicinal Products for Human Use (CHMP) to be within the bounds of a positive benefit-risk balance. Therefore, an assumption in the calculation of the desired sample size is that an observed incidence of

MACE of approximately 20% above the background rate could be considered to be within the 95% margin of error and would indicate no difference from the true background incidence of MACE among patients with PAH. One further assumption is that the true incidence of the background rate of MACE in a real-world context, while unknown, could be presumed to be higher (or lower) than what was observed in the AC-065A302/GRIPHON study with strict inclusion/exclusion criteria. The determination of the precision around the point estimate of 3.0 per 100 person-years should reflect the uncertainty inherent in using clinical trial data to approximate real-world risk. A margin of error of approximately 30% is therefore considered appropriate to accommodate the uncertainty while not obscuring the true incidence of MACE among exposed patients.

For the sample size calculation, to observe a point estimate of 3.0 per 100 person-years with a 95% CI ranging from 2.07 to 3.93, at a minimum observation time of 18 months, approximately 888 UPTRAVI exposed patients are needed. The level of precision of +/– 0.9 per 100 person-years (half the width of the CI) equates to a relative precision of 31% of the point estimate. This provides a reasonable margin of error around the point estimate of the assumed background rate of MACE.

An increased risk for MACE among the UPTRAVI cohort within the PASS study would be indicated if the observed incidence exceeds the upper bound of the 95% CI of the observed background rate in the Other cohort.

Table 2 presents a selection of the permutations reviewed and further information (Table 3, Annex 5) and sensitivity analyses are presented in Annex 5.

Table 2 Number of UPTRAVI exposed patients required to be exposed for a minimum of 18 months in order to achieve various widths of the 95% CI around an IR of 3.0 per 100 person-years

IR	Precision*	Relative precision** (%)	Lower bound of the 95% CI#	Upper bound of the 95% CI#	Study size for UPTRAVI exposed patients (≥ 18 months)
3.00	0.75	25	2.25	3.75	1366
3.00	0.81	27	2.19	3.81	1171
3.00	0.90	30	2.10	3.90	949
3.00	0.93	31	2.07	3.93	888
3.00	1.05	35	1.95	4.05	697
3.00	1.20	40	1.80	4.20	534

* Precision is defined as half the width of the 95% CI
** Relative precision is defined as half the width of the confidence interval and expressed as a percentage of the point estimate incidence rate.
# Based on a Normal Approximation
CI = confidence interval; IR = incidence rate.

In order to achieve comparable treatment groups, the application of the propensity score methodology may result in patients being excluded from the analysis. According to the distribution of patients initiating another PAH-specific therapy in EXPOSURE as of 30 November 2020 data cutoff, additional 50-60% of patients initiating another PAH-specific therapy will be required for propensity score methodology. Thus, the comparator group will need 1450 patients initiating another PAH-specific therapy followed for at least 18 months.

To achieve at least 888 patients exposed to UPTRAVI and 1450 patients initiating another PAH-specific therapy followed for a minimum of 18 months, the study target of enrolment will be 1184 UPTRAVI exposed patients and 1850 patients initiating another PAH-specific therapy, assuming a patient retention rate of 75%.

It is also important to estimate the rate for other important safety concerns within this study. Given the study size, assuming a Poisson distribution with power of 0.80, will allow for the detection of any event above a rate of 0.1 in 100 person-years within the study population of 1100 UPTRAVI exposed patients (Machin 1997).

With a European prevalence of PAH ranging from 15 to 22.6 per million inhabitants (as observed in several European registries), the overall number of people with PAH in the 28 EU member states is estimated to be up to 17000 patients (Humbert 2006, Tueller 200, EscribanoSubias 2012, Jansa 2014). With a maximum study size of 3034 patients with PAH enrolled (ie, 1184 UPTRAVI exposed patients and 1850 patients initiating another PAH-specific therapy), up to 20% of the total PAH population in the EU will be enrolled and observed. Given the voluntary participation in the study and the MAH projection of the estimated UPTRAVI uptake in the European marketplace, it may take at least 3 years to recruit 1184 UPTRAVI exposed patients, and 1850 patients initiating another PAH-specific therapy. The total study duration would be at least 4.5 years.

Results of the propensity score analysis will be examined yearly to assess the number of patients excluded from the analysis by the trimming process. Depending on the findings, the sample size of either cohort may be revised.

9.6 Data management

ICF must be signed prior to start of data collection. Retrospective data collection will be done for those eligible patients who died within the first month of treatment and were not able to provide consent, where permitted by local regulations.

A secure, internet-based EDC system will be used for data entry and hosting. An audit trail will be maintained by the EDC system for all data entries and changes, indicating what entries/changes have been made, who made them, and when. Data will be transferred over

the internet via a secure file transfer protocol and will be stored in a secure database protected from unauthorised access.

Sites will keep a simple site log with information on the number of patients eligible, the number of patients approached about the study, the number of patients who refused to participate, not meeting inclusion/exclusion criteria, or deceased. Reason for refusal to participate or not being eligible will be captured, where possible. For patients who died within 1 month of treatment and before being able to be consented, retrospective data collection will be conducted during the course of the study on a continuous basis.

Data for all participating patients will be entered by the investigator / study coordinator into an eCRF. The investigator/study coordinator is responsible for ensuring the completeness and timeliness of the data reported. All data collected will be de-identified before transmission to the central study coordinating centre. Patient names will not be collected. Other patient identifiers will be collected in order to allow identification of study patients when AEs on study patients are received by the Drug Safety department outside of the PASS, in order to avoid double counting in the Safety database (see Section 11.4).

The treating physician should record the final diagnosis and relevant medical information on the eCRF and, if applicable, the same information is to be reported on an AE/adverse drug reaction (ADR) form.

9.7 Data analysis

A Statistical Analysis Plan (SAP) will be written and finalised before any interim report. The SAP will provide full details of the analyses, the algorithms to be used for data derivations and handling of missing data. SAS® statistical software will be used for analysing the data (SAS Institute, Inc., Cary, North Carolina).

All data analysis will be exploratory. Continuous variables will be summarised using mean, median, standard deviation, minimum, maximum, upper and lower quartiles. Categorical variables will be summarised using counts and percentages. Unless otherwise specified, the number of patients with available data (n) will be used in the calculation of summary statistics.

9.7.1 Analysis sets and groups

The following analysis sets will be defined:

– **All Set** (ALL): All patients present in the database at the time of the database cut (defined annually) with an available PAH-specific therapy initiation date. No analyses are foreseen for this set. This set will only be used to provide the overall number of study patients.

– **Enrolled Set** (ENR): All patients present in the database at the time of the database cut (defined annually) with an available PAH-specific therapy initiation date, and who meet all the eligibility criteria.

– **Follow-Up Set** (FUP): All "Enrolled Set" patients who have at least one follow-up information (ie, follow-up visit date, death date, hospitalisation start date, medication discontinuation date, medication interruption date or medication dose change date) after their PAH-specific therapy initiation date.

– **Propensity Score Analysis Set** (PSA): All patients from the Follow-Up Set contributing to the outcome models in the propensity score analyses.

– **Propensity Score Excluded Set** (PSE): All patients from the Follow-Up Set that do not contribute to the outcome models in the propensity score analyses, due to either missing covariates required to calculate the propensity score, or patients that have been discarded due to trimming of the propensity score (see Section 9.7.5) or other reasons.

Late initiators, defined as patients initiating a PAH-specific therapy other than UPTRAVI at enrolment and initiating UPTRAVI for the first time during the observation period, will contribute person-time to the UPTRAVI and Other cohorts accordingly, as follows:

– **Other (PAH-specific therapy) cohort**:

- Data from patients who initiated any other PAH-specific therapy less than 1 month prior to enrolment or at enrolment and who were never treated with UPTRAVI,
- Data from patients who died within the first month of any other PAH-specific therapy initiation (after study site initiation) and before being able to be consented (enrolment), and
- Data collected during the period of time prior to UPTRAVI initiation for late initiators (ie, patients who initiate treatment with UPTRAVI after enrolment).

– **UPTRAVI cohort**:

- Data from patients who initiated treatment with UPTRAVI less than 1 month prior to enrolment or at enrolment,
- Data from patients who died within the first month of UPTRAVI initiation (after study site initiation) and before being able to be consented (enrolment), and
- Data collected after UPTRAVI initiation for late initiators.

A patient will never contribute to both the UPTRAVI and Other cohorts at the same point in time during the study. Any event will be counted only once (in the exposure category in which the patient is accumulating person-time at the time the event occurs). However, a patient originally initiating a PAH-specific therapy other than UPTRAVI might

subsequently become eligible to enter the UPTRAVI cohort. Per the inclusion criteria, patients initiating a PAH-specific therapy other than UPTRAVI should be naïve to UPTRAVI/selexipag, therefore patients who discontinue UPTRAVI and initiate any other PAH-specific therapy are not eligible to enter the Other cohort.

Cohort entry is therefore defined as the date of UPTRAVI initiation (UPTRAVI cohort) or the date of the other PAH-specific therapy initiation (Other cohort). On the cohort entry date, patient characteristics will be recorded. The cohort entry date will be considered as baseline date in the analyses.

9.7.2 Patient characteristics and clinical course

Clinical characteristics at initiation of a new PAH-specific therapy, demographics, relevant medical history, prior exposure to another PAH-specific therapy and comorbidities will be summarised for all enrolled patients, and separately for the UPTRAVI and Other cohorts at initiation of a new PAH-specific therapy. Summary statistics will include mean, median, standard deviation, minimum, maximum, upper and lower quartiles, and 95% CI. Categorical variables will be summarised using counts, percentages and 95% CI.

These summaries will be produced during the recruitment period on a regular basis and may lead to recruitment restrictions regarding WHO FC for patients initiating a PAH-specific therapy other than UPTRAVI, in order to ensure both cohorts capture similar patient populations. Additionally, these summaries will be used to contrast the characteristics of the EXPOSURE population with the overall European PAH population observed in several contemporaneous large PAH observational cohorts in Europe: COMPERA (academic Pulmonary Hypertension disease registry, large proportion of German representation), UK Audit (PH national disease registry in UK, government driven), French PAH Registry (PAH national disease registry, government driven) and SPAHR (Swedish PH Registry, government driven), in order to assess how the study population reflects the characteristics of patients with PAH in Europe.

Similar descriptive statistics will be provided for European and non-European patient populations in EXPOSURE separately to assess heterogeneity.

The same variables will also be summarised for all patients in the Follow-Up Set, at initiation of any other PAH-specific therapy for the patients initiating a PAH-specific therapy other than UPTRAVI and at UPTRAVI initiation for all UPTRAVI patients.

Clinical characteristics collected during the observation period (as listed in Section 9.3), will be summarised at the last follow-up visit of the observation period for all patients in the Follow-Up Set.

Similar summaries will be produced for all variables as listed in Section 9.3. The complete list of tables to be produced will be developed prior to starting analysis of data and will be included in the SAP.

9.7.3 Exposure to UPTRAVI

Exposure to UPTRAVI will be described in terms of duration, maximum dose received in the titration period, maintenance dose and maintenance dose changes in all exposed patients. The exposure time will be summarised by dose, and the cumulative distribution of exposure time by different class intervals (ie, at least 4 weeks, at least 8 weeks, at least 12 weeks, etc) will be summarised to show the number and percentage of patients in each class interval. Counts and percentages of patients within each individual maintenance dose level will also be summarised.

A patient who discontinues UPTRAVI treatment for more than 7 days will only contribute to the comparison analysis in the UPTRAVI cohort up to the first treatment interruption date + 7 days. The same rule will apply for patients who discontinue any other PAH-specific therapy for more than 7 days in the Other cohort.

9.7.4 UPTRAVI safety profile

In order to further characterise the UPTRAVI safety profile, the frequency and IRs of important identified and potential risks as described in Section 9.3.2 and all-cause death during the exposure period will be calculated in the UPTRAVI exposed patients. For these analyses, all periods of UPTRAVI exposure will be included. A patient may interrupt UPTRAVI treatment and restart at a later date during the observation period. Breaks in UPTRAVI treatment longer than 7 days are excluded. However, breaks shorter than, or equal to 7 days are included.

IRs will be calculated based on the number of patients with the event (numerator) divided by the total duration of the exposure period (denominator) and expressed per 100 person-years, with associated 95% CI, based on a generalised linear model assuming a Poisson distribution, and using log (duration of exposure time) as an offset. For patients experiencing an event, only the exposure until the first event will be included in the calculation of IRs.

Kaplan-Meier estimates of the proportion of event-free patients during the exposure period will be displayed with 95% two-sided confidence limits. For the analysis of events occurring during exposure, the time (months) to first event will be calculated as follows: Time to first event=date of event-treatment start date+1. Patients who do not experience an event will be right censored at the end of the exposure period.

Immortal-time bias methods are described in Section 9.7.6.

9.7.5 MACE and all-cause death

9.7.5.1 Main analysis

The rates of MACE and all-cause death will be compared between UPTRAVI exposed patients and patients initiating another PAH-specific therapy using a propensity score weighting analysis, as this method is more efficient when the sample size and number of events are limited, especially if the number of observations in each stratum is low.

To account for potential survivor bias effect in the analysis (eg, survivor bias either for fatal or non-fatal events during observation period), only the first exposure period of UPTRAVI / other PAH-specific therapy will be included in the UPTRAVI and Other cohorts, respectively. MACE and all-cause death IRs used for this comparison may differ from IRs calculated for safety profile characterisation where safety data will be calculated for all UPTRAVI exposure periods of patients (eg, if there have been two periods of UPTRAVI exposure separated by more than 7 days of treatment interruption, the safety data will include events from both periods of UPTRAVI exposure to address the study objective to characterise the UPTRAVI safety profile). Immortal-time bias methods are described in Section 9.7.6.

The propensity score of each individual patient on entry into the UPTRAVI and Other cohorts will be calculated using a logistic regression model that includes all observed influential covariates such as demographics, clinical characteristics, WHO FC, relevant medical history or current and prior PAH-specific therapies. Selection of variables to adjust and include in the propensity score modelling will be factors that are associated with both treatment exposure and outcomes. Late initiators will have their propensity score re-assessed at the time of UPTRAVI initiation (on entry into the exposed cohort). Further details can be found in the SAP.

Handling and imputation rules for missing covariates will be described in the SAP.

The quality of the propensity scores will be evaluated using two types of comparisons: comparing the distributions of the scores across the two cohorts (common support) and comparing the distributions of each covariate across the two cohorts (balance).

Common support will be assessed graphically, by plotting the distributions of the propensity scores for each cohort. If the distributions do not overlap entirely, or show substantial areas of non-overlap, the samples will be trimmed by discarding cases in the region of non-overlap. Trimming may occur at both ends of the propensity score scale, based on scores below the minimum of the UPTRAVI cohort in a first step and scores above the maximum of the Other cohort in a second step. If non-overlap in propensity scores still extends between the tails, then the steps may be repeated sequentially, removing additional percentiles until the propensity distributions overlap. Trimmed cases will be

flagged, and corresponding patients identified as part of the PSE Set, while cases used in the analyses will be flagged and corresponding patients identified as part of the PSA Set.

The balance of each covariate will also be assessed graphically, by overlaying the cumulative distributions of the propensity score for the two cohorts. Such assessments are focused on the similarity of means in the two cohorts, as well as comparison of variances. Evidence of imbalance will suggest that the propensity score adjustment will not be sufficient to remove the effects of the covariates that are not balanced. In such a circumstance, the statistical model used to create the propensity scores may be re-assessed.

The treatment effect will be estimated using IRs as described in Section 9.7.4. A poisson model will be used to compare the IRs of MACE and all-cause death between UPTRAVI exposed patients and patients initiating another PAH-specific therapy. In case of under or over-dispersion, a negative binomial model will be considered. These analyses will be produced on the PSA Set. The two-sided 95% Wald CI will be calculated for the relative reduction in mean annualised rates for UPTRAVI exposed patients (UPTRAVI cohort) compared with patients initiating another PAH-specific therapy (Other cohort) during the exposure period.

All covariates used to achieve the balance of patients between cohorts will be summarised for both the PSE Set and the PSA Set. The PSE Set will be further described by summarising the IRs of MACE and all-cause death with associated 95% CI, as described above in both UPTRAVI exposed patients and patients initiating another PAH-specific therapy.

The treatment pattern of all PAH-specific drug substances including UPTRAVI (mono and combination therapy) will be observed and described on an annual basis. Exploratory analyses will be performed for comparison between specific drugs or specific combinations of products.

9.7.5.2 Sensitivity analyses

To investigate the effect of late initiators on the PSA sensitivity analyses using the Intention To Treat approach (ie, without considering late initiators) will be performed.

Despite the measures implemented to prevent missing data, it is expected that some of the key covariates data needed in the propensity score model described above will be missing. The impact of missing data will be assessed to check the robustness of the results and to ensure that missing data have not had an undue influence on the results.

Sensitivity analyses demonstrating the influence of different methods of handling missing covariate data on the results will be considered:

- Given the possibility of non-random missing data, an analysis using 'Pattern Mixture' model for propensity score estimation will be conducted. This model will utilize the pattern of missing data in the propensity score model (D'Agostino 2001, Qu 2009). A summary of the patterns will be provided in tabulated format, with number and proportion of values missing for each pattern. This approach will fit a separate propensity score model for each distinct missing covariate data pattern, therefore patterns may be pooled together if the number of observations is not sufficient to run the propensity score model (Qu 2009).
- Multiple imputation will also be used for data missing at random, with the treatment and outcome variables used as covariates in the imputation model (Crowe 2010). Multiple imputation is a Monte Carlo technique in which each missing covariate value is replaced by M > 1 simulated versions. Each of the simulated datasets will therefore be complete and the results will be combined to produce estimates and CI that incorporate missing data uncertainty.

Other sensitivity analyses evaluating the influence of different weighting methods may also be considered. Full details will be described in the SAP.

9.7.5.3 Clinical qualitative assessment

The statistical comparison of IRs will be complemented with a qualitative clinical approach. All qualifying events will be assessed by their primary organ manifestation and demographic characteristics. Any cluster in a specific organ system (central nervous system, coronary system) would be clinically relevant for the purpose of a benefit-risk assessment. For example, if the imbalance is solely driven by haemorrhagic stroke, this finding would be more relevant than if imbalance is composed of a mix of haemorrhagic and ischemic events.

9.7.6 Immortal-time bias methods

Immortal-time bias may occur due to variable new PAH-specific therapy exposure times prior to study enrolment (ie, patients need to survive to the treatment initiation period occurring prior to study enrolment). Both cohorts include patients exposed for up to 1 month prior to enrolment (ICF signed), potentially resulting in immortal bias. This immortal-time bias is eliminated by including in the study database, where feasible per local regulation, patients who initiated a new PAH-specific therapy after study site initiation, died within the first month of treatment and were not able to be consented (ie, eligible patients who did not survive the treatment period occurring before enrolment/ICF signature). Observation period for all patients will start at time of new PAH-specific therapy initiation.

9.7.7 Definition of subgroups

All analytic results from this PASS will be reported at an aggregated level. The comparison of MACE and all-cause death rates will also be presented per country, per European and non-European groups, but used for descriptive purposes only due to study size limitations.

Clinical characteristics of patients at UPTRAVI/other PAH-specific therapy initiation, and the UPTRAVI safety profile will also be described in the subset of patients over the age of 75 years.

9.7.8 Missing data

Due to the non-interventional aspect of the study, some study variables are expected to be missing or incomplete and will be reviewed on a periodic basis for missing data points and incomplete information. Rules for handling of missing or incomplete dates will be described fully in the SAP. Handling and imputation rules for missing covariates used in the propensity score calculations are described in Section 9.7.5.2 and will be fully described in the SAP. The extent of the missing data and the impact on the comparison made between UPTRAVI exposed patients and patients initiating another PAH-specific therapy will be assessed by summarising data in both the PSE Set and the PSA Set as described in Section 9.7.5.

9.8 Quality control

The use of the EDC system will allow for online data quality checks upon data entry. In order to minimise missing information, a data quality plan will be developed per current guidance on best practice for missing data reduction (Gliklich 2014, PARENT 2015). It will focus on reducing the amount of missing data, including identification of variables believed to have a high impact on the robustness of propensity score and study overall. If these variables would be identified as missing, scientific/medical and data plausibility reviews of these results will be performed resulting in queries to the site. The eCRF will have pre-programmed automatic edit checks for data inconsistencies at the time of data entry, and the resulting queries will be addressed by the site.

Clinical research associates (CRAs) dedicated to the study will be assigned per study site. Centralised remote monitoring will be performed regularly via the EDC tool, telephone calls and additional on-site visits may be conducted, if needed. Educational measures and training focused on the importance of capturing all available data will be developed. CRAs will discuss data entry performance thresholds (ie, time intervals of data entry) with study sites.

This approach will allow proactive monitoring and querying of data on an ongoing and regular basis to ensure high data quality. A systematic data query will be implemented for safety profile related data, hospitalisations and all-cause death to retrieve missing

information and encourage AEs reporting. Communication with investigators/study coordinators via dedicated CRAs involvement, newsletters, meetings and other interactions will emphasise the importance of data entry completion. Analytical methods described in Section 9.7.8 will be applied to assess the extent of the missing data and the impact on the comparison made between UPTRAVI exposed patients and patients initiating another PAH-specific therapy.

To minimise the number of patients lost to follow-up, when no data entry occurs for a patient for more than 6 months (based on the assumption that the number of clinical visits on average ranges from 2 to 4 visits per annum), investigators / study coordinators will be asked via the EDC system and/or centralised remote monitoring to either report any visit that may have occurred or record that no visit occurred since last follow-up. If the patient cannot be reached, the study site must make a reasonable effort to contact the patient, document all attempts and enter the loss of follow-up information into the eCRF. Regarding the occurrence of death, the site will be instructed to attempt to retrieve the information from the family or other treating physicians outside of the study site (eg, medical reports, death certificates) at least three times.

If the patient moves from one study site to another during the course of EXPOSURE, data collected in the eCRF from the former site will be linked with data from the new site to ensure data collection continuity without duplication. Study site personnel will be alerted to this process during the site initiation visit and reminded during the course of the study through CRA remote monitoring and topic-focused newsletters.

The study will be conducted in accordance with the International Society for Pharmacoepidemiology (ISPE) *Guidelines for Good Pharmacoepidemiology Practices (GPP)* (ISPE 2015) and in accordance with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) *Guide on Methodological Standards in Pharmacoepidemiology* (ENCePP 2015).

9.9 Limitations of the research methods

This PASS is a non-interventional study examining patients newly exposed to UPTRAVI and patients newly exposed to any other PAH-specific therapy who were never exposed to UPTRAVI in real-world clinical settings. New PAH-specific therapy, including UPTRAVI, will be based on prescriber/investigator decision and will not be influenced by participation in the PASS. The patients will be followed by their physician according to clinical practice. The study protocol will not mandate any treatment, procedures or visits.

Any interpretation of observational study results should consider limitations to observational real-world study designs, including potential sources of selection or information biases, and confounding. Methodological approaches which address relevant design limitations are included below:

To provide a generalisable cohort of patients with PAH within Europe, broad enrolment of patients treated within the different health care systems in Europe is planned (eg, centralised/reference centre versus decentralised/nonreference centre; specialist versus non-specialist prescription). In addition, study population characteristics will be contrasted with the overall European PAH population observed in several contemporaneous large PAH observational cohorts in Europe (from Germany, UK, France and Sweden), to assess how the study population reflects characteristics of patients with PAH in Europe. Descriptive analyses by European vs non-European patient populations in the study will be provided to assess potential heterogeneity and, then European representativeness of the overall study cohort.

A data quality initiative will be put in place to encourage similar data capture across cohorts, as a mitigation strategy. Intensity of follow-up (number of visit per year and per patient) will be assessed for UPTRAVI exposed patients and patients initiating another PAH-specific therapy in order to monitor a potential differential surveillance bias between UPTRAVI exposed patients and patients initiating another PAH-specific therapy, as patients initiating a treatment with a titration phase (UPTRAVI) may be more carefully followed by their physician, and because more data are being requested on UPTRAVI exposed patients versus patients initiating another PAH-specific therapy.

To minimise selection bias, participating sites will be requested to invite all consecutive PAH patients initiating a new PAH-specific therapy who meet the eligibility criteria, regardless of other previous or concomitant PAH-specific therapy received. Reasons for patient refusal to participate and screening failure will be recorded to capture any potential systematic bias in non-participation.

All patients in this PASS will be new users of either UPTRAVI or any other PAH-specific therapy. To eliminate potential immortal-time bias, patients who initiated a new PAH-specific therapy after study site initiation, died within 1 month of treatment and were not able to be consented, will be included in the study database, where feasible according to local regulation. The observation period for all patients will start at time of new PAH-specific therapy initiation. In addition, a patient who discontinues UPTRAVI / other PAH-specific therapy for more than 7 days will only contribute to the comparison analysis in the UPTRAVI/Other cohort up to first treatment interruption date + 7 days.

To ensure that UPTRAVI and Other cohorts capture similar patient populations, descriptive analyses of patient characteristics of the two cohorts will be conducted during the recruitment period and may lead to inclusion/exclusion criteria restrictions (see Section 9.7.2). UPTRAVI exposed patients and patients initiating another PAH-specific therapy may still differ in the distribution of patient characteristics, therefore a stratification method using propensity scores will be applied to assess comparability of the cohorts and avoid channelling bias. MACE and all-cause death rate comparisons will be based on the

overlap of the propensity scores, and the proportion of patients in the region of overlap of the propensity scores will be described. Patient characteristics and IRs of MACE and all-cause death will also be summarised for patients excluded from the propensity scores analysis in order to assess the level of difference with the population used in the analyses (PSE Set and the PSA Set) (see Section 9.7.5).

The targeted study size will represent up to 20% of the total PAH population in Europe. Based on the MAH projection of estimated UPTRAVI uptake (September 2015), patients from the UPTRAVI cohort may represent more than 30% of the overall UPTRAVI treated population in Europe in 2019. Thus, the study size is considered sufficient to generate a large body of data to further characterise the use of UPTRAVI in the European PAH population.

The study design allows a robust description of UPTRAVI use and its safety profile in clinical practice and a comparison of MACE and all-cause death rates of UPTRAVI patients with a contemporaneous cohort of PAH patients newly treated with any other PAH-specific therapy.

9.10 Other aspects

Not applicable.

10 PROTECTION OF HUMAN SUBJECTS

- Institutional Review Board (IRB) / Independent Ethics Committee (IEC) approval:

Depending on local regulations and the physician's institutional policies, and in compliance with local law, the physician may have to submit the study protocol, the form for the Patient Informed Consent, and other relevant information to an IRB/IEC, local health authorities, data protection agency or others. Approval from the IRB/IEC must be obtained before going through a consent procedure with the patient and before entering data into the database. IRB/IEC information/approval should be documented in a letter to the physician, clearly identifying the study, the documents reviewed, and the date of approval.

- Patient informed consent:

The participating physician commits to obtaining approval for the ICF from their respective Research Ethics Board, if required by applicable site policies, national privacy regulations and other state and local laws relating to medical information, prior to commencement of the project. Moreover, the participating physician will obtain a signed ICF from each patient (or legal guardian) whose data will be included in the project. For patients who initiated a new PAH-specific therapy, including UPTRAVI, died within 1 month of treatment and were not able to be consented, local regulations for retrospective data collection on deceased patients will be applied. The ICF will include language to obtain

patient consent for study site personnel to contact current and former treating physicians to obtain relevant data not available at study site (eg, specifics on prior treatment). Consent will also be requested to contact patient family members to obtain information on the patient's vital status in the event that the patient is lost to follow-up.

ICF will be proposed by the physician and signed by the patient only after the decision is taken by the physician to treat or not the patient with a PAH-specific therapy, including UPTRAVI. The patient ICF will be developed as a short and concise document understandable by the participants. This includes short sentences and paragraphs, use of lay language and tables/pictures as appropriate, in compliance with the European clinical trial regulation (EU-CTR 536/2014).

- Patient confidentiality:

By signing the protocol, the participating physician commits to comply with all related applicable local laws and regulations, as well as any applicable EU regulations, such as the *EU Data Protection Act*.

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS / ADVERSE REACTIONS

With reference to collecting, processing and expediting of AE reports, the sponsor of this prospective non-interventional study complies with international and national pharmacovigilance regulations.

Details on the nature of AE reports, seriousness criteria and causality assessments, action taken (such as decreasing, interrupting, or stopping) with UPTRAVI, VELETRI/CARIPUL, OPSUMIT, TRACLEER/STAYVEER, OPSYNVI/YUVANCI, and event outcome are collected within the safety database and are included in the analyses of the consequent periodic benefit-risk evaluation report (PBRER) for the respective product.

For the purpose of AE/ADR solicited in this PASS, the PAH-specific marketed products from the MAH include: UPTRAVI, VELETRI/CARIPUL, OPSUMIT, TRACLEER/STAYVEER, OPSYNVI/YUVANCI.

11.1 Definitions

11.1.1 Adverse event or adverse experience

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding or lack of expected pharmacological action), symptom, or disease

temporally associated with the use of a medicinal product, whether or not related to the medicinal product (annex 1 of Good Pharmacovigilance Practice).

A treatment-emergent AE is any AE which has been found to be temporally associated with the use of a product from the MAH administered in a patient enrolled in this PASS.

AEs include:

- Recurrence or worsening of a pre-existing disease.
- Increase in frequency or intensity of symptoms of a pre-existing disease or medical condition.
- Continuous persistent disease or symptoms present at enrolment/initiation of treatment that worsen following the start of the study.
- Abnormal assessments, eg, vital signs, or physical examination findings, if they represent a clinically significant finding that was not present at enrolment/initiation of treatment or worsened during the course of the study.
- Laboratory test abnormalities if they represent a clinically significant finding, symptomatic or not, which were not present at enrolment/initiation of treatment or worsened during the course of the study or led to interruption or permanent discontinuation of marketed MAH product.
- In addition to AEs, exposure during pregnancy or lactation, product complaints, medication errors, overdose, misuse, abuse, occupational exposure and transmission of an infectious agent via marketed MAH product and the identification of a potential counterfeit medicinal product needs to be reported.
- Reports of UPTRAVI off-label use without an associated AE collected within non-interventional studies shall be included.

AEs do not include:

- Medical procedures such as surgery, endoscopy, tooth extraction. However, the event that led to the intervention is considered an AE.
- Situations in which no undesirable change occurred, such as hospitalisation for cosmetic surgery or for social reasons.

Adverse drug reaction

- An ADR is defined as a response to a medicinal (investigational or non-investigational) product that is noxious and unintended. The phrase “response to a medicinal product” means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. The phrase “a reasonable possibility” means that there are facts, evidence, or arguments to support a causal association with the medicinal product.

- An ADR, in contrast to an AE, is characterized by the fact that a causal relationship between the medicinal product and the occurrence is suspected. All AEs judged by either the reporting physician or the sponsor as having a reasonable causal relationship to a medicinal product qualify as ADRs.

11.1.2 Serious adverse events

A serious adverse event (SAE) is defined by the International Council for Harmonisation guidelines as any AE fulfilling at least one of the following criteria:

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

The following reasons for hospitalisations are exempted from being reported:

- Hospitalisations for cosmetic elective surgery, or social and/or convenience reasons.
- Hospitalisation for pre-planned (prior to initiation of a new PAH-specific therapy) standard monitoring of a pre-existing disease (present at initiation of a new PAH-specific therapy) or medical condition that did not worsen, eg, hospitalisation for coronary angiography in a patient with stable angina pectoris.
- Hospitalisations for elective treatment of a pre-existing disease (present at initiation of a new PAH-specific therapy) or medical condition that did not worsen, eg, elective hip replacement for arthritis.

However, complications that occur during such hospitalisations are AEs or SAEs (for example, if a complication prolongs hospitalisation) and should be reported as described below.

11.1.3 Product Quality Complaints

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labelling, or packaging, ie, any dissatisfaction relative to the identity

quality, durability, reliability, or performance of a distributed product, including its labelling, drug delivery system, or package integrity. A PQC may have an impact on the safety and efficacy of the product. In addition, it includes any technical complaints, defined as any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or the drug delivery system. For the following PAH-specific marketed products from the MAH (UPTRAVI, VELETRI/CARIPUL, OPSUMIT, TRACLEER/STAYVEER, OPSYNVI/YUVANCI), PQCs are to be reported.

For PQC in patients not receiving any PAH-specific products from the MAH, it is the prescriber's/investigator's responsibility to report these PQCs to the corresponding manufacturer, as applicable.

11.1.4 Overdose

For this study, any dose of sponsor-marketed medication (UPTRAVI, VELETRI/CARIPUL, OPSUMIT, TRACLEER/STAYVEER, OPSYNVI/YUVANCI) higher than the planned total daily dose in a single day according to approved medication label will be considered an overdose.

11.1.5 Relationship to the use of marketed PAH-specific product(s) from the MAH

Each AE must be assessed by the investigator as to whether or not there is a reasonable possibility of causal relationship to marketed PAH-specific product(s) from the MAH that were ongoing at the time of AE onset, and reported as either related or unrelated. The determination of the likelihood that the marketed PAH-specific product from the MAH caused the AE shall be provided by an investigator who is a qualified physician.

11.2 AE/SAE reporting

This section describes the rules and processes for AEs/ADRs reported in UPTRAVI exposed patients as well as patients exposed to other PAH-specific products from the MAH during the PASS observation period (see specific variables identified in Table 1 by *, ** and ***).

UPTRAVI exposed patients

For UPTRAVI exposed patients, the EDC system will request completion of an AE/ADR form for all AEs occurring during PASS participation irrespective of seriousness and causality (for definitions please refer to Section 11.1). These AEs/ADRs will be recorded in the safety database and coded using the Medical Dictionary for Regulatory Activities (MedDRA).

The following frequent known adverse reactions associated with the mode of action of selexipag (headache, diarrhoea, jaw pain, nausea, myalgia, vomiting, pain in extremity,

flushing, arthralgia) will not be collected nor reported on an AE/ADR form, unless they fulfil any of the following:

- any seriousness criteria (see Section 11.1.2),
- lead to UPTRAVI discontinuation or dose reduction,
- require symptomatic therapy
- reflect an unusual pattern of severity based on prescriber's/investigator's medical judgment.

For patients who initiated UPTRAVI less than 1 month prior to study enrolment, AE/ADR forms will also be requested to be completed at enrolment for all specific variables identified in Table 1 by *, ** and *** (renal insufficiency, currently pregnant, discontinuation from any PAH-specific product from the MAH if due to AE, underlying or incident comorbidities at time of the visit, hospitalisation, all-cause death and other AEs) for the period of time between UPTRAVI initiation and enrolment. Same will apply to patients who initiated UPTRAVI after study site initiation, died within 1 month of treatment and were not able to be consented, per local regulation.

Patients treated with other PAH-specific products from the MAH

For the variables collected in the eCRF in patients exposed to UPTRAVI, VELETRI/CARIPUL, OPSUMIT, TRACLEER/STAYVEER, OPSYNVI/YUVANCI during the PASS observation period, AEs will be reported from EDC system on the AE/ADR form and recorded in the safety database regardless whether the event is considered causally related to the administration of other PAH-specific product(s) from the MAH (VELETRI/CARIPUL, OPSUMIT, TRACLEER/STAYVEER, OPSYNVI/YUVANCI). In addition, any pregnancy and AEs leading to discontinuation/dose decrease will be also reported and recorded in the safety database. Same will apply to patients who initiated another PAH-specific product from the MAH after study site initiation, died within the first month of treatment and were not able to be consented, per local regulation.

Patients initiating a PAH-specific therapy other than UPTRAVI, not treated with other PAH-specific products from the MAH

For AEs/ADRs occurring in patients not receiving any PAH-specific products from the MAH, it is the prescriber's/investigator's responsibility to report these events to the corresponding manufacturer, as applicable. A notification box will be included in the EDC system for this purpose.

AE/SAE reporting process

Information regarding all AEs/ADRs/SAEs (irrespective of seriousness and causality) is to be collected in the EDC CRF and will be transmitted to the sponsor using the automated

AE/ADR functionality of the EDC system within 24 hours of the investigator's/prescriber's knowledge of the event.

In case of technical difficulty with automated AE reporting system in the EDC, and to ensure timely reporting of SAEs within 24 hours of physician's knowledge, paper based Serious Adverse Event form is made available to sites. This SAE Form must be completed by a physician from the study site within 24 hours of their knowledge of SAE and is to be transmitted in a secure manner to the sponsor. The initial and follow-up SAE reports should be transmitted in a secure manner electronically or by facsimile (fax).

Of note, all SAEs reported initially on the paper SAE Form need to be documented in the EDC CRF as soon as possible.

For AEs/ADRs/SAEs collected from the first documented use of any of the following PAH products from the MAH (UPTRAVI, VELETRI/CARIPUL, OPSUMIT, TRACLEER/STAYVEER, OPSYNVI/YUVANCI), the sponsor's drug safety department will assign the case an Adverse Event Reference Number. The case will then be processed in the Global Safety System and reported to health authorities in accordance with regulatory reporting requirements.

Follow-up of AEs/SAEs

The sponsor will evaluate and process all safety reports received. If follow-up information is required, the sponsor will send a follow-up request directly to the treating physician.

Follow-up information about a previously reported AE must be reported to sponsor within 1 working day of the investigator's/prescriber's first knowledge of the new information.

11.3 Reporting of pregnancy

Any pregnancy occurring in female participants or female partners of male participants during the administration of a marketed PAH-specific product from the MAH (UPTRAVI, VELETRI/CARIPUL, OPSUMIT, TRACLEER/STAYVEER, OPSYNVI/YUVANCI) must be reported within 1 working day of the investigator's/prescriber's knowledge of the event.

Pregnancies must be reported by the prescriber or the participating site personnel on the Pregnancy form available in EDC system, which is faxed or forwarded via the above-mentioned contact information to sponsor directly within 1 working day of the investigator's/prescriber's knowledge of the event.

If follow-up information is required, the sponsor will send a Pregnancy Report Form directly to the investigator/ prescriber. Any pregnancy must be followed to its conclusion and its outcome must be reported to the sponsor directly.

All reports of pregnancy with an abnormal outcome (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) documented in the source data following exposure to UPTRAVI, VELETRI/CARIPUL, OPSUMIT, TRACLEER/STAYVEER, OPSYNVI/YUVANCI must be reported to the sponsor by the participating site personnel within 24 hours of their knowledge of the event using automated AE reporting in EDC or a Serious Adverse Event Form (available only as a backup option of automated AE reporting system in EDC is not working).

11.4 PQC reporting procedures

All PQCs of sponsor-marketed products (UPTRAVI, VELETRI/CARIPUL, OPSUMIT, TRACLEER/STAYVEER, OPSYNVI/YUVANCI) must be reported within 1 working day of the investigator's/prescriber's knowledge of the event.

11.5 Special reporting situations

Safety events of interest on a product under study (UPTRAVI, VELETRI/CARIPUL, OPSUMIT, TRACLEER/STAYVEER, OPSYNVI/YUVANCI) in an interventional study that may require expediated reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor-marketed medication
- Exposure to a sponsor-marketed medication from breastfeeding
- Suspected abuse/misuse of a sponsor-marketed medication
- Inadvertent or accidental exposure to a sponsor-marketed medication
- Any failure of expected pharmacological action (ie, lack of effect) of a product
- Unexpected therapeutic or clinical benefit from use of a product
- Medication error, intercepted medical error, or potential medication error involving a PAH-specific products from the MAH (with or without patient exposure to the PAH-specific products from the MAH, eg, product name confusing, product label confusion, intercepted prescribed or dispending errors)

These safety events may not meet the definition of an adverse event; however, from a policy perspective, they are treated in the same manner as AEs.

Special reporting situations should be recorded in the CRF AE page. Any special reporting situation that meets the criteria of an SAE should be reported within 24 hours of knowledge by the participating site personnel to sponsor.

11.6 Contacting sponsor regarding safety, including product quality

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

11.7 Reconciliation

As defined in Section 11.2, AE/ADR data recorded in this PASS will also be requested to be reported on an AE/ADR form and will be recorded in the safety database.

The sponsor's drug safety department will on a periodic basis compare safety relevant information recorded in the PASS database and safety database and address any discrepancy. If any AE is identified as missing in the safety database during the reconciliation process, sponsor's drug safety department will notify the site to forward all collected information to drug safety. This will be a one-way reconciliation from the PASS database to the safety database.

The safety database will therefore represent the reference AE database used for the medical evaluation and characterisation of identified and potential risks in the UPTRAVI PBRERs.

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The study description and key protocol elements will be published on the ENCePP register. Study reports for submission to the PRAC will be prepared annually (see Milestones, Section 6). Each annual report will be composed by using data from the study eCRF database. Reference will be made to the respective section of the PBRER. Additionally, the interim study abstract will be appended to PBRER.

In the case of communications in other settings (such as conferences or publications), abstracts, presentations, and manuscripts will be prepared in accordance with the MAH's Policies on Disclosure of Clinical Research Information and on Scientific Publications. Publication of the study results will be submitted to a peer reviewed journal, and in accordance with guidelines of the International Committee of Medical Journal Editors standards (ICMJE 2021) and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement (von Elm 2007).

Data collection in EXPOSURE will remain open until study objectives are considered fulfilled by PRAC. The annual data cutoff in November will be maintained and EXPOSURE data will continue to be considered for PBRERs until study closure.

13 REFERENCES

[Chin 2008] Chin KM, Rubin LJ. Pulmonary arterial hypertension. J Am Coll Cardiol. 2008;51(16):1527–1538.

[Crowe 2010] Crowe, B, Lipkovich I, Wang O. Comparison of several imputation methods for missing baseline data in propensity scores analysis of binary outcome. Pharmaceut. Statist. 2010; 9:269–279.

[D'Agostino 2001] D'Agostino R, Lang W, Walkup M, Morgan T. Examining the Impact of Missing Data on Propensity Score Estimation in Determining the Effectiveness of Self-Monitoring of Blood Glucose (SMBG). Health Services & Outcomes Research Methodology. 2001;2:291–315.

[ENCePP 2015] European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. Guide on methodological standards in pharmacoepidemiology (revision 4). EMA/95098/2010 (amended). July 2015 [accessed on 10 June 2016]. Available from: http://www.encepp.eu/standards_and_guidances/methodologicalGuide.shtml.

[EscribanoSubias 2012] Escribano-Subias P, Blanco I, López-Meseguer M, Lopez-Guarch CJ, Roman A, Morales P, et al; on behalf of the REHAP investigators. Survival in pulmonary hypertension in Spain: insights from the Spanish registry. Eur Respir J. 2012;40(3):596-603.

[EU-CTR 536/2014] Regulation (EU) No 536/2014 of the European Parliament and of the council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. Available from: http://ec.europa.eu/health/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf

[Galiè 2016] Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016;37(1):67-119.

[Gliklich 2014] Gliklich R, Dreyer N, Leavy M, eds. Registries for Evaluating Patient Outcomes: A User's Guide. Third edition. Two volumes. AHRQ Publication No. 13(14)-EHC111. Rockville, MD: Agency for Healthcare Research and Quality. April 2014. Available from: http://www.effectivehealthcare.ahrq.gov/registries-guide-3.cfm. Accesses on 31 Oct 2016.

[Humbert 2006] Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, et al. Pulmonary arterial hypertension in France: results from a national registry. Am J Respir Crit Care Med. 2006;173(9):1023-1030.

[ICMJE 2021] International Committee of Medical Journal Editors (ICMJE). Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals. International Committee of Medical Journal Editors; December 2021 [accessed on 21 January 2022]. Available from: http://www.icmje.org

[ISPE 2015] International Society for Pharmacoepidemiology. Guidelines for good pharmacoepidemiology practices (GPP). Revision 3. International Society for Pharmacoepidemiology; 2015 [accessed on 26 April 2016]. Available from: http://www.pharmacoepi.org/resources/guidelines_08027.cfm.

[Jansa 2014] Jansa P, Jarkovsky J, Al-Hiti H, Popelova J, Ambroz D, Zatocil T, et al. Epidemiology and long-term survival of pulmonary arterial hypertension in the Czech Republic: a retrospective analysis of a nationwide registry. BMC Pulm Med. 2014;14:45.

[Machin 1997] Machin D, Campbell M, Fayers, P, Pinol A. Sample size tables for clinical studies. Second Ed. Blackwell Science. 1997;134-5. Available from: http://www.statstodo.com/SSizRareInc_Tab.php.

[McGoon 2009] McGoon MD, Kane GC. Pulmonary hypertension: diagnosis and management. Mayo Clin Proc. 2009;84(2):191–207.

[McLaughlin 2004] McLaughlin V, Presberg K, Doyle R, Abman SH, McCrory DC, Fortin T, et al. Prognosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest. 2004;126(1):78S-92S.

[PARENT 2015] PARENT: Cross-border Patient Registries Initiative. Methodological guidelines and recommendations for efficient and rational governance of patient registries. editors Metka Zaletel, Marcel Kralj. - El. book. - Ljubljana National Institute of Public Health, 2015 October. Available from: http://patientregistries.eu/documents/10184/14613/Methodological+guidelines+and+recommendations+for+efficient+and+rational+governance+of+patient+registries/5bf3ea46-26ca-4d91-b459-47dce18a8846. Accessed on 31 October 2016.

[Pratt 1996] Pratt CM, Greenway PS, Schoenfeld MH, Hibben ML, Reiffel JA. Exploration of the precision of classifying sudden cardiac death. Implications for the interpretation of clinical trials. Circulation. 1996;93(3):519-24.

[Qu 2009] Qu Y, Lipkovich I. Propensity score estimation with missing values using a multiple imputation missingness pattern (MIMP) approach. Statist. Med. 2009;28:1402–1414.

[Simonneau 2013] Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2013;62(25 Suppl):D34–41.

[Sitbon 2015] Sitbon O, Channick R, Chin KM, Frey A, Gaine S, Galiè N, et al. Selexipag for the treatment of pulmonary arterial hypertension. N Engl J Med. 2015;373(26):2522-2533.

[Tueller 2008] Tueller C, Stricker H, Soccal P, Tamm M, Aubert JD, Maggiorini M, et al. Epidemiology of pulmonary hypertension: new data from the Swiss registry. Swiss Med Wkly. 2008;138(25-26):379-384.

[UK Audit 2014] Health and Social Care Information Centre, National Audit of Pulmonary Hypertension. Fifth Annual Report: Key findings from the National Audit of Pulmonary Hypertension for the United Kingdom, Channel Islands, Gibraltar and Isle of Man. Report for the audit period April 2013 to March 2014 [accessed on 14 October 2015]. Available from:
http://www.hscic.gov.uk/catalogue/PUB17264/nati-pulm-hype-audi-2014-rep.pdf

[UPTRAVI SmPC] Summary of product characteristics. European Medicines Agency UPTRAVI product information. Available from:
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003774/WC500207173.pdf.

[von Elm 2007] von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Int J Surg. 2014;12(12):1495-1499.

14 ANNEXES

Annex 1 List of stand-alone documents

None.

Annex 2 ENCePP checklist for study protocols

Doc. Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

Study title:
Post-authorisation safety study (PASS): observational cohort study of PAH patients newly treated with either UPTRAVI (selexipag) or any other PAH-specific therapy, in clinical practice

Study reference number:
EU PAS19085

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[7]	☒	☐	☐	21
1.1.2 End of data collection[8]	☒	☐	☐	21
1.1.3 Study progress report(s)	☒	☐	☐	21
1.1.4 Interim progress report(s)	☒	☐	☐	21
1.1.5 Registration in the EU PAS register	☒	☐	☐	21
1.1.6 Final report of study results.	☒	☐	☐	21

Comments:

1.1.3 & 1.1.4 Study progress report and interim progress report will be combined in one annual report to PRAC.

[7] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[8] Date from which the analytical dataset is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	22
2.1.2 The objective(s) of the study?	☒	☐	☐	23
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	24-25
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☒	☐	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	23-25

Comments:

2.1.4 This is a descriptive study without formal hypothesis to be tested.

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	24-24
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	31-32
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	40-42

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	33-34
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	24
4.2.2 Age and sex?	☒	☐	☐	25; 33-36
4.2.3 Country of origin?	☒	☐	☐	24-25
4.2.4 Disease/indication?	☒	☐	☐	25
4.2.5 Co-morbidity?	☐	☒	☐	
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	24

Comments:

4.2.5 The patient study population is defined with group I PAH, regardless of underlining aetiology (co-morbidities). 4.2.6 Seasonality is not relevant to this study.

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	32
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☒	☐	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	37
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☒	☐	

Comments:

5.2 Prospective ascertainment and assurance of exposure information precedes the occurrence of an outcome are both elements of the new user prospective design used in this study.
5.4 Exposure is classified based on patient-reported start and end date of treatment. No biomarkers are used, nor biological half-life considered.
5.5 A dose-dependent or duration-dependent outcome will not be provided.

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	31-32
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	34-36; 66-67

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	45-47
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	45-47

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	33-34
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	33-34
8.1.3 Covariates?	☒	☐	☐	33-34
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	26-31
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	26-31
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	26-31
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☒	☐	
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	30;51
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☒	☐	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☒	☐	

Comments:

8.3.1 and 8.3.3 There is no coding system used for these data. 8.4 The only source of data for this study is the medical record. No other source will be used.

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	34-36

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☒	☐	☐	42
10.2 Is the choice of statistical techniques described?	☒	☐	☐	37-43
10.3 Are descriptive analyses included?	☒	☐	☐	39-40
10.4 Are stratified analyses included?	☒	☐	☐	32; 41-44
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	41-42
10.6 Does the plan describe methods addressing effect modification?	☒	☐	☐	41-42

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	44
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	36
11.3 Are methods of quality assurance described?	☒	☐	☐	44-45

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	44-45
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

11.5 No independent review board is foreseen.

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	45-47
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	45-47
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	47
12.3 Does the protocol address other limitations?	☒	☐	☐	45-47

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	47-48
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	36; 47-48

Comments:

13.2 protocol, eCRF and ICF will be submitted for IRB and ethics approval prior to study implementation.

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	21

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	55
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	55

Comments:

Annex 3 Definitions of major adverse cardiovascular event categories in the PASS

In this PASS, MACE is defined as the occurrence of at least one condition falling into any of the below categories:

- Death from cardiovascular causes (sudden death, fatal MI, fatal stroke, fatal arrhythmia)
- Non-fatal MI
- Non-fatal stroke (ischaemic stroke and/or haemorrhagic stroke)
- Coronary artery revascularisation
- Unstable angina
- Non-fatal cardiac arrest

Death from cardiovascular causes

Deaths from cardiovascular causes are classified according to the following definitions (sudden death, fatal MI, fatal stroke, fatal arrhythmia)

- **Sudden death/ sudden cardiac arrest**: unexpected occurrence within 1 hour of the onset of a new symptom or a death that was unwitnessed and unexpected (eg, patient found dead in bed in the morning) unless a specific non-cardiac cause of death was confirmed. Per Pratt et al (Pratt 1996), it does not include, for example, a patient whose PAH is deteriorating over the past week and then dies in hospital.
- **Fatal MI**: confirmed by ECG, cardiac enzymes or pathology. Death occurs within 30 days from the episode of MI.
- **Fatal stroke:** confirmed by clinical diagnosis or pathology report.
- **Fatal arrhythmia**: witnessed and documented cardiac arrhythmia.

Non-fatal myocardial infarction

Non-fatal MI should be confirmed by ECG, cardiac enzyme. Clinical symptoms are usually present and characteristics. However non-fatal myocardial infarction can be asymptomatic (silent MI).

Non-fatal stroke

Non-fatal stroke is defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of haemorrhage or infarction.

- **Ischemic stroke**

Ischemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue. Haemorrhage may be a

consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with haemorrhagic transformation and not a haemorrhagic stroke.

- **Haemorrhagic stroke**

Haemorrhagic stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid haemorrhage.

Coronary artery revascularisation

Coronary artery revascularisation is defined as any acute coronary intervention with the goal of establishing patient's coronary blood flow such as coronary arterial bypass grafting, coronary stenting or balloon angioplasty.

Unstable angina

Unstable angina is defined as an unscheduled hospitalisation of a duration greater than 24 hours with documented discharge diagnosis of unstable angina. Unstable angina can be documented by ECG and/or angiography with negative cardiac biomarkers and no evidence of acute MI.

Non-fatal cardiac arrest

Non-fatal cardiac arrest is defined as abrupt cessation of cardiac mechanical function, which was reversible upon a prompt intervention and return of circulation.

[Pratt 1996] Pratt CM, Greenway PS, Schoenfeld MH, et al. Exploration of the precision of classifying sudden cardiac death. Implications for the interpretation of clinical trials. Circulation. 1996; 93(3): 519-24.

Annex 4 Definition of PAH-related death in the PASS

A PAH-related death is defined as any fatal outcome that is directly attributable to a worsening of the underlying disease. An acute condition that led to an aggravation of PAH (eg, pneumonia) and with a fatal outcome, is not to be considered PAH-related.

Annex 5 Study size - additional statistical considerations

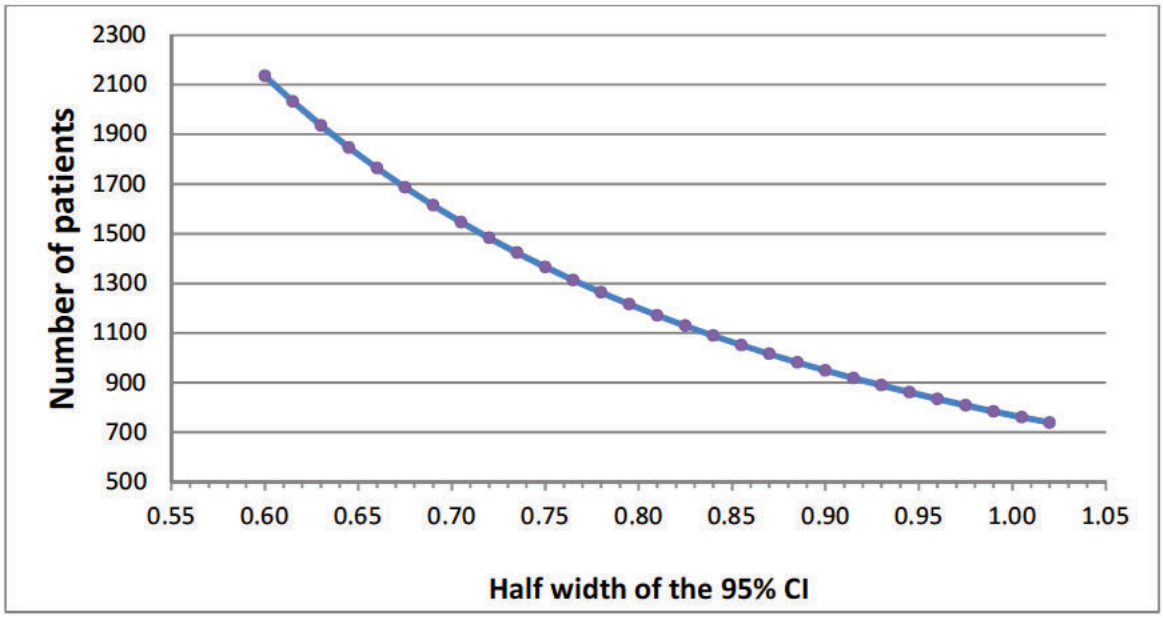
The number of UPTRAVI exposed patients required in order to achieve various widths of the 95% CI around an incidence rate (IR) of 3.0 per 100 person-years are presented in Table 3 and also represented in Figure 1 below.

Table 3 Number of UPTRAVI exposed patients required to be exposed for a minimum of 18 months in order to achieve various widths of the 95% CI around an incidence rate of 3.0 per 100 person-years

Precision*	Relative precision** (%)	Lower bound of the 95% CI#	Upper bound of the 95% CI#	Study size for UPTRAVI exposed patients (≥ 18 months)
0.60	20	2.40	3.60	2135
0.62	20.5	2.39	3.62	2032
0.63	21	2.37	3.63	1936
0.65	21.5	2.36	3.65	1847
0.66	22	2.34	3.66	1764
0.68	22.5	2.33	3.68	1687
0.69	23	2.31	3.69	1614
0.71	23.5	2.30	3.71	1546
0.72	24	2.28	3.72	1483
0.74	24.5	2.27	3.74	1423
0.75	25	2.25	3.75	1366
0.77	25.5	2.24	3.77	1313
0.78	26	2.22	3.78	1263
0.80	26.5	2.21	3.80	1216
0.81	27	2.19	3.81	1171
0.83	27.5	2.18	3.83	1129
0.84	28	2.16	3.84	1089
0.86	28.5	2.15	3.86	1051
0.87	29	2.13	3.87	1016
0.89	29.5	2.12	3.89	981
0.90	30	2.10	3.90	949
0.92	30.5	2.09	3.92	918
0.93	**31**	**2.07**	**3.93**	**888**
0.95	31.5	2.06	3.95	861
0.96	32	2.04	3.96	834
0.98	32.5	2.03	3.98	809
0.99	33	2.01	3.99	784
1.01	33.5	2.00	4.01	761
1.02	34	1.98	4.02	739

* Precision is defined as half the width of the 95% CI
** Relative precision is defined as half the width of the CI and expressed as a percentage of the point estimate incidence rate
# Based on a Normal Approximation
CI = confidence interval.

Figure 1 **Number of UPTRAVI exposed patients required to be exposed for a minimum of 18 months to achieve various widths of the 95% confidence interval (CI) around an incidence rate (IR) of 3.0 per 100 person-years**



Given the above sample size of approximately 888 UPTRAVI exposed patients, it is important to evaluate potential impact on the interpretation in the event that the rate observed is lower, or higher than the expected rate. For example: should the incidence rate observed be much lower than expected, at 2 per 100 person-years the confidence interval will range from 1.24 to 2.76. If the incidence rate observed is higher than expected, eg, at 6 per 100 person-years, the confidence interval will range from 4.68 to 7.32. This reflects a wider confidence interval than seen with the point estimate of 3.0, nonetheless remaining within an acceptable range for the margin of error. The confidence intervals for various incidence rates that may be observed are presented below:

Table 4 Confidence Intervals, Precision, and Relative Precision Levels Achieved with 888 UPTRAVI Exposed Patients for Various Observed Incidence Rates

IR	Lower Bound of the 95% CI[#]	Upper Bound of the 95% CI[#]	Relative precision* (%)	Precision **
1.0	0.46	1.54	53.7	0.54
1.5	0.84	2.16	43.8	0.66
2.0	1.24	2.76	38.0	0.76
2.5	1.65	3.35	34.0	0.85
3.0	**2.07**	**3.93**	**31.0**	**0.93**
3.5	2.50	4.50	28.7	1.00
4.0	2.93	5.07	26.9	1.07
4.5	3.36	5.64	25.3	1.14
5.0	3.80	6.20	24.0	1.20
5.5	4.24	6.76	22.9	1.26
6.0	4.68	7.32	21.9	1.32
6.5	5.13	7.87	21.1	1.37
7.0	5.58	8.42	20.3	1.42
7.5	6.03	8.97	19.6	1.47
8.0	6.48	9.52	19.0	1.52
8.5	6.93	10.07	18.4	1.57
9.0	7.39	10.61	17.9	1.61
9.5	7.84	11.16	17.4	1.66
10.0	8.30	11.70	17.0	1.70
10.5	8.76	12.24	16.6	1.74
11.0	9.22	12.78	16.2	1.78
11.5	9.68	13.32	15.8	1.82

* Relative precision is the precision expressed as a percentage of the point estimate IR.
** Precision is defined as half the width of the 95% CI.
[#]Based on a Normal Approximation.
CI = confidence interval; IR = incidence rate.

PARTICIPATING PHYSICIAN AGREEMENT

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

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

Coordinating Physician:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Responsible Medical Officer:

Name (typed or printed): PPD MD, PhD, Executive Medical Director Cardiopulmonary

Institution: Actelion Pharmaceuticals Ltd. (a Janssen Pharmaceuticals Company of Johnson and Johnson)

_____

_____

_____

Telephone Number: _____

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

Sponsor's Responsible Party (Main Author):

Name (typed or printed): PPD PhD, Senior Director Epidemiology, delegated to PPD, PhD, MPH, Executive Director, Global Epidemiology

Institution: Actelion Pharmaceuticals Ltd. (a Janssen Pharmaceuticals Company of Johnson and Johnson)

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

Qualified Person Pharmacovigilance:

Name (typed or printed):	Laurence Oster-Gozet, QPPV Pharma
Institution:	Actelion Pharmaceuticals Ltd. (a Janssen Pharmaceuticals Company of Johnson and Johnson)

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

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

Signature

User	Date	Reason
PPD	14-Jul-2025 08:13:58 (GMT)	Document Approval
PPD	14-Jul-2025 13:34:47 (GMT)	Document Approval
Oster-Gozet Laurence PPD	15-Jul-2025 09:26:30 (GMT)	Document Approval