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

Non-interventional Postauthorization Safety Study - Protocol

Post-authorisation Safety Study (PASS): Retrospective Medical Chart Review of Patients with PAH Newly Treated With Either Uptravi® (selexipag) or any Other PAH-specific Therapy

EXTRACT (EXploratory hisToRicAl Cohort sTudy)

Protocol (67896049PAH0002)

Uptravi® selexipag

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EU PAS Register Number: (Register Number will be added when available)

Status:	Approved		
Protocol version:	1.0	**Version date:**	10 February 2022
Prepared by:	Actelion Pharmaceuticals Ltd. (a Janssen Pharmaceuticals Company of Johnson and Johnson)		
EDMS number:	EDMS-RIM-588005, 1.0		

Compliance: This study will be conducted in compliance with the protocol and applicable regulatory requirements.

1. PASS INFORMATION

Title:	**Post-authorisation Safety Study (PASS): Retrospective Medical Chart Review of Patients with PAH Newly Treated With Either Uptravi® (selexipag) or any Other PAH-specific Therapy**
Protocol version:	1.0
Date of last version of the protocol:	Original Protocol
EU PAS Register No:	To be assigned
Active substance (INN common name):	Selexipag
Pharmaco-therapeutic group (ATC Code):	Pharmacotherapeutic group: Antithrombotic agents, platelet aggregation inhibitors excluding heparin, ATC code: B01AC27
Medicinal product(s):	Uptravi®
Product reference:	H0003774
Procedure number:	EMEA/H/C/003774/II
Name of Marketing Authorization Holder(s)	Janssen-Cilag International NV
Joint PASS	No
Research question and objectives	This retrospective medical chart review study aims to further characterise the safety profile of Uptravi, and to describe clinical characteristics and outcomes of patients newly treated with Uptravi (Uptravi-exposed patients) or newly treated with any other pulmonary arterial hypertension (PAH)-specific therapy who were never treated wih Uptravi (patients initiating another PAH-specific therapy) in the international post-marketing setting. 1. To describe, overall and in the subset of patients over the age of 75 years, demographics, disease characteristics and clinical course in Uptravi-exposed patients and 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 important identified or potential risks in Uptravi-exposed patients: – Hypotension – Anemia – Hyperthyroidism – Pulmonary oedema associated with pulmonary veno-occlusive disease – Major adverse cardiovascular events (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 describe rates of MACE and all-cause death in Uptravi-exposed patients and patients initiating another PAH-specific therapy.
Country(-ies) of study	Preliminary list of countries where the study is to be conducted: Austria, Canada, Czech Republic, Estonia, Finland, France, Germany, Greece, Italy, Lithuania, Poland, Russia, Slovakia, Spain, Sweden, Switzerland, the Netherlands, the UK and other countries, as needed.
Author	PPD

2. MARKETING AUTHORIZATION HOLDER(S)

Name of Marketing Authorization Holder:	Janssen-Cilag International NV
Address:	Turnhoutseweg 30 B-2340 Beerse Belgium
Contact Details:	Person authorised for communication on behalf of the marketing authorization holder (MAH): PPD
Qualified Person Pharmacovigilance:	
Name:	PPD

3. RESPONSIBLE PARTIES

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

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AMENDMENTS AND UPDATES

Neither the participating physician nor the sponsor will modify this protocol without a formal amendment. All protocol amendments must be issued by the sponsor and will follow the review and approval process in accordance with local regulations.

There are no amendments for this protocol.

4. ABSTRACT

Protocol Title: Post-authorisation Safety Study (PASS): Retrospective Medical Chart Review of Patients with PAH Newly Treated With Either Uptravi® (selexipag) or any Other PAH-specific Therapy (1.0, 10 February 2022)

Background and Rationale

EXTRACT is a multicentre, international, retrospective chart review study of patients with pulmonary arterial hypertension (PAH) newly treated with Uptravi (generic name: selexipag) or other PAH-specific therapies. The aim of EXTRACT is to complement the EXPOSURE study to fulfill the European Medicines Agency (EMA) Post-authorisation safety study (PASS) requirement on Uptravi. EXPOSURE (AC-065A401) is a PASS (EU PAS 19085) for Uptravi included in the Europeon Union (EU) Risk Management Plan (RMP) as Additional Pharmacovigilance Activities agreed with the Pharmacovigilance Risk Assessment Committee (PRAC) during the initial MAA in 2016. EXPOSURE is a multicentre, international, prospective, real-world, observational cohort study of patients with PAH newly treated with a PAH-specific therapy. It was developed to describe characteristics of patients with PAH, to further characterize the safety profile of Uptravi, and to compare the outcomes of major adverse cardiovascular events (MACE) and all-cause death in patients newly treated with Uptravi with those in patients newly treated with other PAH-specific therapies in the real-world, post-marketing setting.

EXPOSURE was initiated several months after Uptravi reimbursement was available in the enroling countries, and contained a strict enrolment requirement that PAH-specific therapy should have been initiated within a maximum of 30 days prior to informed consent form signature by patients. These resulted in a substantial number of patients who initiated Uptravi more than 30 days prior to the study start not eligible for enrolment in EXPOSURE.

In addition, following initiation of EXPOSURE, the recruitment of new Uptravi users in EXPOSURE was slower than initially projected. It is projected that, at the initially planned time for final data-cut (November 2022), approximately 50% of the expected 1184 patients will be enrolled in the Uptravi cohort.

EXTRACT will complement EXPOSURE with atleast 391 retrospectively identified patients with PAH who have been newly treated with Uptravi (as monotherapy or in combination with other PAH-specific therapy) before EXPOSURE was initiated, in order to achieve the desired sample size. This is done in order to avoid significant delay in completing EXPOSURE and assessing the study objectives. A comparator group consisting of 510 patients with PAH newly treated with other PAH-specific therapies will serve as an internal comparator cohort in EXTRACT and allow for pooling of the cohorts of EXPOSURE and EXTRACT in comparative analyses.

Research Question and Objectives

This retrospective medical chart review study aims 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 or newly treated with any other PAH-specific therapy who were never treated with Uptravi in the international post-marketing setting.

The objectives of the study 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
- Anemia
- Hyperthyroidism
- Pulmonary oedema associated with pulmonary veno-occlusive disease (PVOD)
- 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 describe rates of MACE and all-cause death in Uptravi exposed patients and patients initiating another PAH-specific therapy.

Study Design

This is a retrospective, non-interventional, multicenter, international, chart review study in patients with PAH newly treated with Uptravi or other PAH-specific therapies. Only data available within normal clinical practice will be collected in this study.

The enrolment period is from the start of reimbursement of Uptravi in a specific country, to the earlier of either

a) 31 days before the respective EXPOSURE site initiation visit (to prevent enrolment of any patients who are eligible for EXPOSURE to enrol in EXTRACT), or

b) 30 June 2021 (to allow a minimum of 12 months of potential follow-up after enrolment, as observation period ends on 30 June 2022)

The observation period is from the date of initiation of new PAH-specific therapy until death, loss to follow-up, or 30 June 2022 (the day before planned ethics committee submission for EXTRACT for the first site), whichever is earlier.

Setting and Patient Population

Patients in this non-interventional study will have been newly treated with Uptravi or other PAH-specific therapies in routine clinical settings.

Study sites are encouraged to enroll all consecutive patients that fulfill enrolment criteria to avoid selection bias. Only countries and sites where waivers of informed consent can be obtained for this study will be included in EXTRACT to avoid survival bias.

Inclusion criteria at enrolment:

1. Patients ≥18 years old, and
2. Clinically diagnosed with Group 1 PAH, and
3. Patients whose medical charts are available for data collection during observation period
4. Uptravi cohort: Patients who initiated Uptravi for the first time
5. Other PAH-specific therapy cohort:

- Prevalent patients (≥ 6 months from first clinically diagnosed PAH), and
- Patients initiating a PAH-specific therapy other than Uptravi for the first time as part of a combination therapy

Exclusion criteria at enrolment:

1. Previously treated with Uptravi/selexipag
2. Patients initiating another PAH-specific therapy must not have been previously treated with the same drug
3. Enrolled in EXPOSURE
4. Patients enrolled in any ongoing interventional clinical study during observation period of EXTRACT

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).

- Study specifics (visit date, termination of data entry: date, reason)
- Demographics (age, gender, country)
- Clinical characteristics (PAH classification, aetiology, date of first PAH diagnosis and World Health Organization (WHO) functional class (FC) at diagnosis, WHO FC, 6-minute walk distance [6MWD], incremental shuttle walking test [ISWT], height, weight, right heart catheterisation haemodynamics, % predicted diffusion capacity of the lungs for carbon monoxide (DL_{CO}), pericardial effusion, vital signs, transplantation list / pre-transplantation visit, renal insufficiency)
- Laboratory data (haemoglobin, thyroid hormone, N-terminal of the prohormone brain natriuretic peptide [NT-proBNP], brain natriuretic peptide [BNP])
- Medical history
  - Cardiovascular/cerebrovascular disease history (history of myocardial ischaemia, MI, cardiac arrest, ischaemic cerebrovascular disorders, haemorrhagic cerebrovascular disorders, revascularisation procedure [coronary and/or carotid] 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, smoking status, hyperlipidaemia, systemic hypertension, hypercoagulable state, sleep apnoea syndrome)
  - Other relevant medical history (hypotension, anemia, pulmonary oedema associated with PVOD, hyperthyroidism, renal impairment, bleeding events, light-dependent non-melanoma skin malignancy, ophthalmological effects associated with retinal disorder, intestinal intussusception manifested as intestinal obstruction / ileus)
- Medication
  - Uptravi or any other PAH-specific therapy (drug name of all individual PAH-specific drug substances, start date, dosing regimen [date of up/down titration & dose at each step, maintenance dosing change], dose change, interruption or discontinuation [date, reason], history of any PAH-specific therapy within the previous 12 months)

- Outcomes
  - Incident important identified or potential risks, defined as 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, and MACE, defined as the occurrence of at least one condition falling into any of the below categories[a]:
    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
  - Hospitalisation (PAH related or not, admission /discharge dates, reason)
  - Death (PAH related or not, date, reason)
  - Any new diagnosis or adverse events considered by the reporter (ie, site personnel who entered patient data into medical chart) to be explicitly causally related to a PAH-specific Janssen product, ie adverse drug reaction (ADR) of a PAH-specific Janssen product

Data Sources

The primary data source for this study will be the medical records of each patient. Source documentation should be in patients' records for all data entered into the eCRF.

The EXTRACT eCRF is a stand-alone program, however it will be aligned with the data structure of EXPOSURE eCRF. Data will be collected by the investigator / study coordinator for each patient throughout the observation period based on the existing medical records.

Study Size

Sample size in EXTRACT is determined based on the difference between the overall sample size needed in the Uptravi cohort in EXPOSURE (ie, 1184 patients) and the projected number of patients that can be enrolled in the Uptravi cohort in EXPOSURE by June 2023 (ie, by the end of data collection in EXTRACT), while maintaining a similar ratio with the comparator cohort as in EXPOSURE. No formal sample size calculation has been performed for EXTRACT. Based on current projection, EXPOSURE is expected to enroll 793 patients in the Uptravi cohort by in June 2023. Therefore, EXTRACT is planned to enroll at least 391 patients in the Uptravi cohort, to reach the enrolment target of about 1184 Uptravi patients in the combined EXPOSURE and EXTRACT dataset. In addition, at least 510 patients will be enrolled in the Other PAH-specific therapy cohort in EXTRACT to serve as an internal comparator of the Uptravi cohort.

Data Analysis

The following analyses will be performed in the EXTRACT dataset, which follows the same approach as agreed with the PRAC for EXPOSURE:

a) Summary statistics of demographics, disease characteristics and clinical course in Uptravi exposed patients and patients initiating other PAH-specific therapies.

[a] See definition in Annex 3.

b) Occurrence and incidence rate during Uptravi exposure period of all-cause death and the important identified and potential risks of Uptravi, including MACE, in the Uptravi exposed patients.

c) Occurrence and incidence rates of MACE and all-cause death in the Uptravi cohort and the Other PAH-specific cohort.

Analyses will include descriptive statistics of the Uptravi cohort and the Other PAH-specific therapy cohort, at initiation of a new PAH-specific therapy and during the observation period. To further characterise the Uptravi safety profile, the frequency and incidence rates will be calculated for important identified and potential risks of Uptravi and all-cause death in the Uptravi cohort. Frequency and incidence rates of all ADRs related to PAH-specific Janssen product will be calculated.

In addition, homogeneity between EXPOSURE and EXTRACT (after adjusting for differences in patient characteristics by matching or weighting methods) will be assessed using descriptive statistics and standardized mean differences of patient characteristics at time of new PAH-specific therapy initiation of both populations. If homogeneity between the two populations is deemed acceptable, pooled analysis using data from both EXPOSURE and EXTRACT will be performed and reported. Otherwise, descriptive statistics will be provided for each study separately. Further details about the analyses and homogeneity assessment will be provided in the SAP.

Milestones

Milestone	**Planned date**
Start of data collection	4Q2022
End of data collection	2Q2023
Registration in the EU PAS register	At time of PRAC protocol approval
Combined final report of study results from EXPOSURE and EXTRACT	1Q2024

ECRF DATA COLLECTION SCHEDULE (AS AVAILABLE PER CLINICAL PRACTICE FROM THE EXISTING MEDICAL RECORD)

Variable	At initiation of a new PAH-specific therapy	Follow-up (any available data recorded in the medical chart after initiation of the new PAH-specific therapy)
1 – Study specifics		
Visit date (if available in medical chart)	**X**	**X**
Termination of data entry: date, reason (incl death, lost to follow-up, lung transplant)		**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)	**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**
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**	
Renal insufficiency	**X**	**X**
4 – Laboratory data (within 3 months prior or at initiation of a new PAH-specific therapy)		

Variable	At initiation of a new PAH-specific therapy	Follow-up (any available data recorded in the medical chart after initiation of the new PAH-specific therapy)
Haemoglobin	**X**	
Thyroid hormone (hs-TSH)	**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, smoking status, hyperlipidaemia, systemic hypertension, hypercoagulable state, sleep apnoea syndrome]	**X**	
Other relevant medical history (incl. year of occurrence, number of episodes) *apply for any patient initiating Uptravi* [Hypotension, anemia, pulmonary oedema associated with PVOD, hyperthyroidism, renal impairment, bleeding events, light-dependent non-melanoma skin malignancy, ophthalmological effects associated with retinal disorder, intestinal intussusception manifested as intestinal obstruction / ileus]	**X**	
6 – Medication		
Uptravi or any other PAH-specific treatment - Drug name of all individual PAH-specific drug substances - Start date - Dosing regimen (date of up/down titration & dose at each step, maintenance dosing change)	**X**	**X**
- Dose change, interruption or discontinuation (date, reason)		**X**
- History of any PAH-specific therapy within the previous 12 months	**X**	
7 – Outcomes		

Variable	At initiation of a new PAH-specific therapy	Follow-up (any available data recorded in the medical chart after initiation of the new PAH-specific therapy)
Underlying or incident comorbidities during observation period (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 - anemia (if yes, haemoglobin value) - pulmonary oedema associated with PVOD - hyperthyroidism (if yes, hs-TSH tests value) - light-dependent non-melanoma skin malignancy - ophthalmological effects associated with retinal vascular system - intestinal intussusception manifested as intestinal obstruction / ileus	**X**	**X**
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**

Variable	At initiation of a new PAH-specific therapy	Follow-up (any available data recorded in the medical chart after initiation of the new PAH-specific therapy)
Any new diagnosis or adverse events considered by the reporter (ie, site personnel who entered patient data into medical chart) to be explicitly causally related to a PAH-specific Janssen product[1] , ie adverse drug reaction (ADR) of a PAH-specific Janssen product		
apply for patients treated with any PAH-specific product from Janssen[1]		**X**
- any ADR of PAH-specific Janssen[1] products, irrespective of seriousness (if yes[2])		

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.

[1] PAH-specific Janssen products include Uptravi, Veletri® / Caripul®, Opsumit®, Tracleer® or STAYVEER®

[2] All ADRs will be recorded in CRF and reported to GMS.

5. MILESTONES

The initial planned dates for key milestones in this study are outlined below.

Milestone:	Planned Date:
Start of data collection	4Q2022
End of data collection	2Q2023
Registration in the EU PAS register	At time of PRAC protocol approval
Combined final report of study results from EXPOSURE and EXTRACT	1Q2024

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

6MWD	6-minute walk distance
ADR	Adverse drug reaction
BMI	Body mass index
BNP	Brain natriuretic peptide
CHMP	Committee for Medicinal Products for Human Use
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
EU	European Union
EXPOSURE	EXPloratory observational study of Uptravi in real-life
EXTRACT	EXploratory hisToRicAl Cohort sTudy
FC	Functional class
GMS	Global Medical Safety
ICF	Informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISWT	Incremental shuttle walking test
MAA	Marketing Authorization Application
MACE	major adverse cardiovascular event
MAH	Marketing Authorisation Holder
MI	Myocardial infarction
NT-proBNP	N-terminal of the prohormone brain natriuretic peptide
PAH	pulmonary arterial hypertension
PASS	Post-authorisation safety study
PQC	Product quality complaint
PRAC	Pharmacovigilance Risk Assessment Committee
PVOD	Pulmonary veno-occlusive disease
RHC	Right heart catheterisation
RMP	Risk Management Plan
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
USPI	United States Prescribing Information
WHO	World Health Organization

6. BACKGROUND AND RATIONALE

6.1. Background

EXTRACT is a multicentre, international, retrospective chart review study of patients with pulmonary arterial hypertension (PAH) newly treated with Uptravi (generic name: selexipag) or

other PAH-specific therapy. The aim of EXTRACT is to complement the EXPOSURE study (AC-065A401; EU PAS 19085) to fulfill the EMA PASS requirement on Uptravi. EXPOSURE is a post-authorisation safety study for Uptravi included in the European Union (EU) Risk Management Plan (RMP) as Additional Pharmacovigilance Activities agreed with the Pharmacovigilance Risk Assessment Committee (PRAC) during the initial Marketing Authorization Application (MAA) in 2016. (RMP 2020) EXPOSURE is a multicentre, international, prospective, real-world, observational cohort study of patients with PAH newly treated with a PAH-specific therapy. It was developed to describe characteristics of patients with PAH, to further characterize the safety profile of Uptravi, and to compare the outcomes of major adverse cardiovascular events (MACE) and all-cause death in patients newly treated with Uptravi with those in patients newly treated with other PAH-specific therapies in the real-world, post-marketing setting.

EXPOSURE was initiated several months after Uptravi reimbursement was available in the enrolling countries and contained a strict enrolment requirement that PAH-specific therapy should have been initiated within a maximum of 30 days prior to informed consent form signature by patients. These resulted in a substantial number of patients who initiated Uptravi more than 30 days prior to the study start not eligible for enrolment in EXPOSURE.

The enrolment period is from the start of reimbursement of Uptravi in a specific country to either a) 31 days before the respective EXPOSURE site initiation visit (to prevent enrolment of any patients who are eligible for EXPOSURE to enrol in EXTRACT), or b) 30 June 2021 (to allow a minimum of 12 months of potential follow-up after enrolment, as observation period ends on 30 June 2022), whichever is earlier.

The recruitment of new Uptravi users is slower than projected and cannot be achieved within the planned timelines of EXPOSURE. It is projected that, at the initially planned time for final data-cut (November 2022), approximately 50% of the expected 1184 patients will be enrolled in the Uptravi cohort in EXPOSURE.

6.2. Overall Rationale for the Study

EXTRACT will complement EXPOSURE with atleast 391 retrospectively identified patients with PAH who have been newly treated with Uptravi (as monotherapy or in combination with other PAH-specific therapy) before EXPOSURE was initiated, in order to achieve the desired sample size. This is done in order to avoid significant delay in completing EXPOSURE and assessing the study objectives. A comparator group consisting of 510 patients with PAH newly treated with other PAH-specific therapies will be included to serve as an internal comparator cohort in EXTRACT and allow for pooling of the cohorts of EXPOSURE and EXTRACT in comparative analyses.

7. RESEARCH QUESTION AND OBJECTIVES

Research Question

The purpose of this Post-authorisation safety study (PASS) is to complement EXPOSURE 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 or newly treated with any other PAH-specific therapy who were never treated with Uptravi in the international post-marketing setting.

Objective(s) and Measure(s) of Interest

The objectives of the study 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 and 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 important identified or potential risks:
   - Hypotension
   - Anemia
   - Hyperthyroidism
   - Pulmonary oedema associated with pulmonary veno-occlusive disease (PVOD)
   - 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 describe rates of MACE and all-cause death in Uptravi exposed patients and patients initiating another PAH-specific therapy

8. RESEARCH METHODS

8.1. Study Design

8.1.1. Overview of Study Design

This is a retrospective, non-interventional, multicenter, international, chart review study of patients with PAH newly treated with Uptravi or other PAH-specific therapies.

Only data available within normal clinical practice will be collected in this study.

The enrolment period is from start of reimbursement of Uptravi in a specific country, to the earlier of either

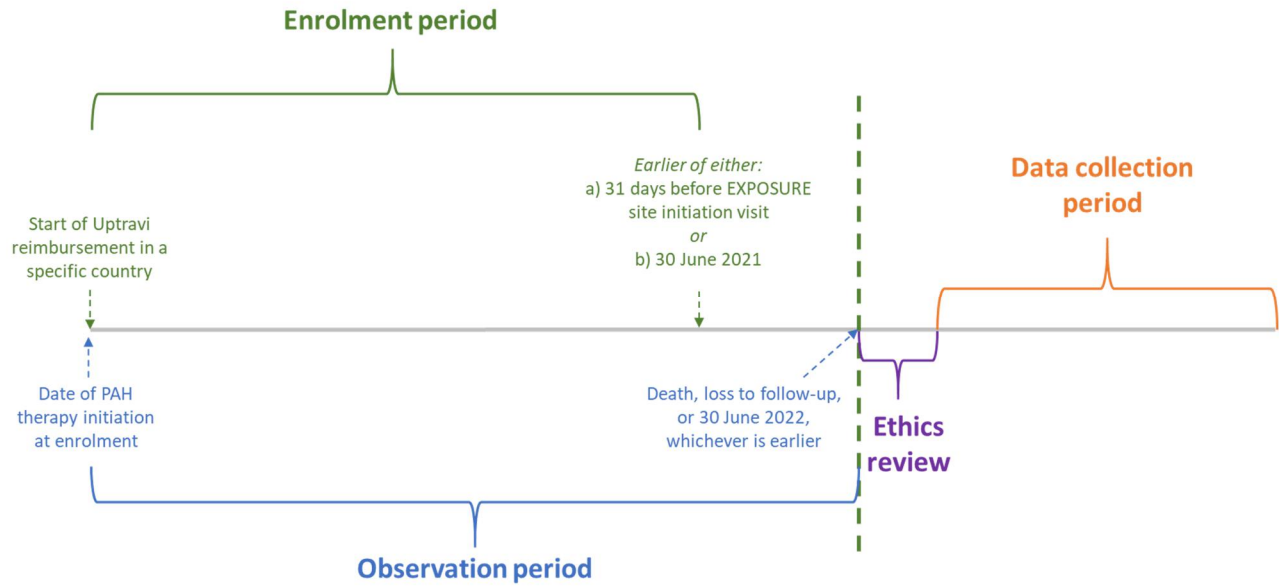
a) 31 days before the respective EXPOSURE site initiation visit (SIV) (to avoid enrolment of any patients who are eligible for EXPOSURE to enrol in EXTRACT), or

b) 30 June 2021 (to allow a minimum of 12 months of potential follow-up after enrolment, as the observation period ends on 30 June 2022)

The observation period is from the date of new PAH-specific therapy initiation until death, loss to follow-up, or 30 June 2022 (the day before planned ethics committee submission for EXTRACT for the first site), whichever is earlier.

A diagram of the study design is provided below.

Figure 1: Diagram of the Study Design



PAH= pulmonary arterial hypertension

Pulmonary arterial hypertension therapies in scope for this study are as follows (Table 1):

Table 1: PAH-specific Therapies in Scope for This Study

Class of Therapy	Therapy Name
Endothelin receptor antagonist	Macitentan [a] Ambrisentan Bosentan [a]
Phosphodiesterase type 5 inhibitor	Tadalafil Sildenafil
Soluble guanylate cyclase stimulator	Riociguat
Prostacyclin receptor agonist	Selexipag [a]
Prostacyclin analogues	Epoprostenol IV [a] Iloprost IV/inhaled Treprostinil IV/SC/inhaled/oral Beraprost sodium

IV=intravenous; PAH=pulmonary arterial hypertension; SC=subcutaneous

[a] The drug is a Janssen PAH-specific therapy: Uptravi® (selexipag), Veletri® / Caripul® (epoprostenol), Opsumit®(macitentan), Tracleer® / STAYVEER® (bosentan)

8.1.2. Rationale for Study Design Elements

A retrospective, non-interventional design is chosen for EXTRACT in order to enroll patients who were not eligible for EXPOSURE due to having initiated PAH-specific therapy more than 30 days before EXPOSURE initiation. The Other PAH-specific therapy cohort will serve as internal control and allow data pooling with EXPOSURE for comparative analyses.

The Other PAH-specific therapy cohort in EXTRACT will enroll prevalent patients with PAH who initiated a new PAH-specific therapy as part of a combination regimen. Since the majority of patients newly initiating Uptravi are prevalent patients treated in combination therapy, these criteria increase the proportion of patients with characteristics similar to patients in the Uptravi cohort, thereby increasing the effective sample for comparative analyses.

8.2. Setting and Patient Population

8.2.1. Study Setting and Duration

Patients in this non-interventional study will have been treated with Uptravi or other PAH-specific therapies in a routine clinical setting.

No treatment will be provided by the sponsor and patients will not be reimbursed for purchasing any treatments that they need to treat their pathology.

The retrospective data will document data available from the date of initiation of new PAH-specific therapy until death, loss to follow-up, or 30 June 2022 (the day before planned ethics committee submission for EXTRACT for the first site), whichever is earlier.

All treatment decisions would have been made at the discretion of the treating physician. Starting or stopping therapies for PAH during the observation period will not impact data collection for this study. If a patient discontinued treatment before the end of the observational period, all relevant following treatments and assessments will be documented.

Patients who are enrolled in any ongoing interventional clinical trial during observation period of this study are excluded from enrolment in this study. Study sites are encouraged to enroll all consecutive patients that fulfill enrolment criteria to avoid selection bias. Only countries and sites where waivers of informed consent can be obtained for this study will be included in EXTRACT to avoid survival bias.

The study is considered completed when the last data item for the last patient participating in the study is entered in the electronic case report form (eCRF). Participating sites will be closed upon study completion. Further details of study completion and termination procedures are presented in Annex 1.11.

8.2.2. Selection Criteria

The number of patients planned to be enrolled in the study is atleast 391 Uptravi exposed patients and 510 patients initiating other PAH-specific therapies from participating PAH expert centres.

At each participating site, the participating physician will evaluate patient's medical records to determine their eligibility for data collection in this study based on the selection criteria described below. If there is a question about any of the selection criteria, the participating physician should consult with the appropriate sponsor representative before enrolling the patient.

Each potential participant must satisfy the following criteria to be eligible for data collection in this study:

1. Patients ≥18 years old
2. Clinically diagnosed with Group 1 PAH
3. Patients whose medical charts are available for data collection during the observation period
4. Uptravi cohort:
    - Patients who initiated Uptravi for the first time
5. Other PAH-specific therapy cohort:
    - Prevalent patients (≥ 6 months from first clinically diagnosed PAH)
    - Patients initiating a PAH-specific therapy other than Uptravi for the first time as part of a combination therapy

Potential participants who meet any of the following criteria will not be eligible for this study:

1. Previously treated with Uptravi/selexipag
2. Patients initiating another PAH-specific therapy that had been previously treated with the same drug
3. Enrolled in EXPOSURE
4. Patients enrolled in any ongoing interventional clinical study during the observation period of EXTRACT

8.3. Variables

The eCRF DATA COLLECTION SCHEDULE that follows the abstract summarizes the variables collected at initiation of a new PAH-specific therapy and/or during the observation period, if available, per clinical practice. Only data available from a patient's source medical records will be collected. Data will be entered by the investigator / study coordinator into a standardised eCRF.

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 eCRF.

- Study specifics (visit date, termination of data entry: date, reason)
- Demographics (age, gender, country)
- Clinical characteristics (PAH classification, aetiology, date of first PAH diagnosis and World Health Organization (WHO) functional class (FC) at diagnosis, WHO FC, 6-minute walk distance [6MWD], incremental shuttle walking test [ISWT], height, weight, right heart catheterisation haemodynamics, % predicted diffusion capacity of the lungs for carbon monoxide [DL_{CO}], pericardial effusion, vital signs, transplantation list/pre-transplantation visit, renal insufficiency)
- Laboratory data (haemoglobin, thyroid hormone, N-terminal of the prohormone brain natriuretic peptide [NT-proBNP], brain natriuretic peptide [BNP])
- Medical history
  - Cardiovascular/cerebrovascular disease history (history of myocardial ischaemia, myocardial infarction [MI], cardiac arrest, ischaemic cerebrovascular disorders, haemorrhagic cerebrovascular disorders, revascularisation procedure [coronary and/or carotid] 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, smoking status, hyperlipidaemia, systemic hypertension, hypercoagulable state, sleep apnoea syndrome)
  - Other relevant medical history (hypotension, anaemia, pulmonary oedema associated with PVOD, hyperthyroidism, renal impairment, bleeding events, light-dependent non-melanoma skin malignancy, ophthalmological effects associated with retinal disorder, intestinal intussusception manifested as intestinal obstruction / ileus)
- Medication
  - Uptravi or any other PAH-specific therapy (See Table 1) (drug name of all individual PAH-specific drug substances, start date, dosing regimen [date of up/down titration & dose at each step, maintenance dosing change], dose change, interruption or discontinuation [date, reason], history of any PAH-specific therapy within the previous 12 months)
- Outcomes
  - Incident important identified or potential risks, defined as 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 intestinal obstruction, and MACE, defined as the occurrence of at least one condition falling into any of the below categories[a]:

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

- Hospitalisation (PAH related or not, admission /discharge dates, reason)
- Death
- Any new diagnosis or adverse events considered by the reporter (ie, site personnel who entered patient data into medical chart) to be explicitly causally related to a PAH-specific Janssen product, ie adverse drug reaction (ADR) of a PAH-specific Janssen product

8.3.1. 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
2. WHO FC change

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

1. Occurrence of all-cause death
2. Occurrence of the following important identified or potential risks:
   - Hypotension
   - Anaemia
   - Pulmonary oedema associated with PVOD
   - Hyperthyroidism
   - MACE (Annex 3)
   - Acute renal failure and renal function impairment
   - Bleeding events
   - Light-dependent non-melanoma skin malignancy
   - Ophthalmological effects associated with retinal vascular system
   - Intestinal intussusception manifested as an intestinal obstruction / ileus

[a] See definition in Annex 3.

To describe rates of MACE and all-cause death, the following outcomes will be evaluated in Uptravi exposed patients and patients initiating other PAH-specific therapies:

1. Occurrence of MACE (Annex 3)
2. Occurrence of all-cause death

8.3.2. PAH-Specific Medication Exposure Definition and Measures

The observation period is from the date of initiation of new PAH-specific therapy until death, loss to follow- up, or 30 June 2022 (the day before planned ethics committee sumbmission for EXTRACT for the first site), whichever is earlier.

The exposure period is defined as time from initiation of new PAH-specific therapy to the earliest of discontinuation + 7 days of this therapy, death, last available follow-up, or end of the study.

Patients in the Other PAH-specific therapy cohort who initiated Uptravi for the first time during the observation period (defined as late initiators for analysis purposes in Section 8.6) will be followed, from that point forward, as Uptravi exposed patients for analysis.

As per the patient selection criteria, (Section 8.2.2) patients initiating a PAH-specific therapy other than Uptravi should be naïve to Uptravi/selexipag; therefore, patients who discontinued Uptravi during the observation period are not eligible to enter the Other PAH-specific therapy cohort.

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

8.3.3. Covariate Definition and Measures

Based on known characteristics of PAH, the following variables will be considered for analysis as confounding factors or effect modifiers in the pooled analysis with EXPOSURE, and their relationship to the safety-related outcomes will be explored:

1. Age, time of PAH-specific therapy initiation, gender
2. PAH characteristics at time of PAH-specific therapy initiation:
    - PAH etiology, time since PAH diagnosis
    - WHO FC, 6MWD, ISWT, haemodynamics from most recent right heart catheterisation (RHC)
3. Medical history of previous and ongoing clinically significant underlying diseases and comorbid conditions (eg, cardiovascular risk factors, renal insufficiency, diabetes mellitus)
4. PAH-specific therapy and its treatment duration, dose and regimen.

8.4. Data Sources

Identification of participating countries

The study will include patients predominantly in 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 may include Austria, Czech Republic, Estonia, Finland, France, Germany, Greece, Italy, Lithuania, Poland, Slovakia, Spain, Sweden, Switzerland, the Netherlands, the UK and other countries, as needed, as Uptravi becomes commercially available.

eCRF data collection

The EXTRACT eCRF is a stand-alone program. Data will be collected by the investigator / study coordinator for each patient throughout the observation period based on the existing medical records.

The primary data source for this study will be the medical records of each patient. Source documentation should be in patients' records for all data entered into the CRF.

Source documentation should be available for the following to confirm data collected in the CRF for this study: patient identification, eligibility and study identification, and date of study completion. The author of any entry in the source documents should be identifiable. The type and level of detail of source data available for a patient should be consistent with that commonly recorded at the participating site as a basis for standard medical care. Specific details required as source data for the study will be reviewed with the participating physician before the study.

8.5. Study Size

Sample size in EXTRACT is determined based on the difference between the overall sample size needed in the Uptravi cohort in EXPOSURE (ie, 1184 patients) and the projected number of patients that can be enrolled in the Uptravi cohort in EXPOSURE by June 2023 (ie, by the end of data collection in EXTRACT), while maintaining a similar ratio with the comparator cohort as in EXPOSURE. No formal sample size calculation has been performed for EXTRACT. Based on current projection, EXPOSURE is expected to have 793 patients enrolled in the Uptravi cohort by June 2023. Therefore, EXTRACT is planned to enroll at least 391 patients in the Uptravi cohort, to reach the enrolment target of about 1184 Uptravi patients in the combined EXPOSURE and EXTRACT dataset. In addition, at least 510 patients will be enrolled the Other PAH-specific therapy cohort in EXTRACT to serve as an internal comparator of the Uptravi cohort. Overview of sample size is provided in Table 2:

Table 2: Overview of Sample Size

	Uptravi cohort	Other PAH-specific therapy cohort
Sample size as per EXPOSURE protocol version 7	1184	1850
Expected number of patients in EXPOSURE as of Jun 2023	793	1850
Number of patients needed in EXTRACT as of June 2023	391	510
Total sample size in the combined dataset of EXPOSURE and EXTRACT	1184	2360

8.5.1. Data Management

Participating sites will enter data into the eCRF using electronic data capture (eDC) via a secure internet-based eDC system. The CRF will direct the site regarding which data are required for collection. Participating sites will be trained on the use of the eDC system. Data collected should be recorded accurately, legibly and promptly for each patient during the study. Further details of CRF completion procedures are presented in Annex 1.7.

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 from study patients are received by the Drug Safety department outside of the PASS to avoid double counting in the Safety database.

8.6. Data Analysis

Statistical analyses will be performed by or under the authority of the sponsor once all data have been collected at the end of the study. A general description of the planned statistical methods is presented in the following subsections. Additional details will be provided in the statistical analysis plan (SAP).

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.

Additional analysis for other research questions not specified in this protocol may be conducted, including use of study data in combination with other data sources to address relevant research questions. Separate study protocols and/or SAPs will be developed for additional analyses.

8.6.1. Analysis Sets and Groups

The following analysis sets will be defined:

– **All Set** (ALL): All patients present in the database 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 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 information on at least one follow-up visit or event (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.

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 at enrolment and who were never treated with Uptravi,
- 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 at enrolment,
- 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. As 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).

8.6.2. Main Summary Measures

The main summary measures are:

- Summary statistics of demographics, disease characteristics and clinical course in Uptravi-exposed patients and patients initiating another PAH-specific therapy.
- Occurrence and incidence rate during Uptravi exposure period of all-cause death and the important identified and potential risks of Uptravi, including MACE, in Uptravi-exposed patients**.**
- Occurrence and incidence rates of MACE and all-cause death in Uptravi-exposed patients and patients initiating another PAH-specific therapy.

8.6.3. Main Statistical Methods

To account for potential survivor bias effect in the analysis (eg, survivor bias either for fatal or non-fatal events during the observation period), only the first exposure period of Uptravi / other PAH-specific therapy within the study period will be included in the Uptravi and Other cohorts, respectively. The Other PAH-specific therapy cohort will also include data prior to Uptravi initiation for late initiators (for the definition of late initiators, refer to Section 8.3.2).

8.6.4. Uptravi Safety Profile

In order to further characterise the Uptravi safety profile, the frequency and incidence rates of important identified and potential risks as described in Section 8.3 and all-cause death during all exposure period will also be calculated in the Uptravi cohort. For these analyses, all periods of Uptravi exposure will be included (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).

Frequency and incidence rates of all ADRs related to PAH-specific Janssen product will be calculated.

Analytic results from this retrospective chart review study will be reported at an aggregated level.

Clinical characteristics of patients at the time of 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.

8.6.5. Pooled Analyses of EXTRACT and EXPOSURE

Homogeneity between EXPOSURE and EXTRACT (after adjusting for differences in patient characteristics by matching or weighting methods) will be assessed using descriptive statistics and standardized mean differences of patient characteristics at time of new PAH-specific therapy initiation of both populations. If homogeneity between the two populations is deemed acceptable, pooled analysis using data from both EXPOSURE and EXTRACT will be performed and reported. Otherwise, descriptive statistics will be provided for each study separately. Further details about the analyses and homogeneity assessment will be provided in the SAP.

8.6.6. Missing Values

Due to the non-interventional and retrospective nature of the study, some study variables are expected to be missing or incomplete. Rules for handling of missing or incomplete dates will be fully described in the SAP.

8.6.7. Sensitivity Analyses

Not applicable.

8.6.8. Interim Analysis

No interim analysis of EXTRACT will be performed.

8.7. Quality Control

Procedures to ensure the accuracy and reliability of data will include the selection of qualified physicians and appropriate participating sites, review of data collection procedures with the participating physician and site personnel before the study, and periodic monitoring visits and/or remote monitoring by the sponsor (if applicable) (see Section 8.5.1).

Guidelines for CRF completion will be provided and reviewed with the participating site personnel before the start of the study (see Annex 1.7). The sponsor will review CRFs for accuracy and completeness during on-site monitoring visits (where applicable) and after transmission to the sponsor; any discrepancies will be resolved with the participating physician or designee, as appropriate.

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 and feasible. Educational measures and training focused on the importance of capturing all available data will be developed. (Annex 1.8).

The participating physician and/or site will maintain all CRFs and source documentation that support the data collected for each patient, as well as all study documents specified by the applicable regulatory requirement(s) (see Annex 1.3). The participating physician and/or site will take measures to prevent accidental or premature destruction of these documents. Essential documents must be retained for at least 5 years after the completion of the final study report but will be retained for a longer period if required by applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the participating physician and/or site as to when these documents no longer need to be retained. Further details of record retention policies are provided in Annex 1.10.

Representatives of the sponsor may visit the participating site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and/or company policy. Similar procedures may also be conducted by a regulatory body. Further details of on-site audit policies are presented in Annex 1.9.

8.8. Limitations of the Research Methods

This PASS is a non-interventional study examining patients newly exposed to Uptravi and patients newly exposed to other PAH-specific therapies in real-world clinical settings. Due to the retrospective and observational nature of this study, treatment with new PAH-specific therapies, including Uptravi, was based on prescriber/investigator decision and was not influenced by participation in the PASS. The patients were followed by their physician according to clinical practice.

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. To minimise selection bias, participating sites will be encouraged to enrol all patients

with PAH initiating a new PAH-specific therapy who meet the eligibility criteria, regardless of other previous or concomitant PAH-specific therapy received.

Due to the observational and retrospective nature of this study, some study variables, including patient and disease characteristics, exposure and outcomes, may be missing or inaccurate. Procedures to improve the completeness, accuracy and reliability of data will include the selection of qualified physicians and appropriate participating sites, review of data collection procedures with the participating physician and site personnel before the study, periodic review of data collected by the sponsor, monitoring visits and/or remote monitoring by the sponsor (see Section 8.7). Guidelines for CRF completion will be provided and reviewed with the participating site personnel before the start of the study (see Annex 1.7).

Due to the difference in design between EXTRACT (retrospective) and EXPOSURE (prospective), data quality (eg, missingness, accuracy) might differ between the two studies. Poolability of EXTRACT with EXPOSURE data for comparative analyses will be assessed through homogeneity assessment. Homogeneity assessment of the EXTRACT and EXPOSURE are descripted in Section 8.6.5.

PROTECTION OF HUMAN SUBJECTS

Based on the arguments below, it is concluded that no patient informed consent is needed to conduct this study. Therefore, a request for waiver of informed consent will be submitted to the Independent Ethics Committee (IEC)/Institutional Review Board (IRB). The criteria qualifying for waiver of consent for this study are:

- This EXTRACT study will supplement EXPOSURE with retrospectively identified patients. EXTRACT has been developed to achieve the desired sample size of EXPOSURE, the post-marketing requirement for Uptravi (EU PAS 19085)
- There is minimal risk to harm the subject:
  - EXTRACT involves no more than minimal risk to participants and involves no procedures for which signed consent is normally required. There are no experimental procedures involved or medication use proposed.
  - EXTRACT is a retrospective observational study limited to reviewing and collecting pre-existing patient medical chart data.
  - The risk to the patient in the study is the potential release of protected health information, or loss of confidentiality. Strict confidentiality will be maintained through a secure internet-based electronic data collection (EDC) system and de-identification of patient data at the study site level.
- Since EXTRACT is a retrospective review of existing data, the rights and welfare of the patients will not be adversely affected. The visits and treatment have already occurred. Thus, inclusion in the study will have no influence on the treatment of the patient. No patient contact is required.
- The study could not practicably be carried out without the waiver:

  - Patients who are deceased cannot be contacted for informed consent due to the 1- and 3-years published survival rates, this would be the case for 15% to 32% of eligible patients.
  - Some patients will have moved, changed physicians, or have no known address available.

- Any ADRs, product quality complaints or special situations found to be documented in medical chart as being explicitly causally related to PAH-specific Janssen products (ie, Uptravi® (selexipag), Veletri® / Caripul® (epoprostenol), Opsumit® (macitentan), or Tracleer® / STAYVEER® (bosentan); see Table 1) will be collected and reported to GMS.

Obtaining informed consent to use data from a retrospective chart review for research purposes is considered impracticable and a possible source of selection bias. If waiving informed consent is not possible at a particular site, that site will not participate in the study.

Where appropriate, as required by local regulations, this study will be undertaken only after the IEC/IRB has given full approval of the final protocol, any applicable amendments, and the waiver of informed consent form (ICF), and the sponsor has received a copy of this approval (see Annex 1.4).

Personal data collected from patients enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study, and will be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations (see Annex 1.6).

9. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of patients, physicians, and the sponsor, and are mandated by regulatory agencies worldwide. All studies conducted by the sponsor or its affiliates will be conducted in accordance with established procedures and regulatory requirements worldwide to ensure appropriate reporting of safety information.

9.1. Procedures

In this retrospective, non-interventional, chart review study, Uptravi or other PAH-specific therapies are the therapies under study.

The sponsor will provide appropriate pharmacovigilance training to participating site personnel. The sponsor assumes responsibility for appropriate reporting of (serious) adverse events and significant safety information originating from the data collected for Janssen medicinal products to the regulatory authorities (see country-specific attachments).

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product safety issues and/or quality issues are listed on the contact information page(s), which is/are provided separately.

9.1.1. Adverse Drug Reactions

All ADRs and special situations documented in the source data following exposure to a PAH-specific Janssen product(s) under study (see Table 1) are to be recorded in the CRF and reported to GMS, regardless of seriousness. ADRs should be collected within the protocol-defined data collection period until 30 days after the last documented use of the PAH-specific Janssen product(s) under study, or until the end of observation period, defined in Section 8.1.1, whichever is earlier.

All serious ADRs for a Janssen product under study should be reported directly by the participating site, within 24 hours of them becoming aware, to the local sponsor using a Serious Adverse Event Report Form. For non-serious ADR, line listings will be generated from the clinical database by Data Management (DM) at least every 30 days, and will be submitted to GMS directly. When necessary, the sponsor will inform the local health authorities following applicable requirements for expedited and aggregated reporting.

All collected ADRs will be summarized in the final study report.

9.1.2. Pregnancy

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 a PAH-specific Janssen product under study must be reported to the sponsor by the participating site personnel within 24 hours of their knowledge of the event using a Serious Adverse Event Form.

9.1.3. Product Quality Complaints

A product quality complaint (PQC) may have an impact on the safety and effectiveness of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of patients, physicians, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

All initial PQCs involving a Janssen product must be reported to the local sponsor by the participating site personnel within 24 hours after being made aware of the event. The names (and corresponding telephone numbers) of the individuals who should be contacted regarding PQCs for a Janssen product are listed on the contact information page(s), which is/are provided separately.

If the defect for a Janssen product is combined with a serious adverse event, the study-site personnel must report the PQC to the local sponsor according to the serious adverse event reporting timelines. A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

9.2. Definitions and Classifications

9.2.1. Adverse Event Definitions

Adverse Event

An adverse event is any untoward medical occurrence in a patient administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can be any unfavorable and unintended sign (including an abnormal finding or lack of expected pharmacological action), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition based on International Council for Harmonization [ICH]).

This includes any occurrence that is new in onset or aggravated in severity from the baseline condition, or abnormal results of any diagnostic procedures that are conducted per clinical practice.

Adverse Drug Reaction

An adverse drug reaction (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 adverse event, is characterized by the fact that a causal relationship between the medicinal product and the occurrence is suspected. All adverse events judged by either the reporting physician or the sponsor as having a reasonable causal relationship to a medicinal product qualify as ADRs.

Serious Adverse Event

A serious adverse event, based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use, is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (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 if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is medically important*

* Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above.

Unlisted (Unexpected) Adverse Event

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. The expectedness of an adverse event will be determined by whether or not it is listed in the applicable reference safety information such as United States Prescribing Information (USPI), Summary of Product Characteristics (SmPC), and other approved product information documents for PAH-specific Janseen products, ie, Uptravi® (selexipag), Veletri® / Caripul® (epoprostenol), Opsumit®(macitentan), or Tracleer® / STAYVEER® (bosentan).

NOTE: Unlistedness of an event is only relevant for the sponsor's reporting obligations but does not determine reporting requirements of the participating physician to the sponsor or Marketing Authorization Holder.

Product Quality Complaint

A product quality complaint is any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or drug delivery system.

9.2.2. Attribution Definitions

Assessment of Causality

The causal relationship to treatment is determined by a physician and should be used to assess all adverse events. The causal relationship can be one of the following:

Related

There is a reasonable causal relationship between administration of the medicinal product(s) (Janssen PAH-specific therapy: Uptravi® [selexipag], Veletri® / Caripul® [epoprostenol], Opsumit® [macitentan], or Tracleer® / STAYVEER® [bosentan]) and the adverse event.

Not Related

There is not a reasonable causal relationship between administration of the the product under study (Uptravi® [selexipag], Veletri® / Caripul® [epoprostenol], Opsumit® [macitentan], or Tracleer® / STAYVEER® [bosentan]) and the adverse event.

The term "reasonable causal relationship" means there is evidence to support a causal relationship.

9.3. Special Situations

Safety events of interest for a Janssen product under study that require reporting and/or safety evaluation by Janssen include, but are not limited to:

- Overdose of a product
- Exposure to a product from breastfeeding
- Suspected abuse/misuse of a product
- Inadvertent or accidental exposure to a product
- 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 medication error, or potential medication error involving a Janssen medicinal product (with or without patient exposure to the Janssen medicinal product, eg, product name confusion, product label confusion, intercepted prescribing or dispensing 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 adverse events.

10. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The study description and key protocol elements will be published on the ENCePP register. The results of the study will be reported in a clinical study report generated by the sponsor, which will contain data collected from all study sites that participated in the study. The sponsor will register and/or disclose the existence of and the results of clinical studies as required by law.

Patient identifiers will not be used in the publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the participating physician) shall be the property of the sponsor as author and owner of copyright in such work.

Further details of publication policies and practices are provided in Annex 1.12.

11. REFERENCES

Pratt CM (1996), 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.

European Union Risk Management Plan (UPTRAVI [selexipag]) Version 9.2. Janssen Research & Development (20 Dec 2020).

ANNEX 1: STAND-ALONE DOCUMENTS AND ADDITIONAL INFORMATION

Annex 1.1: List of Standalone Documents

None

Annex 1.2: Information to be Provided to Participating Physicians

The participating physician will be provided with the following supplies:

- CRF completion guideline

Annex 1.3: Regulatory Documentation

Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, where applicable. A study may not be initiated until any applicable local regulatory requirements are met.

Required Prestudy Documentation

The following documents must be provided to the sponsor before starting the study:

- Protocol and amendment(s), if any, signed and dated by the participating physician
- Where appropriate, as required by local regulations, a copy of the dated and signed written IEC/IRB approval of the protocol, amendments, waiver of ICF, and any recruiting materials.
- Where appropriate, as required by local regulations, a copy of the dated and signed written Designated Regulatory Body (DRB) approval of the protocol, protocol amendments, waiver of ICF, and any other recruiting materials. This approval must clearly identify the specific protocol by title and number and must be signed by the chairman or authorized designee.
- Where appropriate, as required by local regulations, the name and address of the DRB (with a statement that it is organized and operates according to applicable laws and regulations). If a participating physician or a member of the participating site personnel is a member of the DRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote or opinion of the study.
- Regulatory authority approval or notification, if applicable
- Documentation of the qualifications (eg, curriculum vitae) of the participating physician, where appropriate
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first patient:

- Signed and dated study agreement, which includes the financial agreement

Annex 1.4: Ethics Compliance

Independent Ethics Committee or Institutional Review Board

Before the start of data collection, the participating physician (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, protocol amendments
- Participating physician's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding name of the sponsor, institutional affiliations, other potential conflicts of interest
- Any other documents that the IEC/IRB requests to fulfill its obligation

Where appropriate, as required by local regulations, this study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding those that are purely administrative, with no consequences for data collection), the waiver of ICF, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the participating physician (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding those that are purely administrative, with no consequences for data collection)
- If applicable, new or revised patient recruiting materials approved by the sponsor
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB
- Reports of adverse events that are serious, unlisted/unexpected, and temporally associated with the product under study
- New information that may adversely affect the safety of the patients or the conduct of the study
- Report of deaths of patients under the participating physician's care
- Notification if a new physician is responsible at the participating site
- Any other requirements of the IEC/IRB

At the end of the study, where required by local regulations, the participating physician (or sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the study completion notification will be submitted through the head of the participating site).

Annex 1.5: Patient Identification and Enrollment

The participating physician agrees to complete a patient identification and enrollment log to permit easy identification of each patient during and after the study. This document will be reviewed by

the sponsor and participating site contact for completeness. The patient identification and enrollment log will be treated as confidential and will be filed by the participating physician in the study file. To ensure patient confidentiality, no copy will be made. All reports and communications relating to the study will identify patients by patient identification and age at enrolment.

Where applicable, the participating physician should also complete a patient screening log, which documents all patients who were evaluated to determine eligibility for data collection in the study.

Annex 1.6: Patient Data Protection

The collection and processing of personal data from patients enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study, which must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of patients confidential.

Annex 1.7: Case Report Form Completion

Case report forms are provided for each patient in electronic format.

Electronic Data Capture (eDC) will be used for this study. The study data will be transcribed from the source documents onto an electronic CRF by personnel at each participating site, and transmitted in a secure manner to the sponsor within the timeframe agreed upon between the sponsor and the site. The electronic file will be considered to be the CRF.

The participating physician must verify that all data entries in the CRFs are accurate and correct. All CRF entries, corrections, and alterations must be made by the participating physician or other authorized participating site personnel. If necessary, queries will be generated in the eDC tool. The participating physician or participating site personnel must adjust the CRF (if applicable) and complete the query.

If corrections to a CRF are needed after the initial entry into the CRF, this can be done in 3 different ways:

- Personnel at each participating site can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- The manager of the participating site can generate a query for resolution by the personnel at that site.
- Clinical data manager can generate a query for resolution by the participating site personnel.

Annex 1.8: Monitoring

- Direct access to source documentation must be allowed for the purpose of verifying that the data recorded in the CRF are consistent with the original source data. Findings from this review of CRFs and source documents will be discussed with the participating site personnel. The sponsor expects that, during monitoring visits, the relevant participating site personnel

will be available, the source documentation will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the participating physician on a regular basis during the study to provide feedback on the study conduct.

Annex 1.9: On-Site Audits

- Any audits conducted by the sponsor at a participating site will require access to all study records, including source documents, for inspection and comparison with the CRFs. Patient privacy must, however, be respected. The participating physician and participating site personnel are responsible for being present and available for consultation during routinely scheduled site audit visits conducted by the sponsor or its designees.

Annex 1.10: Record Retention

If the responsible participating physician retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the participating physician relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the participating physician and/or site must permit access to such reports.

Annex 1.11: Study Completion/Termination

The final data from the participating site will be sent to the sponsor (or designee) after completion of the final data collection time point at that site.

The sponsor reserves the right to close a participating site for data collection or to terminate the study at any time for any reason at the sole discretion of the sponsor.

A participating site is considered closed when all required documents and study specific supplies have been collected and a site closure assessment has been performed.

The participating physician may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a participating site by the sponsor or participating physician may include but are not limited to:

- Failure of the participating physician to comply with the protocol, requirements of the local health authorities, or the sponsor's procedures
- Inadequate recruitment of patients by the participating physician

The participating physician should immediately notify the sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection.

Annex 1.12: Use of Information and Publication

All information, including but not limited to information regarding PAH-specific therapies under study or the sponsor's operations (eg, patent applications, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the participating physician and not previously published, and any data generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The participating physician agrees to maintain this information in confidence, to use this information only to accomplish this study, and not to use it for other purposes without the sponsor's prior written consent.

The participating physician understands that the information obtained in the study will be used by the sponsor in connection with the continued development of PAH-specific therapies under study, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information obtained to be used, the participating physician is obligated to provide the sponsor with all data obtained in the study.

Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the participating physician as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish the primary (multicenter) data and information without approval from the participating physician. The participating physician has the right to publish data specific to the associated participating site after the primary data are published. If a participating physician wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the participating physician will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the participating physician. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, participating physicians will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

ANNEX 2: ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Section 1: Research question	Yes	No	N/A	Page Number(s)
1.1 Does the formulation of the research question clearly explain:				
1.1.1 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)	☒	☐	☐	18
1.1.2 The objectives of the study?	☒	☐	☐	20
1.2 Does the formulation of the research question specify:				
1.2.1 The target population? (i.e. population or subgroup to whom the study results are intended to be generalized)	☒	☐	☐	Section 8.2
1.2.2 Which formal hypothesis(-es) is (are) to be tested?	☐	☒	☐	
1.2.3 if applicable, that there is no a priori hypothesis?	☒	☐	☐	Section 8.2

Comments:

1.2.2: This is a descriptive study without formal hypothesis to be tested

Section 2: Source and study populations	Yes	No	N/A	Page Number(s)
2.1 Is the source population described?	☒	☐	☐	Section 8.2
2.2 Is the planned study population defined in terms of:				
2.2.1 Study time period?	☒	☐	☐	Section 8.2
2.2.2 Age and sex?	☒	☐	☐	Section 8.2
2.2.3 Country of origin?	☒	☐	☐	27
2.2.4 Disease/indication?	☒	☐	☐	Section 8.2
2.2.5 Co-morbidity?	☒	☐	☐	Section 8.2
2.2.6 Seasonality?	☐	☐	☒	
2.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	

Comments:

2.2.6: Seasonality is not relevant for this study

Section 3: Study design	Yes	No	N/A	Page Number(s)
3.1 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	25
3.2 Is the study design described? (e.g. cohort, case-control, randomized controlled trial, new or alternative design)	☒	☐	☐	20
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)	☒	☐	☐	20
3.4 Is sample size considered?	☒	☐	☐	27
3.5 Is statistical power calculated?	☐	☒	☐	

Comments:

3.5 No formal hypothesis testing planned in this study

Section 4: Data sources	Yes	No	N/A	Page Number(s)
4.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
4.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc)	☒	☐	☐	27
4.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc)	☒	☐	☐	27
4.1.3 Covariates?	☒	☐	☐	27
4.2 Does the protocol describe the information available from the data source(s) on:				
4.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	27
4.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	27
4.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	27
4.3 Is the coding system described for:				
4.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☐	☒	
4.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☐	☐	☒	
4.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☐	☒	
4.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

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)	☒	☐	☐	26
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)	☒	☐	☐	31
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	26
5.4 Is exposure classified based on biological mechanism of action?	☐	☒	☐	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☒	☐	

Comments:

5.4 Exposure is classified based on start and end date of treatment in CRF. 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?	☒	☐	☐	25
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)	☒	☐	☐	28, 31

Comments:

Section 7: Biases and Effect modifiers	Yes	No	N/A	Page Number(s)
7.1 Does the protocol address:				
7.1.1 Selection biases?	☒	☐	☐	31
7.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	31
7.2 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	31
7.3 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	31
7.4 Does the protocol address other limitations?	☒	☐	☐	31

Comments:

Section 8: Analysis plan	Yes	No	N/A	Page Number(s)
8.1 Does the plan include measurement of absolute effects?	☒	☐	☐	28
8.2 Is the choice of statistical techniques described?	☒	☐	☐	28
8.3 Are descriptive analyses included?	☒	☐	☐	28
8.4 Are stratified analyses included?	☒	☐	☐	28
8.5 Does the plan describe the methods for identifying:				
8.5.1 Confounders?	☒	☐	☐	26
8.5.2 Effect modifiers?	☒	☐	☐	26
8.6 Does the plan describe how the analysis will address:				
8.6.1 Confounding?	☒	☐	☐	26
8.6.2 Effect modification?	☒	☐	☐	26

Comments:

Section 9: Quality assurance, feasibility and reporting	Yes	No	N/A	Page Number(s)
9.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	28
9.2 Are methods of quality assurance described?	☒	☐	☐	28, 31
9.3 Does the protocol describe quality issues related to the data source(s)?	☒	☐	☐	31
9.4 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	27
9.5 Does the protocol specify timelines for				
9.5.1 Start of data collection?	☒	☐	☐	17
9.5.2 Any progress report?	☒	☐	☐	17
9.5.3 End of data collection?	☒	☐	☐	17
9.5.4 Reporting? (i.e. interim reports, final study report)	☒	☐	☐	17
9.6 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	7
9.7 Are communication methods to disseminate results described?	☒	☐	☐	37
9.8 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

9.8: No independent review board is planned.

Section 10: Ethical issues	Yes	No	N/A	Page Number(s)
10.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	32
10.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
10.3 Have data protection requirements been described?	☒	☐	☐	32

Comments:

10.2: EXTRACT protocol will be submitted to IRC/IEC prior to study implementation.

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

Death 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. As 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 myocardial infarction**: confirmed by electrocardiogram (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 myocardial infarction 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)

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.

Principal Participating Physician:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer (Main Author):

Name (typed or printed): PPD

Institution: PPD

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

Institution: PPD

Signature: electronic signature appended at the end of the protocol Date: _____

Qualified Person Pharmacovigilance:

Name (typed or printed): PPD

Institution: PPD

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		