European Union Risk Management Plan
UPTRAVI (selexipag)

Data-lock point for current RMP	20 December 2020	Version number	11.2

Procedure EMEA/H/C/003774/MEA/003.5/Health Authority Approval Date 08 November 2024 (CHMP Opinion)
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PPD

PPD

QPPV Name(s):	Dr. Laurence Oster-Gozet, PharmD, PhD
QPPV Signature:	The MAH QPPV has either reviewed and approved this RMP, or approved with an electronic signature appended to this RMP, as applicable.

Details of this RMP Submission	
Version Number	11.1
Rationale for submitting an updated RMP (if applicable)	Per CHMP feedback on the MAH's request (Procedure EMEA/H/C/003774/MEA/003.5) to conclude the EDUCATE PASS (AC-065A403) as per timelines detailed in the RMP Version 10.1, the MAH agreed to continue patient recruitment to the EDUCATE PASS and update study milestones accordingly.
Summary of significant changes in this RMP	• Update of the EDUCATE PASS milestone date for end of data collection from "2023" to "At the time of PRAC agreement that commitment is fulfilled" and final study report submission milestone date from "2024" to "12 months after the PRAC agreement." • Addition of the completion date of the EDUCATE HCP survey collection (16 June 2023).

Details of this RMP Submission	
Version Number	11.2
Rationale for submitting an updated RMP (if applicable)	Per Request for Supplementary Information received on the MAH's request (Procedure EMEA/H/C/003774/MEA/003.5) to update EDUCATE PASS study milestones. The MAH aligned the study milestones as presented in the HA-approved EDUCATE PASS (AC-065A403).
Summary of significant changes in this RMP	• Update of the status of the EDUCATE PASS from "planned" to "ongoing". • Update of the EDUCATE PASS milestone date for start of data collection from "2022" to "02 December 2022". • Addition of the second interim report submission milestone for EDUCATE PASS (once 100 patients' questionnaires are completed).

Other RMP Versions Under Evaluation:

RMP Version Number	Submitted On	Procedure Number
Not applicable		

Details of the Currently Approved RMP:

Version number of last agreed RMP:	10.1
Approved within procedure	EMEA/H/C/003774/X/0038
Date of approval (Competent authority opinion date)	27 March 2024 (EC Decision)

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PART I:PRODUCT(S) OVERVIEW

Active substance(s) (INN or common name)	Selexipag
Pharmaco-therapeutic group(s) (ATC Code)	B01AC27
Marketing Authorization Holder	Janssen-Cilag International NV
Medicinal products to which the RMP refers	1
Invented name(s) in the EEA	UPTRAVI® (selexipag)
Marketing authorization procedure	Centralized
Brief description of the product	Selexipag is a selective IP receptor agonist distinct from prostacyclin and its analogues. Selexipag is hydrolysed by carboxylesterases to yield its active metabolite, which is approximately 37-fold more potent than selexipag. Selexipag and the active metabolite are high affinity IP receptor agonists with a high selectivity for the IP receptor versus other prostanoid receptors (EP_1-EP_4, DP, FP, and TP). Stimulation of the IP receptor by selexipag and the active metabolite leads to vasodilatory as well as anti-proliferative and anti-fibrotic effects. The selexipag active substance 2-{4-[(5,6-diphenylpyrazin-2-yl) (isopropyl) amino] butoxy}-N-(methylsulfonyl) acetamide is of chemical origin.
Reference to the Product Information	UPTRAVI Annexes I–III submitted in Module 1.3.1.
Indication(s) in the EEA	UPTRAVI is indicated for the long-term treatment of PAH in adult patients with WHO FC II–III, either as combination therapy in patients insufficiently controlled with an ERA and/or a PDE-5 inhibitor, or as monotherapy in patients who are not candidates for these therapies. Efficacy has been shown in a PAH population, including idiopathic and heritable PAH, PAH associated with CTD, and PAH associated with corrected simple CHD.
Dosage in the EEA	*Individualized dose titration* Each patient should be up-titrated to the highest individually tolerated dose, which can range from 200 µg bid to 1600 µg bid (individualized maintenance dose).

Pharmaceutical form(s) and strengths	Film-coated tablet for oral use 100, 200, 400, 600, 800, 1000, 1200, 1400 and 1600 µg
Is/will the product be subject to additional monitoring in the EU?	☐ **Yes** ☑ **No**

PART II: SAFETY SPECIFICATION

Module SI: Epidemiology of the Indication(s) and Target Population(s)

Indication: PAH

Incidence and Prevalence:

In the US, approximately 500 to 1000 new cases of PAH are diagnosed each year (NORD 2012). Based on the US Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL), the incidence of all adult patients with Group 1 PAH is estimated at 2.3 cases per million in the US (Frost 2011).

A recent critical appraisal of the literature reported epidemiology estimates of approximately 5.8 adult patients per million for PAH incidence and 47.6 to 54.7 per million for PAH prevalence (Leber 2021) using recent (<5 years) national systematic registry data from centralized healthcare systems (NHS Digital 2021, Kjellström 2020).

The Orphanet 2021 report estimates the overall prevalence of PAH in Europe to be about 20 cases per million. PAH can be further classified into subtypes according to etiology. These are IPAH, heritable PAH, PAH induced by exposure to drugs and toxins, or PAH associated with other conditions, such as connective tissue disease (CTD-PAH) and congenital heart disease (CHD-PAH). For the most common PAH subtypes, incidences and prevalences per million population are reported in systematic national registries: for IPAH 2.6 to 7.6 and 9.0 to 18.3; CTD-PAH 2.8 and 10.0 to 13.0; and CHD-PAH 2.2 and 7.0 to 19.0, respectively (Peacock 2007, Skride 2018, NHS Digital 2021).

The Orphanet 2021 report describes prevalence for IPAH of 11 cases per million and heritable PAH of 0.8 cases per million (Orphanet 2021). The prevalence of CTD-PAH and CHD-PAH are reported as 2.5 and 5.7 cases per million, respectively.

From the REVEAL registry, a lower estimate for adult prevalence for Group 1 PAH is calculated at 12.4 cases per million in the US (Frost 2011). Both the incidence and prevalence of PAH confirm the rarity of the condition.

The US IPAH incidence estimate from the REVEAL registry is 0.9 patients per million, which is lower compared with European data (McGoon 2013) (Table SI.1).

Table SI.1: Annual Incidence and Prevalence of PAH Identified from National Systematic and Multicenter Registries in Adults

Publication	Country	Time period	Annual incidence (patients per million)	Prevalence (patients per million)
Peacock 2007 (SPVU)	UK (Scotland)	2005	IPAH: 2.6 CTD-PAH: 2.8 CHD-PAH: 2.2	IPAH: 9.0 CTD-PAH: 10.0 CHD-PAH: 7.0
Skride 2018	Latvia	2007-2016	IPAH: 7.6	IPAH: 18.3
NHS Digital 2021	UK	2019-2020	-	IPAH: 16.8* CTD-PAH: 13.0* CHD-PAH: 19.0*
McGoon 2013 (REVEAL)	USA	2006-2009	IPAH: 0.9	-

Note: *Numerator: number of active PAH patients on March 2020 (IPAH n = 1128; CTD-PAH n = 873; CHD-PAH n = 1273); denominator: Great Britain population 2020 mid-year (N = 87,081,000).

Demographics of the Population within the Authorized Indication and Risk Factors for the Disease

Demographics of Patients With PAH

A median or mean age of 50 to 64 years at diagnosis is commonly reported from PAH registries across European countries, with a higher proportion of females (66% to 80%) (Escribano-Subias 2012, Kopeć 2020, Hoeper 2016b, Ling 2012, Hurdman 2012). In the REVEAL registry, patients had a mean age of 50 years at diagnosis and were more likely to be females (80%) (Badesch 2010). The same observation was reported from a pulmonary hypertension expert center in Southeast Asia, where the mean age was 51 years and 77% were female (Lim 2019).

Ethnicity distribution in patients with PAH is reported to be similar to the general population. REVEAL data reflect the contemporaneous US Census data with 73% of the included patients being White non-Hispanic, 12% Black, 9% Hispanic, 3% Asian, and 3% other categories (Medrek 2018, Frost 2011). Similarly, racial distribution in Southeast Asian patients with PAH was consistent with the Southeast Asia population census (Lim 2019).

Risk Factors for the Disease

Any factor or condition that is suspected to play a predisposing or facilitating role in the development of the disease is defined as a risk factor. A number of risk factors for the development of PAH have been identified that include family history, drugs and chemicals, diseases, age, and sex (Simonneau 2019).

IPAH and heritable PAH

IPAH corresponds to sporadic disease in which there is neither a family history of PAH nor an identified risk factor, and represents the most frequent form of PAH. When PAH occurs in a familial context, germ-line mutations in the bone morphogenetic protein receptor type 2 gene, a

member of the transforming growth factor beta signaling family, can be detected in approximately 70% to 80% of cases. Mutations of this gene can also be detected in 10% to 20% of apparently sporadic cases, thus representing the major genetic predisposing factor for PAH (Morrell 2019).

Drug- and toxin-induced PAH

There are several well-known toxin and drug risk factors for PAH including aminorex, fenfluramine derivatives, methamphetamines, dasatinib, and toxic rapeseed oil. Possible associations are suspected for cocaine, phenylpropanolamine, L-tryptophan, St John's wort, amphetamines, interferon α and β, alkylating agents, bosutinib, direct-acting antiviral agents against hepatitis C virus, leflunomide, and indirubin (Simonneau 2019).

PAH associated with underlying conditions/diseases

PAH may also occur in association with other diseases. Associated conditions include CTD, CHD, PoPH, HIV infection, and schistosomiasis (Galiè 2015a). Frequent causes of PAH in countries where these diseases are endemic are schistosomiasis, HIV infection, post-streptococcal rheumatic heart disease, and sickle cell disease (Hoeper 2016a).

CTD-PAH represents about 15% to 25% of adult patients with PAH. Several CTDs are associated with PAH, such as mixed CTD and systemic lupus erythematosus but is most commonly seen with SSc (Mukerjee 2003, Hachulla 2005, Humbert 2006, Escribano-Subias 2012, Hoeper 2016a).

A significant proportion of adult patients with CHD, in particular those with relevant systemic-to-pulmonary shunts, will develop PAH if left untreated (Simonneau 2013). Eisenmenger syndrome represents the most advanced form of CHD-PAH (Simonneau 2013). CHD-PAH represents about 7% to 15% of cases in the adult PAH population (Humbert 2006, Escribano-Subias 2012, Hoeper 2016a).

PoPH is a form of PAH associated with portal hypertension with or without underlying chronic liver disease. In the French Pulmonary Hypertension Network registry, PoPH represented 18% of all PAH patients, the majority of whom had alcohol-related cirrhosis (58%) (Savale 2020).

PAH associated with PoPH accounted for 4.9% of PAH patients in the REVEAL Registry (Krowka 2012).

PAH is a rare complication of HIV infection (Simonneau 2013). In France, the prevalence of this condition was estimated at 0.5% of the PAH population in 2005 (Sitbon 2008).

Main Existing Treatment Options:

Supportive therapy

A range of conventional therapies have been shown to provide some degree of symptomatic benefit to PAH patients. However, they have a limited effect on the disease process or prognosis.

Among those conventional treatments are oxygen for patients with dyspnea associated with PAH, anticoagulants to decrease the risk for intrapulmonary thrombosis and thromboembolism, diuretics for patients with decompensated RHF associated with PAH, and calcium channel blockers, which may be of benefit in PAH patients with a positive vasoreactive response during right heart catheterization (Simonneau 2019, Fuso 2011).

Advanced therapy (also termed PAH-specific therapy)

PAH-specific therapies target one of three major pathways (known to be involved in the development of PAH): the prostacyclin and nitric oxide pathways, which are underexpressed in patients with PAH, and the endothelin pathway, which is overexpressed. Route of administration varies between the drugs (IV, subcutaneous, oral, or inhaled). These PAH-specific therapies are either prescribed alone or in combination, which can be either provided as initial or sequential therapies (Galiè 2019).

- PDE-5 inhibitors: these oral agents act on the nitric oxide pathway to induce vasodilation. They also have antiproliferative effects on vascular smooth muscle cells. A systematic review and meta-analyses of clinical trials reported that treatment with PDE-5 inhibitors has a beneficial effect on exercise capacity, hemodynamic parameters, WHO FC, and survival in patients with PAH (Barnes 2019).
- ERAs: endothelin is implicated in the pathogenesis of PAH through its actions on the pulmonary vasculature. Endothelin is elevated in patients with PAH and levels are directly related to disease severity and prognosis. ERAs are oral treatments that act by blocking the binding of endothelin to either one (single antagonist) or both (dual antagonist) of its receptors. Clinical trials have shown that treatment with ERAs has a beneficial effect on exercise capacity, WHO FC, hemodynamics and time to clinical worsening in patients with PAH (Mehta 2017, Pulido 2013). Currently marketed ERA therapies are bosentan (dual antagonist), macitentan (dual antagonist), and ambrisentan (single antagonist).
- Drugs targeting the prostacyclin pathway: synthetic prostacyclins (eg, epoprostenol), prostacyclin analogs (eg, treprostinil, beraprost, iloprost), and IP receptor agonists (eg, selexipag) act by correcting the deficiency of endogenous prostacyclin seen in patients with PAH. The clinical use of IV administered prostacyclins in patients with PAH has been extended by the synthesis of more stable analogs that can be given by subcutaneous infusion, by inhalation, or by oral administration. Clinical trials with prostacyclin and prostacyclin analogs have shown improvement in PAH symptoms (eg, epoprostenol, iloprost, treprostinil), exercise capacity (eg, beraprost, epoprostenol, iloprost, treprostinil), hemodynamics (eg, epoprostenol, iloprost, treprostinil, selexipag), and survival (eg, epoprostenol, selexipag) (Sitbon 2015, Galiè 2015b).
- sGC stimulator (riociguat) acts in synergy with endogenous nitric oxide and directly stimulates sGC to produce intracellular cyclic guanosine monophosphate, which influences vascular tone, proliferation, fibrosis, and inflammation. Short-term clinical trials (12 weeks) have demonstrated a statistically significant improvement in exercise capacity, WHO FC, and delay in clinical worsening with riociguat (Galiè 2015c).

Natural History of the Indicated Condition , Including Mortality and Morbidity:

PAH is a disease of the small pulmonary arteries, characterized by vascular proliferation and remodeling. These vascular changes result in a progressive increase of pulmonary vascular resistance leading to right ventricular failure and premature death. There is currently no cure for PAH. Common symptoms of PAH are shortness of breath, fatigue, non-productive cough, angina pectoris, fainting or syncope, peripheral edema, rarely hemoptysis, and other signs and symptoms of cardiovascular decompensation. With disease progression, exercise tolerance is markedly decreased, and life expectancy is reduced (Galiè 2015a).

Survival estimates in adult patients with PAH

In the French, UK, Russian and US registries, published survival rates at 1 year were 85% to 99%; after 2 years were 76% to 81%; after 3 years were 67% to 94%; and after 5 years were 57% to 86% (Humbert 2010, Hurdman 2012, Benza 2012, Chazova 2019; Table SI.2). Survival with PAH is worse in men (Thenappan 2018).

Table SI.2: Survival Estimates in Adult Patients with PAH

Study Name, Region, Reference	Analysis period	Population characteristics	Survival (years), %			
			1	2	3	5
REVEAL, USA (Benza 2012)	2006-2009	n = 2,635, ≥3 months	85	-	68	57
Russian National Registry (Chazova 2019)	2012-2017	n = 470, >18 years	99	-	94	86
French PAH Registry, France (Humbert 2010)	2002-2003	n = 674, ≥18 years	87*	76*	67*	-
ASPIRE, UK (Hurdman 2012)	2001-2010	n = 598, adults	88[1]	81*[1]	68[1]	57*[1]

Note: *Extracted from graph; [1]Transplant-free survival.

Important Comorbidities:

The co-occurrence of PAH and comorbidities increases the complexity of disease management for patients who may require multiple pharmacological interventions to treat both PAH and the comorbidity. In PAH, approximately three quarters of patients have at least one comorbidity, with patients aged 65 years and older having a greater number of comorbidities. Current research suggests that the presence of comorbid conditions in patients with PAH negatively affects outcomes (Lang 2019).

A variety of comorbid conditions, not representing the principal cause of the development of PAH, have been identified in patients with PAH. The REVEAL Registry (2006 to 2007) reported the following comorbidities in more than 10% of all IPAH patients: systemic hypertension, obesity, sleep apnea, clinical depression, obstructive airway disease, thyroid disease, diabetes mellitus, and ischemic cardiovascular events (Lang 2019). In the US Pulmonary Hypertension Scientific Registry conducted almost 10 years later (2015 to 2018), obesity, diabetes, hypertension, hypothyroidism, and clinical depression were found to be among the most common comorbid conditions (Badlam 2021).

Additional comorbidities associated with PAH include anemia, chronic kidney disease, chronic liver disease, chronic pain, chronic muscle disease, frailty, peripheral vascular disease, cancer, dementia, cirrhosis, renal insufficiency, and atrial fibrillation (Lang 2019). The main causes of death reported in PAH patients are cardiovascular events, including heart failure and sudden death, which account for 44% to 89% of deaths in PAH patients (Tonelli 2013, Ruiz-Cano 2009).

Patients with PAH may develop various severe liver complications (due to severe congestive hepatopathy induced by RHF and/or due to autoimmune disease/CTD) (Wells 2018, Nickel 2021).

PART II: SAFETY SPECIFICATION

Module SII: Nonclinical Part of the Safety Specification

The nonclinical safety assessment was focused on the active metabolite (ACT-333679) because it is the main contributor to efficacy and potential safety-relevant effects.

The results from the non-clinical toxicology, carcinogenicity, reproductive toxicity, and DDI studies are adequately reflected in the SmPC for UPTRAVI.

Key Safety Findings	Relevance to Human Usage
Toxicity	
Selexipag has undergone a complete programme of toxicity studies in rodents, rabbits, and dogs.	
Single & repeat-dose toxicity	
Clinical observations (flaccidity, decreased activity) in rats at 39-fold the human exposure at 1600 µg bid were due to strong blood pressure decrease at high doses. Effects on food consumption and body weight development were secondary to the blood pressure decrease and reversible during the treatment period.	This effect is considered to reflect exaggerated PD in rat toxicity studies and is not expected to occur similarly in humans at therapeutic doses.
In dogs less than 1 year of age, intestinal intussusception occurred in both sexes and generally developed during the first 4 weeks of treatment in acute to chronic toxicity studies and in the 39 week juvenile toxicity study. Mortality or early necropsy of animals in these studies was directly related to this finding. Clinical signs included decreased food consumption, bloody stool, and anus protrusion. Macroscopically, intussusception was characterized by the invagination of proximal bowel segments (jejunum and/or ileum) into a distal segment (eg, colon). Histopathologically, intussusception led to necrosis, haemorrhage, and congestion of the intestinal mucosa of the affected bowel segments. Intestinal intussusception (invagination) in individual dogs below 1 year of age is considered to be a result of exaggerated PD, related to the IP-receptor mediated disturbance of gastric motility. The effect occurred at 5-fold the human exposure (ie, corrected for potency; 415-fold based on total exposure). Safety margins based on no-observed-adverse-effect levels for the active metabolite, corrected for difference in receptor potency between human and dog, were 2-fold in relation to human exposure at a dose of 1600 µg of selexipag bid. Intussusception was not observed in mice or rats.	Due to the known susceptibility of young dogs to develop intussusception and the safety margin of 2-fold (ie, corrected for potency; at 180-fold based on total exposure) for the active metabolite, the finding is considered as not relevant for adult humans. However, in infants and young children, intussusception is the most common cause of intestinal obstruction. Available epidemiological data show that 75–90% of cases arise before 2 years of age (Waseem 2008, Stringer 1992). The peak incidence is between 5 and 9 months of age, and then starts to decline (Newman 1987, Hutchison 1980, Pollack 1991). The high background incidence of and susceptibility to intussusception in young children may pose a risk in this patient population when treated with selexipag. Considering the toxicological and epidemiological data, a waiver on safety grounds for pediatric development in children from birth to less than 2 years of age was justified.
Treatment of juvenile or adult dogs with selexipag induces a particular pattern of bone and bone marrow findings after 2 to 39 weeks of treatment. These findings consisted of increased ossification, bands of fibroblasts	The particular pattern of bone or bone marrow findings after treatment of dogs with selexipag is explained by an off-target activation of EP_4 receptors in dogs. As human EP_4 receptors are not activated by selexipag and its active metabolite, the finding is dog specific and not

Key Safety Findings	Relevance to Human Usage
and collagen fibers and variable appearance of hematopoietic tissue. These findings are considered to be related to activation of EP_4 receptor in dogs, which is activated with similar potency as the IP receptor in this species. Increased ossification and the occurrence of fibrocytes with collagen fibres in bone in dog studies are considered to be related to the activation of EP_4 receptors by selexipag.	relevant for humans.
Minimal decrease in platelet counts in rat studies were reversible and were not accompanied by effects on blood coagulation. Decreased platelet counts in dog studies were due to low individual values in animals in very poor general condition because of intussusception.	This finding is not considered to be relevant for the clinical use of selexipag because of the minimal severity and reversibility in rats, and the fact that it was seen as an effect secondary to individual poor condition in dogs. The thrombocytopenia AE data and the platelet count data recorded in the clinical studies confirm the conclusion that selexipag has no effect on platelets in patients with PAH.
Tortuosity and dilation of retinal vessels were observed at ophthalmological examination in Week 104 at 95-fold the human exposure. The NOEL was 10 mg/kg/day, corresponding to 35-fold the human exposure.	Retinal tortuosity is considered to reflect exaggerated PD resulting in continuous blood vessel dilation for the whole lifespan. Because of high safety margins, it is not considered relevant for the clinical use of selexipag. The potential relevance to humans was evaluated in the Phase 2 and Phase 3 clinical studies. Based on clinical data, the non-clinical finding is not relevant to humans.
Reproductive toxicity	
Reproductive toxicity of selexipag was assessed in fertility and embryofetal studies and pre-/post-natal development studies. These studies were complemented by a dog juvenile toxicity study, including exposure assessment. Selexipag was not teratogenic in rats and rabbits, and had no effect on fertility of male and female rats. In the rat pre- and post-natal development study, selexipag induced no effects on maternal and pup reproductive function. In rats, selexipag or its metabolites are excreted in milk.	Nonclinical data do not indicate a safety concern for humans. UPTRAVI is not recommended during pregnancy and in women of childbearing potential not using contraception. It is unknown whether selexipag or its metabolites are excreted in human milk. A risk to the suckling child cannot be excluded. UPTRAVI should not be used during breast-feeding.
Developmental toxicity	
Toxicity of selexipag was determined in pre-/post-natal development studies. There were no effects on maternal and pup reproductive function.	Nonclinical data do not indicate a safety concern for humans.
Genotoxicity	
Selexipag and the active metabolite are not genotoxic on the basis of the overall evidence of conducted	Nonclinical data do not indicate a safety concern for humans.

Key Safety Findings	Relevance to Human Usage
genotoxicity studies.	
Carcinogenicity	
In the mouse carcinogenicity study, the incidence of thyroid adenomas was increased at 250 mg/kg/day corresponding to 113-fold the human exposure.	The finding in mice is considered secondary to hepatic enzyme induction, which leads to degradation of thyroid hormones, up-regulation of TSH release, and continuous stimulation of the thyroid. This mechanism is rodent specific, and the findings were observed at exposures more than 25-fold above human exposure and are, therefore, not relevant for humans. Hyperthyroidism was identified as an important risk in clinical studies based on a different mechanism of action.
In the rat carcinogenicity study, the incidence of Leydig cell adenomas and hyperplasia was marginally increased at the high dose of 100 mg/kg/day, corresponding to 458-fold the human exposure. A NOEL for adenoma development was 30 mg/kg/day, corresponding to 95-fold the human exposure.	As rats are known to be particularly susceptible to develop Leydig cell adenomas and because of the high effect and safety margins more than 25-fold above human exposure, this finding is not relevant for humans.
Other toxicity-related information or data	
Selexipag was phototoxic in vitro.	The relevance to humans was investigated in a dedicated Phase 1 clinical study that did not show phototoxic potential.

Summary of Nonclinical Safety Concerns

Important identified risks	None
Important potential risks	None
Missing information	None

PART II: SAFETY SPECIFICATION

Module SIII: Clinical Trial Exposure

SIII.1. Brief Overview of Development

UPTRAVI oral tablets have been developed and marketed for long-term treatment of PAH in adult patients with WHO FC II–III, either as combination therapy in patients insufficiently controlled with an ERA and/or a PDE-5 inhibitor, or as monotherapy in patients who are not candidates for these therapies.

The overall number of patients exposed and the duration of exposure to selexipag in the Phase 2, Phase 3 and Phase 4 studies in adults in the approved indication of PAH are presented in the tables below, and include the following 8 studies:

- **AC-065A302 (GRIPHON)**: Randomized, placebo-controlled, double-blind, parallel groups (completed study, 2 October 2014) and Treatment Extension Period (completed 27 February 2015).
- **AC-065A303 (GRIPHON OL)**: Uncontrolled extension of AC-065A302, completed (data cut-off date is 20 December 2020).
- **NS-304/-02:** Uncontrolled single dose of selexipag including two treatment periods: an acute hemodynamic period and a randomized, placebo-controlled, double-blind, parallel-group period, which were handled as if they were two studies (completed study, 20 January 2010).
- **NS-304/-03:** Uncontrolled, open-label extension of NS-304/-02 (completed study, 16 October 2018).
- **AC-065A201:** Uncontrolled, open-label study to assess the efficacy, safety and PK of selexipag in patients with PAH (completed study, 14 February 2018).
- **AC-065A304 (TRANSIT):** Open-label, single-group study to assess the tolerability and safety of the transition from inhaled treprostinil to oral selexipag in adult patients (completed study, 1 December 2017).
- **AC-065A308 (TRITON):** Double-blind, placebo-controlled, Phase 3b study to assess the efficacy and safety of initial triple versus initial dual oral combination therapy in patients with newly diagnosed PAH (completed study, 9 December 2020).
- **AC-065A404 (TRACE):** Double-blind, placebo-controlled, Phase 4 study in patients with PAH to assess the effect of selexipag on daily life, physical activity and patient's self-reported symptoms and their impacts (completed study, 15 December 2020).

SIII.2. Clinical Trial Exposure

Randomized Clinical Trials Population

Exposure to selexipag in the randomized clinical trials population is summarized in Tables SIII.1 through SIII.5 for all participants by duration, by age group and sex, by dose, and by variable stratifications relevant to the product (eg, ethnic origin, by concomitant PAH-specific medication at baseline). These data are based on the completed randomized studies: AC-065A302, NS-304/-02, AC-065A308 and AC-065A404 in PAH.

Table SIII.1: Duration of Exposure: Randomized Clinical Trials Population

	Selexipag N=779	
Total Population	**Persons**	**Person Time (year)**
Duration of exposure		
<1 m	40	1.8
1 to <3 m	47	7.5
3 to <6 m	131	53.7
6 to <12 m	73	52.7
12 to <24 m	235	354.5
24 to <36 m	163	407.8
36 to <48 m	88	291.9
48 to <60 m	2	8.7
≥60 m	0	0.0
Total	**779**	**1178.7**

Based on the completed randomized, double-blind studies: AC-065A302, NS-304/-02, AC-065A308 and AC-065A404 in PAH.

Table SIII.2: Age Group and Sex: Randomized Clinical Trials Population

	Selexipag N=779			
Total Population	**Persons Male**	**Person Time (year) Male**	**Persons Female**	**Person Time (year) Female**
Age group				
<18 years	0	0.0	0	0.0
18 to 64 years	141	206.1	492	780.7
65 to 74 years	26	31.8	108	138.8
75 to 84 years	3	6.6	9	14.7
≥85 years	0	0.0	0	0.0
Total	**170**	**244.5**	**609**	**934.2**

Based on the completed randomized, double-blind studies: AC-065A302, NS-304/-02, AC-065A308 and AC-065A404 in PAH.

Table SIII.3: Dose of exposure: Randomized Clinical Trials Population

	Selexipag N=779	
Total Population	**Persons**	**Person time (year)**
Dose of exposure		
<200 µg bid	11	0.6
200 to 600 µg bid	251	320.5
>600 to <1600 µg bid	304	467.6
≥1600 µg bid	213	389.9
Total	**779**	**1178.7**

Individual maximum tolerated dose (µg bid) in the titration period.
Based on the completed randomized, double-blind studies: AC-065A302, NS-304/-02, AC-065A308 and AC-065A404 in PAH.

Table SIII.4: Race/Ethnicity: Randomized Clinical Trials Population

	Selexipag N=779	
Total Population	**Persons**	**Person time (year)**
Race/ethnicity		
Caucasian / Hispanic	601	904.3
Asian	138	213.8
Black	20	31.2
Other	12	17.2
Unknown	3	1.4
Missing	5	10.7
Total	**779**	**1178.7**

Based on the completed randomized, double-blind studies: AC-065A302, NS-304/-02, AC-065A308 and AC-065A404 in PAH.

Table SIII.5: Concomitant PAH-special Medication at Baseline: Randomized Clinical Trials Population

	Selexipag N=779	
Total Population	**Persons**	**Person time (year)**
Concomitant PAH-special medication at baseline		
No PAH medication	112	204.1
ERA alone	108	150.3
PDE5-i/sGC stimulator alone	198	317.7
≥2 PAH medications	361	506.6
Total	**779**	**1178.7**

Based on the completed randomized, double-blind studies: AC-065A302, NS-304/-02, AC-065A308 and AC-065A404 in PAH.

Exposure in All Clinical Trials

The All Clinical Trials Population includes 8 trials:

- **AC-065A302 (GRIPHON)**: Randomized, placebo-controlled, double-blind, parallel groups (completed study, 27 February 2015).
- **AC-065A303 (GRIPHON OL)**: Uncontrolled extension of AC-065A302 (completed; data cut-off date is 20 December 2020).
- **NS-304/-02:** Uncontrolled single dose of selexipag including two treatment periods: an acute hemodynamic period and a randomized, placebo-controlled, double-blind, parallel-group period, which were handled as if they were two studies (completed study, 20 January 2010).
- **NS-304/-03:** Uncontrolled extension of NS-304/-02 (completed study, 16 October 2018).
- **AC-065A201:** Uncontrolled, open-label study to assess the efficacy, safety and PK of selexipag in patients with PAH (completed study, 14 February 2018).
- **AC-065A304 (TRANSIT):** Open-label, single-group study to assess the tolerability and safety of the transition from inhaled treprostinil to oral selexipag in adult patients (completed study, 1 December 2017).
- **AC-065A308 (TRITON):** Double-blind, placebo-controlled, Phase 3b study to assess the efficacy and safety of initial triple versus initial dual oral combination therapy in patients with newly diagnosed PAH (completed study, 9 December 2020).
- **AC-065A404 (TRACE):** Double-blind, placebo-controlled, Phase 4 study in patients with PAH to assess the effect of selexipag on daily life, physical activity and patient's self-reported symptoms and their impacts (completed study, 15 December 2020).

Table SIII.6: Duration of Exposure: All Clinical Trials Population

	Selexipag N=1237	
Total Population	**Persons**	**Person Time (year)**
Duration of exposure		
<1 m	58	2.4
1 to <3 m	75	11.8
3 to <6 m	137	54.4
6 to <12 m	114	83.9
12 to <24 m	210	323.3
24 to <36 m	149	370.2
36 to <48 m	92	312.9
48 to <60 m	92	413.9
≥60 m	310	2288.1
Total	**1237**	**3860.9**

Based on the completed studies (before cut-off date 20 Dec 2020): AC-065A302 + AC-065A303, NS-304/-02 + NS-304/-03, AC-065A201, AC-065A304, AC-065A308 and AC-065A404 in PAH.
AC-065A303 study with data cut-off at 20 Dec 2020.

Table SIII.7: Age Group and Sex: All Clinical Trials Population

	Selexipag N=1237			
Total Population	**Persons Male**	**Person Time (year) Male**	**Persons Female**	**Person Time (year) Female**
Age group				
<18 years	0	0.0	0	0.0
18 to 64 years	210	591.5	811	2754.6
65 to 74 years	37	60.3	150	378.0
75 to 84 years	7	22.5	22	54.1
≥85 years	0	0.0	0	0.0
Total	**254**	**674.3**	**983**	**3186.6**

Based on the completed studies (before cut-off date 20 Dec 2020): AC-065A302 + AC-065A303, NS-304/-02 + NS-304/-03, AC-065A201, AC-065A304, AC-065A308 and AC-065A404 in PAH.
AC-065A303 study with data cut-off at 20 Dec 2020.

Table SIII.8: Dose of Exposure : All Clinical Trials Population

	Selexipag N=1237	
Total Population	**Persons**	**Person Time (year)**
Dose of exposure		
<200 µg bid	20	9.6
200 to 600 µg bid	420	1256.6
>600 to <1600 µg bid	477	1448.3
≥1600 µg bid	320	1146.4
Total	**1237**	**3860.9**

Individual maximum tolerated dose (µg bid) in the titration period.
Based on the completed studies (before cut-off date 20 Dec 2020): AC-065A302 + AC-065A303, NS-304/-02 + NS-304/-03, AC-065A201, AC-065A304, AC-065A308 and AC-065A404 in PAH.
AC-065A303 study with data cut-off at 20 Dec 2020.

Table SIII.9: Race/Ethnicity : All Clinical Trials Population

	Selexipag N=1237	
Total Population	**Persons**	**Person Time (year)**
Race/ethnicity		
Caucasian / Hispanic	914	2681.0
Asian	269	1064.8
Black	29	56.0
Other	17	47.0
Unknown	3	1.4
Missing	5	10.7
Total	**1237**	**3860.9**

Based on the completed studies (before cut-off date 20 Dec 2020): AC-065A302 + AC-065A303, NS-304/-02 + NS-304/-03, AC-065A201, AC-065A304, AC-065A308 and AC-065A404 in PAH.
AC-065A303 study with data cut-off at 20 Dec 2020.

Table SIII.10: Concomitant PAH-special Medication at Baseline: All Clinical Trials Populations

	Selexipag N=1237	
Total Population	**Persons**	**Person Time (year)**
Concomitant PAH-special medication at baseline		
No PAH medication	185	864.1
ERA alone	163	508.4
PDE5-i/sGC stimulator alone	339	1317.3
≥2 PAH medications	550	1171.1
Total	**1237**	**3860.9**

Based on the completed studies (before cut-off date 20 Dec 2020): AC-065A302 + AC-065A303, NS-304/-02 + NS-304/-03, AC-065A201, AC-065A304, AC-065A308 and AC-065A404 in PAH.
AC-065A303 study with data cut-off at 20 Dec 2020.

Table SIII.11: Exposures in Studies: All Clinical Trials Populations

	Selexipag N=1237	
Total Population	**Persons**	**Person Time (year)**
Study		
AC-065A302 + AC-065A303	953	3315.4
NS-304/-02 + NS-304/-03	41	190.4
AC-065A201	37	111.8
AC-065A304	34	14.1
AC-065A308	119	207.1
AC-065A404	53	22.2
Total	**1237**	**3860.9**

Based on the completed studies (before cut-off date 20 Dec 2020): AC-065A302 + AC-065A303, NS-304/-02 + NS-304/-03, AC-065A201, AC-065A304, AC-065A308 and AC-065A404 in PAH.
AC-065A303 study with data cut-off at 20 Dec 2020.

PART II: SAFETY SPECIFICATION

Module SIV: Populations Not Studied in Clinical Trials

SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Table SIV.1: Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 1	**Patients with moderate or severe hepatic impairment (ie, Child-Pugh class B and C)**
Reason for being an exclusion criterion	PAH patients with moderate or severe hepatic impairment were excluded from the clinical studies as a precautionary measure due to the limited amount of data on the PK of selexipag in patients with severe hepatic impairment at the time of the start of the study.
Considered to be included as missing information: Yes/No	No
Rationale (if not included as missing information)	As stated in the SmPC, selexipag should not be used in patients with severe liver impairment (Child-Pugh class C). The exposure to selexipag and its active metabolite is increased in participants with moderate hepatic impairment (Child-Pugh class B; SmPC section 5.2). For patients with moderate hepatic impairment, the starting dose of treatment should be 100 µg bid or 200 µg qd and increased at weekly intervals by increments of 100 µg bid or 200 µg qd until adverse reactions reflecting the mode of action of selexipag that cannot be tolerated or medically managed are experienced (SmPC section 4.2). No additional pharmacovigilance activities are planned to further characterize the use in patients with moderate to severe hepatic impairment.
Criterion 2	**Patients with severe renal insufficiency (estimated creatinine clearance <30 mL/min, or serum creatinine >2.5 mg/dL)**
Reason for being an exclusion criterion	PAH patients with severe renal impairment were excluded from the clinical studies as a precautionary measure due to the limited amount of data on the PK of selexipag in patients with renal impairment at the time of the start of the study.
Considered to be included as missing information: Yes/No	No
Rationale (if not included as missing information)	As stated in the SmPC, no adjustment to the dose regimen is needed in patients with mild or moderate renal impairment. No change in starting dose is required in patients with severe renal impairment (estimated glomerular filtration rate <30 mL/min/1.73 m^2), dose titration should be done with caution in these patients (SmPC sections 4.2 and 4.4). There is no experience with selexipag in patients undergoing dialysis (SmPC section 5.2), therefore selexipag should not be used in these patients. Dialysis is however unlikely to affect plasma concentrations of the drug because selexipag and its active metabolite are highly protein bound (SmPC section 4.9). No additional pharmacovigilance activities are planned to further characterize the use in patients with severe renal insufficiency.

Table SIV.1: Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 3	**Patients with moderate or severe obstructive lung disease**
Reason for being an exclusion criterion	Patients with moderate or severe obstructive lung disease were excluded to ensure that patients with PH group 3 were not enrolled in the study.
Considered to be included as missing information: Yes/No	No
Rationale (if not included as missing information)	Selexipag is not indicated for treatment of patients with PH due to lung diseases and/or hypoxia (Group 3).
Criterion 4	**Patients with moderate or severe restrictive lung disease**
Reason for being an exclusion criterion	Patients with moderate or severe restrictive lung disease were excluded to ensure that patients with PH group 3 were excluded from the study, in order to prevent co-morbidities interfering with the diagnosis of PAH.
Considered to be included as missing information: Yes/No	No
Rationale (if not included as missing information)	Selexipag is not indicated for treatment of patients with PH due to lung diseases and/or hypoxia (Group 3).
Criterion 5	**Patients with documented left ventricular dysfunction**
Reason for being an exclusion criterion	Left heart disease represents the most frequent cause of PH and belongs to PH group 2. Patients with documented left ventricular dysfunction were excluded to ensure that patients with PH group 2 were excluded from the study, in order to prevent co morbidities interfering with the diagnosis of PAH.
Considered to be included as missing information: Yes/No	No
Rationale (if not included as missing information)	Selexipag is not indicated for treatment of patients with PH due to left heart disease (Group 2).
Criterion 6	**Patients with BMI <18.5 kg/m^2**
Reason for being an exclusion criterion	Patients with BMI <18.5 kg/m^2 were excluded in order to limit variability of drug exposure and facilitate interpretation of study results.
Considered to be included as missing information: Yes/No	No
Rationale (if not included as missing information)	No implications are expected for the treatment of PAH patients. Individualized dosing based on tolerability.

Table SIV.1: Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 7	**Psychotic, addictive, or any other disorder**
Reason for being an exclusion criterion	The exclusion of patients with this condition from the clinical trial was based on practicality of conducting the clinical trial, as psychotic, addictive or any other disorder would limit the ability to provide informed consent or to comply with study requirements.
Considered to be included as missing information: Yes/No	No
Rationale (if not included as missing information)	No implications are expected for the treatment of PAH patients.
Criterion 8	**Lactating or pregnant (positive pre-randomization serum pregnancy test) women or those who planned to become pregnant during the study**
Reason for being an exclusion criterion	Pregnancy: a) There were no data on the use of selexipag in pregnant women. Animal studies did not indicate direct or indirect harmful effects with respect to reproductive toxicity. b) Current treatment guidelines recommend to avoid pregnancy in PAH patients, as this is associated with high risk of mortality for the mother. Pregnant women or those who planned to become pregnant were excluded as the condition could interfere with the assessment of the efficacy of selexipag in a mortality/morbidity event-driven clinical trial. Lactating: It is unknown whether selexipag or its metabolites are excreted in human milk. In rats, selexipag or its metabolites are excreted in milk.
Considered to be included as missing information: Yes/No	Yes
Rationale (if not included as missing information)	Not applicable.
Criterion 9	**Known hypersensitivity to any of the excipients of the drug formulations**
Reason for being an exclusion criterion	These individuals were excluded from clinical trials to avoid potentially severe and life-threatening allergic/hypersensitivity reactions
Considered to be included as missing information: Yes/No	No
Rationale (if not included as missing information)	Required by QRD template of the SmPC, these criteria will remain as a contraindication in section 4.3 of the SmPC.

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions.

SIV.3. Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Program(s)

Table SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women Breastfeeding women	Cumulatively, since the IBD (21 December 2015) and up to the data cut-off date of 20 December 2020, 46 confirmed pregnancies in selexipag-treated patients have been reported, including 11 from interventional clinical trials, 17 from noninterventional solicited clinical studies, and 18 from spontaneous sources (1 spontaneous case was from a literature source). Drug exposure was during the first trimester in 22 cases; selexipag was started 6 weeks prior to birth in 1 case; time of exposure was unknown in 19 cases; and pregnancy was confirmed after selexipag discontinuation in 4 cases. To date, no reports of selexipag use during lactation have been received.
Populations with relevant different ethnic origin	In the All Clinical Trials Population included in this RMP, of the 1237 patients treated with selexipag, 73.9% of the participants were Caucasian / Hispanic; 21.7% were Asian; and 2.3% were Black (Table SIII.9). Pharmacokinetics The results from study NS304/P1/01, which mainly included Japanese participants, suggested higher plasma concentrations of both selexipag and its active metabolite when compared to study QGUY/2006/NS304/-01, which mainly included Caucasian participants. Upon review, the differences in PK were explained by differences in body weight. In study AC-065A302, race/ethnicity was not identified as a significant covariate towards the PK of selexipag and its active metabolite (D-14.470). In this study, the majority of patients were Caucasian (ie, White/Hispanic; 74.7%) or Asian (21.3%). There were some demographic/baseline characteristic differences between Asian and non-Asian populations, with Asian patients generally being younger and exhibiting less severe PAH disease as assessed by NYHA / WHO FC. There were no important differences between Asian and non-Asian populations regarding duration of exposure to study drug, selexipag dose achieved, or exposure to selexipag in population PK analysis. Safety In the Phase 3 study, the safety findings were similar across geographical regions / ethnicities. Efficacy In contrast to findings in other subgroups, the observed treatment effect in the primary endpoint was small in the Asian population / Asia geographic subgroup. As fewer patients in the placebo group in Asia had a MM event compared to the rest of the world (probably linked to the higher proportion of less severe disease status at baseline), it was more challenging to demonstrate an effect in the active treatment arm.

Table SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
	While no single factor was identified that could explain lower efficacy of selexipag in Asian patients compared to non-Asian patients, it was concluded that the results are likely to represent random variation; however, an influence of unidentified racial/ethnic factors cannot be excluded. The analysis requested by CHMP, using the definition of a composite MM endpoint in accordance with the EMEA/CHMP/EWP/356954/2008 guideline, shows that the treatment effect in the Asian geographical region is consistent with the overall observed treatment effect (hazard ratio selexipag versus placebo of 0.76 [99% CI: 0.46, 1.25] and of 0.73 [99% CI: 0.6, 0.91], respectively). This could be due to the difference in the definition of an MM component: the CHMP guideline, allowing an isolated deterioration in either WHO FC, or 6-minute walk distance, or signs and symptoms of RHF to qualify as PAH-related deterioration.
Subpopulations carrying relevant genetic polymorphisms	In study AC-065-117 investigating the effect of a moderate inhibitor of CYP2C8 on selexipag in healthy male participants, the following CYP2C8 genotypes were present in the study: *1/*1 (wild-type) (n = 13) *1/*3 (n = 6) and *1/*4 (n= 2). Investigations according to genetic polymorphisms have not been included in the remaining clinical development program. Enzymatic hydrolysis of selexipag by carboxylesterase 1 and 2 yields ACT-333679, the active metabolite of selexipag (D-14.482, Selexipag IB, Imai 2018). *In vitro* functional studies indicated that certain CES gene mutations could lead to dysfunctional CES activity in humans. However, there are no known CES genetic variants that can be utilised as biomarkers to predict the activity of CES in clinical practice (Zhu 2008, Zhu 2013, Merali 2014). The most important polymorphisms in CYP enzymes are those for CYP2C9, CYP2C19, and CYP2D6 (McGraw 2012, Zhou 2009), which can result in reduced therapeutic efficacy or increased incidence of adverse reactions. These enzymes are not involved in the metabolism of selexipag and ACT-333679. For CYP2C8, which is an important enzyme in elimination of ACT-333679, there are several alleles. Three alleles, known as *CYP2C8*2*, *CYP2C8*3*, and *CYP2C8*4*, account for the majority of polymorphic variants of the *CYP2C8* gene in humans. Other alleles, such as *CYP2C8*5, CYP2C8*7,* or *CYP2C8*8*, are very rare variants (Daily 2009, Backman 2016). Some of these variants might affect the activity of the CYP2C8 enzyme, but, for example, *CYP2C8*4* does not seem to have a significant effect on enzyme activity (Bahadur 2002). The frequency of these variants differs significantly between ethnic groups. For example, *CYP2C8*2* has been detected in the Black population (Dai 2001), but was not found in Caucasians. *CYP2C8*3* is commonly found in Caucasians (10% to 23%) but it is rare in African and Asian populations (Totah 2005, Daily 2009, Bahadur 2002). *CYP2C8*5* has been found in the Japanese population. There are also

Table SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
	reports about the presence of this variant in the Black population (Brown 2016, Ishikawa 2004, Nakajima 2003). During the development of selexipag, and in the population PK analysis performed in study AC-065A302 (GRIPHON) with patients with PAH, as well as additional exploratory subgroup PK analyses, there was some variability but no clear correlation between ethnicity and PK of selexipag. In the DDI study between selexipag and gemfibrozil (AC-065-113) a large inter-individual variability was observed in the magnitude of the gemfibrozil effect on the PK of selexipag and ACT-333679, with increases in ACT-33679 exposure ranging from 4-fold to 20-fold (out of 20 enrolled participants, 18 were Caucasian and 2 Asian). In the absence of a genetic analysis in this study, it is not known if there is any correlation between *CYP2C8*3* carriers and the observed variability in gemfibrozil effect. Based on the non-clinical findings and data from a dedicated clinical DDI study, concomitant administration of selexipag with strong inhibitors of CYP2C8 (eg, gemfibrozil) is contraindicated. Concomitant administration of selexipag with clopidogrel (300 mg as a loading dose or maintenance doses of 75 mg qd), a moderate inhibitor of CYP2C8, had no relevant effect on the exposure to selexipag but increased the exposure to the active metabolite by approximately 2.2-fold and 2.7-fold following loading dose and maintenance dose, respectively (AC-065-117). In the presence of clopidogrel (both loading and maintenance doses), comparable increased exposure to ACT-333679 was observed in all identified CYP2C8 genotypes present in the study (genotypes *1/*1, *1/*3, and *1/*4). When co-administered with moderate CYP2C8 inhibitors (e.g., clopidogrel, deferasirox, teriflunomide), the total daily dose of selexipag should be reduced by half. This can be achieved by either administering half the dose of selexipag bid or reducing the dosing frequency of selexipag to qd. When co-administration of a moderate CYP2C8 inhibitor is stopped, the total daily dose of selexipag should be increased by either increasing each dose or reverting to bid dosing, as applicable. The maximum dose of 1600 µg bid should not be exceeded (SmPC section 4.2). In the presence of rifampicin, an inducer of CYP2C8 (and UGT enzymes), the exposure to selexipag did not change, whereas exposure to the active metabolite was reduced by half. Dose adjustment of Uptravi may be required with concomitant administration of inducers of CYP2C8 (eg, rifampicin, carbamazepine, phenytoine).

Table SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Children	As of 20 December 2020, 50 pediatric patients received selexipag during the currently ongoing AC-065A203 study. Selexipag starting dose is based on their body weight: 100 µg for participants from ≥9 to <25 kg, 150 µg for participants from ≥25 to <50 kg, and 200 µg for participants ≥50 kg. Since initiation of the study, the planned first and the second interim PK analyses for age Cohort 1 (≥12 to <18 years of age) and Cohort 2 (≥6 to <12 years of age) were completed. Selexipag starting doses and up-titration increments according to patient's weight category (≥9 to <25 kg; ≥25 to 50 kg; and ≥50 kg) were confirmed for patients aged ≥6 to <18 years of age. Enrollment to Cohort 3 (≥2 to <6 years of age) has been initiated and is still ongoing. Based on data from Cohorts 1 and 2, no significant safety findings were identified from the clinical trial that had an impact on the benefit-risk balance of selexipag. The safety and efficacy of selexipag in children aged 0 to less than 18 years have not yet been established. No data are available. Administration of selexipag in the pediatric population is not recommended. Animal studies indicated an increased risk of intussusception, but the clinical relevance of these findings is unknown (SmPC section 4.2). In the current PIP, a waiver was granted for children from birth to less than 2 years (EMEA 000997 PIP01 10-M02).
Elderly	Data for patients aged between 65 (according to the definition of 'elderly' used by the ICH guideline E7) and 80 years are available. Experience in the elderly is substantial, based on 99 patients treated with selexipag and 107 with placebo in the Phase 3 study AC-065A302. Of the 99 patients on selexipag, 91 were aged between 65 and 74 years, and 8 patients were ≥75 years old (range: 75-80 years). In the placebo group, 102 patients were 65-74 years old, and 5 patients were ≥75 years old. No patients >80 years old were exposed in the clinical programme of selexipag. In the EXPOSURE PASS, as of 30 November 2021, 151 selexipag-treated patients were aged between 65 and 75 years and 67 selexipag-treated patients were >75 years old. There is no clinically relevant effect of age on the PK of selexipag and its active metabolite in healthy participants or PAH patients. Therefore, no adjustment to the dosing regimen is needed in elderly patients. No important differences for efficacy or safety were observed between elderly and non-elderly patients. However, the experience in patients >75 years old is limited. The recommendations regarding the use of selexipag in the elderly are described in the SmPC in sections 4.2 and 4.4.

Table SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Patients with relevant comorbidities:	
Patients with hepatic impairment	PAH patients with moderate and severe hepatic impairment were excluded from the clinical studies as a precautionary measure due to the absence of data on the PK of selexipag in patients with hepatic impairment before the start of Phase 2 or 3 clinical trials. The PK, safety, and tolerability of a single dose of selexipag (400 µg) were assessed in participants with different degrees of liver impairment (Child-Pugh class A or B) in a single-centre, OL, Phase 1 study (AC-065-104). Results showed a 2-fold increase of exposure to selexipag ($AUC_{0-\infty}$) in participants with mild liver impairment (Child-Pugh class A) compared to healthy participants, while exposure to the active metabolite remained unchanged. In participants with moderate liver impairment (Child-Pugh class B), $AUC_{0-\infty}$ of selexipag and its active metabolite increased approximately 4-fold and 2-fold, respectively. Only 2 participants with severe hepatic impairment (Child-Pugh class C) were dosed with selexipag. Exposure to selexipag and its active metabolite in these 2 participants was similar to that in participants with moderate hepatic impairment (Child-Pugh class B). Based on modelling and simulation data from this study, the exposure to selexipag at steady state in participants with moderate hepatic impairment (Child-Pugh class B) after a qd regimen is predicted to be approximately 2-fold higher than that in healthy participants during a bid regimen. The exposure to the active metabolite at steady state in these participants during a qd regimen is predicted to be similar to that in healthy participants during a bid regimen. Participants with severe hepatic impairment (Child-Pugh class C) showed similar predicted exposure at steady state as participants with moderate hepatic impairment during a qd regimen. In patients with moderate hepatic impairment, the total daily dose of selexipag should be reduced (SmPC section 4.4). See SmPC section 4.2 ‘Posology and method of administration’ under ‘hepatic impairment’, section 4.4 ‘Special warnings and precautions for use’ under ‘hepatic impairment’, and section 5.2 ‘Pharmacokinetic properties’.
Patients with renal impairment	Patients with severe renal insufficiency (estimated creatinine clearance <30 mL/min, or serum creatinine >2.5 mg/dL) were excluded from the clinical studies in the pre-authorization phase as the data on the specific dedicated Phase 1 study in patients with renal impairment were lacking at the time of planning of the Phase 3 trials. The PK, safety, and tolerability of a single oral dose of selexipag (400 µg) in participants with renal function impairment were investigated in a single-centre, OL study (AC-065-105). Results showed that a 1.4- to 1.7-fold increase in exposure to selexipag and its active metabolite was observed in participants with severe renal function impairment (estimated glomerular filtration rate <30 mL/min/1.73 m^2). The increase in exposure was not associated with any unexpected AEs in participants with severe renal function impairment and was not

Table SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
	considered large enough to require investigation in participants with moderate renal function impairment. Selexipag is not expected to be dialysable as selexipag, and its active metabolite are highly bound to plasma proteins (approximately 99% in total and to the same extent to albumin and alpha1-acid glycoprotein). Laboratory data in the Phase 3 study indicated no detrimental effect of selexipag on renal function. See SmPC section 4.2 'Posology and method of administration' under 'renal impairment', section 4.4 'Special warnings and precautions for use' under 'renal impairment', and section 5.2 'Pharmacokinetic properties'.
Patients with cardiovascular impairment	Not included in the clinical development program.
Immunocompromised patients	Not included in the clinical development program.
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program.

Summary of Missing Information Due to Limitations of the Clinical Trial Program

Missing information	Use in elderly over 75 years old
	Use during pregnancy and lactation
	Concomitant use with strong inhibitors of UGT1A3 and UGT2B7

PART II: SAFETY SPECIFICATION

Module SV:: Postauthorization Experience

SV.1. Postauthorization Exposure

SV.1.1. Method Used to Calculate Exposure

The number of patients exposed to selexipag during the post-marketing period is estimated via controlled distribution systems or from the number of packages sold. The cut-off date used for the postauthorization exposure for the purpose of this document is 30 November 2020.

SV.1.2. Exposure

Cumulatively, since IBD (21 December 2015) and up to the data cut-off point of 30 November 2020, an estimated 21,142 patients (corresponding to 31,267 patient years) were exposed to commercial selexipag worldwide, including 4,815 patients in the EEA (22.8%), 10,830 patients in the US (51.2%), 3,005 patients in Japan (14.2%), and 2,492 patients in the ROW (11.8%). Selexipag is currently approved in PAH (WHO group 1), and the vast majority of patients for whom an indication was provided had PAH.

The estimated cumulative exposure to commercial selexipag by region is presented in Table SV.1.

Table SV.1: Cumulative Exposure to Selexipag by Region (Launch to 30 November 2020)

Region	Patient-Years	Number of Patients Exposed
EEA	5,378	4,815
US	15,031	10,830
Japan	8,075	3,005
ROW	2,783	2,492
Total	**31,267**	**21,142**

The estimated cumulative exposure to commercial selexipag in the EEA, by country, is presented in Table SV.2.

Table SV.2: Estimated Cumulative Post-marketing Exposure in the EEA (Launch to 30 November 2020)

Country	Number of Patients Exposed
Austria	84
Belgium	156
Croatia	1
Cyprus	15
Czech Republic	51
Denmark	38
Estonia	3
Finland	41
France	650
Germany	1,263
Greece	178
Hungary	42
Iceland	7

Table SV.2: Estimated Cumulative Post-marketing Exposure in the EEA (Launch to 30 November 2020)

Country	Number of Patients Exposed
Ireland	32
Italy	483
Lithuania	6
Luxembourg	3
Malta	1
Netherlands	472
Norway	64
Poland	3
Portugal	95
Slovakia	39
Spain	536
Sweden	205
United Kingdom	347
Total	**4,815**

The split into gender and age groups was estimated based on data collected in the US in the context of controlled distribution; due to local data privacy regulations, such information cannot consistently be collected outside the US.

According to cumulative exposure data available from the US, 72.0% of the exposed patients were females and 28.0% were males (this matches the gender distribution for the indication of PAH); 41% of the exposed patients were elderly (including 16.1% ≥75 years), 57.0% were adults, 1.0% were aged between 12 and 18 years, and 1.0% were younger than 12 years (Table SV.3)

Table SV.3: Estimated Cumulative Post-marketing Exposure in the US – Number of Patients by Age Group and Gender

	Age	Number of Patients Exposed					
		Females		Males		Total	
Pediatric Patients	**<12 y**	48	0.4%	62	0.6%	110	**1.0%**
	≥12 to 18 y	69	0.6%	42	0.4%	111	**1.0%**
Adult Patients	**≥18 to <65 y**	4,476	41.3%	1,697	15.7%	6,173	**57.0%**
Elderly Patients	**≥65 to <75 y**	1,953	18.1%	739	6.8%	2,692	**24.9%**
	≥75 to <85 y	1,084	10.0%	439	4.1%	1,523	**14.1%**
	≥85 y	172	1.6%	49	0.4%	221	**2.0%**
Total		**7,802**	**72.0%**	**3,028**	**28.0%**	**10,830**	**100.0%**

Note: Estimated cumulative post-marketing exposure in the US: number of patients by age group and sex (21 December 2015 to 30 November 2020). The methodology regarding patient age calculation is based on patient age at the time of first product shipment. Percentages were obtained based on the proportion of the US patients in the concerned category and are displayed in this table as values rounded up or down to 1 decimal point.

The estimated cumulative exposure in the US corresponds to 15,031 patient-years (Table SV.4).

Table SV.4: Estimated Cumulative Post-marketing Exposure in the US – Patient-Years by Age Group and Gender

	Age	Number of Patient-years		
		Females	**Males**	**Total**
Pediatric Patients	**≥2y to <12 y**	85	82	168
	≥12 to 18 y	87	66	153
Adult Patients	**≥18 to <65 y**	6,932	2,437	9,369
Elderly Patients	**≥65 to <75 y**	2,543	922	3,465
	≥75 to <85 y	1,242	448	1,690
	≥85 y	145	43	188
Total		**11,034**	**3,998**	**15,033**

Note: Estimated cumulative post-marketing exposure in the US: number of patient-years, by age group and sex (21 December 2015 to 30 November 2020). The methodology regarding patient age calculation is based on patient age at the time of first product shipment.

PART II: SAFETY SPECIFICATION

Module SVI: Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

Based on the pharmacology and mechanism of action of selexipag, it is considered highly unlikely that selexipag has the potential for abuse. No systematic examination of the abuse potential of selexipag has been performed in nonclinical and clinical studies; however, there have been no reports of misuse for illegal use or dependence during the clinical development or post-approval use of selexipag. There are no data suggesting that selexipag has the potential for illicit use, abuse, or dependency.

PART II: SAFETY SPECIFICATION

Module SVII: Identified and Potential Risks

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

Not applicable.

SVII.1.1. Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

Reason for not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP:

Not applicable.

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

SVII.2. New Safety Concerns and Reclassification With a Submission of an Updated RMP

None.

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

Important Identified Risks

1. Hypotension
2. Anemia, decrease in hemoglobin concentration
3. Hyperthyroidism
4. Concomitant use of strong inhibitors of CYP2C8

Important Potential Risks

1. Pulmonary edema associated with PVOD
2. MACE
3. Renal function impairment / acute renal failure
4. Bleeding events
5. Light-dependent non-melanoma skin malignancies
6. Ophthalmological effects associated with retinal vascular system
7. GI disturbances denoting intestinal intussusception (manifested as ileus or obstruction)
8. Medication error

Missing Information:

1. Use in pediatric patients
2. Use in elderly patients over 75 years old
3. Use during pregnancy and lactation
4. Concomitant use with strong inhibitors of UGT1A3 and UGT2B7

MedDRA version 22.0 was used to classify the clinical trials AE information that is summarized in this section.

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

SVII.3.1.1. Important Identified Risk: Hypotension

Potential Mechanisms:

As with other pulmonary vasodilators (ie, ERAs, PDE-5 inhibitors, and other prostanoids), treatment with selexipag may be associated with a reduction in blood pressure due to its vasodilatory effects.

Evidence Source(s) and Strength of Evidence:

Selexipag as well as other pulmonary vasodilators widens blood vessels, and there is a risk that patients could have a small drop in blood pressure.

In the double-blind GRIPHON study, about 7 out of every 100 patients (7%) who took selexipag had low blood pressure compared to 4 out of every 100 patients (4%) who took placebo. The pattern and frequency of hypotension events in GRIPHON OL (AC-065A303) was consistent with what was reported for the double-blind studies. In GRIPHON OL, there was no indication of an increased risk of low blood pressure in selexipag-treated patients over long-term treatment.

In the TRITON study, about 9 out of every 100 patients (9%) who took selexipag had low blood pressure compared to 7 out of every 100 patients (7%) who took placebo. No patients who took selexipag in the TRACE study had low blood pressure.

Characterization of the Risk:

Randomized, double-blind studies

Table SVII.1: Important Identified Risk: Treatment-emergent Adverse Events of Hypotension in Randomized, Double-blind Studies

Indication	Trial Number	Incidence Rate, m/N (%)		Relative Risk (95%CI)	Annualized Event Rate (%) [person time (year)]	
		Selexipag	Placebo		Selexipag	Placebo
PAH	AC-065A302	38 / 574 (6.6%)	22 / 578 (3.8%)	1.739 (1.042 - 2.903)	0.0481 [936.4]	0.0274 [875.9]
PAH	NS-304/-02	2 / 33 (6.1%)	0 / 10 (0)	NA	0.1534 [13.0]	0 [3.7]
PAH	AC-065A308	11 / 119 (9.2%)	8 /120 (6.7%)	1.387 (0.578 - 3.325)	0.0531 [207.1]	0.0482 [186.9]
PAH	AC-065A404	0 / 53 (0%)	1 /55 (1.8%)	NA	0 [22.2]	0.0390 [25.7]

All selexipag studies

Table SVII.2: Important Identified Risk: Treatment-emergent Adverse Events of Hypotension in All Studies

Indication	Trial Number	Selexipag	
		Incidence Rate, m/N (%)	Annualized Event Rate (%) [person time (year)]
PAH	AC-065A302 + AC-065A303	82 / 953 (8.6%)	0.0308 [3315.4]
PAH	NS-304/-02 + NS-304/-03	7 / 41 (17.1%)	0.0368 [190.4]
PAH	AC-065A201	8 / 37 (21.6%)	0.1073 [111.8]
PAH	AC-065A304	2 / 34 (5.9%)	0.1421 [14.1]
PAH	AC-065A308	11 / 119 (9.2%)	0.0531 [207.1]
PAH	AC-065A404	0 / 53 (0%)	0 [22.2]

Table SVII.3: Important Identified Risk: Treatment-emergent AESIs in Randomized, Double-blind Studies: Hypotension

	All Studies		AC-065A302		NS-304/-02		AC-065A308		AC-065A404	
	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo
Hypotension										
Analysis set: Safety set	779	763	574	578	33	10	119	120	53	55
Patients with at least one AESI	51 (6.5%)	31 (4.1%)	38 (6.6%)	22 (3.8%)	2 (6.1%)	0	11 (9.2%)	8 (6.7%)	0	1 (1.8%)
Serious	7 (0.9%)	5 (0.7%)	5 (0.9%)	4 (0.7%)	0	0	2 (1.7%)	1 (0.8%)	0	0
Leading to discontinuation	0	2 (0.3%)	0	2 (0.3%)	0	0	0	0	0	0
Fatal outcome	1 (0.1%)	0	1 (0.2%)	0	0	0	0	0	0	0
Relative Risk	1.611	-	1.739	-	NA	-	1.387	-	NA	-
95% CI	(1.043 - 2.490)		(1.042 - 2.903)				(0.578 - 3.325)			
Number of recurrent AESI	58	34	45	24	2	0	11	9	0	1
Patient-years of observation	1178.69	1092.10	936.44	875.87	13.04	3.70	207.05	186.86	22.15	25.67
Average annualized event rate	0.0492	0.0311	0.0481	0.0274	0.1534	0	0.0531	0.0482	0	0.0390
Severity (worst)*										
Mild	17 (2.2%)	10 (1.3%)	12 (2.1%)	6 (1.0%)	1 (3.0%)	0	4 (3.4%)	3 (2.5%)	0	1 (1.8%)
Moderate	27 (3.5%)	19 (2.5%)	19 (3.3%)	14 (2.4%)	1 (3.0%)	0	7 (5.9%)	5 (4.2%)	0	0
Severe	7 (0.9%)	2 (0.3%)	7 (1.2%)	2 (0.3%)	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0	0	0

* The event experienced by the patient with the worst severity is used.
AEs are coded using MedDRA Version 22.0

Table SVII.4: Important Identified Risk: Treatment-emergent AESIs in Selexipag Treated Patients: Hypotension

	Selexipag Treated in Studies					
	All Selexipag	AC-065A302 and/or AC-065A303	NS-304/-02 and/or NS-304/-03	AC-065A304	AC-065A308	AC-065A404
Hypotension						
Analysis set: Safety set	1200	953	41	34	119	53
Patients with at least one AESI	102 (8.5%)	82 (8.6%)	7 (17.1%)	2 (5.9%)	11 (9.2%)	0
Serious	15 (1.3%)	13 (1.4%)	0	0	2 (1.7%)	0
Leading to discontinuation	1 (0.1%)	1 (0.1%)	0	0	0	0
Fatal outcome	1 (0.1%)	1 (0.1%)	0	0	0	0
Number of recurrent AESI	122	102	7	2	11	0
Patient-years of observation	3749.11	3315.43	190.40	14.07	207.05	22.15
Average annualized event rate	0.0325	0.0308	0.0368	0.1421	0.0531	0
Severity (worst)*						
Mild	38 (3.2%)	30 (3.1%)	3 (7.3%)	1 (2.9%)	4 (3.4%)	0
Moderate	53 (4.4%)	41 (4.3%)	4 (9.8%)	1 (2.9%)	7 (5.9%)	0
Severe	11 (0.9%)	11 (1.2%)	0	0	0	0
Missing	0	0	0	0	0	0

AC-065A303 (open label extension study of AC-065A302) was ongoing at the cut-off date.
* The event experienced by the patient with the worst severity is used.
AEs are coded using MedDRA Version 22.0

Table SVII.5: AESIs: Hypotension

	NS-304 N = 37 n (%)
Patients with at least one AESI	8 (21.6%)
Patients with at least one AESI leading to discontinuation	1 (2.7%)
Patients with at least one serious AESI	1 (2.7%)
Patients with at least one AESI with a fatal outcome	0
Number of recurrent AESIs	12
Patient-years of observation	111.81
Average annualized event rate	0.1073
Severity (worst) (b)	
Asymptomatic	0
Mild	4 (10.8%)
Moderate	3 (8.1%)
Severe	1 (2.7%)
Missing	0

MedDRA version 22.0 was used to classify the AESIs. (b) The subject is counted only once in the most severe event when (s)he has multiple events.

MedDRA Terms Used in Database Search:

Refer to Annex 7.3 for the list of MedDRA PTs for the risk of Hypotension.

Post-marketing data sources

Cumulatively, since IBD up to 20 December 2020, 1,644 cases containing events of hypotension or blood pressure decrease have been received from post-marketing data sources. Taking into account the estimated exposure of 21,142 patients, the estimated cumulative reporting rate is 7.8%.

Data from post-marketing data sources were consistent with data observed in the clinical studies. Altogether, in the majority of cases, the events of hypotension occurred in a context of severe medical conditions or other comorbidities that can lead to decrease in blood pressure, eg, PAH worsening, cardiac failure, syncope, infection/sepsis, chronic kidney disease, acute renal failure, hypovolaemia or dehydration, or was associated with a bleeding event; and in patients treated with multiple concomitant medications with hypotensive effects (eg, ERAs, riociguat, PDE-5 inhibitors, anti-hypertensives [beta-blocking agents, anti-adrenergic agents, angiotensin converting enzyme inhibitors, angiotensin II antagonists], and/or diuretics).

Risk Factors and Risk Groups:

General risk factors for hypotension are, eg, a history of systemic hypotension, vegetative dysfunction, concurrent infections or dehydration; and polytherapy with vasodilators and/or other hypotensive medications (eg, ERAs, riociguat, PDE-5 inhibitors, anti-hypertensives, and/or diuretics).

Hypotension is a main prognostic factor of poor outcome related to RHF hospitalization. Four-fold increase of in-hospital mortality for patients with systolic blood pressure <100 mmHg upon admission is observed among PAH patients hospitalized for RHF.

Preventability:

In the case of clinically significant blood-pressure reduction, appropriate measures should be taken as per usual clinical practice.

The following information is included in the SmPC:

Section 4.4 'Special warnings and precautions for use'

"Hypotension

Selexipag has vasodilatory properties that may result in lowering of blood pressure. Before prescribing UPTRAVI, physicians should carefully consider whether patients with certain underlying conditions could be adversely affected by vasodilatory effects (eg, patients on antihypertensive therapy or with resting hypotension, hypovolemia, severe left ventricular outflow obstruction or autonomic dysfunction)."

In section 4.8 'Undesirable effects', hypotension is listed as a commonly reported adverse reaction.

Impact on the Risk-Benefit Balance of the Product:

Blood pressure is measurable, monitorable, and can typically be managed, eg, by adjusting administered medications. Taking into account the severity of the indication, this risk does not have a medically relevant impact on the benefit-risk balance of the product.

Public Health Impact:

Hypotension may require blood pressure monitoring and, in severe cases, may lead to hospitalization.

Annex 1 MedDRA Term:

MedDRA PT: Hypotension.

SVII.3.1.2. Important Identified Risk: Anemia, decrease in hemoglobin concentration

Potential Mechanisms:

Selexipag therapy is associated with a modest decrease in mean hemoglobin concentration. The mechanism has not been elucidated. There is no evidence of hemolysis, occult or overt bleeding or bone-marrow depression associated with selexipag treatment.

Evidence Source(s) and Strength of Evidence:

Selexipag may lower the amount of hemoglobin in the blood. In the double-blind GRIPHON study, a decrease in hemoglobin was reported in about 11 out of 100 patients (11%) who took selexipag and 9 out of 100 (9%) patients who took placebo. In this study, treatment-emergent decreases in hemoglobin from baseline to <10 g/dL were reported for 8.6% of patients who took selexipag and 5.0% of patients who took placebo. In GRIPHON OL, there was no indication of increased occurrence of anemia in selexipag-treated patients over long-term treatment. Anemia events were mostly reported as non-serious and were clinically manageable, with no participant discontinuing selexipag due to anemia.

In the TRITON study, a decrease in hemoglobin was reported in about 27 out of 100 patients (27%) who took selexipag and 17 out of 100 (17%) patients who took placebo. In the TRITON study, treatment-emergent decreases from baseline to <8 g/dL in hemoglobin were reported for 6.8% of patients who took selexipag and 4.1% of patients who took placebo. In TRITON, mean changes in hemoglobin from baseline up to Month 18 ranged from −1.8 to −1.3 g/dL in the selexipag group and −1.6 to −1.3 g/dL in the placebo group.

In the TRACE study, a decrease in hemoglobin was reported in about 4 out of 100 patients (4%) who took selexipag or placebo.

Characterization of the Risk:

Randomized, double-blind studies

Table SVII.6: Important Identified Risk: Treatment-emergent Adverse Events of Anemia in Randomized, Double-blind Studies

Indication	Trial Number	Incidence Rate, m/N (%)		Relative Risk (95%CI)	Annualized Event Rate (%) [person time (year)]	
		Selexipag	Placebo		Selexipag	Placebo
PAH	AC-065A302	64 / 574 (11.1%)	49 / 578 (8.5%)	1.315 (0.923 - 1.873)	0.0854 [936.4]	0.0719 [875.9]
PAH	NS-304/-02	0 / 33 (0)	0 / 10 (0)	NA	0 [13.0]	0 [3.7]
PAH	AC-065A308	31 / 119 (26.1%)	20 / 120 (16.7%)	1.563 (0.946 - 2.581)	0.2077 [207.1]	0.1391 [186.9]
PAH	AC-065A404	2 /53 (3.8%)	2 / 55 (3.6%)	1.038 (0.152 - 7.102)	0.0903 [22.2]	0.0779 [25.7]

All selexipag studies

Table SVII.7: Important Identified Risk: Treatment-emergent Adverse Events of Anemia in All Studies

Indication	Trial Number	Selexipag	
		Incidence Rate, m/N (%)	Annualized Event Rate (%) [person time (year)]
PAH	AC-065A302 + AC-065A303	153 / 953 (16.1%)	0.0615 [3315.4]
PAH	NS-304/-02 + NS-304/-03	8 / 41 (19.5%)	0.0683 [190.4]
PAH	AC-065A201	10 / 37 (27.0%)	0.1163 [111.8]
PAH	AC-065A304	1 / 34 (2.9%)	0.0711 [14.1]
PAH	AC-065A308	31 / 119 (26.1%)	0.2077 [207.1]
PAH	AC-065A404	2 /53 (3.8%)	0.0903 [22.2]

Table SVII.8: Important Identified Risk: Treatment-emergent AESIs in Randomized, Double-blind Studies: Anemia

	All Studies		AC-065A302		NS-304/-02		AC-065A308		AC-065A404	
	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo
Anemia										
Analysis set: Safety set	779	763	574	578	33	10	119	120	53	55
Patients with at least one AESI	97 (12.5%)	71 (9.3%)	64 (11.1%)	49 (8.5%)	0	0	31 (26.1%)	20 (16.7%)	2 (3.8%)	2 (3.6%)
Serious	14 (1.8%)	7 (0.9%)	7 (1.2%)	5 (0.9%)	0	0	7 (5.9%)	2 (1.7%)	0	0
Leading to discontinuation	0	0	0	0	0	0	0	0	0	0
Fatal outcome	0	0	0	0	0	0	0	0	0	0
Relative Risk	1.338	-	1.315	-	NA	-	1.563	-	1.038	-
95% CI	(1.002 - 1.787)		(0.923 - 1.873)				(0.946 - 2.581)		(0.152 - 7.102)	
Number of recurrent AESI	125	91	80	63	0	0	43	26	2	2
Patient-years of observation	1178.69	1092.10	936.44	875.87	13.04	3.70	207.05	186.86	22.15	25.67
Average annualized event rate	0.1060	0.0833	0.0854	0.0719	0	0	0.2077	0.1391	0.0903	0.0779
Severity (worst)*										
Mild	53 (6.8%)	29 (3.8%)	38 (6.6%)	21 (3.6%)	0	0	15 (12.6%)	7 (5.8%)	0	1 (1.8%)
Moderate	30 (3.9%)	34 (4.5%)	18 (3.1%)	22 (3.8%)	0	0	10 (8.4%)	11 (9.2%)	2 (3.8%)	1 (1.8%)
Severe	13 (1.7%)	8 (1.0%)	7 (1.2%)	6 (1.0%)	0	0	6 (5.0%)	2 (1.7%)	0	0
Missing	1 (0.1%)	0	1 (0.2%)	0	0	0	0	0	0	0

* The event experienced by the patient with the worst severity is used.
AEs are coded using MedDRA Version 22.0

Table SVII.9: Important Identified Risk: Treatment-emergent AESIs in Selexipag Treated Patients: Anemia

	Selexipag Treated in Studies					
	All Selexipag	AC-065A302 and/or AC-065A303	NS-304/-02 and/or NS-304/-03	AC-065A304	AC-065A308	AC-065A404
Anemia						
Analysis set: Safety set	1200	953	41	34	119	53
Patients with at least one AESI	195 (16.3%)	153 (16.1%)	8 (19.5%)	1 (2.9%)	31 (26.1%)	2 (3.8%)
Serious	28 (2.3%)	19 (2.0%)	2 (4.9%)	0	7 (5.9%)	0
Leading to discontinuation	1 (0.1%)	1 (0.1%)	0	0	0	0
Fatal outcome	1 (0.1%)	1 (0.1%)	0	0	0	0
Number of recurrent AESI	263	204	13	1	43	2
Patient-years of observation	3749.11	3315.43	190.40	14.07	207.05	22.15
Average annualized event rate	0.0702	0.0615	0.0683	0.0711	0.2077	0.0903
Severity (worst)*						
Mild	96 (8.0%)	80 (8.4%)	1 (2.4%)	0	15 (12.6%)	0
Moderate	69 (5.8%)	52 (5.5%)	4 (9.8%)	1 (2.9%)	10 (8.4%)	2 (3.8%)
Severe	27 (2.3%)	18 (1.9%)	3 (7.3%)	0	6 (5.0%)	0
Missing	3 (0.3%)	3 (0.3%)	0	0	0	0

AC-065A303 (open label extension study of AC-065A302) was ongoing at the cut-off date.
* The event experienced by the patient with the worst severity is used.
AEs are coded using MedDRA Version 22.0

Table SVII.10 : AESIs: Anemia

	NS-304 N = 37 n (%)
Patients with at least one AESI	10 (27.0%)
Patients with at least one AESI leading to discontinuation	0
Patients with at least one serious AESI	0
Patients with at least one AESI with a fatal outcome	0
Number of recurrent AESIs	13
Patient-years of observation	111.81
Average annualized event rate	0.1163
Severity (worst) (b)	
Asymptomatic	0
Mild	5 (13.5%)
Moderate	5 (13.5%)
Severe	0
Missing	0

MedDRA version 22.0 was used to classify the AESIs. (b) The subject is counted only once in the most severe event when (s)he has multiple events.

MedDRA Terms Used in Database Search:

Refer to Annex 7.3 for the list of MedDRA PTs for the risk of Anemia, decrease in hemoglobin concentration.

Post-marketing data sources

Cumulatively, since IBD up to 20 December 2020, 921 post-marketing cases with events of anemia and/or decreased hemoglobin have been received. The estimated reporting rate was 4.4% (921 cases/21,142 exposed patients). Transfusion was documented in 214 of the 921 cases of anemia.

Data from post-marketing data sources were consistent with data observed in Study AC-065A302 (GRIPHON). In the TRITON study, a higher incidence of AEs denoting anemia was observed in both the triple (selexipag) and double (placebo) combination therapy groups. More patients in the triple (selexipag) as compared to the double therapy (placebo) group experienced an anemia event; however, there was no difference in the magnitude of hemoglobin decrease as well as the proportion of patients with hemoglobin decrease between the treatment groups (measured from baseline until end-of-study).

In the majority of cases received from all sources, the events of anemia, including those treated by transfusion, occurred in a context of severe medical conditions or other comorbidities that can lead to progressive anemia, such as cardiac failure, renal failure, CTD, or bleeding, or in patients concomitantly treated with medications such as anti-thrombotics, platelet aggregation inhibitors, or other medications including ERA with known effects on blood hemoglobin levels.

Risk Factors and Risk Groups:

General risk factors for anemia are, eg, iron deficiency, history of anemia, concomitant platelet inhibitors, anticoagulants, steroids, pre-existing or concurrent bleeding.

Preventability:

Anemia is measurable, monitorable, and treatable.

Anemia and hemoglobin decreased are listed in section 4.8 of the UPTRAVI SmPC as common reported adverse reactions based on data from the GRIPHON study. Section 4.8 of the SmPC also includes a description that anemia was reported at a higher frequency in the TRITON study.

In addition, the following information is provided in section 4.8 under 'Laboratory abnormalities':

"Haemoglobin decrease

In a Phase 3 placebo-controlled study in patients with PAH, mean absolute changes in haemoglobin at regular visits compared to baseline ranged from -0.34 to -0.02 g/dL in the selexipag group compared to -0.05 to 0.25 g/dL in the placebo group. A decrease from baseline in haemoglobin concentration to below 10 g/dL was reported in 8.6% of selexipag-treated patients and 5.0% of placebo treated patients."

Impact on the Risk-benefit Balance of the Product:

Anemia is measurable, monitorable, and treatable. Taking into account the severity of the indication, this risk does not have a medically relevant impact on the benefit-risk balance of the product.

Public Health Impact:

Anemia may require blood transfusion.

Annex 1 MedDRA Term:

MedDRA PT: Anaemia.

SVII.3.1.3. Important Identified Risk: Hyperthyroidism

Potential Mechanisms:

Prostacyclin plays an important role in the modulation of thyroid function (Silva 2009). It was suggested that prostacyclin stimulates TSH secretion (Marvisi 2006). Previous investigations have shown that prostacyclin stimulate intracellular thyroid processes through interaction with specific surface membrane-bound receptors and mimic many of the effects of TSH on the thyroidal metabolism and in vivo stimulate the synthesis and secretion of thyroid hormone (Virgolini 1988).

Evidence Source(s) and Strength of Evidence:

In the double-blind GRIPHON study, signs of an overactive thyroid gland were seen in about 3 out of every 100 patients (3%) who took selexipag and 1 out of every 100 patients (1%) who took placebo. In GRIPHON OL, overall, the pattern and frequency of hyperthyroidism events was comparable to that seen in the double-blind studies.

In the TRITON and TRACE studies, no patients who took selexipag had signs of an overactive thyroid gland.

Characterization of the Risk:

Randomized, double-blind studies

Table SVII.11: Important Identified Risk: Treatment-emergent Adverse Events of Hyperthyroidism in Randomized, Double-blind Studies

Indication	Trial Number	Incidence Rate, m/N (%)		Relative Risk (95%CI)	Annualized Event Rate (%), [person time (year)]	
		Selexipag	Placebo		Selexipag	Placebo
PAH	AC-065A302	15 / 574 (2.6%)	8 / 578 (1.4%)	1.888 (0.807 - 4.419)	0.0203 [936.4]	0.0126 [875.9]
PAH	NS-304/-02	0 / 33 (0)	0 / 10 (0)	NA	0 [13.0]	0 [3.7]
PAH	AC-065A308	0 / 119 (0)	1 / 120 (0.8%)	NA	0 [207.1]	0.0054 [186.9]
PAH	AC-065A404	0 / 53 (0)	0 / 55 (0)	NA	0 [22.2]	0 [25.7]

All selexipag studies

Table SVII.12: Important Identified Risk: Treatment-emergent Adverse Events of Hyperthyroidism in All Studies

Indication	Trial Number	Selexipag	
		Incidence Rate, m/N (%)	Annualized Event Rate (%) [person time (year)]
PAH	AC-065A302 + AC-065A303	31 / 953 (3.3%)	0.0109 [3315.4]
PAH	NS-304/-02 + NS-304/-03	0 / 41 (0)	0 [190.4]
PAH	AC-065A201	0 / 37 (0)	0 [111.8]
PAH	AC-065A304	0 / 34 (0)	0 [14.1]
PAH	AC-065A308	0 / 119 (0)	0 [207.1]
PAH	AC-065A404	0 / 53 (0)	0 [22.2]

Table SVII.13: Important Identified Risk: Treatment-emergent AESIs in Randomized, Double-blind Studies: Hyperthyroidism

	All Studies		AC-065A302		NS-304/-02		AC-065A308		AC-065A404	
	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo
Hyperthyroidism										
Analysis set: Safety set	779	763	574	578	33	10	119	120	53	55
Patients with at least one AESI	15 (1.9%)	9 (1.2%)	15 (2.6%)	8 (1.4%)	0	0	0	1 (0.8%)	0	0
Serious	2 (0.3%)	0	2 (0.3%)	0	0	0	0	0	0	0
Leading to discontinuation	2 (0.3%)	1 (0.1%)	2 (0.3%)	1 (0.2%)	0	0	0	0	0	0
Fatal outcome	0	0	0	0	0	0	0	0	0	0
Relative Risk	1.632	-	1.888	-	NA	-	NA	-	NA	-
95% CI	(0.719 - 3.708)		(0.807 - 4.419)							
Number of recurrent AESI	19	12	19	11	0	0	0	1	0	0
Patient-years of observation	1178.69	1092.10	936.44	875.87	13.04	3.70	207.05	186.86	22.15	25.67
Average annualized event rate	0.0161	0.0110	0.0203	0.0126	0	0	0	0.0054	0	0
Severity (worst)*										
Mild	13 (1.7%)	3 (0.4%)	13 (2.3%)	3 (0.5%)	0	0	0	0	0	0
Moderate	2 (0.3%)	4 (0.5%)	2 (0.3%)	3 (0.5%)	0	0	0	1 (0.8%)	0	0
Severe	0	0	0	0	0	0	0	0	0	0
Missing	0	2 (0.3%)	0	2 (0.3%)	0	0	0	0	0	0

* The event experienced by the patient with the worst severity is used.
AEs are coded using MedDRA Version 22.0

Table SVII.14: Important Identified Risk: Treatment-emergent AESIs in Selexipag Treated Patients: Hyperthyroidism

	Selexipag Treated in Studies					
	All Selexipag	AC-065A302 and/or AC-065A303	NS-304/-02 and/or NS-304/-03	AC-065A304	AC-065A308	AC-065A404
Hyperthyroidism						
Analysis set: Safety set	1200	953	41	34	119	53
Patients with at least one AESI	31 (2.6%)	31 (3.3%)	0	0	0	0
Serious	5 (0.4%)	5 (0.5%)	0	0	0	0
Leading to discontinuation	2 (0.2%)	2 (0.2%)	0	0	0	0
Fatal outcome	0	0	0	0	0	0
Number of recurrent AESI	36	36	0	0	0	0
Patient-years of observation	3749.11	3315.43	190.40	14.07	207.05	22.15
Average annualized event rate	0.0096	0.0109	0	0	0	0
Severity (worst)*						
Mild	17 (1.4%)	17 (1.8%)	0	0	0	0
Moderate	12 (1.0%)	12 (1.3%)	0	0	0	0
Severe	2 (0.2%)	2 (0.2%)	0	0	0	0
Missing	0	0	0	0	0	0

AC-065A303 (open label extension study of AC-065A302) was ongoing at the cut-off date.
* The event experienced by the patient with the worst severity is used.
AEs are coded using MedDRA Version 22.0

Table SVII.15: AESIs: Hyperthyroidism

	NS-304 N = 37 n (%)
No patient observed	

MedDRA version 22.0 was used to classify the AESIs.

MedDRA Terms Used in Database Search:

Refer to Annex 7.3 for the list of MedDRA PTs for the risk of Hyperthyroidism.

Post-marketing data sources

Cumulatively, since IBD up to 20 December 2020, 97 post-marketing reports including events of hyperthyroidism were received. Taking into account the estimated exposure of 21,142 patients, the estimated cumulative reporting rate is 0.5%.Data from post-marketing data sources were consistent with data observed in the clinical studies.

Risk Factors and Risk Groups:

Patients susceptible to the stimulatory effect of an IP receptor at the thyroid gland may be at risk.

In some studies, prostacyclin treatment has been reported concomitantly with thyroid disorder occurrence (Chu 2002). Prostacyclins stimulate intracellular thyroid processes and mimic the effects of TSH on the thyroidal metabolism and stimulate the synthesis and secretion of thyroid hormone (Virgolini 1988). A possible role of epoprostenol (Chadha 2009, Ferris 2001, Fojas 2016, Richter 2016, Srimatkandada 2014) and of treprostinil (Gu 2016) in triggering hyperthyroid disease was suspected in PAH patients.

Preventability:

Hyperthyroidism (subclinical or overt) is measurable, monitorable and treatable.

The following information is included in the SmPC:

Section 4.4 ‘Special warnings and precautions for use’

“*Hyperthyroidism*

Hyperthyroidism has been observed with UPTRAVI. Thyroid function tests are recommended as clinically indicated in the presence of signs or symptoms of hyperthyroidism.”

In section 4.8 ‘Undesirable effects’, hyperthyroidism and TSH decreased are listed as a commonly reported adverse reactions.

In addition, the following information is provided in section 4.8 under 'Laboratory abnormalities':

'Thyroid function tests

In a Phase 3 placebo-controlled study in patients with PAH, hyperthyroidism was reported for 1.6% of patients in the selexipag group, compared to no case in the placebo group (see section 4.4). A reduction (up to –0.3 MU/L from a baseline median of 2.5 MU/L) in median TSH was observed at most visits in the selexipag group. In the placebo group, little change in median values was apparent. There were no mean changes in triiodothyronine or thyroxine in either group.'

Impact on the Risk-Benefit Balance of the Product:

Hyperthyroidism (subclinical or overt) is measurable, monitorable, and treatable. Taking into account the severity of the indication, this risk does not have a medically relevant impact on the benefit-risk balance of the product.

Public Health Impact:

Hyperthyroidism requires dedicated treatment and may require hospitalization.

Annex 1 MedDRA Term:

MedDRA PT: Hyperthyroidism.

SVII.3.1.4. Important Identified Risk: Concomitant use with strong inhibitors of CYP2C8

Potential Mechanisms:

Selexipag and its active metabolite both undergo oxidative metabolism by CYP2C8. Gemfibrozil is the only known strong CYP2C8 inhibitor based on experimental DDI data obtained with multiple dosing (Niemi 2003).

Evidence Source(s) and Strength of Evidence:

In the presence of 600 mg gemfibrozil, twice a day, a strong inhibitor of CYP2C8, exposure to selexipag increased approximately 2-fold, whereas exposure to the active metabolite increased approximately 11-fold (AC-065-113). Concomitant administration of UPTRAVI with strong inhibitors of CYP2C8 (eg, gemfibrozil) is therefore contraindicated.

Characterization of the Risk:

No patient was treated concomitantly with a strong CYP2C8 inhibitor during the GRIPHON, TRITON and TRACE double-blind studies.

MedDRA Terms Used in Database Search:

Refer to Annex 7.3 for the list of for the list of medications which are strong inhibitors of CYP2C8.

Post-marketing data sources

Cumulatively, since IBD up to 20 December 2020, co-administration of strong CYP2C8 inhibitors with selexipag where patients initiated selexipag on top of ongoing concomitant gemfibrozil was reported in 3 post-marketing cases. 1 of the patients was unable to titrate selexipag beyond 200 µg bid, due to the severity of prostacyclin-associated events; both gemfibrozil and selexipag were discontinued. In the second patient, the maximum documented dose of selexipag was 1,400 µg bid, which was gradually down-titrated due to ADRs; lower doses were reported to be associated with unchanged pulmonary pressures and fewer side effects. The third patient was prescribed gemfibrozil when on selexipag treatment (1,200 µg bid) and experienced severe pain after one dose of gemfibrozil; atorvastatin and gemfibrozil were discontinued, and action taken with selexipag was unknown.

Risk Factors and Risk Groups:

Patients treated with gemfibrozil and selexipag.

Preventability:

Substances that strongly inhibit the activity of these CYP2C8 enzymes should not be used with selexipag and are contraindicated (SmPC section 4.3). The doctor and the patient will be told about the interaction between selexipag and gemfibrozil in the product information documents.

Impact on the Risk-Benefit Balance of the Product:

This identified DDI does not have a medically relevant impact on the benefit-risk balance of the product.

Public Health Impact:

Prescribers need to monitor concomitant treatments given to selexipag-treated patients.

Annex 1 MedDRA Term:

MedDRA PT: Drug interaction.

SVII.3.1.5. Important Potential Risk: Pulmonary edema associated with PVOD

Potential Mechanisms:

Pulmonary edema following administration of any pulmonary vasodilator used for treatment of PAH could be due to previously unrecognized secondary angioproliferative process caused by post-capillary obstruction, eg, PVOD and/or due to combined pre capillary and post-capillary pulmonary hypertension (Galiè 2015b, Galiè 2016, Opitz 2016).

Evidence Source(s) and Strength of Evidence:

Experience with other pulmonary vasodilators, ie, ERAs, PDE-5 inhibitors, riociguat, prostacyclin and its analogue.

Cases of pulmonary edema have been reported with vasodilators (mainly prostacyclins) when used in patients with previously undiagnosed PVOD. Close monitoring for such events continues for emerging data from clinical studies as well as in post-approval use.

In the double-blind GRIPHON study, about 1 out of every 100 patients (1%) who took selexipag or placebo had pulmonary edema associated with PVOD. In GRIPHON OL, overall, the pattern and frequency of PVOD associated with pulmonary edema AESIs was consistent with that seen in the double-blind studies.

In the TRITON study, about 2 out of every 100 patients (2%) who took selexipag and 1 out of every 100 patients (1%) who took placebo had pulmonary edema associated with PVOD. No patients who took selexipag or placebo in the TRACE study had pulmonary edema associated with PVOD.

Characterization of the Risk:

Randomized, double-blind studies

Table SVII.16: Important Potential Risk: Treatment-emergent Adverse Events of Pulmonary Edema Associated with PVOD in Randomized, Double-blind Studies

Indication	Trial Number	Incidence Rate, m/N (%)		Relative Risk (95%CI)	Annualized Event Rate (%) [person time (year)]	
		Selexipag	Placebo		Selexipag	Placebo
PAH	AC-065A302	4 / 574 (0.7%)	5 / 578 (0.9%)	0.806 (0.217 - 2.985)	0.0053 [936.4]	0.0069 [875.9]
PAH	NS-304/-02	0 / 33 (0)	0 / 10 (0)	NA	0 [13.0]	0 [3.7]
PAH	AC-065A308	2 / 119 (1.7%)	1 /120 (0.8%)	2.017 (0.185 - 21.945)	0.0145 [207.1]	0.0054 [186.9]
PAH	AC-065A404	0 / 53 (0)	0 / 55 (0)	NA	0 [22.2]	0 [25.7]

All selexipag studies

Table SVII.17: Important Potential Risk: Treatment-emergent Adverse Events of Pulmonary Edema Associated with PVOD in All Studies

Indication	Trial Number	Selexipag	
		Incidence Rate, m/N (%)	Annualized Event Rate (%) [person time (year)]
PAH	AC-065A302 + AC-065A303	9 / 953 (0.9%)	0.0030 [3315.4]
PAH	NS-304/-02 + NS-304/-03	0 / 41 (0)	0 [190.4]
PAH	AC-065A201	1 / 37 (2.7%)	0.0089 [111.8]
PAH	AC-065A304	0 / 34 (0)	0 [14.1]
PAH	AC-065A308	2 / 119 (1.7%)	0.0145 [207.1]
PAH	AC-065A404	0 / 53 (0)	0 [22.2]

Table SVII.18: Important Potential Risk: Treatment-emergent AESIs in Randomized, Double-blind Studies: PVOD Associated with Pulmonary Edema

	All Studies		AC-065A302		NS-304/-02		AC-065A308		AC-065A404	
	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo
PVOD Associated with Pulmonary Edema										
Analysis set: Safety set	779	763	574	578	33	10	119	120	53	55
Patients with at least one AESI	6 (0.8%)	6 (0.8%)	4 (0.7%)	5 (0.9%)	0	0	2 (1.7%)	1 (0.8%)	0	0
Serious	3 (0.4%)	3 (0.4%)	2 (0.3%)	2 (0.3%)	0	0	1 (0.8%)	1 (0.8%)	0	0
Leading to discontinuation	2 (0.3%)	0	2 (0.3%)	0	0	0	0	0	0	0
Fatal outcome	0	1 (0.1%)	0	0	0	0	0	1 (0.8%)	0	0
Relative Risk	0.979	-	0.806	-	NA	-	2.017	-	NA	-
95% CI	(0.317 - 3.024)		(0.217 - 2.985)				(0.185 - 21.945)			
Number of recurrent AESI	8	7	5	6	0	0	3	1	0	0
Patient-years of observation	1178.69	1092.10	936.44	875.87	13.04	3.70	207.05	186.86	22.15	25.67
Average annualized event rate	0.0068	0.0064	0.0053	0.0069	0	0	0.0145	0.0054	0	0
Severity (worst)*										
Mild	0	0	0	0	0	0	0	0	0	0
Moderate	3 (0.4%)	4 (0.5%)	2 (0.3%)	4 (0.7%)	0	0	1 (0.8%)	0	0	0
Severe	3 (0.4%)	2 (0.3%)	2 (0.3%)	1 (0.2%)	0	0	1 (0.8%)	1 (0.8%)	0	0
Missing	0	0	0	0	0	0	0	0	0	0

* The event experienced by the patient with the worst severity is used.
AEs are coded using MedDRA Version 22.0

Table SVII.19: Important Potential Risk: Treatment-emergent AESIs in Selexipag Treated Patients: PVOD Associated with Pulmonary Edema

	Selexipag Treated in Studies					
	All Selexipag	AC-065A302 and/or AC-065A303	NS-304/-02 and/or NS-304/-03	AC-065A304	AC-065A308	AC-065A404
PVOD Associated with Pulmonary Edema						
Analysis set: Safety set	1200	953	41	34	119	53
Patients with at least one AESI	11 (0.9%)	9 (0.9%)	0	0	2 (1.7%)	0
Serious	5 (0.4%)	4 (0.4%)	0	0	1 (0.8%)	0
Leading to discontinuation	2 (0.2%)	2 (0.2%)	0	0	0	0
Fatal outcome	2 (0.2%)	2 (0.2%)	0	0	0	0
Number of recurrent AESI	13	10	0	0	3	0
Patient-years of observation	3749.11	3315.43	190.40	14.07	207.05	22.15
Average annualized event rate	0.0035	0.0030	0	0	0.0145	0
Severity (worst)*						
Mild	1 (0.1%)	1 (0.1%)	0	0	0	0
Moderate	4 (0.3%)	3 (0.3%)	0	0	1 (0.8%)	0
Severe	6 (0.5%)	5 (0.5%)	0	0	1 (0.8%)	0
Missing	0	0	0	0	0	0

AC-065A303 (open label extension study of AC-065A302) was ongoing at the cut-off date.
* The event experienced by the patient with the worst severity is used.
AEs are coded using MedDRA Version 22.0

Table SVII.20: AESIs: PVOD Associated with Pulmonary Edema

	NS-304 N = 37 n (%)
Patients with at least one AESI	1 (2.7%)
Patients with at least one AESI leading to discontinuation	0
Patients with at least one serious AESI	0
Patients with at least one AESI with a fatal outcome	0
Number of recurrent AESIs	1
Patient-years of observation	111.81
Average annualized event rate	0.0089
Severity (worst) (b)	
Asymptomatic	0
Mild	1 (2.7%)
Moderate	0
Severe	0
Missing	0

MedDRA version 22.0 was used to classify the AESIs. (b) The subject is counted only once in the most severe event when (s)he has multiple events.

MedDRA Terms Used in Database Search:

Refer to Annex 7.3 for the list of MedDRA PTs for the risk of Pulmonary edema associated with PVOD.

Post-marketing data sources

Cumulatively, since IBD up to 20 December 2020, 34 post-marketing reports including events of PVOD or veno-occlusive disease have been received, corresponding to a cumulative reporting rate of 0.16% (34 cases / 21,142 exposed patients). Concurrent events of pulmonary edema/acute pulmonary edema were reported in 10 of these 34 cases; selexipag was discontinued in 4 cases and remained ongoing in 6 cases (at a decreased dose in 1 case).

Data from post-marketing data sources were consistent with data observed in the clinical studies.

Risk Factors and Risk Groups:

Patients with undiagnosed PVOD and on concurrent medications leading to pulmonary vasodilatation.

Preventability:

Undiagnosed pre-existing PVOD or post-capillary pulmonary artery disease may unmask itself with administration of PAH-specific therapies that are pulmonary vasodilators. The use of any PAH-specific therapies in PVOD patients may therefore lead to pulmonary edema.

As stated in SmPC section 4.4 (‘Special warnings and precautions for use’): “Cases of pulmonary edema have been reported with vasodilators (mainly prostacyclins) when used in patients with

PVOD. Consequently, if signs of pulmonary edema occur when UPTRAVI is administered in patients with PAH, the possibility of PVOD should be considered. If confirmed, treatment is to be discontinued."

Impact on the Risk-Benefit Balance of the Product:

Taking into account the severity of the PAH indication, and pathological, genetic, and clinical similarities between PVOD and PAH resulting in a diagnostic and therapeutic challenge, this potential risk does not have a medically relevant impact on the benefit-risk balance of the product.

Public Health Impact:

Some patients with a specific blockage of the blood vessels in the lungs may have a very rare type of high blood pressure in the lungs called PVOD. These patients can get a build-up of fluid in the lungs if they take UPTRAVI or other medicines that widen blood vessels in the lung. If there are signs of a build-up of fluid in the lungs that the doctor thinks might be due to this disease, treatment with UPTRAVI should be stopped.

The diagnosis of PVOD / pulmonary capillary hemangiomatosis can be established with a high probability by the combination of clinical suspicion, physical examination, bronchoscopy, and radiological findings. Diagnosis of PVOD may require hospitalization and change in the therapy administered.

Annex 1 MedDRA Term:

MedDRA PT: Pulmonary veno-occlusive disease.

SVII.3.1.6. Important Potential Risk: MACE

Potential Mechanisms:

No deleterious effect of selexipag on MACE is evident. Neither scientific literature nor non-clinical data indicate a risk of harmful effects of prostacyclin and its analogues on MACE.

Evidence Source(s) and Strength of Evidence:

Results of adjudication performed by the external cardiologist and the Critical Event Committee in study AC-065A302 (GRIPHON) [D-15.136].

In the pivotal double-blind Phase 3 AC-065A302/GRIPHON study, MACE was observed in 4.4% of selexipag-treated patients versus 4.0% of placebo-treated patients. The long-term safety data for MACE showed a decreasing trend in average annualized event rates. There was no evidence of a causal association between these events and selexipag administration in participants treated with selexipag in clinical studies.

In the TRITON study, about 3 out of every 100 patients (3%) who took selexipag had MACE compared to 6 out of every 100 patients (6%) who took placebo. No patients who took selexipag or placebo in the TRACE study had MACE.

Close monitoring of such events continues for emerging data from clinical studies as well as in post-approval use.

Characterization of the Risk:

Randomized, double-blind studies

Table SVII.21: Important Potential Risk: Treatment-emergent Adverse Events of MACE in Randomized, Double-blind Studies

Indication	Trial Number	Incidence Rate, m/N (%)		Relative Risk (95%CI)	Annualized Event Rate (%), [person time (year)]	
		Selexipag	Placebo		Selexipag	Placebo
PAH	AC-065A302	25 / 574 (4.4%)	23 / 578 (4.0%)	1.095 (0.629 - 1.905)	0.0310 [936.4]	0.0308 [875.9]
PAH	NS-304/-02	0 / 33 (0)	0 / 10 (0)	NA	0 [13.0]	0 [3.7]
PAH	AC-065A308	3 / 119 (2.5%)	7 /120 (5.8%)	0.432 (0.114 - 1.632)	0.0145 [207.1]	0.0482 [186.9]
PAH	AC-065A404	0 / 53 (0)	0 / 55 (0)	NA	0 [22.2]	0 [25.7]

All selexipag studies

Table SVII.22: Important Potential Risk: Treatment-emergent Adverse Events of MACE in All Studies

Indication	Trial Number	Selexipag	
		Incidence Rate, m/N (%)	Annualized Event Rate (%) [person time (year)]
PAH	AC-065A302 + AC-065A303	77 / 953 (8.1%)	0.0256 [3315.4]
PAH	NS-304/-02 + NS-304/-03	8 / 41 (19.5%)	0.0473 [190.4]
PAH	AC-065A201	1 / 37 (2.7%)	0.0089 [111.8]
PAH	AC-065A304	0 / 34 (0)	0 [14.1]
PAH	AC-065A308	3 / 119 (2.5%)	0.0145 [207.1]
PAH	AC-065A404	0 / 53 (0)	0 [22.2]

Table SVII.23: Important Potential Risk: Treatment-emergent AESIs in Randomized, Double-blind Studies: MACE

	All Studies		AC-065A302		NS-304/-02		AC-065A308		AC-065A404	
	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo
MACE										
Analysis set: Safety set	779	763	574	578	33	10	119	120	53	55
Patients with at least one AESI	28 (3.6%)	30 (3.9%)	25 (4.4%)	23 (4.0%)	0	0	3 (2.5%)	7 (5.8%)	0	0
Serious	23 (3.0%)	21 (2.8%)	23 (4.0%)	16 (2.8%)	0	0	0	5 (4.2%)	0	0
Leading to discontinuation	12 (1.5%)	5 (0.7%)	12 (2.1%)	4 (0.7%)	0	0	0	1 (0.8%)	0	0
Fatal outcome	15 (1.9%)	12 (1.6%)	15 (2.6%)	10 (1.7%)	0	0	0	2 (1.7%)	0	0
Relative Risk	0.914	-	1.095	-	NA	-	0.432	-	NA	-
95% CI	(0.552 - 1.515)		(0.629 - 1.905)				(0.114 - 1.632)			
Number of recurrent AESI	32	36	29	27	0	0	3	9	0	0
Patient-years of observation	1178.69	1092.10	936.44	875.87	13.04	3.70	207.05	186.86	22.15	25.67
Average annualized event rate	0.0271	0.0330	0.0310	0.0308	0	0	0.0145	0.0482	0	0
Severity (worst)*										
Mild	3 (0.4%)	4 (0.5%)	1 (0.2%)	3 (0.5%)	0	0	2 (1.7%)	1 (0.8%)	0	0
Moderate	6 (0.8%)	8 (1.0%)	5 (0.9%)	6 (1.0%)	0	0	1 (0.8%)	2 (1.7%)	0	0
Severe	18 (2.3%)	17 (2.2%)	18 (3.1%)	13 (2.2%)	0	0	0	4 (3.3%)	0	0
Missing	1 (0.1%)	1 (0.1%)	1 (0.2%)	1 (0.2%)	0	0	0	0	0	0

* The event experienced by the patient with the worst severity is used.
AEs are coded using MedDRA Version 22.0

Table SVII.24: Important Potential Risk: Treatment-emergent AESIs in Selexipag Treated Patients: MACE

	Selexipag Treated in Studies					
	All Selexipag	AC-065A302 and/or AC-065A303	NS-304/-02 and/or NS-304/-03	AC-065A304	AC-065A308	AC-065A404
MACE						
Analysis set: Safety set	1200	953	41	34	119	53
Patients with at least one AESI	88 (7.3%)	77 (8.1%)	8 (19.5%)	0	3 (2.5%)	0
Serious	76 (6.3%)	68 (7.1%)	8 (19.5%)	0	0	0
Leading to discontinuation	16 (1.3%)	15 (1.6%)	1 (2.4%)	0	0	0
Fatal outcome	59 (4.9%)	53 (5.6%)	6 (14.6%)	0	0	0
Number of recurrent AESI	97	85	9	0	3	0
Patient-years of observation	3749.11	3315.43	190.40	14.07	207.05	22.15
Average annualized event rate	0.0259	0.0256	0.0473	0	0.0145	0
Severity (worst)*						
Mild	6 (0.5%)	4 (0.4%)	0	0	2 (1.7%)	0
Moderate	12 (1.0%)	10 (1.0%)	1 (2.4%)	0	1 (0.8%)	0
Severe	66 (5.5%)	59 (6.2%)	7 (17.1%)	0	0	0
Missing	4 (0.3%)	4 (0.4%)	0	0	0	0

AC-065A303 (open label extension study of AC-065A302) was ongoing at the cut-off date.
* The event experienced by the patient with the worst severity is used.
AEs are coded using MedDRA Version 22.0

Table SVII.25: AESIs: MACE

	NS-304 N = 37 n (%)
Patients with at least one AESI	1 (2.7%)
Patients with at least one AESI leading to discontinuation	0
Patients with at least one serious AESI	1 (2.7%)
Patients with at least one AESI with a fatal outcome	1 (2.7%)
Number of recurrent AESIs	1
Patient-years of observation	111.81
Average annualized event rate	0.0089
Severity (worst) (b)	
Asymptomatic	0
Mild	0
Moderate	0
Severe	1 (2.7%)
Missing	0

MedDRA version 22.0 was used to classify the AESIs. (b) The subject is counted only once in the most severe event when (s)he has multiple events.

MedDRA Terms Used in Database Search:

Refer to Annex 7.3 for the list of MedDRA PTs for the risk of MACE.

Post-marketing data sources

Cumulatively, since IBD up to 20 December 2020, 457 post-marketing cases containing MACE have been received. The estimated cumulative reporting rate is 2.2% (457 cases / 21,142 patients exposed).

Consistent with data from Study AC-065A302/GRIPHON and all other completed studies, MACE were reported in patients with severe PAH disease, receiving multiple medications, and occurred in a context of other pre-existing cardiovascular comorbidities or prior history of stroke or myocardial infarction, which are known to represent independent factors increasing the risk for adverse cardiovascular or cerebrovascular events. There was no evidence of a causal association between these events and selexipag administration in participants treated with selexipag in clinical studies or with commercial product.

Risk Factors and Risk Groups:

As in the general population, patients with high cardiovascular risk due to intercurrent atherosclerotic disease requiring antihypertensive and/or lipid-lowering and/or antidiabetic treatment are identified as groups at risk. Systematic multidisciplinary approach, which addresses lifestyle, cardiovascular risk factor and underlying cardiovascular comorbidities treatment, is part of general medical management of each patient.

Preventability:

Proper management of patients with pre-existing cardiac disease (either in the context of underlying PAH, CTD, or other cardiac co morbidities) as per clinical practice.

In addition, as stated in the UPTRAVI SmPC in section 4.3 'Contraindications', selexipag treatment is contraindicated in patients with the following conditions:

- Severe coronary heart disease or unstable angina.
- Myocardial infarction within the last 6 months.
- Decompensated cardiac failure if not under close medical supervision.
- Severe arrhythmias.
- Cerebrovascular events (eg, transient ischemic attack, stroke) within the last 3 months.
- Congenital or acquired valvular defects with clinically relevant myocardial function disorders not related to pulmonary hypertension.

Impact on the Risk-benefit Balance of the Product:

Taking into account the severity of the PAH indication, and additional impact of the cardiovascular and cerebrovascular comorbidities associated with more severe clinical symptoms and a lower exercise tolerance, this potential risk does not have a medically relevant impact on the benefit-risk balance of the product.

Public Health Impact:

Events may require hospitalization of various duration, conservative and/or surgical treatment, may affect the activities of daily living and prognosis of these patients.

Annex 1 MedDRA Term:

MedDRA PT: Myocardial infarction.

SVII.3.1.7. Important Potential Risk: Renal function impairment / acute renal failure

Potential Mechanisms:

No deleterious effect of selexipag on renal function is evident. Neither scientific literature nor non-clinical data indicate a risk of harmful effects of prostacyclin and its analogues on renal function. In contrast, the activation of IP receptors by endogenous prostacyclin is critical for normal renal function, including regulating renal blood flow, glomerular filtration rate, secretion of renin, glomerular and tubular growth, tubular transport processes, and cell fate (Nasrallah 2005).

Evidence Source(s) and Strength of Evidence:

In the double-blind GRIPHON study, a numerically small imbalance in AEs of renal failure between selexipag and the placebo group was observed. These events were transient and reversible in nature, and the majority of renal events resolved while treatment with selexipag was maintained. The long-term safety data for renal function impairment / acute renal failure showed a decreasing trend in average annualized event rates.

In the TRITON study, about 10 out of every 100 patients (10%) who took selexipag had events of renal failure compared to 4 out of every 100 patients (4%) who took placebo. In the TRACE study, no patients who took selexipag had events of renal failure compared to about 2 out of every 100 patients (2%) who took placebo.

In the TRITON and GRIPHON studies, no numerical imbalance in estimated glomerular filtration rate <60 mL/min and overall mean increases in creatinine clearance from baseline to regular visits were observed in the selexipag or placebo groups, suggesting no overall detrimental effect of selexipag on renal function.

Close monitoring of such events continues for emerging data from clinical studies as well as in post-approval use.

Characterization of the Risk:

Randomized, double-blind studies

Table SVII.26: Important Potential Risk: Treatment-emergent Adverse Events of Renal Function Impairment / Acute Renal Failure in Randomized, Double-blind Studies

Indication	Trial Number	Incidence Rate, m/N (%)		Relative Risk (95%CI)	Annualized Event Rate (%), [person time (year)]	
		Selexipag	Placebo		Selexipag	Placebo
PAH	AC-065A302	33 / 574 (5.7%)	19 / 578 (3.3%)	1.749 (1.007 - 3.039)	0.0406 [936.4]	0.0251 [875.9]
PAH	NS-304/-02	0 / 33 (0)	1 / 10 (10.0%)	NA	0 [13.0]	0.5407 [3.7]
PAH	AC-065A308	12 / 119 (10.1%)	5 /120 (4.2%)	2.420 (0.880 - 6.658)	0.0628 [207.1]	0.0321 [186.9]
PAH	AC-065A404	0 / 53 (0)	1 / 55 (1.8%)	NA	0 [22.2]	0.0390 [25.7]

All selexipag studies

Table SVII.27: Important Potential Risk: Treatment-emergent Adverse Events of Renal Function Impairment / Acute Renal Failure in All Studies

Indication	Trial Number	Selexipag	
		Incidence Rate, m/N (%)	Annualized Event Rate (%), [person time (year)]
PAH	AC-065A302 + AC-065A303	72 / 953 (7.6%)	0.0277 [3315.4]
PAH	NS-304/-02 + NS-304/-03	3 / 41 (7.3%)	0.0158 [190.4]
PAH	AC-065A201	1 / 37 (2.7%)	0.0089 [111.8]
PAH	AC-065A304	0 / 34 (0)	0 [14.1]
PAH	AC-065A308	12 / 119 (10.1%)	0.0628 [207.1]
PAH	AC-065A404	0 / 53 (0)	0 [22.2]

Table SVII.28: Important Potential Risk: Treatment-emergent AESIs in Randomized, Double-blind Studies: Renal Function Impairment / Acute Renal Failure

	All Studies		AC-065A302		NS-304/-02		AC-065A308		AC-065A404	
	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo
Renal Function Impairment / Acute Renal Failure										
Analysis set: Safety set	779	763	574	578	33	10	119	120	53	55
Patients with at least one AESI	45 (5.8%)	26 (3.4%)	33 (5.7%)	19 (3.3%)	0	1 (10.0%)	12 (10.1%)	5 (4.2%)	0	1 (1.8%)
Serious	14 (1.8%)	9 (1.2%)	10 (1.7%)	7 (1.2%)	0	0	4 (3.4%)	2 (1.7%)	0	0
Leading to discontinuation	2 (0.3%)	2 (0.3%)	2 (0.3%)	2 (0.3%)	0	0	0	0	0	0
Fatal outcome	3 (0.4%)	3 (0.4%)	2 (0.3%)	3 (0.5%)	0	0	1 (0.8%)	0	0	0
Relative Risk	1.695	-	1.749	-	NA	-	2.420	-	NA	-
95% CI	(1.057 - 2.719)		(1.007 - 3.039)				(0.880 - 6.658)			
Number of recurrent AESI	51	31	38	22	0	2	13	6	0	1
Patient-years of observation	1178.69	1092.10	936.44	875.87	13.04	3.70	207.05	186.86	22.15	25.67
Average annualized event rate	0.0433	0.0284	0.0406	0.0251	0	0.5407	0.0628	0.0321	0	0.0390
Severity (worst)*										
Mild	13 (1.7%)	9 (1.2%)	11 (1.9%)	6 (1.0%)	0	0	2 (1.7%)	2 (1.7%)	0	1 (1.8%)
Moderate	20 (2.6%)	10 (1.3%)	14 (2.4%)	7 (1.2%)	0	1 (10.0%)	6 (5.0%)	2 (1.7%)	0	0
Severe	12 (1.5%)	6 (0.8%)	8 (1.4%)	5 (0.9%)	0	0	4 (3.4%)	1 (0.8%)	0	0
Missing	0	1 (0.1%)	0	1 (0.2%)	0	0	0	0	0	0

* The event experienced by the patient with the worst severity is used.
AEs are coded using MedDRA Version 22.0

Table SVII.29: Important Potential Risk: Treatment-emergent AESIs in Selexipag Treated Patients: Renal Function Impairment / Acute Renal Failure

	Selexipag Treated in Studies					
	All Selexipag	AC-065A302 and/or AC-065A303	NS-304/-02 and/or NS-304/-03	AC-065A304	AC-065A308	AC-065A404
Renal function impairment / acute renal failure						
Analysis set: Safety set	1200	953	41	34	119	53
Patients with at least one AESI	87 (7.3%)	72 (7.6%)	3 (7.3%)	0	12 (10.1%)	0
Serious	23 (1.9%)	18 (1.9%)	1 (2.4%)	0	4 (3.4%)	0
Leading to discontinuation	2 (0.2%)	2 (0.2%)	0	0	0	0
Fatal outcome	3 (0.3%)	2 (0.2%)	0	0	1 (0.8%)	0
Number of recurrent AESI	108	92	3	0	13	0
Patient-years of observation	3749.11	3315.43	190.40	14.07	207.05	22.15
Average annualized event rate	0.0288	0.0277	0.0158	0	0.0628	0
Severity (worst)*						
Mild	28 (2.3%)	26 (2.7%)	0	0	2 (1.7%)	0
Moderate	39 (3.3%)	31 (3.3%)	2 (4.9%)	0	6 (5.0%)	0
Severe	19 (1.6%)	14 (1.5%)	1 (2.4%)	0	4 (3.4%)	0
Missing	1 (0.1%)	1 (0.1%)	0	0	0	0

AC-065A303 (open label extension study of AC-065A302) was ongoing at the cut-off date.
* The event experienced by the patient with the worst severity is used.
AEs are coded using MedDRA Version 22.0

Table SVII.30: AESIs: Renal Function Impairment / Acute Renal Failure

	NS-304 N = 37 n (%)
Patients with at least one AESI	1 (2.7%)
Patients with at least one AESI leading to discontinuation	0
Patients with at least one serious AESI	0
Patients with at least one AESI with a fatal outcome	0
Number of recurrent AESIs	1
Patient-years of observation	111.81
Average annualized event rate	0.0089
Severity (worst) (b)	
Asymptomatic	0
Mild	1 (2.7%)
Moderate	0
Severe	0
Missing	0

MedDRA version 22.0 was used to classify the AESIs. (b) The subject is counted only once in the most severe event when (s)he has multiple events.

MedDRA Terms Used in Database Search:

Refer to Annex 7.3 for the list of MedDRA PTs for the risk of Renal function impairment/acute renal failure.

Post-marketing data sources

Cumulatively, since IBD up to 20 December 2020, 592 post-marketing cases describing renal function impairment / acute renal failure events have been received. The estimated cumulative post-marketing reporting rate is 2.8% (592 cases / 21,142 exposed patients).

Consistent with data from Study AC-065A302/GRIPHON and all other completed studies, the majority of these events were temporally associated with hemodynamic compromise due to PAH disease progression / right ventricular failure, or in association with other concurrent illnesses (eg, sepsis, hypovolemic shock) that can result in a transient effect on renal function as a secondary complication, or were attributed to other concomitant medications (ie, diuretics, digoxin) that can affect renal function.

Reported events of renal failure or renal function impairment are considered unlikely to be related to selexipag administration. The absence of an adverse effect of selexipag on renal function is supported by the short term and reversible nature of the majority of these events while selexipag treatment was continued. Renal function usually improved with improved cardiac function.

Risk Factors and Risk Groups:

General risk factors include hemodynamic decompensation in the context of PAH worsening, RHF, or other concurrent illnesses (eg, sepsis, hypovolemic shock) or as a complication in patients with pre-existing renal impairment.

Preventability:

Regular monitoring of renal functions as per standard medical care of each patient with acute heart failure or other concurrent illnesses leading to hemodynamic decompensation.

Impact on the Risk-Benefit Balance of the Product:

Taking into account the severity of the indication and high prevalence of associated renal function impairment in PAH patients, this potential risk does not have a medically relevant impact on the benefit-risk balance of the product.

Public Health Impact:

Impaired renal function is measurable, monitorable and treatable. Acute renal failure / renal impairment requires therapeutic intervention, hospitalization or dialysis. Measuring renal function in PAH patients during regular monitoring is recommended in the current *ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension* as part of the comprehensive evaluation for any evidence of clinical deterioration due to progression of PH (right ventricular dysfunction, right ventricular failure, and/or secondary organ dysfunction) or due to a concomitant illness (Galiè 2016).

Annex 1 MedDRA Term:

MedDRA PT: Renal impairment.

SVII.3.1.8. Important Potential Risk: Bleeding events

Potential Mechanisms:

Selexipag is a weak platelet aggregation inhibitor (in vitro experiment). In healthy participants, selexipag did not show any effects on PD and PK of warfarin. In healthy participants and PAH or chronic thromboembolic pulmonary hypertension patients, selexipag use was associated with a decrease in mean plasma vWF; however, no decrease in individual vWF below the lower limit of the normal range was observed, nor were associated hemorrhagic AEs of concern reported.

Evidence Source(s) and Strength of Evidence:

Known effects of other prostacyclins.

In the double-blind GRIPHON study, the overall proportions of patients with bleeding events in the selexipag and placebo groups were similar (approximately 17 out of 100 patients [17%]). The long-term safety data for bleeding events showed a decreasing trend in average annualized event rates. There was no indication of an increased bleeding risk upon long-term treatment with selexipag.

In the TRITON study, about 22 out of every 100 patients (22%) who took selexipag or placebo had bleeding events. In the TRACE study, about 13 out of every 100 patients (13%) who took selexipag or placebo had bleeding events.

As shown in in-vitro experiments, selexipag is a weak platelet aggregation inhibitor and close monitoring of such events continues for emerging data from clinical studies as well as in post-approval use.

Characterization of the Risk:

Randomized, double-blind studies

Table SVII.31: Important Potential Risk: Treatment-emergent Adverse Events of Bleeding Events in Randomized, Double-blind Studies

Indication	Trial Number	Incidence Rate, m/N (%)		Relative Risk (95%CI)	Annualized Event Rate (%), [person time (year)]	
		Selexipag	Placebo		Selexipag	Placebo
PAH	AC-065A302	95 / 574 (16.6%)	96 / 578 (16.6%)	0.996 (0.769 - 1.291)	0.1602 [936.4]	0.1530 [875.9]
PAH	NS-304/-02	3 / 33 (9.1%)	2 / 10 (20.0%)	0.455 (0.088 - 2.351)	0.2301 [13.0]	0.8111 [3.7]
PAH	AC-065A308	26 / 119 (21.8%)	27 /120 (22.5%)	0.971 (0.604 - 1.562)	0.2028 [207.1]	0.2034 [186.9]
PAH	AC-065A404	7 / 53 (13.2%)	7 / 55 (12.7%)	1.038 (0.391 - 2.758)	0.4062 [22.2]	0.3116 [25.7]

All selexipag studies

Table SVII.32: Important Potential Risk: Treatment-emergent Adverse Events of Bleeding Events in All Studies

Indication	Trial Number	Selexipag	
		Incidence Rate, m/N (%)	Annualized Event Rate (%), [person time (year)]
PAH	AC-065A302 + AC-065A303	196 / 953 (20.6%)	0.0995 [3315.4]
PAH	NS-304/-02 + NS-304/-03	14 / 41 (34.1%)	0.0945 [190.4]
PAH	AC-065A201	18 / 37 (48.6%)	0.3667 [111.8]
PAH	AC-065A304	4 / 34 (11.8%)	0.2842 [14.1]
PAH	AC-065A308	26 / 119 (21.8%)	0.2028 [207.1]
PAH	AC-065A404	7 / 53 (13.2%)	0.4062 [22.2]

Table SVII.33: Important Potential Risk: Treatment-emergent AESIs in Randomized, Double-blind Studies: Bleeding Events

	All Studies		AC-065A302		NS-304/-02		AC-065A308		AC-065A404	
	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo
Bleeding Events										
Analysis set: Safety set	779	763	574	578	33	10	119	120	53	55
Patients with at least one AESI	131 (16.8%)	132 (17.3%)	95 (16.6%)	96 (16.6%)	3 (9.1%)	2 (20.0%)	26 (21.8%)	27 (22.5%)	7 (13.2%)	7 (12.7%)
Serious	30 (3.9%)	27 (3.5%)	23 (4.0%)	22 (3.8%)	0	0	7 (5.9%)	5 (4.2%)	0	0
Leading to discontinuation	2 (0.3%)	5 (0.7%)	2 (0.3%)	4 (0.7%)	0	0	0	1 (0.8%)	0	0
Fatal outcome	2 (0.3%)	3 (0.4%)	2 (0.3%)	2 (0.3%)	0	0	0	1 (0.8%)	0	0
Relative Risk	0.972	-	0.996	-	0.455	-	0.971	-	1.038	-
95% CI	(0.780 - 1.211)		(0.769 - 1.291)		(0.088 - 2.351)		(0.604 - 1.562)		(0.391 - 2.758)	
Number of recurrent AESI	204	183	150	134	3	3	42	38	9	8
Patient-years of observation	1178.69	1092.10	936.44	875.87	13.04	3.70	207.05	186.86	22.15	25.67
Average annualized event rate	0.1731	0.1676	0.1602	0.1530	0.2301	0.8111	0.2028	0.2034	0.4062	0.3116
Severity (worst)*										
Mild	67 (8.6%)	70 (9.2%)	49 (8.5%)	46 (8.0%)	1 (3.0%)	1 (10.0%)	11 (9.2%)	18 (15.0%)	6 (11.3%)	5 (9.1%)
Moderate	45 (5.8%)	42 (5.5%)	31 (5.4%)	35 (6.1%)	2 (6.1%)	1 (10.0%)	11 (9.2%)	4 (3.3%)	1 (1.9%)	2 (3.6%)
Severe	19 (2.4%)	20 (2.6%)	15 (2.6%)	15 (2.6%)	0	0	4 (3.4%)	5 (4.2%)	0	0
Missing	0	0	0	0	0	0	0	0	0	0

* The event experienced by the patient with the worst severity is used.
AEs are coded using MedDRA Version 22.0

Table SVII.34: Important Potential Risk: Treatment-emergent AESIs in Selexipag Treated Patients: Bleeding Events

	Selexipag Treated in Studies					
	All Selexipag	AC-065A302 and/or AC-065A303	NS-304/-02 and/or NS-304/-03	AC-065A304	AC-065A308	AC-065A404
Bleeding Events						
Analysis set: Safety set	1200	953	41	34	119	53
Patients with at least one AESI	247 (20.6%)	196 (20.6%)	14 (34.1%)	4 (11.8%)	26 (21.8%)	7 (13.2%)
Serious	73 (6.1%)	61 (6.4%)	4 (9.8%)	1 (2.9%)	7 (5.9%)	0
Leading to discontinuation	6 (0.5%)	6 (0.6%)	0	0	0	0
Fatal outcome	10 (0.8%)	9 (0.9%)	1 (2.4%)	0	0	0
Number of recurrent AESI	403	330	18	4	42	9
Patient-years of observation	3749.11	3315.43	190.40	14.07	207.05	22.15
Average annualized event rate	0.1075	0.0995	0.0945	0.2842	0.2028	0.4062
Severity (worst)*						
Mild	109 (9.1%)	87 (9.1%)	3 (7.3%)	2 (5.9%)	11 (9.2%)	6 (11.3%)
Moderate	88 (7.3%)	67 (7.0%)	8 (19.5%)	1 (2.9%)	11 (9.2%)	1 (1.9%)
Severe	50 (4.2%)	42 (4.4%)	3 (7.3%)	1 (2.9%)	4 (3.4%)	0
Missing	0	0	0	0	0	0

AC-065A303 (open label extension study of AC-065A302) was ongoing at the cut-off date.
* The event experienced by the patient with the worst severity is used.
AEs are coded using MedDRA Version 22.0

Table SVII.35: AESIs: Bleeding Events

	NS-304 N = 37 n (%)
Patients with at least one AESI	18 (48.6%)
Patients with at least one AESI leading to discontinuation	0
Patients with at least one serious AESI	1 (2.7%)
Patients with at least one AESI with a fatal outcome	0
Number of recurrent AESIs	41
Patient-years of observation	111.81
Average annualized event rate	0.3667
Severity (worst) (b)	
Asymptomatic	3 (8.1%)
Mild	11 (29.7%)
Moderate	4 (10.8%)
Severe	0
Missing	0

MedDRA version 22.0 was used to classify the AESIs. (b) The subject is counted only once in the most severe event when (s)he has multiple events.

MedDRA Terms Used in Database Search:

Refer to Annex 7.3 for the list of MedDRA PTs for the risk of Bleeding events.

Post-marketing data sources

Cumulatively, since IBD up to 20 December 2020, 1,329 post-marketing cases containing bleeding events have been received; the estimated cumulative reporting rate is stable at 6.3% (1,329 cases / 21,142 exposed patients).

Consistent with data from Study AC-065A302/GRIPHON and all other completed studies, the post-marketing data sources showed that the majority of the bleeding events at various sites occurred in PAH patients with pre-existing risk factors, such as concomitant use of anticoagulants and antithrombotic agents, or occurred in a temporal association with underlying PAH disease progression / right ventricular failure, other concurrent illnesses (eg, gastritis, pre-existing vascular abnormalities in patients with CTD, infections), or in association with diagnostic or surgical procedures or injuries.

Risk Factors and Risk Groups:

Available data do not support any overall increased risk of bleeding with selexipag or any synergically increased risk of bleeding if selexipag is co-administered with anticoagulants or other antithrombotics. No specific risk factor has been identified to predict the occurrence of bleeding events in selexipag-treated patients.

Preventability:

As no specific risk factors other than the underlying PAH disease have been identified to date, no proposal for preventability is feasible.

Impact on the Risk-Benefit Balance of the Product:

Taking into account the severity of the indication and high prevalence of concomitant use of anticoagulant and antithrombotic medications in PAH patients, this potential risk does not have a medically relevant impact on the benefit-risk balance of the product.

Public Health Impact:

The public health impact depends on the nature and severity of the bleeding event that may require hospitalization, therapeutic or surgical intervention.

Annex 1 MedDRA Term:

MedDRA PT: Hemoptysis.

SVII.3.1.9. Important Potential Risk: Light-dependent non-melanoma skin malignancies

Potential Mechanisms:

No propensity of selexipag for the development of malignancies, including skin malignancies was observed in non-clinical carcinogenicity studies in animals. The observed clinical pattern and incidence of BCC in GRIPHON is consistent with the expected incidence in the general and connective tissue disease patient populations. There is currently no evidence of causal association between selexipag treatment and occurrence of light-dependent non-melanoma skin malignancies.

Evidence Source(s) and Strength of Evidence:

During the double-blind GRIPHON study, 4 patients aged >68 years in the selexipag group were diagnosed with BCC compared to none in the placebo group. Confounding factors were present in all cases (eg, immunosuppressant use, history of malignancy, or short duration of exposure). In GRIPHON OL, there was no indication of an increased risk of light-dependent non-melanoma skin malignancies associated with long-term selexipag treatment.

In the TRITON study, less than 1 out of every 100 patients (<1%) who took selexipag had skin malignancies compared to 2 out of every 100 patients (2%) who took placebo. In the TRACE study, no patients who took selexipag or placebo had skin malignancies.

Close monitoring of such events continues for emerging data from clinical studies as well as in post-approval use.

Characterization of the Risk:

Randomized, double-blind studies

Table SVII.36: Important Potential Risk: Treatment-emergent Adverse Events of Light-dependent Non-melanoma Skin Malignancies in Randomized, Double-blind Studies

Indication	Trial Number	Incidence Rate, m/N (%)		Relative Risk (95%CI)	Annualized Event Rate (%), [person time (year)]	
		Selexipag	Placebo		Selexipag	Placebo
PAH	AC-065A302	4 / 574 (0.7%)	0 / 578 (0)	NA	0.0075 [936.4]	0 [875.9]
PAH	NS-304/-02	0 / 33 (0)	0 / 10 (0)	NA	0 [13.0]	0 [3.7]
PAH	AC-065A308	1 / 119 (0.8%)	2 / 120 (1.7%)	0.504 (0.046 - 5.486)	0.0048 [207.1]	0.0107 [186.9]
PAH	AC-065A404	0 / 53 (0)	0 / 55 (0)	NA	0 [22.2]	0 [25.7]

All selexipag studies

Table SVII.37: Important Potential Risk: Treatment-emergent Adverse Events of Light-dependent Non-melanoma Skin Malignancies in All Studies

Indication	Trial Number	Selexipag	
		Incidence Rate, m/N (%)	Annualized Event Rate (%), [person time (year)]
PAH	AC-065A302 + AC-065A303	6 / 953 (0.6%)	0.0027 [3315.4]
PAH	NS-304/-02 + NS-304/-03	0 / 41 (0)	0 [190.4]
PAH	AC-065A201	1 / 37 (2.7%)	0.0089 [111.8]
PAH	AC-065A304	0 / 34 (0)	0 [14.1]
PAH	AC-065A308	1 / 119 (0.8%)	0.0048 [207.1]
PAH	AC-065A404	0 / 53 (0)	0 [22.2]

Table SVII.38: Important Potential Risk: Treatment-emergent AESIs in Randomized, Double-blind Studies: Light-dependent Non-melanoma Skin Malignancies

	All Studies		AC-065A302		NS-304/-02		AC-065A308		AC-065A404	
	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo
Light-dependent Non-melanoma Skin Malignancies										
Analysis set: Safety set	779	763	574	578	33	10	119	120	53	55
Patients with at least one AESI	5 (0.6%)	2 (0.3%)	4 (0.7%)	0	0	0	1 (0.8%)	2 (1.7%)	0	0
Serious	1 (0.1%)	0	1 (0.2%)	0	0	0	0	0	0	0
Leading to discontinuation	0	0	0	0	0	0	0	0	0	0
Fatal outcome	0	0	0	0	0	0	0	0	0	0
Relative Risk	2.449	-	NA	-	NA	-	0.504	-	NA	-
95% CI	(0.477 - 12.583)						(0.046 - 5.486)			
Number of recurrent AESI	8	2	7	0	0	0	1	2	0	0
Patient-years of observation	1178.69	1092.10	936.44	875.87	13.04	3.70	207.05	186.86	22.15	25.67
Average annualized event rate	0.0068	0.0018	0.0075	0	0	0	0.0048	0.0107	0	0
Severity (worst)*										
Mild	1 (0.1%)	1 (0.1%)	0	0	0	0	1 (0.8%)	1 (0.8%)	0	0
Moderate	3 (0.4%)	1 (0.1%)	3 (0.5%)	0	0	0	0	1 (0.8%)	0	0
Severe	1 (0.1%)	0	1 (0.2%)	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0	0	0

* The event experienced by the patient with the worst severity is used.
AEs are coded using MedDRA Version 22.0

Table SVII.39: Important Potential Risk: Treatment-emergent AESIs in Selexipag Treated Patients: Light-dependent Non-melanoma Skin Malignancies

	Selexipag Treated in Studies					
	All Selexipag	AC-065A302 and/or AC-065A303	NS-304/-02 and/or NS-304/-03	AC-065A304	AC-065A308	AC-065A404
Light-dependent Non-melanoma Skin Malignancies						
Analysis set: Safety set	1200	953	41	34	119	53
Patients with at least one AESI	7 (0.6%)	6 (0.6%)	0	0	1 (0.8%)	0
Serious	1 (0.1%)	1 (0.1%)	0	0	0	0
Leading to discontinuation	0	0	0	0	0	0
Fatal outcome	0	0	0	0	0	0
Number of recurrent AESI	10	9	0	0	1	0
Patient-years of observation	3749.11	3315.43	190.40	14.07	207.05	22.15
Average annualized event rate	0.0027	0.0027	0	0	0.0048	0
Severity (worst)*						
Mild	2 (0.2%)	1 (0.1%)	0	0	1 (0.8%)	0
Moderate	3 (0.3%)	3 (0.3%)	0	0	0	0
Severe	2 (0.2%)	2 (0.2%)	0	0	0	0
Missing	0	0	0	0	0	0

AC-065A303 (open label extension study of AC-065A302) was ongoing at the cut-off date.
* The event experienced by the patient with the worst severity is used.
AEs are coded using MedDRA Version 22.0

Table SVII.40: AESIs: Light-dependent Non-melanoma Skin Malignancies

	NS-304 N = 37 n (%)
Patients with at least one AESI	1 (2.7%)
Patients with at least one AESI leading to discontinuation	0
Patients with at least one serious AESI	0
Patients with at least one AESI with a fatal outcome	0
Number of recurrent AESIs	1
Patient-years of observation	111.81
Average annualized event rate	0.0089
Severity (worst) (b)	
Asymptomatic	0
Mild	1 (2.7%)
Moderate	0
Severe	0
Missing	0

MedDRA version 22.0 was used to classify the AESIs. (b) The subject is counted only once in the most severe event when (s)he has multiple events.

MedDRA Terms Used in Database Search:

Refer to Annex 7.3 for the list of MedDRA PTs for the risk of Light-dependent non-melanoma skin malignancies.

Post-marketing data sources

Cumulatively, since IBD up to 20 December 2020, 17 post-marketing reports including events denoting non-melanoma skin malignancies have been received. The incidence of reported skin malignancies appears consistent with the expected incidence in the general population, with an expected higher rate in patients with CTD compared to other PAH etiologies.

At present, there is no evidence that selexipag is associated with an increased risk of skin malignancies.

Risk Factors and Risk Groups:

PAH is known to be associated with autoimmune disease as the underlying cause of PAH or associated co-morbidity. Therefore, clinical management of these conditions frequently requires administration of medications with immunosuppressant effect.

In general, sunlight exposure is considered as a relevant susceptibility factor.

Preventability:

Regular skin check as per clinical practice.

Impact on the Risk-Benefit Balance of the Product:

Considering the severity of the indication, this potential risk does not have a medically relevant impact on the benefit-risk balance of the product.

Public Health Impact:

Intervention or hospitalization.

Annex 1 MedDRA Term:

MedDRA PT: Squamous cell carcinoma.

SVII.3.1.10. Important Potential Risk: Ophthalmological effects associated with retinal vascular system

Potential Mechanisms:

Retinal vessel tortuosity in rats is considered to reflect exaggerated PD resulting in continuous blood vessel dilatation for the whole lifespan. There is no evidence of retinal vascular abnormalities associated with selexipag treatment in humans.

Evidence Source(s) and Strength of Evidence:

Nonclinical findings of tortuosity and dilatation of retinal blood vessels in rats at the end of a 2-year carcinogenicity study (D-14.104).

During the double-blind GRIPHON study, there was no evidence of an increase in relevant adverse ocular effects in selexipag-treated patients compared to placebo-treated patients. In the AC-065A302/GRIPHON ophthalmology sub-study, no new post-baseline fundoscopy findings or worsening of pre-existing retinal arterial tortuosity were reported in the selexipag group (D-14.407).

The long-term safety data for ophthalmological events and events associated with the retinal vascular system showed a decreasing trend in average annualized event rates. The pattern and frequency of ophthalmological events and events associated with the retinal vascular system remained similar for long-term selexipag treatment as had been reported for the double-blind studies. There was no indication of any adverse effect of selexipag on retinal vasculature upon long-term treatment, and the non-clinical findings of retinal arteriolar tortuosity continue to be considered of limited clinical relevance.

In the TRITON study, about 5 out of every 100 patients (5%) who took selexipag had relevant adverse ocular effects compared to 7 out of every 100 patients (7%) who took placebo. In the TRACE study, no patients who took selexipag had relevant adverse ocular effects.

Characterization of the Risk:

Randomized, double-blind studies

Table SVII.41: Important Potential Risk: Treatment-emergent Adverse Events of Ophthalmological Effects Associated with Retinal Vascular System in Randomized, Double-blind Studies

Indication	Trial Number	Incidence Rate, m/N (%)		Relative Risk (95%CI)	Annualized Event Rate (%), [person time (year)]	
		Selexipag	Placebo		Selexipag	Placebo
PAH	AC-065A302	24 / 574 (4.2%)	15 / 578 (2.6%)	1.611 (0.854 - 3.039)	0.0299 [936.4]	0.0194 [875.9]
PAH	NS-304/-02	1 / 33 (3.0%)	0 / 10 (0)	NA	0.0767 [13.0]	0 [3.7]
PAH	AC-065A308	6 / 119 (5.0%)	8 / 120 (6.7%)	0.756 (0.271 - 2.114)	0.0386 [207.1]	0.0428 [186.9]
PAH	AC-065A404	0 / 53 (0)	2 / 55 (3.6%)	NA	0 [22.2]	0.0779 [25.7]

All selexipag studies

Table SVII.42: Important Potential Risk: Treatment-emergent Adverse Events of Ophthalmological Effects Associated with Retinal Vascular System in All Studies

Indication	Trial Number	Selexipag	
		Incidence Rate, m/N (%)	Annualized Event Rate (%), [person time (year)]
PAH	AC-065A302 + AC-065A303	37 / 953 (3.9%)	0.0124 [3315.4]
PAH	NS-304/-02 + NS-304/-03	1 / 41 (2.4%)	0.0053 [190.4]
PAH	AC-065A201	4 / 37 (10.8%)	0.0358 [111.8]
PAH	AC-065A304	2 / 34 (5.9%)	0.1421 [14.1]
PAH	AC-065A308	6 / 119 (5.0%)	0.0386 [207.1]
PAH	AC-065A404	0 / 53 (0)	0 [22.2]

Table SVII.43: Important Potential Risk: Treatment-emergent AESIs in Randomized, Double-blind Studies: Ophthalmological Effects Associated with Retinal Vascular System

	All Studies		AC-065A302		NS-304/-02		AC-065A308		AC-065A404	
	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo
Ophthalmological Effects Associated with Retinal Vascular System										
Analysis set: Safety set	779	763	574	578	33	10	119	120	53	55
Patients with at least one AESI	31 (4.0%)	25 (3.3%)	24 (4.2%)	15 (2.6%)	1 (3.0%)	0	6 (5.0%)	8 (6.7%)	0	2 (3.6%)
Serious	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0	1 (0.8%)	0	0	1 (1.8%)
Leading to discontinuation	1 (0.1%)	0	1 (0.2%)	0	0	0	0	0	0	0
Fatal outcome	0	0	0	0	0	0	0	0	0	0
Relative Risk	1.215	-	1.611	-	NA	-	0.756	-	NA	-
95% CI	(0.724 - 2.037)		(0.854 - 3.039)				(0.271 - 2.114)			
Number of recurrent AESI	37	27	28	17	1	0	8	8	0	2
Patient-years of observation	1178.69	1092.10	936.44	875.87	13.04	3.70	207.05	186.86	22.15	25.67
Average annualized event rate	0.0314	0.0247	0.0299	0.0194	0.0767	0	0.0386	0.0428	0	0.0779
Severity (worst)*										
Mild	19 (2.4%)	17 (2.2%)	15 (2.6%)	9 (1.6%)	0	0	4 (3.4%)	7 (5.8%)	0	1 (1.8%)
Moderate	9 (1.2%)	8 (1.0%)	7 (1.2%)	6 (1.0%)	1 (3.0%)	0	1 (0.8%)	1 (0.8%)	0	1 (1.8%)
Severe	2 (0.3%)	0	1 (0.2%)	0	0	0	1 (0.8%)	0	0	0
Missing	1 (0.1%)	0	1 (0.2%)	0	0	0	0	0	0	0

* The event experienced by the patient with the worst severity is used.
AEs are coded using MedDRA Version 22.0

Table SVII.44: Important Potential Risk: Treatment-emergent AESIs in Selexipag Treated Patients: Ophthalmological Effects Associated with Retinal Vascular System

	Selexipag Treated in Studies					
	All Selexipag	AC-065A302 and/or AC-065A303	NS-304/-02 and/or NS-304/-03	AC-065A304	AC-065A308	AC-065A404
Ophthalmological Effects Associated with Retinal Vascular System						
Analysis set: Safety set	1200	953	41	34	119	53
Patients with at least one AESI	46 (3.8%)	37 (3.9%)	1 (2.4%)	2 (5.9%)	6 (5.0%)	0
Serious	4 (0.3%)	3 (0.3%)	0	0	1 (0.8%)	0
Leading to discontinuation	1 (0.1%)	1 (0.1%)	0	0	0	0
Fatal outcome	0	0	0	0	0	0
Number of recurrent AESI	52	41	1	2	8	0
Patient-years of observation	3749.11	3315.43	190.40	14.07	207.05	22.15
Average annualized event rate	0.0139	0.0124	0.0053	0.1421	0.0386	0
Severity (worst)*						
Mild	29 (2.4%)	23 (2.4%)	0	2 (5.9%)	4 (3.4%)	0
Moderate	13 (1.1%)	11 (1.2%)	1 (2.4%)	0	1 (0.8%)	0
Severe	3 (0.3%)	2 (0.2%)	0	0	1 (0.8%)	0
Missing	1 (0.1%)	1 (0.1%)	0	0	0	0

AC-065A303 (open label extension study of AC-065A302) was ongoing at the cut-off date.
* The event experienced by the patient with the worst severity is used.
AEs are coded using MedDRA Version 22.0

Table SVII.45: AESIs: Ophthalmological Effects Associated with Retinal Vascular System

	NS-304 N = 37 n (%)
Patients with at least one AESI	4 (10.8%)
Patients with at least one AESI leading to discontinuation	0
Patients with at least one serious AESI	0
Patients with at least one AESI with a fatal outcome	0
Number of recurrent AESIs	4
Patient-years of observation	111.81
Average annualized event rate	0.0358
Severity (worst) (b)	
Asymptomatic	0
Mild	3 (8.1%)
Moderate	1 (2.7%)
Severe	0
Missing	0

MedDRA version 22.0 was used to classify the AESIs. (b) The subject is counted only once in the most severe event when (s)he has multiple events.

MedDRA Terms Used in Database Search:

Refer to Annex 7.3 for the list of MedDRA PTs for the risk of Ophthalmological effects associated with retinal vascular system.

Post-marketing data sources

Cumulatively, since IBD up to 20 December 2020, 440 post-marketing cases containing events under the 'Retinal disorders' SMQ (broad search) have been received. There were 40 post-marketing cases identified using the 'Retinal disorders' SMQ (narrow scope). None of these events were confirmed to be associated with retinal arterial tortuosity.

At present, there is no evidence that selexipag is associated with the occurrence of ophthalmological effects associated with the retinal vascular system.

Risk Factors and Risk Groups:

The findings of tortuosity and dilation of retinal arterioles in rats were considered by the independent experts in ophthalmology to be animal species-specific and of limited clinical relevance. Therefore, no particular risk group can be determined.

Preventability:

Not applicable.

Impact on the Risk-Benefit Balance of the Product:

Considering the severity of the indication, this potential risk does not have a medically relevant impact on the benefit-risk balance of the product.

Public Health Impact:

More severe cases of symptomatic retinal vascular abnormality may require therapeutic and/or surgical intervention, and/or modification in the concomitant treatment (eg, anticoagulants).

Annex 1 MedDRA Term:

MedDRA PT: Retinal vascular disorder.

SVII.3.1.11. Important Potential Risk: GI disturbances denoting intestinal intussusception (manifested as ileus or obstruction)

Potential Mechanisms:

Intestinal intussusception was identified in young dogs, but not in rodents. This can be ascribed to IP-mediated effects on intestinal motility in a sensitive species at a particularly sensitive age; therefore, it is unlikely to be of relevance to the adult target population. Due to the known susceptibility of young dogs to develop intussusception and the safety margin of 2-fold (ie, corrected for potency; at 180-fold based on total exposure) for the active metabolite, the finding is considered as not relevant for adult humans.

Evidence Source(s) and Strength of Evidence:

In pre-clinical studies, intestinal intussusception upon selexipag treatment was identified in young dogs, but not in rodents. Because of the species-specific sensitivity of dogs to develop intussusception and the safety margin, this finding is considered not relevant for adult humans.

In the double-blind GRIPHON study, less than 1 out of every 100 patients (<1%) who took selexipag or placebo had GI disturbances denoting intestinal intussusception. The long-term safety data for GI disturbances denoting intestinal intussusception showed a decreasing trend in average annualized event rates. There was no evidence of a causal association between these events and selexipag administration in participants treated with selexipag in clinical studies. In the TRITON study, less than 1 out of every 100 patients (<1%) who took selexipag had GI disturbances denoting intestinal intussusception compared to no patients who took placebo. In the TRACE study, no patients who took selexipag or placebo had GI disturbances denoting intestinal intussusception.

Characterization of the Risk:

Randomized, double-blind studies

Table SVII.46: Important Potential Risk: Treatment-emergent Adverse Events of GI Disturbances Denoting Intestinal Intussusception in Randomized, Double-blind Studies

Indication	Trial Number	Incidence Rate, m/N (%)		Relative Risk (95%CI)	Annualized Event Rate (%) [person time (year)]	
		Selexipag	Placebo		Selexipag	Placebo
PAH	AC-065A302	1 / 574 (0.2%)	1 / 578 (0.2%)	1.007 (0.063 - 16.060)	0.0011 [936.4]	0.0023 [875.9]
PAH	NS-304/-02	0 / 33 (0)	0 / 10 (0)	NA	0 [13.0]	0 [3.7]
PAH	AC-065A308	1 / 119 (0.8%)	0 / 120 (0)	NA	0.0097 [207.1]	0 [186.9]
PAH	AC-065A404	0 / 53 (0)	0 / 55 (0)	NA	0 [22.2]	0 [25.7]

All selexipag studies

Table SVII.47: Important Potential Risk: Treatment-emergent Adverse Events of GI Disturbances Denoting Intestinal Intussusception in All Studies

Indication	Trial Number	Selexipag	
		Incidence Rate, m/N (%)	Annualized Event Rate (%) [person time (year)]
PAH	AC-065A302 + AC-065A303	3 / 953 (0.3%)	0.0009 [3315.4]
PAH	NS-304/-02 + NS-304/-03	0 / 41 (0)	0 [190.4]
PAH	AC-065A201	0 / 37 (0)	0 [111.8]
PAH	AC-065A304	0 / 34 (0)	0 [14.1]
PAH	AC-065A308	1 / 119 (0.8%)	0.0097 [207.1]
PAH	AC-065A404	0 / 53 (0)	0 [22.2]

Table SVII.48: Important Potential Risk: Treatment-emergent AESIs in Randomized, Double-blind Studies: GI Disturbances Denoting Intestinal Intussusception (Manifested as Ileus or Obstruction)

	All Studies		AC-065A302		NS-304/-02		AC-065A308		AC-065A404	
	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo
GI Disturbances Denoting Intestinal Intussusception (Manifested as Ileus or Obstruction)										
Analysis set: Safety set	779	763	574	578	33	10	119	120	53	55
Patients with at least one AESI	2 (0.3%)	1 (0.1%)	1 (0.2%)	1 (0.2%)	0	0	1 (0.8%)	0	0	0
Serious	2 (0.3%)	1 (0.1%)	1 (0.2%)	1 (0.2%)	0	0	1 (0.8%)	0	0	0
Leading to discontinuation	0	0	0	0	0	0	0	0	0	0
Fatal outcome	0	0	0	0	0	0	0	0	0	0
Relative Risk	1.959	-	1.007	-	NA	-	NA	-	NA	-
95% CI	(0.178 - 21.559)		(0.063 - 16.060)							
Number of recurrent AESI	3	2	1	2	0	0	2	0	0	0
Patient-years of observation	1178.69	1092.10	936.44	875.87	13.04	3.70	207.05	186.86	22.15	25.67
Average annualized event rate	0.0025	0.0018	0.0011	0.0023	0	0	0.0097	0	0	0
Severity (worst)*										
Mild	0	0	0	0	0	0	0	0	0	0
Moderate	0	0	0	0	0	0	0	0	0	0
Severe	2 (0.3%)	1 (0.1%)	1 (0.2%)	1 (0.2%)	0	0	1 (0.8%)	0	0	0
Missing	0	0	0	0	0	0	0	0	0	0

* The event experienced by the patient with the worst severity is used.
AEs are coded using MedDRA Version 22.0

Table SVII.49: Important Potential Risk: Treatment-emergent AESIs in Selexipag Treated Patients: GI Disturbances Denoting Intestinal Intussusception (Manifested as Ileus or Obstruction)

	Selexipag Treated in Studies					
	All Selexipag	AC-065A302 and/or AC-065A303	NS-304/-02 and/or NS-304/-03	AC-065A304	AC-065A308	AC-065A404
GI Disturbances Denoting Intestinal Intussusception (Manifested as Ileus or Obstruction)						
Analysis set: Safety set	1200	953	41	34	119	53
Patients with at least one AESI	4 (0.3%)	3 (0.3%)	0	0	1 (0.8%)	0
Serious	3 (0.3%)	2 (0.2%)	0	0	1 (0.8%)	0
Leading to discontinuation	0	0	0	0	0	0
Fatal outcome	0	0	0	0	0	0
Number of recurrent AESI	5	3	0	0	2	0
Patient-years of observation	3749.11	3315.43	190.40	14.07	207.05	22.15
Average annualized event rate	0.0013	0.0009	0	0	0.0097	0
Severity (worst)*						
Mild	1 (0.1%)	1 (0.1%)	0	0	0	0
Moderate	0	0	0	0	0	0
Severe	3 (0.3%)	2 (0.2%)	0	0	1 (0.8%)	0
Missing	0	0	0	0	0	0

AC-065A303 (open label extension study of AC-065A302) was ongoing at the cut-off date.
* The event experienced by the patient with the worst severity is used.
AEs are coded using MedDRA Version 22.0

Table SVII.50: AESIs: GI Disturbances Denoting Intestinal Intussusception (Manifested as Ileus or Obstruction)

	NS-304 N = 37 n (%)
No patient observed	

MedDRA version 22.0 was used to classify the AESIs.

MedDRA Terms Used in Database Search:

Refer to Annex 7.3 for the list of MedDRA PTs for the risk of GI disturbances denoting intestinal intussusception (manifested as ileus or obstruction).

Post-marketing data sources

Cumulatively, since IBD up to 20 December 2020, 72 post-marketing cases including 1 or more GI disturbances suggestive of intestinal obstruction have been reported. Overall, 3 cases involved the PT Intestinal intussusception: (1) One elderly patient was diagnosed with appendix cancer; the event was assessed as not related by the reporter. (2) One case referred to an adult patient with ulcerative colitis who experienced intestinal intussusception after starting selexipag, with no causality assessment reported. (3) The 3rd case pertained to a patient diagnosed with diffuse large B-cell lymphoma 1.5 years after selexipag initiation who 1 year later experienced bilateral pneumonia, abdominal pain and developed life-threatening invagination of intestine. The reporter assessed these events as not related to selexipag and possibly associated with intestinal lesions due to diffuse large B-cell lymphoma. The remaining 69 cases pertained to other relevant comorbidities known to be associated with GI obstruction, such as partial colectomy, intestinal resection, gallstone ileus, diverticulitis; intestinal polyps, *Clostridium difficile* infection, or a medical history of connective tissue disease or scleroderma.

Risk Factors and Risk Groups:

Patients with PAH associated with systemic scleroderma represent patients at particular risk of GI motility disorder in the adult patient population.

In infants and young children, intussusception is the most common cause of intestinal obstruction. Available epidemiological data show that 75% to 90% of cases arise before 2 years of age (Waseem 2008, Stringer 1992). The peak incidence is between 5 and 9 months of age and then starts to decline (Newman 1987).

Preventability:

As no specific risk factors other than the underlying PAH disease associated with SSc have been identified to date, no proposal for preventability is feasible. In the current PIP, a waiver was granted for children from birth to less than 2 years (EMEA 000997 PIP01 10-M02).

See UPTRAVI SmPC, section 4.2:

"*Pediatric population*

The safety and efficacy of selexipag in children aged 0 to less than 18 years have not yet been established. No data are available. Administration of selexipag in the pediatric population is not recommended. Animal studies indicated an increased risk of intussusception, but the clinical relevance of these findings is unknown (see section 5.3)."

Impact on the Risk-Benefit Balance of the Product:

Taking into account the severity of the indication, this potential risk does not have a medically relevant impact on the benefit-risk balance of the product.

Public Health Impact:

Occurrence of intestinal obstruction requires prompt therapeutic and/or surgical intervention.

Annex 1 MedDRA Term:

MedDRA PT: Intussusception.

SVII.3.1.12. Important Potential Risk: Medication error

Potential Mechanisms:

Selexipag is available only on prescription. A total of 9 dosage strengths (100, 200, 400, 600, 800, 1000, 1200, 1400, and 1600 µg film-coated tablets) are available.

Evidence Source(s) and Strength of Evidence:

As compared to controlled clinical trials in adult patients, where only selexipag 200 µg tablets were administered, a total of 9 dosage strengths (100, 200, 400, 600, 800, 1000, 1200, 1400, and 1600 µg film-coated tablets) are available on the market. Data regarding instructions on recommended daily dosing, titration and transition to maintenance dose are given in the respective national UPTRAVI product labelling documents and further educational materials provided to patients and HCPs. Information regarding medication errors during selexipag initial titration and transition to maintenance dose is therefore only collected from post-approval use.

Characterization of the Risk:

Selexipag is available in 9 dosage strengths (100, 200, 400, 600, 800, 1000, 1200, 1400, and 1600 µg film-coated tablets), and the commercial presentations for UPTRAVI include the following: one titration pack of 140 tablets (200 µg) , one titration pack of 140 tablets (100 µg) for adult patients concomitantly treated with moderate CYP2C8 inhibitors or with moderate hepatic impairment, one pack of 10 tablets (200 µg), and 9 different packs of 60 tablets each (100, 200, 400, 600, 800, 1000, 1200, 1400, 1600 µg).

Starting patients on UPTRAVI involves dose titration, according to tolerability, to reach the individually appropriate dose for each patient.

General Population

For the general population, the recommended starting dose of UPTRAVI is 200 µg bid, approximately 12 hours apart. The dose is increased in increments of 200 µg bid, usually at weekly intervals until adverse pharmacological effects that cannot be tolerated or medically managed are experienced or until a maximum dose of 1600 µg bid is reached. If a patient reaches a dose that cannot be tolerated, the dose should be reduced to the previous dose level (down-titration).

To aid the titration stage, UPTRAVI 200 µg bid film-coated tablets are used for up-titration to a dose of 800 µg bid. If a patient reaches a dose above 800 µg bid during the titration period, UPTRAVI 200 µg film-coated tablets together with one UPTRAVI 800 µg film-coated tablet should be used.

Once the maintenance dose is achieved, an equivalent single-tablet strength for the individualized maintenance dose can be prescribed (200-1600 µg tablets available). This allows the patient to take one tablet in the morning and one in the evening.

In clinical practice, the administration of multiple units (eg, tablets) required to achieve a single dose may be associated with dosing errors because of users making miscalculations or forgetting how many units have already been administered. For patients reaching doses of 300, 500 or 700 µg bid, the individualized maintenance dose will require prescription of two tablet strengths.

Patients concomitantly treated with moderate CYP2C8 inhibitors and patients with moderate hepatic impairment requiring a 50% reduction in the daily dose of selexipag

When co-administered with moderate CYP2C8 inhibitors, the total daily dose of selexipag is reduced by half. This can be achieved by either administering half the dose of selexipag bid or reducing the dosing frequency of selexipag to qd (SmPC section 4.2). The dosing frequency is based on the physician's choice.

For patients with moderate hepatic impairment (Child-Pugh class B), the starting dose of treatment should be 100 µg bid or 200 µg qd and increased at weekly intervals by increments of 100 µg bid or 200 µg qd until adverse reactions, reflecting the mode of action of selexipag, that cannot be tolerated or medically managed are experienced (SmPC section 4.2). The starting dose (100 µg bid or 200 µg qd) is based on physician choice.

MedDRA Terms Used in Database Search:

Refer to Annex 7.3 for the list of MedDRA PTs for the risk of Medication error associated with selexipag tablets.

Post-marketing data sources

Cumulatively, since IBD up to 20 December 2020, 2,005 post-marketing cases containing events denoting medication errors have been received from worldwide sources. Of these, 162 cases originated from EEA.

In 134 out of 162 cases reported from EEA, the reported medication error referred to a single occasion of accidental error, such as drug dose omission, extra dose, wrong technique in product usage process, wrong strength and/or voluntary/intentional change in selexipag dose or dosing regimen, accidental overdose or unspecified incorrect dose/dosage, inappropriate schedule of product administration, product prescribing error, also commonly seen with other medications without an initial up-titration process.

Twenty-eight out of 162 cases reported events denoting medication errors which reportedly occurred during selexipag initiation, titration and transition to maintenance dose. Nine cases referred to medication errors associated with selexipag titration and 19 cases referred to voluntary/intentional change in selexipag dose or dosing scheme modifications during titration phase that were reported as medication errors.

Analysis of cases of medication errors suggestive of selexipag titration errors did not indicate any trend for a specific systematic medication error during the selexipag initial titration phase. If associated AEs were reported, they mostly referred to non-serious well known ADRs with selexipag which also commonly occur in patients following initial up-titration scheme as described in the SmPC. No unanticipated pattern of medication error or AEs was identified.

Taking into account the estimated cumulative exposure since approval/launch in the EEA the estimated cumulative reporting rate of medication errors during selexipag initiation, titration and transition to maintenance dose was at 0.19% (9 cases/ 4,815 exposed patients).

Risk Factors and Risk Groups:

Patients during initial selexipag up-titration phase.

Preventability:

Treatment with selexipag should only be initiated by a certified physician experienced in the treatment of PAH and familiar with educational materials included in the Prescriber Kit.

Clear instructions on recommended daily dosing, titration and transition to maintenance dose are given in the respective national UPTRAVI product labelling documents and corresponding patient information leaflets. In addition, further educational materials are provided to patients and HCPs.

In the EU/EEA, as documented in Annex 6, all HCPs identified via a Controlled Access System (implemented nationally) who intend to prescribe and/or dispense selexipag are provided with educational material in a Prescriber Kit containing the following:

- Cover letter to the HCP.

- The SmPC.
- An HCP A4 laminated titration guide for the physician specifically describing treatment initiation and titration with a selexipag starting dose of 100 µg bid.
- An HCP A4 laminated titration guide for the physician specifically describing treatment initiation and titration with a selexipag starting dose of 200 µg bid.
- Patient Titration Guide included in the titration pack of the 100 µg tablets.
- Patient Titration Guide included in the titration pack of the 200 µg tablets.
- Package leaflet.

Impact on the Risk-Benefit Balance of the Product:

This potential risk does not have a medically relevant impact on the benefit-risk balance of the product.

Public Health Impact:

If a medication error is detected, correction and treatment adjustment may need to be performed.

At present, routine and additional risk minimization measures in place clearly and extensively educate HCPs as well as patients and appropriately address its purpose to minimize the occurrence of medication errors during initial selexipag up-titration or transition to individual maximum tolerated maintenance dose in the clinical practice.

A Category 3 PASS (EDUCATE) with the objective of evaluating medication error risk minimization measures during the selexipag titration phase is ongoing (see Part III.2.). The objectives in the current EDUCATE PASS protocol address the concepts of the educational materials for treatment initiation using 200 µg. These objectives are also considered applicable to the 100 µg selexipag tablets because the additional risk minimization measures are replicated for treatment initiation with the 100 µg selexipag tablets. Therefore, no modifications to the EDUCATE PASS are deemed necessary.

Furthermore, following introduction of the 100 µg selexipag tablet, the MAH will continue to provide dedicated analyses on all cases of medication error in the upcoming PBRERs, including information on the selexipag starting dose (100 µg or 200 µg), if available.

Annex 1 MedDRA Term:

MedDRA PT: Drug titration error.

SVII.3.2. Presentation of the Missing Information

Missing Information: Use in pediatric patients

Evidence Source: Based on current medical practice and due to the lack of registered treatments for pediatric PAH as well as the high medical need (Abman 2015, Hansmann 2016, Hansmann 2017), it is not uncommon for treating physicians to prescribe pediatric patients drugs approved in adult PAH.

Cumulatively, since IBD up to 20 December 2020, 514 post-marketing cases have been received for children.

Consistent with the adult and elderly patient population, the most frequently reported AEs in pediatric patients were those reflecting the mode of action of selexipag, and typically occurred during the initial selexipag dose titration. The nature of the reported events in pediatric patients was similar to other age groups, and consistent with expected events in patients with PAH and its associated comorbidities.

Population in Need of Further Characterization: Pediatric patients under the age of 18 years. In the current PIP, a waiver was granted for children from birth to less than 2 years (EMEA 000997 PIP01 10-M02).

Anticipated Risk/Consequence of the Missing Information: To date, no safety concern has been identified from the review of selexipag use in this patient population. There is no evidence that the safety profile of selexipag is expected to be different from that in the general (adult) target population.

To date, no safety concern has been identified from the review of selexipag use in this patient population.

Missing Information: Use in elderly patients over 75 years old

Evidence Source: In the pivotal Phase 3 AC-065A302/GRIPHON study, 99 elderly patients were treated with selexipag and 107 with placebo. Of the 99 patients on selexipag, 91 were aged between 65 and 74 years, and 8 patients were ≥75 years old (range 75–80 years).

In the TRITON study, 27 (22.0%) and 26 (21.0%) participants in the selexipag and placebo groups, respectively, were ≥65 years-of-age. No patients were >75 years old (range 21-75 years). In the TRACE study, 11 (20.8%) and 12 (21.8%) participants in the selexipag and placebo groups, respectively, were ≥65 years-of-age. No patients were >75 years old (range 19-75 years).

No patients >80 years were exposed to selexipag during the clinical development programme.

There is no clinically relevant effect of age on the PK of selexipag and its active metabolite in healthy participants or PAH patients. Therefore, no adjustment to the dosing regimen is needed in elderly patients. No important differences regarding efficacy or safety were observed between elderly and non-elderly patients.

Cumulatively, since IBD up to 20 December 2020, 3339 post-marketing cases have been received for patients aged ≥75 years.

Cumulative safety information pertaining to patients aged ≥75 years showed that the nature and pattern of reported events were comparable between patients aged ≥18 to <75 years and those aged ≥75 years. As expected, the majority of AEs reflected the mode of action of selexipag, ie, known prostacyclin-like reactions typically occurring during initial dose titration, and symptoms of the underlying PAH disease.

Population in Need of Further Characterization: Patients >75 years old.

Anticipated Risk/Consequence of the Missing Information: There is no evidence that the safety profile of selexipag is expected to be different than that in the general (adult) target population. To date, no safety concern has been identified from the review of selexipag use in this patient population.

Missing Information: Use during pregnancy and lactation

Evidence Source: Pregnant or breast-feeding women were excluded from the clinical trials with selexipag.

As described in the current ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension, pregnancy is associated with a very high risk to mother and fetus, and should be discouraged. Effective contraception is considered mandatory (Galiè 2016).

Per UPTRAVI SmPC, section 4.6 'Fertility, pregnancy and lactation':

"Women of Childbearing Potential

Women of childbearing potential should practice effective contraception while taking selexipag (see section 4.4).

Pregnancy

There are no data from the use of selexipag in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Selexipag and its main metabolite showed 20- to 80-times lower IP receptor potency *in vitro* for animal species used in reproductive toxicity testing compared to humans. Therefore, safety margins for potential IP receptor-mediated effects on reproduction are accordingly lower than for non-IP-related effects (see section 5.3).

UPTRAVI is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

It is unknown whether selexipag or its metabolites are excreted in human milk. In rats, selexipag or its metabolites are excreted in milk (see section 5.3). A risk to the suckling child cannot be excluded. UPTRAVI should not be used during breast-feeding."

Cumulatively, since IBD (21 December 2015) and up to the data cut-off point for the most recent PBRER/PSUR (20 December 2020), 46 confirmed pregnancies in selexipag-treated patients have been reported, including 11 from interventional clinical trials, 17 from noninterventional solicited clinical studies, and 18 from spontaneous source (1 spontaneous case was from a literature source). Drug exposure was during the first trimester in 22 cases; selexipag was started 6 weeks prior to birth in 1 case; time of exposure was unknown in 19 cases; and pregnancy was confirmed after selexipag discontinuation in 4 cases.

To date, 15 pregnant patients gave birth. Of these, 1 case reported live birth of a term baby, 3 cases reported live births with gestational age not reported and the remaining 11 cases reported live births of premature neonates. Eleven patients gave birth via Caesarean section: 8 babies were premature, born at Week 26 (1 case), Week 28 (1 case), Week 31 (2 cases), Week 33, Week 35, probably Week 36, and Week 36+3 days of gestation; 1 baby was born at Week 37; and gestational age was not reported for 2 babies.

Three of the prematurely born babies had respiratory distress syndrome and foetal distress syndrome: 1 baby (born at Week 35) required continuous positive airway pressure and had secundum atrial septal defect seen on neonatal echocardiogram; however, the baby was "doing well" at 10 weeks of age. One baby (born at Week 31) was admitted to a neonatal intensive care unit with neonatal respiratory distress syndrome, requiring positive pressure ventilation due to cyanosis, then continuous positive airway pressure and doses of surfactant. The remaining baby case (born at Week 28) reported that the mother was admitted to the hospital as the baby was in distress; the baby was a female with a birth weight of 815 grams, Apgar scores were not provided, and the mother died after birth.

There were no neonatal abnormalities reported for the remaining babies.

Eighteen pregnancies had an outcome of abortion (10 induced abortions, 8 spontaneous/missed abortions), ongoing pregnancy was reported in 10 cases, 1 pregnancy was lost to follow-up in a patient

who died, 1 case of pregnancy had an unknown outcome, 1 case reported ectopic pregnancy.

No safety concern has been identified from the review of data referring to patients who became pregnant while being treated with selexipag.

To date, no reports of selexipag use during lactation have been received.

Population in Need of Further Characterization: Pregnant and lactating women.

Anticipated Risk/Consequence of the Missing Information: To date, no safety concern has been identified from the review of selexipag use in this patient population. Studies in animals do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

Missing Information: Concomitant use with strong inhibitors of UGT1A3 and UGT2B7

Evidence Source: Based on non-clinical data, CYP2C8 and CYP3A4 were considered to be involved in the metabolism of both selexipag and its active metabolite, ACT-333679. CYP2C8 was identified as the only CYP isoform catalyzing the aromatic hydroxylation of ACT 333679 to P10, one of the major metabolites detected in human feces and in vitro with human liver microsomes. UGT1A3 and UGT2B7 are involved in the glucuronidation of the active metabolite.

The effect of inhibitors of UGT1A3 and UGT2B7 (such as valproic acid, probenecid, and fluconazole) on exposure to selexipag or its active metabolite has not been studied.

Cumulatively, since IBD up to 20 December 2020, 51 cases with concomitant use of UGT1A3 and UGT2B7 inhibitors, ie, fluconazole (19 cases), valproate/valpromide (28 cases), valproic acid (2 cases) or probenecid (2 cases) were reported.

To date, no safety concern has been identified from the review of data referring to selexipag patients concomitantly treated with inhibitors of UGT1A3 and UGT2B7.

Population in Need of Further Characterization: Patients treated with inhibitors of UGT1A3 and UGT2B7 (such as valproic acid, probenecid and fluconazole).

PART II: SAFETY SPECIFICATION

Module SVIII: Summary of the Safety Concerns

Table SVIII.1: Summary of Safety Concerns

Important Identified Risks	Hypotension
	Anemia
	Hyperthyroidism
	Concomitant use with strong inhibitors of CYP2C8
Important Potential Risks	Pulmonary edema associated with PVOD
	MACE
	Renal functional impairment / acute renal failure
	Bleeding events
	Light-dependent non-melanoma skin malignancies
	Ophthalmological effects associated with retinal vascular system
	GI disturbances denoting intestinal intussusception (manifested as ileus or obstruction)
	Medication error
Missing Information	Use in pediatric patients
	Use in elderly over 75 years old
	Use during pregnancy and lactation
	Concomitant use with strong inhibitors of UGT1A3 and UGT2B7

PART III: PHARMACOVIGILANCE PLAN (Including Postauthorization Safety Studies)

III.1. Routine Pharmacovigilance Activities Beyond Adverse Reaction Reporting and Signal Detection

Specific Follow-up Questionnaires for Safety Concerns	
Safety Concern	Purpose/Description
Not applicable	

Other Forms of Routine Pharmacovigilance Activities		
Activity	Objective/Description	Milestones
Not applicable		

III.2. Additional Pharmacovigilance Activities

Additional Pharmacovigilance Activities	
Study	
Study name and title	**AC-065A401 EXPOSURE: EXPloratory Observational Study of Uptravi in Real-lifE** PASS: observational cohort study of PAH patients newly treated with either UPTRAVI® (selexipag) or any other PAH-specific therapy, in clinical practice.
Rationale and study objectives	To further characterize the safety profile in PAH patients treated with UPTRAVI in routine clinical practice; including additional experience of the use of UPTRAVI in patients over the age of 75 years; and to compare mortality and MACE rates with PAH patients not treated with UPTRAVI.
Safety concern(s) addressed	The safety concerns addressed are: • Hypotension • Anemia • Hyperthyroidism • Pulmonary edema associated with PVOD • MACE • Renal function impairment / acute renal failure • Bleeding events • Light-dependent non-melanoma skin malignancies • Ophthalmological effects associated with retinal vascular system • GI disturbances denoting intestinal intussusception (manifested as ileus or obstruction) • Use in elderly over 75 years old

Additional Pharmacovigilance Activities	
Study design	This is a multicenter, prospective, real-world, observational cohort study.
Study population	The cohort study includes patients with PAH who either initiated treatment with UPTRAVI less than 1 month prior to enrolment, at enrolment, or during observation, or initiated any other PAH-specific therapy less than 1 month prior to enrolment or at enrolment and who were never treated with UPTRAVI.
Milestones	• Seq0078\m1\eu\18-pharmacovigilance\182-riskmgt-system • Start of data collection: 2017 • Registration in the EU PAS register (ENCePP): 2017 • Regular updates for mortality data in selexipag cohort: Reporting within the PBRERs • Annual updates: Progress reports on enrolment and intermediate analysis results will be provided yearly • Submission of combined final report of study results from EXPOSURE and EXTRACT for PRAC agreement: 2024 • End of data collection: at time of PRAC agreement that commitment is fulfilled • Final study report: 12 months after PRAC agreement
Study name and title	**67896049PAH0002 EXTRACT: EXploratory hisToRicAl Cohort sTudy** PASS: retrospective medical chart review of PAH patients newly treated with either UPTRAVI® (selexipag) or any other PAH-specific therapy.
Rationale and study objectives	In order to avoid significant delay in completing EXPOSURE and assessing the study objectives, EXTRACT will be used to complement EXPOSURE with 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 overall sample size. A comparator group consisting of patients with PAH newly treated with other PAH-specific therapy will serve as an internal comparator cohort in EXTRACT and allow for pooling of the cohorts of EXPOSURE and EXTRACT in comparative analyses. The Other PAH-specific therapy cohort for EXTRACT will only include disease prevalent patients (ie, ≥6 months from first PAH diagnosis) who initiated a PAH-specific therapy other than UPTRAVI for the first time as part of a combination therapy. The purpose of this PASS is to complement EXPOSURE to further characterize the safety profile in PAH patients treated with UPTRAVI in routine clinical practice; including additional experience of the use of UPTRAVI in patients over the age of 75 years; and to describe mortality and MACE rates with PAH patients not treated with UPTRAVI.

Additional Pharmacovigilance Activities	
Safety concern(s) addressed	The safety concerns addressed are: • Hypotension • Anemia • Hyperthyroidism • Pulmonary edema associated with PVOD • MACE • Renal function impairment / acute renal failure • Bleeding events • Light-dependent non-melanoma skin malignancies • Ophthalmological effects associated with retinal vascular system • GI disturbances denoting intestinal intussusception (manifested as ileus or obstruction) • Use in elderly over 75 years old
Study design	The study is an international, multicenter, retrospective chart review of new initiators of UPTRAVI or other PAH-specific therapies.
Study population	Patients with PAH who have been newly treated with UPTRAVI or other PAH-specific therapies in a clinical practice setting.
Milestones	• Seq0078\m1\eu\18-pharmacovigilance\182-riskmgt-system • Start of data collection: 2022 • End of data collection: 2023 • Registration in the EU PAS register: at time of PRAC protocol approval • Submission of combined final report of study results from EXPOSURE and EXTRACT for PRAC agreement: 2024

Study name and title	**AC-065A403 EDUCATE** PASS to evaluate risk minimization measures for medication errors with UPTRAVI during the titration phase in patients with PAH in clinical practice.
Rationale and study objectives	The objectives of this study are to assess HCPs' and patients' awareness (process), knowledge (impact), and comprehension (impact) of the risk minimization materials and to record the occurrence of patient-reported "wrong dose" medication errors (outcome) at completion of titration or discontinuation of UPTRAVI during titration.
Safety concern(s) addressed	The safety concern addressed is the occurrence of medication errors during the UPTRAVI titration phase.
Study design	The study is an observational, cross-sectional survey of awareness, knowledge, and self-reported behavior.

Additional Pharmacovigilance Activities	
Study population	The study population will involve patients and HCPs from Europe and Australia, including centralized healthcare systems (ie, national PAH reference centers) and decentralized systems.
Milestones	• Seq0077\m1\eu\18-pharmacovigilance\182-riskmgt-system • Start of data collection: 02 December 2022 • Collection of targeted number (60) of HCP surveys completed: 16 June 2023 • Second interim report submission: Once 100 patients' questionnaires are completed • End of data collection: At time of PRAC agreement that commitment is fulfilled • Final study report submission: 12 months after PRAC agreement

III.3. Summary Table of Additional Pharmacovigilance Activities

Table Part III.1:Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable.				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable.				
Category 3 - Required additional pharmacovigilance activities				
AC-065A401 EXPOSURE PASS: observational cohort study of PAH patients newly treated with either UPTRAVI® (selexipag) or any other PAH-specific therapy, in clinical practice. Ongoing	To further characterize the safety profile in PAH patients treated with UPTRAVI in routine clinical practice; including additional experience of the use of UPTRAVI in patients over the age of 75 years; and to compare mortality and MACE rates with PAH patients not treated with UPTRAVI.	• Hypotension • Anemia • Hyperthyroidism • Pulmonary edema associated with PVOD • MACE • Renal function impairment / acute renal failure • Bleeding events • Light-dependent non-melanoma skin malignancies • Ophthalmological effects associated with retinal vascular system	Annual updates Final study report	Progress reports on enrolment and intermediate analysis results will be provided yearly, including mortality data. Submission of combined final study report of study results from EXPOSURE and EXTRACT for PRAC agreement: 2024.

Table Part III.1:Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
		• GI disturbances denoting intestinal intussusception (manifested as ileus or obstruction) • Use in elderly over 75 years old		Final study report 12 months after PRAC agreement
67896049PAH0002 EXTRACT PASS: retrospective medical chart review of PAH patients newly treated with either UPTRAVI® (selexipag) or any other PAH-specific therapy Planned	The purpose of this PASS is to complement EXPOSURE to further characterize the safety profile in PAH patients treated with UPTRAVI in routine clinical practice; including additional experience of the use of UPTRAVI in patients over the age of 75 years; and to describe mortality and MACE rates with PAH patients not treated with UPTRAVI.	• Hypotension • Anemia • Hyperthyroidism • Pulmonary edema associated with PVOD • MACE • Renal function impairment / acute renal failure • Bleeding events • Light-dependent non melanoma skin malignancies • Ophthalmological effects associated with retinal vascular system • GI disturbances denoting intestinal intussusception (manifested as ileus or obstruction) • Use in elderly over 75 years old	Final study report	Submission of combined final report of study results from EXPOSURE and EXTRACT for PRAC agreement: 2024
AC-065A403 EDUCATE PASS to evaluate risk minimization measures for medication errors with UPTRAVI during the titration	The objectives of this study are to assess HCPs' and patients' awareness (process), knowledge (impact), and comprehension (impact) of the risk minimization materials and to record the occurrence of	Occurrence of medication errors during the UPTRAVI titration phase.	Collection of targeted number (60) of HCP surveys Second interim report submission	Completed: 16 June 2023 Once 100 patients' questionnaires are completed

Table Part III.1:Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
phase in patients with pulmonary arterial hypertension (PAH) in clinical practice. Ongoing	patient-reported “wrong dose” medication errors (outcome) at completion of titration or discontinuation of UPTRAVI during titration.		Final study report	Final study report submission: 12 months after PRAC agreement.

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

There are no ongoing or planned imposed postauthorization efficacy studies included in the selexipag pharmacovigilance plan.

PART V: RISK MINIMIZATION MEASURES (Including Evaluation of the Effectiveness of Risk Minimization Activities)

Risk Minimization Plan

V.1. Routine Risk Minimization Measures

Table Part V.1: Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Hypotension	**Routine risk communication:** SmPC section 4.4: 'Special warnings and precautions for use'. SmPC section 4.8: 'Undesirable effects' in the ADR table as a common adverse reaction. PL section 2: 'What you need to know before you take UPTRAVI'. PL section 4: 'Possible side effects'. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription.
Anemia	**Routine risk communication:** SmPC section 4.8: 'Undesirable effects' in the ADR table as a common adverse reaction based on data from the GRIPHON study. Section 4.8 of the SmPC also includes a description that anemia was reported at a higher frequency in the TRITON study. PL section 4: 'Possible side effects'. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription.
Hyperthyroidism	**Routine risk communication:** SmPC section 4.4: 'Special warnings and precautions for use'. SmPC section 4.8: 'Undesirable effects' in the ADR table as a common adverse reaction. PL section 2: 'What you need to know before you take UPTRAVI'. PL section 4: 'Possible side effects'. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** Legal status: Medicinal product subject to restricted medical prescription.

Table Part V.1:	Description of Routine Risk Minimization Measures by Safety Concern
Safety Concern	**Routine Risk Minimization Activities**
Concomitant use with strong inhibitors of CYP2C8	**Routine risk communication:** SmPC section 4.3: 'Contraindications'. SmPC section 4.5: 'Interaction with other medicinal products and other forms of interaction'. PL section 2: 'What you need to know before you take UPTRAVI'. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** Legal status: Medicinal product subject to restricted medical prescription.
Pulmonary edema associated with PVOD	**Routine risk communication:** SmPC section 4.4: 'Special warnings and precautions for use'. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** Legal status: Medicinal product subject to restricted medical prescription.
MACE	**Routine risk communication:** SmPC section 4.3: 'Contraindications'. PL section 2: 'What you need to know before you take UPTRAVI'. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** Legal status: Medicinal product subject to restricted medical prescription.
Renal function impairment / acute renal failure	**Routine risk communication:** SmPC section 4.2: 'Posology and method of administration'. SmPC section 4.4: 'Special warnings and precautions for use'. SmPC section 5.2: 'Pharmacokinetic properties'. PL section 2: 'What you need to know before you take UPTRAVI'. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** Legal status: Medicinal product subject to restricted medical prescription.

Table Part V.1:	Description of Routine Risk Minimization Measures by Safety Concern
Safety Concern	**Routine Risk Minimization Activities**
Bleeding events	**Routine risk communication:** SmPC section 4.5: 'Interaction with other medicinal products and other forms of interaction'. PL section 2: 'What you need to know before you take UPTRAVI'. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** Legal status: Medicinal product subject to restricted medical prescription.
Light-dependent non melanoma skin malignancies	**Routine risk communication:** None **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** Legal status: Medicinal product subject to restricted medical prescription.
Ophthalmological effects associated with retinal vascular system	**Routine risk communication:** SmPC section 5.3: 'Preclinical safety data'. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** Legal status: Medicinal product subject to restricted medical prescription.
GI disturbances denoting intestinal intussusception (manifested as ileus or obstruction)	**Routine risk communication:** SmPC section 4.2: 'Posology and method of administration'. SmPC section 5.3: 'Preclinical safety data'. PL section 2: 'What you need to know before you take UPTRAVI'. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** Legal status: Medicinal product subject to restricted medical prescription.

Table Part V.1:	Description of Routine Risk Minimization Measures by Safety Concern
Safety Concern	**Routine Risk Minimization Activities**
Medication error	**Routine risk communication:** SmPC section 4.2: 'Posology and method of administration'. PL section 2: 'What you need to know before you take UPTRAVI'. PL section 3: 'How to take UPTRAVI'. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** Legal status: Medicinal product subject to restricted medical prescription. The authorized pack size is chosen to ensure that the medicine is used correctly.
Missing information in use in pediatric patients	**Routine risk communication:** SmPC section 4.2: 'Posology and method of administration'. SmPC section 5.1: 'Pharmacodynamic properties'. PL section 2: 'What you need to know before you take UPTRAVI'. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** Legal status: Medicinal product subject to restricted medical prescription.
Missing information in use in elderly over 75 years old	**Routine risk communication:** SmPC section 4.2: 'Posology and method of administration'. SmPC section 4.4: 'Special warnings and precautions for use'. PL section 2: 'What you need to know before you take UPTRAVI'. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** Legal status: Medicinal product subject to restricted medical prescription.

Table Part V.1:	Description of Routine Risk Minimization Measures by Safety Concern
Safety Concern	**Routine Risk Minimization Activities**
Missing information in use during pregnancy and lactation	**Routine risk communication:** SmPC section 4.4: 'Special warnings and precautions for use'. SmPC section 4.6: 'Fertility, pregnancy and lactation'. SmPC section 5.3: 'Preclinical safety data'. PL section 2: 'What you need to know before you take UPTRAVI'. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** Legal status: Medicinal product subject to restricted medical prescription.
Missing information in concomitant use with strong inhibitors of UGT1A3 and UGT2B7	**Routine risk communication:** SmPC section 4.5: 'Interactions with other medicinal products and other forms of interaction'. SmPC section 5.2: 'Pharmacokinetic properties'. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** Legal status: Medicinal product subject to restricted medical prescription.

V.2. Additional Risk Minimization Measures

Additional Risk Minimization Activity 1

Additional Risk Minimization Activity 1

Educational material in a Prescriber Kit:

- Cover letter to the HCP.
- The SmPC.
- An HCP A4 laminated titration guide for the physician specifically describing treatment initiation and titration with a selexipag starting dose of 100 µg bid.
- An HCP A4 laminated titration guide for the physician specifically describing treatment initiation and titration with a selexipag starting dose of 200 µg bid.
- Patient Titration Guide included in the titration pack of the 100 µg tablets.
- Patient Titration Guide included in the titration pack of the 200 µg tablets.
- Package leaflet.

Objective(s):	To explain that the purpose of the educational materials is to reduce the risk of medication error due to the availability of multiple tablets and dose strengths. To provide a list of the content of the prescriber kit. To provide the HCP with information on the dosing and titration concept, the move to the maintenance dose, and expectations and management of AEs. To encourage the HCP to communicate clearly with the patient during their first visit; and to take responsibility to contact the patient during the titration phase, facilitating communication between HCP and the patient. To demonstrate and discuss with patients the safe and effective use of UPTRAVI. To be aware of the information and the titration guide that the patient will receive in the pack together with the package leaflet. To ensure that patients receive the patient titration guide in lay language. The patient titration guide will facilitate UPTRAVI use and serve as a reminder for the patients (eg, to contact her/his doctor), and a place to record intake of tablets.
Rationale for the additional risk minimization activity:	These efforts reinforce patient knowledge regarding the safe use of UPTRAVI, thereby mitigating the risks associated with UPTRAVI treatment.
Target audience and planned distribution path:	Prescribers and other HCPs (eg, pharmacists, nurses) involved in the prescription and delivery of UPTRAVI or in the education of patients who are prescribed UPTRAVI.

Plans to evaluate the effectiveness of the interventions and criteria for success:	Title: Category 3 PASS, EDUCATE, AC-065A403 "PASS to evaluate risk minimization measures for medication errors with UPTRAVI during the titration phase in patients with PAH in clinical practice." The study is an observational, cross-sectional survey of awareness, knowledge and self-reported behavior in the following groups: • HCPs (physicians, pharmacists and nurses); collection of targeted number (60) of HCP surveys was completed on 16 June 2023 • Patients at completion of titration or discontinuation of UPTRAVI during titration (ie, ≤4 weeks after reaching individual maintenance dose or ≤4 weeks after discontinuation during titration). The objectives of this study are to assess HCPs' and patients' awareness (process), knowledge (impact), and comprehension (impact) of the risk minimization materials and to record the occurrence of patient-reported "wrong dose" medication errors (outcome) at completion of titration or discontinuation of UPTRAVI during titration. The surveys will contain questions about: a. Process indicators: • Whether and how HCPs and patients use the respective materials, b. Impact assessment: • Measuring HCPs' and patients' awareness and knowledge (understanding) of the UPTRAVI titration c. Outcome indicator: • Patient self-reported occurrence of medication errors

Additional Risk Minimization Activity 2

Additional Risk Minimization Activity 2 Controlled Access System	
Objective(s):	To facilitate the identification of prescribers and approach them with the appropriate information on the safe and effective use of UPTRAVI, and provide them with risk minimization tools, especially regarding the potential risk of medication error.
Rationale for the additional risk minimization activity:	The Controlled Access System includes three key principles that will be incorporated within each system in all Member States. These are: • The identification and maintenance of a list of all UPTRAVI prescribers. • The distribution of kits to all identified prescribers to minimize the risks of medication error. • Tracking of the receipt of the kits by prescribers.
Target audience and planned distribution path:	UPTRAVI prescribers and other HCPs.

Plans to evaluate the effectiveness of the interventions and criteria for success:	There are no regulatory commitments regarding measuring the effectiveness.

V.2.1. Removal of Additional Risk Minimization Activities

Not applicable.

V.3. Summary of Risk Minimization Measures and Pharmacovigilance Activities

Table Part V.3: Summary Table of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Hypotension	**Routine risk minimization measures:** SmPC section 4.4: 'Special warnings and precautions for use'. SmPC section 4.8: 'Undesirable effects' in the ADR table as a common adverse reaction. PL section 2: 'What you need to know before you take UPTRAVI'. PL section 4: 'Possible side effects'. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** AC-065A401 EXPOSURE 67896049PAH0002 EXTRACT Submission of combined final report of study results from AC-065A401 EXPOSURE and 67896049PAH0002 EXTRACT for PRAC agreement: 2024 Final study report for EXPOSURE: 12 months after PRAC agreement
Anemia	**Routine risk minimization measures:** SmPC section 4.8: 'Undesirable effects' in the ADR table as a common adverse reaction based on data from the GRIPHON study. Section 4.8 of the SmPC also includes a description that anemia was reported at a higher frequency in the TRITON study. PL section 4: 'Possible side effects'. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** AC-065A401 EXPOSURE 67896049PAH0002 EXTRACT Submission of combined final report of study results from AC-065A401 EXPOSURE and 67896049PAH0002 EXTRACT for PRAC agreement: 2024 Final study report for EXPOSURE: 12 months after PRAC agreement

Table Part V.3: Summary Table of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Hyperthyroidism	**Routine risk minimization measures:** SmPC section 4.4: 'Special warnings and precautions for use'. SmPC section 4.8: 'Undesirable effects' in the ADR table as a common adverse reaction. PL section 2: 'What you need to know before you take UPTRAVI'. PL section 4: 'Possible side effects'. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** AC-065A401 EXPOSURE 67896049PAH0002 EXTRACT Submission of combined final report of study results from AC-065A401 EXPOSURE and 67896049PAH0002 EXTRACT for PRAC agreement: 2024 Final study report for EXPOSURE: 12 months after PRAC agreement
Concomitant use with strong inhibitors of CYP2C8	**Routine risk minimization measures:** SmPC section 4.3: 'Contraindications'. SmPC section 4.5: 'Interaction with other medicinal products and other forms of interaction'. PL section 2: 'What you need to know before you take UPTRAVI'. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Pulmonary edema associated with PVOD	**Routine risk minimization measures:** SmPC section 4.4: 'Special warnings and precautions for use'. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** AC-065A401 EXPOSURE 67896049PAH0002 EXTRACT Submission of combined final report of study results from AC-065A401 EXPOSURE and 67896049PAH0002 EXTRACT for PRAC agreement: 2024 Final study report for EXPOSURE: 12 months after PRAC agreement

Table Part V.3: Summary Table of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
MACE	**Routine risk minimization measures:** SmPC section 4.3: 'Contraindications'. PL section 2: 'What you need to know before you take UPTRAVI'. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** AC-065A401 EXPOSURE 67896049PAH0002 EXTRACT Submission of combined final report of study results from AC-065A401 EXPOSURE and 67896049PAH0002 EXTRACT for PRAC agreement: 2024 Final study report for EXPOSURE: 12 months after PRAC agreement
Renal function impairment / acute renal failure	**Routine risk minimization measures:** SmPC section 4.2: 'Posology and method of administration'. SmPC section 4.4: 'Special warnings and precautions for use'. SmPC section 5.2: 'Pharmacokinetic properties'. PL section 2: 'What you need to know before you take UPTRAVI'. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** AC-065A401 EXPOSURE 67896049PAH0002 EXTRACT Submission of combined final report of study results from AC-065A401 EXPOSURE and 67896049PAH0002 EXTRACT for PRAC agreement: 2024 Final study report for EXPOSURE: 12 months after PRAC agreement

Table Part V.3: Summary Table of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Bleeding events	**Routine risk minimization measures:** SmPC section 4.5: 'Interaction with other medicinal products and other forms of interaction'. PL section 2: 'What you need to know before you take UPTRAVI'. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** AC-065A401 EXPOSURE 67896049PAH0002 EXTRACT Submission of combined final report of study results from AC-065A401 EXPOSURE and 67896049PAH0002 EXTRACT for PRAC agreement: 2024 Final study report for EXPOSURE: 12 months after PRAC agreement
Light-dependent non-melanoma skin malignancies	**Routine risk minimization measures:** None **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** AC-065A401 EXPOSURE 67896049PAH0002 EXTRACT Submission of combined final report of study results from AC-065A401 EXPOSURE and 67896049PAH0002 EXTRACT for PRAC agreement: 2024 Final study report for EXPOSURE: 12 months after PRAC agreement

Table Part V.3: Summary Table of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Ophthalmological effects associated with retinal vascular system	**Routine risk minimization measures:** SmPC section 5.3: 'Preclinical safety data'. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** AC-065A401 EXPOSURE 67896049PAH0002 EXTRACT Submission of combined final report of study results from AC-065A401 EXPOSURE and 67896049PAH0002 EXTRACT for PRAC agreement: 2024 Final study report for EXPOSURE: 12 months after PRAC agreement
GI disturbances denoting intestinal intussusception (manifested as ileus or obstruction)	**Routine risk minimization measures:** SmPC section 4.2: 'Posology and method of administration'. SmPC section 5.3: 'Preclinical safety data'. PL section 2: 'What you need to know before you take UPTRAVI'. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** AC-065A401 EXPOSURE 67896049PAH0002 EXTRACT Submission of combined final report of study results from AC-065A401 EXPOSURE and 67896049PAH0002 EXTRACT for PRAC agreement: 2024 Final study report for EXPOSURE: 12 months after PRAC agreement

Table Part V.3: Summary Table of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Medication error	**Routine risk minimization measures:** SmPC section 4.2: 'Posology and method of administration'. PL section 2: 'What you need to know before you take UPTRAVI'. PL section 3: 'How to take UPTRAVI'. **Additional risk minimization measures:** Controlled Access System Educational material in a Prescriber Kit containing: • Cover Letter to the HCP and pharmacist • A4 laminated card HCP titration guide (specific for starting doses of 100 µg or 200 µg) • SmPC • Package leaflet and patient titration guide Specific patient titration guides are included in the titration packs of the 100 µg and 200 µg tablets.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** AC-065A403 EDUCATE Collection of targeted number (60) of HCP surveys completed: 16 June 2023 Second interim report submission: Once 100 patients' questionnaires are completed Final study report: 12 months after PRAC agreement
Use in pediatric patients	**Routine risk minimization measures:** SmPC section 4.2: 'Posology and method of administration'. SmPC section 5.1: 'Pharmacodynamic properties'. PL section 2: 'What you need to know before you take UPTRAVI'. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Table Part V.3: Summary Table of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Use in elderly over 75 years old	**Routine risk minimization measures:** SmPC section 4.2: 'Posology and method of administration' SmPC section 4.4: 'Special warnings and precautions for use'. PL section 2: 'What you need to know before you take UPTRAVI'. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** AC-065A401 EXPOSURE 67896049PAH0002 EXTRACT Submission of combined final report of study results from AC-065A401 EXPOSURE and 67896049PAH0002 EXTRACT for PRAC agreement: 2024 Final study report for EXPOSURE: 12 months after PRAC agreement
Use during pregnancy and lactation	**Routine risk minimization measures:** SmPC section 4.4: 'Special warnings and precautions for use'. SmPC section 4.6: 'Fertility, pregnancy and lactation'. SmPC section 5.3: 'Preclinical safety data'. PL section 2: 'What you need to know before you take UPTRAVI'. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Concomitant use with strong inhibitors of UGT1A3 and UGT2B7	**Routine risk minimization measures:** SmPC section 4.5: 'Interactions with other medicinal products and other forms of interactions'. SmPC section 5.2: 'Pharmacokinetic properties'. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for UPTRAVI® (selexipag)

This is a summary of the risk management plan (RMP) for UPTRAVI. The RMP details important risks of UPTRAVI, how these risks can be minimized, and how more information will be obtained about UPTRAVI's risks and uncertainties (missing information).

UPTRAVI's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how UPTRAVI should be used.

This summary of the RMP for UPTRAVI should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of UPTRAVI's RMP.

I. The Medicine and What it is Used For

UPTRAVI is authorized for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients with WHO functional class (FC) II–III, either as combination therapy in patients insufficiently controlled with an endothelin receptor antagonist (ERA) and/or a phosphodiesterase type 5 (PDE-5) inhibitor, or as monotherapy in patients who are not candidates for these therapies.

Efficacy has been shown in a PAH population including idiopathic and heritable PAH, PAH associated with connective tissue disorders, and PAH associated with corrected simple congenital heart disease. (see SmPC for the full indication).

It contains selexipag as the active substance and it is given by oral route of administration.

Further information about the evaluation of UPTRAVI's benefits can be found in UPTRAVI's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

https://www.ema.europa.eu/medicines/human/EPAR/UPTRAVI

II. Risks Associated With the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of UPTRAVI, together with measures to minimize such risks and the proposed studies for learning more about UPTRAVI's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

1. Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
2. Important advice on the medicine's packaging;

3. The authorized pack size — the amount of medicine in a pack is chosen to ensure that the medicine is used correctly;
4. The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of UPTRAVI, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed including Periodic Safety Update Report (PSUR)/Periodic Benefit-risk Evaluation Report (PBRER) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of UPTRAVI is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of UPTRAVI are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of UPTRAVI. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine);

List of Important Risks and Missing Information	
Important identified risks	• Hypotension • Anemia • Hyperthyroidism • Concomitant use with strong inhibitors of CYP2C8
Important potential risks	• Pulmonary edema associated with PVOD • MACE • Renal function impairment / acute renal failure • Bleeding events • Light-dependent non-melanoma skin malignancies • Ophthalmological effects associated with retinal vascular system • GI disturbances denoting intestinal intussusception (manifested as ileus or obstruction) • Medication error

Missing information	• Use in pediatric patients • Use in elderly over 75 years old • Use during pregnancy and lactation • Concomitant use with strong inhibitors of UGT1A3 and UGT2B7

II.B. Summary of Important Risks

Important Identified Risk: Hypotension	
Evidence for linking the risk to the medicine	Selexipag as well as other pulmonary vasodilators widens blood vessels, and there is a risk that patients could have a small drop in blood pressure. In the double-blind GRIPHON study, about 7 out of every 100 patients (7%) who took selexipag had low blood pressure compared to 4 out of every 100 patients (4%) who took placebo. The pattern and frequency of hypotension events in GRIPHON OL (AC-065A303) was consistent with what was reported for the double-blind studies. In GRIPHON OL, there was no indication of an increased risk of low blood pressure in selexipag-treated patients over long-term treatment. In the TRITON study, about 9 out of every 100 patients (9%) who took selexipag had low blood pressure compared to 7 out of every 100 patients (7%) who took placebo. No patients who took selexipag in the TRACE study had low blood pressure.
Risk factors and risk groups	General risk factors for hypotension are, eg, a history of systemic hypotension, vegetative dysfunction, concurrent infections or dehydration; and polytherapy with vasodilators and/or other hypotensive medications (eg, ERAs, riociguat, PDE-5 inhibitors, anti-hypertensives and/or diuretics). Hypotension is a main prognostic factor of poor outcome related to RHF hospitalization. Four-fold increase of in-hospital mortality for patients with systolic blood pressure <100 mmHg upon admission is observed among PAH patients hospitalized for RHF.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.4: ‘Special warnings and precautions for use’. SmPC section 4.8 ‘Undesirable effects’ in the ADR table as a common adverse reaction. PL section 2: ‘What you need to know before you take UPTRAVI’. PL section 4: ‘Possible side effects’. Additional risk minimization measures: None

Important Identified Risk: Hypotension	
Additional pharmacovigilance activities	Additional pharmacovigilance activities: AC-065A401 EXPOSURE 67896049PAH0002 EXTRACT Submission of combined final report of study results from AC-065A401 EXPOSURE and 67896049PAH0002 EXTRACT for PRAC agreement: 2024 Final study report for EXPOSURE: 12 months after PRAC agreement See Section II.C. of this summary for an overview of the postauthorization development plan.

Important Identified Risk: Anemia	
Evidence for linking the risk to the medicine	Selexipag may lower the amount of hemoglobin in the blood. In the double-blind GRIPHON study, a decrease in hemoglobin was reported in about 11 out of 100 patients (11%) who took selexipag and 9 out of 100 (9%) patients who took placebo. In this study, treatment-emergent decreases in hemoglobin from baseline to <10 g/dL were reported for 8.6% of patients who took selexipag and 5.0% of patients who took placebo. In GRIPHON OL, there was no indication of increased occurrence of anemia in selexipag-treated patients over long-term treatment. Anemia events were mostly reported as non-serious and were clinically manageable, with no participant discontinuing selexipag due to anemia. In the TRITON study, a decrease in hemoglobin was reported in about 27 out of 100 patients (27%) who took selexipag and 17 out of 100 (17%) patients who took placebo. In the TRITON study, treatment-emergent decreases from baseline to <8 g/dL in hemoglobin were reported for 6.8% of patients who took selexipag and 4.1% of patients who took placebo. In TRITON, mean changes in hemoglobin from baseline up to Month 18 ranged from −1.8 to −1.3 g/dL in the selexipag group and −1.6 to −1.3 g/dL in the placebo group. In the TRACE study, a decrease in hemoglobin was reported in about 4 out of 100 patients (4%) who took selexipag or placebo.
Risk factors and risk groups	General risk factors for anemia are, eg, iron deficiency, history of anemia, concomitant platelet inhibitors, anticoagulants, steroids, pre-existing or concurrent bleeding.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.8 ‘Undesirable effects’ in the ADR table as a common adverse reaction based on data from the GRIPHON study. Section 4.8 of the SmPC also includes a description that anemia was reported at a higher frequency in the TRITON study. PL section 4: ‘Possible side effects’. Additional risk minimization measures: None

Important Identified Risk: Anemia	
Additional pharmacovigilance activities	Additional pharmacovigilance activities: AC-065A401 EXPOSURE 67896049PAH0002 EXTRACT Submission of combined final report of study results from AC-065A401 EXPOSURE and 67896049PAH0002 EXTRACT for PRAC agreement: 2024 Final study report for EXPOSURE: 12 months after PRAC agreement See Section II.C. of this summary for an overview of the postauthorization development plan.

Important Identified Risk: Hyperthyroidism	
Evidence for linking the risk to the medicine	In the double-blind GRIPHON study, signs of an overactive thyroid gland were seen in about 3 out of every 100 patients (3%) who took selexipag and 1 out of every 100 patients (1%) who took placebo. In GRIPHON OL, overall, the pattern and frequency of hyperthyroidism events was comparable to that seen in the double-blind studies. In the TRITON and TRACE studies, no patients who took selexipag had signs of an overactive thyroid gland.
Risk factors and risk groups	Patients susceptible to the stimulatory effect of an IP receptor at the thyroid gland may be at risk. In some studies, prostacyclin treatment has been reported concomitantly with thyroid disorder occurrence (Chu 2002). Prostacyclins stimulate intracellular thyroid processes and mimic the effects of TSH on the thyroidal metabolism and stimulate the synthesis and secretion of thyroid hormone (Virgolini 1988). A possible role of epoprostenol (Chadha 2009, Ferris 2001, Fojas 2016, Richter 2016, Srimatkandada 2014) and of treprostinil (Gu 2016) in triggering hyperthyroid disease was suspected in PAH patients.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.4: ‘Special warnings and precautions for use’. SmPC section 4.8: ‘Undesirable effects’ in the ADR table as a common adverse reaction. PL section 2: ‘What you need to know before you take UPTRAVI’. PL section 4: ‘Possible side effects’. Additional risk minimization measures: None

Important Identified Risk: Hyperthyroidism	
Additional pharmacovigilance activities	Additional pharmacovigilance activities: AC-065A401 EXPOSURE 67896049PAH0002 EXTRACT Submission of combined final report of study results from AC-065A401 EXPOSURE and 67896049PAH0002 EXTRACT for PRAC agreement: 2024 Final study report for EXPOSURE: 12 months after PRAC agreement See Section II.C. of this summary for an overview of the postauthorization development plan.

Important Identified Risk: Concomitant use with Strong Inhibitors of CYP2C8	
Evidence for linking the risk to the medicine	In the presence of 600 mg gemfibrozil, twice a day, a strong inhibitor of CYP2C8, exposure to selexipag increased approximately 2-fold, whereas exposure to the active metabolite increased approximately 11-fold (AC-065-113). Concomitant administration of UPTRAVI with strong inhibitors of CYP2C8 (eg, gemfibrozil) is therefore contraindicated.
Risk factors and risk groups	Patients treated with gemfibrozil and selexipag.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.3: ‘Contraindications’. SmPC section 4.5: ‘Interaction with other medicinal products and other forms of interaction’. PL section 2: ‘What you need to know before you take UPTRAVI’. Additional risk minimization measures: None.

Important Potential Risk: Pulmonary Edema Associated with PVOD	
Evidence for linking the risk to the medicine	Experience with other pulmonary vasodilators, ie, ERAs, PDE-5 inhibitors, riociguat, prostacyclin and its analogue. Cases of pulmonary edema have been reported with vasodilators (mainly prostacyclins) when used in patients with previously undiagnosed PVOD. Close monitoring for such events continues for emerging data from clinical studies as well as in post-approval use. In the double-blind GRIPHON study, about 1 out of every 100 patients (1%) who took selexipag or placebo had pulmonary edema associated with PVOD. In GRIPHON OL, overall, the pattern and frequency of PVOD associated with pulmonary edema AESIs was consistent with that seen in the double-blind studies. In the TRITON study, about 2 out of every 100 patients (2%) who took selexipag and 1 out of every 100 patients (1%) who took placebo had pulmonary edema associated with PVOD. No patients who took selexipag or placebo in the TRACE study had pulmonary edema associated with PVOD.
Risk factors and risk groups	Patients with undiagnosed PVOD and on concurrent medications leading to pulmonary vasodilatation.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.4: ‘Special warnings and precautions for use’. Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: AC-065A401 EXPOSURE 67896049PAH0002 EXTRACT Submission of combined final report of study results from AC-065A401 EXPOSURE and 67896049PAH0002 EXTRACT for PRAC agreement: 2024 Final study report for EXPOSURE: 12 months after PRAC agreement See Section II.C. of this summary for an overview of the postauthorization development plan.

Important Potential Risk: MACE	
Evidence for linking the risk to the medicine	Results of adjudication performed by the external cardiologist and the Critical Event Committee in Study AC-065A302 (GRIPHON) [D-15.136]. In the pivotal double-blind Phase 3 AC-065A302/GRIPHON study, MACE was observed in 4.4% of selexipag-treated patients versus 4.0% of placebo-treated patients. The long-term safety data for MACE showed a decreasing trend in average annualized event rates. There was no evidence of a causal association between these events and selexipag administration in participants treated with selexipag in clinical studies. In the TRITON study, about 3 out of every 100 patients (3%) who took selexipag had MACE compared to 6 out of every 100 patients (6%) who took placebo. No patients who took selexipag or placebo in the TRACE study had MACE.
Risk factors and risk groups	As in the general population, patients with high cardiovascular risk due to intercurrent atherosclerotic disease requiring antihypertensive and/or lipid-lowering and/or antidiabetic treatment are identified as groups at risk. Systematic multidisciplinary approach, which addresses lifestyle and cardiovascular risk factor management, is part of general medical management of each patient.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.3: ‘Contraindications’. PL section 2: ‘What you need to know before you take UPTRAVI’. Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: AC-065A401 EXPOSURE 67896049PAH0002 EXTRACT Submission of combined final report of study results from AC-065A401 EXPOSURE and 67896049PAH0002 EXTRACT for PRAC agreement: 2024 Final study report for EXPOSURE: 12 months after PRAC agreement See Section II.C. of this summary for an overview of the postauthorization development plan.

Important Potential Risk: Renal Function Impairment / Acute Renal Failure	
Evidence for linking the risk to the medicine	In the double-blind GRIPHON study, a numerically small imbalance in AEs of renal failure between selexipag and the placebo group was observed. These events were transient and reversible in nature, and the majority of renal events resolved while treatment with selexipag was maintained. The long-term safety data for renal function impairment / acute renal failure showed a decreasing trend in average annualized event rates. In the TRITON study, about 10 out of every 100 patients (10%) who took selexipag had events of renal failure compared to 4 out of every 100 patients (4%) who took placebo. In the TRACE study, no patients who took selexipag had events of renal failure compared to about 2 out of every 100 patients (2%) who took placebo. In the TRITON and GRIPHON studies, no numerical imbalance in estimated glomerular filtration rate <60 mL/min and overall mean increases in creatinine clearance from baseline to regular visits were observed in the selexipag or placebo groups, suggesting no overall detrimental effect of selexipag on renal function. Close monitoring of such events continues for emerging data from clinical studies as well as in post-approval use.
Risk factors and risk groups	General risk factors include hemodynamic decompensation in the context of PAH worsening, RHF, or other concurrent illnesses (eg, sepsis, hypovolemic shock) or as a complication in patients with pre-existing renal impairment.
Risk minimization measures	Risk minimization measures: SmPC section 4.2: ‘Posology and method of administration’. SmPC section 4.4: ‘Special warnings and precautions for use’. SmPC section 5.2: ‘Pharmacokinetic properties’. PL section 2: ‘What you need to know before you take UPTRAVI’. Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: AC-065A401 EXPOSURE 67896049PAH0002 EXTRACT Submission of combined final report of study results from AC-065A401 EXPOSURE and 67896049PAH0002 EXTRACT for PRAC agreement: 2024 Final study report for EXPOSURE: 12 months after PRAC agreement See Section II.C. of this summary for an overview of the postauthorization development plan.

Important Potential Risk: Bleeding Events	
Evidence for linking the risk to the medicine	Known effects of other prostacyclins. In the double-blind GRIPHON study, the overall proportions of patients with bleeding events in the selexipag and placebo groups were similar (approximately 17 out of 100 patients [17%]). The long-term safety data for bleeding events showed a decreasing trend in average annualized event rates. There was no indication of an increased bleeding risk upon long-term treatment with selexipag. In the TRITON study, about 22 out of every 100 patients (22%) who took selexipag or placebo had bleeding events. In the TRACE study, about 13 out of every 100 patients (13%) who took selexipag or placebo had bleeding events. As shown in in-vitro experiments, selexipag is a weak platelet aggregation inhibitor and close monitoring of such events continues for emerging data from clinical studies as well as in post-approval use.
Risk factors and risk groups	Available data do not support any overall increased risk of bleeding with selexipag or any synergically increased risk of bleeding if selexipag is co-administered with anticoagulants or other antithrombotics. No specific risk factor has been identified to predict the occurrence of bleeding events in selexipag-treated patients.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.5: 'Interaction with other medicinal products and other forms of interaction'. PL section 2: 'What you need to know before you take UPTRAVI'. Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: AC-065A401 EXPOSURE 67896049PAH0002 EXTRACT Submission of combined final report of study results from AC-065A401 EXPOSURE and 67896049PAH0002 EXTRACT for PRAC agreement: 2024 Final study report for EXPOSURE: 12 months after PRAC agreement See Section II.C. of this summary for an overview of the postauthorization development plan.

Important Potential Risk: Light-dependent Non-melanoma Skin Malignancies	
Evidence for linking the risk to the medicine	During the double-blind GRIPHON study, 4 patients aged >68 years in the selexipag group were diagnosed with BCC compared to none in the placebo group. Confounding factors were present in all cases (eg, immunosuppressant use, history of malignancy, or short duration of exposure). In GRIPHON OL, there was no indication of an increased risk of light-dependent non-melanoma skin malignancies associated with long-term selexipag treatment. In the TRITON study, less than 1 out of every 100 patients (<1%) who took selexipag had skin malignancies compared to 2 out of every 100 patients (2%) who took placebo. In the TRACE study, no patients who took selexipag or placebo had skin malignancies. Close monitoring of such events continues for emerging data from clinical studies as well as in post-approval use.
Risk factors and risk groups	PAH is known to be associated with autoimmune disease as the underlying cause of PAH or associated co-morbidity. Therefore clinical management of these conditions frequently requires administration of medications with immunosuppressant effect. In general, sunlight exposure is considered as a relevant susceptibility factor.
Risk minimization measures	No risk minimization measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: AC-065A401 EXPOSURE 67896049PAH0002 EXTRACT Submission of combined final report of study results from AC-065A401 EXPOSURE and 67896049PAH0002 EXTRACT for PRAC agreement: 2024 Final study report for EXPOSURE: 12 months after PRAC agreement See Section II.C. of this summary for an overview of the postauthorization development plan.

Important Potential Risk: Ophthalmological Effects Associated with Retinal Vascular System	
Evidence for linking the risk to the medicine	Nonclinical findings of tortuosity and dilatation of retinal blood vessels in rats at the end of a 2-year carcinogenicity study (D-14.104). During the double-blind GRIPHON study, there was no evidence of an increase in relevant adverse ocular effects in selexipag-treated patients compared to placebo-treated patients. In the AC-065A302/GRIPHON ophthalmology sub-study, no new post-baseline fundoscopy findings or worsening of pre-existing retinal arterial tortuosity were reported in the selexipag group (D-14.407). The long-term safety data for ophthalmological events and events associated with the retinal vascular system showed a decreasing trend in average annualized event rates. The pattern and frequency of ophthalmological events and events associated with the retinal vascular system remained similar for long-term selexipag treatment as had been reported for the double-blind studies. There was no indication of any adverse effect of selexipag on retinal vasculature upon long-term treatment, and the non-clinical findings of retinal arteriolar tortuosity continue to be considered of limited clinical relevance. In the TRITON study, about 5 out of every 100 patients (5%) who took selexipag had relevant adverse ocular effects compared to 7 out of every 100 patients (7%) who took placebo. In the TRACE study, no patients who took selexipag had relevant adverse ocular effects.
Risk factors and risk groups	The findings of tortuosity and dilation of retinal arterioles in rats were considered by the independent experts in ophthalmology to be animal species-specific and of limited clinical relevance. Therefore no particular risk group can be determined.
Risk minimization measures	Routine risk minimization measures: SmPC section 5.3: ‘Preclinical safety data’. Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: AC-065A401 EXPOSURE 67896049PAH0002 EXTRACT Submission of combined final report of study results from AC-065A401 EXPOSURE and 67896049PAH0002 EXTRACT for PRAC agreement: 2024 Final study report for EXPOSURE: 12 months after PRAC agreement See Section II.C. of this summary for an overview of the postauthorization development plan.

Important Potential Risk: GI Disturbances Denoting Intestinal Intussusception (Manifested as Ileus or Obstruction)	
Evidence for linking the risk to the medicine	In pre-clinical studies, intestinal intussusception upon selexipag treatment was identified in young dogs, but not in rodents. Because of the species-specific sensitivity of dogs to develop intussusception and the safety margin, this finding is considered not relevant for adult humans. In the double-blind GRIPHON study, less than 1 out of every 100 patients (<1%) who took selexipag or placebo had GI disturbances denoting intestinal intussusception. The long-term safety data for GI disturbances denoting intestinal intussusception showed a decreasing trend in average annualized event rates. There was no evidence of a causal association between these events and selexipag administration in participants treated with selexipag in clinical studies. In the TRITON study, less than 1 out of every 100 patients (<1%) who took selexipag had GI disturbances denoting intestinal intussusception compared to no patients who took placebo. In the TRACE study, no patients who took selexipag or placebo had GI disturbances denoting intestinal intussusception.
Risk factors and risk groups	Patients with PAH associated with systemic scleroderma represent patients at particular risk of GI motility disorder in the adult patient population. In infants and young children, intussusception is the most common cause of intestinal obstruction. Available epidemiological data show that 75% to 90% of cases arise before 2 years of age (Waseem 2008, Stringer 1992). The peak incidence is between 5 and 9 months of age and then starts to decline (Newman 1987).
Risk minimization measures	Routine risk minimization measures: SmPC section 4.2: ‘Posology and method of administration’. SmPC section 5.3: ‘Preclinical safety data’. PL section 2: ‘What you need to know before you take UPTRAVI’. Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: AC-065A401 EXPOSURE 67896049PAH0002 EXTRACT Submission of combined final report of study results from AC-065A401 EXPOSURE and 67896049PAH0002 EXTRACT for PRAC agreement: 2024 Final study report for EXPOSURE: 12 months after PRAC agreement See Section II.C. of this summary for an overview of the postauthorization development plan.

Important Potential Risk: Medication Error	
Evidence for linking the risk to the medicine	As compared to controlled clinical trials, where only selexipag 200 µg tablets were administered, a total of 9 dosage strengths (100, 200, 400, 600, 800, 1000, 1200, 1400, and 1600 µg film-coated tablets) are available on the market. Data regarding instructions on recommended daily dosing, titration and transition to maintenance dose are given in the respective national UPTRAVI product labelling documents and further educational materials provided to patients and healthcare professionals (HCPs). Information regarding medication errors with tablets during selexipag initial titration and transition to maintenance dose is therefore only collected from post-approval use.
Risk factors and risk groups	Patients during initial selexipag up-titration phase.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.2: 'Posology and method of administration'. PL section 2: 'What you need to know before you take UPTRAVI'. PL section 3: 'How to take UPTRAVI'. Additional risk minimization measures: Controlled Access System Educational material in a Prescriber Kit containing: • Cover Letter to the HCP and pharmacist • A4 laminated card HCP titration guide (specific for starting doses of 100 µg or 200 µg) • SmPC • Package leaflet and patient titration guide Specific patient titration guides are included in the titration packs of the 100 µg and 200 µg tablets.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: AC-065A403 EDUCATE Collection of targeted number (60) of HCP surveys completed: 16 June 2023 Second interim report submission: Once 100 patients' questionnaires are completed Final study report: 12 months after PRAC agreement See Section II.C. of this summary for an overview of the postauthorization development plan.

Missing Information: Use in Pediatric Patients	
Risk minimization measures	Routine risk minimization measures: SmPC section 4.2: 'Posology and method of administration'. SmPC section 5.1: 'Pharmacodynamic properties'. PL section 2: 'What you need to know before you take UPTRAVI'. Additional risk minimization measures: None

Missing Information: Use in Elderly Over 75 Years Old	
Risk minimization measures	Routine risk minimization measures: SmPC section 4.2: 'Posology and method of administration'. SmPC section 4.4: 'Special warnings and precautions for use'. PL section 2: 'What you need to know before you take UPTRAVI'. Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: AC-065A401 EXPOSURE 67896049PAH0002 EXTRACT Submission of combined final report of study results from AC-065A401 EXPOSURE and 67896049PAH0002 EXTRACT for PRAC agreement: 2024 Final study report for EXPOSURE: 12 months after PRAC agreement See Section II.C. of this summary for an overview of the postauthorization development plan.

Missing Information: Use During Pregnancy and Lactation	
Risk minimization measures	Routine risk minimization measures: SmPC 4.4: 'Special warnings and precautions for use'. SmPC 4.6 'Fertility, pregnancy and lactation'. SmPC section 5.3: 'Preclinical safety data'. PL section 2: 'What you need to know before you take UPTRAVI'. Additional risk minimization measures: None

Missing Information: Concomitant Use with Strong Inhibitors of UGT1A3 and UGT2B7	
Risk minimization measures	Routine risk minimization measures: SmPC section 4.5 'Interactions with other medicinal products and other forms of interaction'. SmPC section 5.2: 'Pharmacokinetic properties'. Additional risk minimization measures: None

II.C. Postauthorization Development Plan

II.C.1. Studies Which are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of UPTRAVI.

II.C.2. Other Studies in Postauthorization Development Plan

AC-065A401 EXPOSURE

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

Purpose of the study:

To further characterize the safety profile in PAH patients treated with UPTRAVI in routine clinical practice; including additional experience of the use of UPTRAVI in patients over the age of 75 years; and to compare mortality and MACE rates with PAH patients not treated with UPTRAVI.

67896049PAH0002 EXTRACT

PASS: retrospective medical chart review of PAH patients newly treated with either UPTRAVI® (selexipag) or any other PAH-specific therapy.

Purpose of the study:

In order to avoid significant delay in completing EXPOSURE and assessing the study objectives, EXTRACT will be used to complement EXPOSURE with 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 overall sample size. A comparator group consisting of patients with PAH newly treated with other PAH-specific therapy will serve as an internal comparator cohort in EXTRACT and allow for pooling of the cohorts of EXPOSURE and EXTRACT in comparative analyses. The Other PAH-specific therapy cohort for EXTRACT will only include disease prevalent patients (ie, ≥6 months from first PAH diagnosis) who initiated a PAH-specific therapy other than UPTRAVI for the first time as part of a combination therapy.

The purpose of this PASS is to complement EXPOSURE to further characterize the safety profile in PAH patients treated with UPTRAVI in routine clinical practice; including additional experience of the use of UPTRAVI in patients over the age of 75 years; and to describe mortality and MACE rates with PAH patients not treated with UPTRAVI.

AC-065A403 EDUCATE

PASS to evaluate risk minimization measures for medication errors with UPTRAVI during the titration phase in patients with PAH in clinical practice.

Purpose of the study:

The objectives of this study are to assess HCPs' and patients' awareness (process), knowledge (impact), and comprehension (impact) of the risk minimization materials and to record the occurrence of patient-reported "wrong dose" medication errors (outcome) at completion of titration or discontinuation of UPTRAVI during titration.

The safety concern addressed is the occurrence of medication errors during the UPTRAVI titration phase.

PART VII: ANNEXES

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Annex 4: Specific ADR Follow-up Forms

Not applicable.

Annex 6: Details of Proposed Additional Risk Minimization Activities

Approved Key Messages of the Additional Risk Minimization Measures

Physician educational material:

1. The SmPC will contain information on approved indications and posology in order to ensure appropriate prescription of UPTRAVI, the warnings and the precautions as well as symptoms and signs of any potential ADRs.
2. Cover letter to HCPs
   a. To explain that the purpose of the educational materials is to reduce the risk of medication error due to the availability of multiple tablets and dose strengths. The Cover letter will include an explanation regarding availability of 100 µg or 200 µg tablet strengths for initial up-titration.
   b. To provide a list of the content of the prescriber kit.
3. HCP A4 laminated titration guides describing treatment initiation and titration with UPTRAVI 100 µg or with UPTRAVI 200 µg dosage strengths
   a. To provide the HCP with information on the dosing and titration concept, the move to the maintenance dose, and expectations and management of AEs.
   b. To encourage the HCP to communicate clearly with the patient during their first visit; as well as to take responsibility to contact the patient during the titration phase, facilitating communication between HCP and the patient.
   c. To demonstrate and discuss with patients the safe and effective use of UPTRAVI.
4. Patient Titration Guide and patient leaflet to be used by the HCP during discussions with the patient (included in the titration packs containing 140 tablets of 100 µg or 200 µg selexipag specifically for patients initiating UPTRAVI at starting dose of 100 µg or 200 µg bid).
   a. To demonstrate and discuss with patients the safe and effective use of UPTRAVI.
   b. To be aware of the information and the titration guide that the patient will receive in the pack together with the package leaflet.

Controlled Access System:

1. To facilitate the identification of prescribers and approach them with the appropriate information on the safe and effective use of UPTRAVI, and provide them with risk minimization tools, especially regarding the potential risk of medication error.