Common Drug Review
Clinical Review Report

September 2017

Drug	selexipag (Uptravi)
Indication	Long-term treatment of idiopathic pulmonary arterial hypertension, heritable pulmonary arterial hypertension (HPAH), pulmonary arterial hypertension (PAH) associated with connective tissue disorders and PAH associated with congenital heart disease, in adult patients with WHO functional class (FC) II–III to delay disease progression.
Listing request	As per indication
Dosage form(s)	200 mcg, 400 mcg, 600 mcg, 800 mcg, 1,000 mcg, 1,200 mcg, 1,400 mcg, 1,600 mcg tablets for oral administration
NOC date	20 January 2016
Manufacturer	Actelion Pharmaceuticals Canada Inc.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in treating pulmonary arterial hypertension (PAH) who provided input on the conduct of the review and the interpretation of findings.

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ABBREVIATIONS

6MWD	six-minute walk distance
AE	adverse event
CDEC	CADTH Canadian Drug Expert Committee
CEC	Critical Event Committee
CI	confidence interval
CDR	CADTH Common Drug Review
DB	double-blind
ERA	endothelin receptor antagonist
FAS	full analysis set
FC	functional class
MCID	minimal clinically important difference
mPAP	mean pulmonary arterial pressure
NR	not reported
NT-proBNP	N-terminal pro-brain natriuretic peptide
PAH	pulmonary arterial hypertension
PDE5	phosphodiesterase type 5
PH	pulmonary hypertension
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
sGC	soluble guanylate cyclase
SSC	Scleroderma Society of Canada
WDAE	withdrawal due to adverse event
WHO	World Health Organization

EXECUTIVE SUMMARY

Introduction

Pulmonary arterial hypertension (PAH) is an uncommon, debilitating, progressive, and life-threatening disease of the pulmonary vasculature, characterized by vascular proliferation and remodelling of small pulmonary arteries. It can lead to right heart failure and premature death. PAH is defined by an increase in mean pulmonary arterial pressure (mPAP) ≥ 25 mm Hg.[1] The four main categories of PAH (classified as Group 1 pulmonary hypertension) include idiopathic PAH, heritable or familial PAH, drug- and toxin-induced PAH, and PAH associated with other conditions such as connective tissue disease, HIV infection, portal hypertension, congenital heart disease, or schistosomiasis.[2] The symptoms of PAH include breathlessness, fatigue, weakness, chest pain, light-headedness or fainting, and edema or ascites. PAH has a significant impact on the lives of patients and caregivers. Patients with PAH have a day-to-day life that is difficult and exhausting, and they progressively lose the ability to care for themselves. While therapy may delay progression, reduce the severity of symptoms and make certain tasks easier, there is still no cure for PAH.

Health Canada has previously approved nine advanced treatment options covering four different classes of drugs for PAH, Group 1:

- Prostacyclin therapies (epoprostenol, treprostinil)
- Endothelin receptor antagonists (ERAs) (bosentan, ambrisentan, macitentan)
- Phosphodiesterase type 5 (PDE5) inhibitors (sildenafil, tadalafil)
- Soluble guanylate cyclase (sGC) stimulator (riociguat)

In 2014, CADTH conducted a Therapeutic Review to assess the comparative efficacy and safety and to determine the cost-effectiveness of pharmacologic treatments for adults with PAH.[3]

Based on the Therapeutic Review and patient group input, the CADTH Canadian Drug Expert Committee (CDEC) recommended the following:

- That sildenafil or tadalafil be the preferred initial therapy for adult patients with functional class (FC) II and III PAH; and
- Add-on therapy should be used in adult PAH patients who are unable to achieve disease control with a single drug.[4]

Selexipag is an oral, selective, prostacyclin receptor agonist, and is structurally and pharmacologically distinct from prostacyclin and its analogues. The recommended starting dose is 200 mcg given twice daily. The dose is increased in increments of 200 mcg given twice daily, usually at weekly intervals, until adverse pharmacological effects that cannot be tolerated or medically managed are experienced, or until a maximum dose of 1,600 mcg twice daily is reached.

The objective of this systematic review is to evaluate the beneficial and harmful effects of selexipag tablets for the treatment of PAH in adults (World Health Organization [WHO] FC II or III).

Results and Interpretation

Included Studies

The evidence for this review came from one randomized, placebo-controlled, event-driven, group-sequential trial in patients with symptomatic PAH. Patients, treating physicians, and investigators who assessed the primary outcome were blinded to treatment. The objective of the trial was to demonstrate

the effect of selexipag on time to first morbidity and/or mortality event (primary composite outcome) in patients with PAH. A total of 1,156 patients, mainly with WHO FC II or III, were randomized to selexipag or placebo (1:1) and titrated to the highest tolerated dose (range: 200 mcg to 1,600 mcg orally twice daily). Groups received study treatment as monotherapy or as add-on to stable single or double background PAH drugs (PDE5 inhibitor and/or ERA). The median duration on treatment in the selexipag group was 70.7 weeks and was 63.7 weeks in the placebo group.

The majority of patients were female (80%), had idiopathic PAH (56%), were classified as WHO FC II (46%) or III (53%) and had a mean time since PAH diagnosis of slightly greater than two years. Eighty per cent of patients were receiving stable doses of one or two concomitant medications for PAH at baseline. [redacted] were enrolled in Canada. Prognostic factors at baseline were well balanced, but the initiation of concomitant medications for PAH (e.g., PDE5 inhibitors and ERAs) during the study occurred in [redacted] of patients in the selexipag and [redacted] in the placebo groups and this may have introduced treatment bias. The direction of the bias cannot be ascertained with precision, but if [redacted]

The primary outcome in the GRIPHON study was time to first Critical Event Committee–confirmed morbidity or mortality event up to seven days after the last study drug intake. This was a composite of all cause of death or PAH-related morbidity events, including disease progression or worsening of PAH that resulted in hospitalization, initiation of parenteral prostanoid therapy or long-term oxygen therapy, or the need for lung transplantation or balloon atrial septostomy. Disease progression was defined as a decrease from baseline of at least 15% in the six-minute walk distance (6MWD), accompanied by a worsening in WHO FC or the need for additional treatment of PAH. Secondary outcomes were subject to a hierarchical statistical testing procedure.

The number of patients who discontinued the study drug prior to study closure was high and was slightly lower in the selexipag group (49%) compared with placebo (55%).

Selexipag is indicated for mono, dual, or triple therapy. Treatment with stable doses of ERAs and/or PDE5s was permitted at the study start and new ERAs or PDE5s could be added during the study. The overall trial population was heterogeneous with respect to the number and type of concomitant PAH drugs and the trial was not specifically designed to compare monotherapy versus dual therapy versus triple therapy. Therefore, there is uncertainty regarding the population to which the results are generalizable, with respect to concomitant therapies.

Efficacy

The occurrence of death as a first primary outcome event from any cause up to seven days after the last dose of study drug was [redacted] in the selexipag group [redacted] compared with the placebo group [redacted]. This analysis of deaths is difficult to interpret because of competing events in the primary composite outcome. There were several other analyses of deaths that included a total of 100 and 105 patients in the selexipag and placebo groups, respectively, who died up to study closure (hazard ratio [HR] 0.97; 99% confidence interval [CI], 0.68 to 1.39).

The annualized numbers of hospitalizations per year for all causes were [redacted] for the selexipag group and [redacted] for the placebo group. There were no statistically significant differences in overall hospitalization rates or number of days spent in hospital after these rates were adjusted for cumulative time on study at the group level.

Overall, 140 selexipag patients (24.4%) and 212 patients (36.4%) had a clinical worsening (morbidity/mortality event; primary composite outcome). The results of the primary outcome were driven by hospitalization for PAH and disease progression. The HR for the primary outcome in the selexipag group was 0.61 (99% CI, 0.46 to 0.81), relative to placebo. This corresponds to a relative risk reduction of 39% and absolute risk reduction of 12% (see Table 1). The group-sequential trial design used a one-sided, family-wise, overall type I error rate of 0.005 for the primary and secondary end points based on a conditional hierarchy.

Absence of worsening from baseline in WHO FC at week 26 was reported for 444 of 571 (77.8%) of patients in the selexipag group and 430 of 574 (74.9%) in the placebo group (odds ratio [OR] 1.16; 99% CI, 0.81 to 1.66; *P* = 0.19). There was no statistically significant difference in absence of WHO FC worsening and the hierarchical testing procedure was therefore halted at this stage. The 6MWD was the first secondary end point in the hierarchy to be tested. There were statistically significant improvements in the 6MWD results favouring selexipag compared with placebo (median difference of change 12 m), but this change is lower than the estimated minimal clinically important change of 33 m (see Appendix 5). The Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) questionnaire was used in a subset of GRIPHON patients to assess PAH symptom changes, functioning, and quality of life; only changes on the Symptoms and Breathlessness scales were analyzed in the trial. There were no statistically significant differences between selexipag and placebo in the CAMPHOR questionnaire subscales. There were no statistically significant differences between selexipag and placebo in dyspnea score as measured by the Borg dyspnea index.

Harms

Most patients experienced an adverse event during GRIPHON and the difference in incidence of specific adverse events between selexipag and placebo was 5% or greater for headache, diarrhea, pain in jaw, nausea, myalgia, vomiting, pain in extremity, and flushing. Prostacyclin-like adverse events such as headache, diarrhea, nausea, pain in jaw, myalgia, pain in extremity, vomiting, and flushing were more common during the titration phase than in the maintenance dose phase.

Serious adverse events were reported in 252 patients (44%) in the selexipag group compared with 272 patients (47%) in the placebo group. Other than PAH worsening, the most common serious adverse events were right ventricular failure, pneumonia, dyspnea, syncope, and atrial fibrillation, all of which occurred at similar rates in the selexipag and placebo groups.

Fewer patients discontinued the study drug regimen in the selexipag group (32%) compared with the placebo group (37%). This was mainly due to worsening of PAH (Table 1).

Overall, 182 patients (32%) in the selexipag group and 214 patients (37%) in the placebo group discontinued their study regimen prematurely because of an adverse event. The most frequent adverse events leading to discontinuation in the selexipag group (events for which there was a greater than 1% difference between the selexipag and placebo groups) were headache (3%), diarrhea (2%), and nausea (2%). Hyperthyroidism occurred in eight patients in the selexipag group and led to treatment discontinuation in one patient.

Potential Place in Therapy

This information in this section is based on that provided in draft form by the clinical expert consulted by CADTH Common Drug Review (CDR) reviewers for the purpose of this review.

The clinical expert consulted by CDR discussed the unmet needs in this patient population, which included:

- Persistent symptoms and significant morbidity and mortality in patients despite aggressive combination therapy
- Lack of therapeutic options for patients with persistent symptoms who are not candidates for intravenous prostacyclin therapy.[5]

According to the clinical expert, selexipag has the potential to address both unmet needs, and it has a place in the pharmacotherapy of PAH. The data from the GRIPHON study suggest that selexipag delays clinical worsening in a population of patients that would be very similar to those whom PAH specialists treat in Canada. There is no way to make conclusions with respect to the comparative benefits and safety with selexipag versus other drugs, as no head-to-head studies or indirect comparisons have been done.

In practice, selexipag would not be a replacement for intravenous prostacyclins in patients who require and are candidates for such therapy, according to the clinical expert consulted. In addition, given the complexity of the drug with respect to administration and monitoring, relative to others available, it would likely not be used as a first-line drug.

The place in therapy rests on patients who fail to meet treatment goals despite background mono or dual therapy. This might include a New York Health Association (NYHA) II or early NYHA III patient who does not yet require escalation to intravenous prostacyclins; selexipag can be an option in this population, similar to all other oral drugs when making this decision. The other potential use for this drug would be in patients who are not candidates for intravenous prostacyclin therapies, such as those with advanced WHO FC III (IIIB) or IV symptoms, and/or those with cognitive, physical, or medical contraindications that would preclude safe use of a chronic indwelling intravenous catheter. This represents a very small percentage of patients; however, there is no evidence from the reviewed trial on outcomes for this specific subpopulation.

There are no additional specific diagnostic tests required to prescribe this drug beyond what is routinely done. The monitoring and titration is more complex, but with patient support programs, much of this could be done remotely.

The barriers to prescribing will largely involve tolerance, as the adverse effect profile is considerable and in line with other drugs targeting the prostacyclin pathway.

Conclusions

Results of one randomized controlled trial indicated that selexipag is associated with clinically and statistically significant improvements in time to clinical worsening (composite outcome) compared with placebo in patients with PAH on a heterogeneous background of PAH therapies or no PAH therapy. No clinically significant improvements were observed in the 6MWD test for selexipag compared with placebo. No clear evidence of improvement was observed for selexipag compared with placebo for overall deaths, PAH-related deaths, hospitalization rates, WHO FC changes, quality of life, symptoms of PAH, breathlessness, or dyspnea.

Based on the results of GRIPHON, some patients would be expected to discontinue selexipag due to headache, diarrhea, or nausea. Adverse events associated with prostacyclin use are more likely to occur

during the dose-adjustment phase, compared with the maintenance phase. These include headache, diarrhea, nausea, pain in jaw, myalgia, pain in extremity, vomiting, and flushing.

A number of important gaps in information remain. The presence of different background PAH therapies, or no PAH therapy, in the trial population creates uncertainty regarding the generalizability of the data from the GRIPHON study. No evidence was identified that allowed an assessment of the effects of selexipag relative to other oral PAH therapies or prostacyclin therapies.

TABLE 1: SUMMARY OF RESULTS

Outcome	GRIPHON Study		
	Selexipag N = 574	Placebo N = 582	
Median Exposure to Study Treatment (Range), Weeks	70.7 (0.3 to 217)	63.7 (0.7 to 192)	
Primary Composite Outcome, n (%)	140 (24.4)	212 (36.4)	HR 0.61; 99% CI, 0.46 to 0.81; *P* < 0.0001
Death — all cause to EOT + 7 days, n (%)[a]	25 (4.4)	16 (2.7)	
Hospitalization for PAH worsening, n (%)	71 (12.4)	95 (16.5)	
PAH worsening resulting in need for lung transplant or balloon atrial septostomy	1 (0.2)	2 (0.3)	
Parenteral prostanoid therapy or chronic oxygen therapy	11 (1.9)	14 (2.4)	
Disease progression	32 (5.6)	84 (14.4)	
6MWD			
Mean baseline 6MWD, m	359 (76)	348 (83)	–
Mean change from baseline (SD) at week 26, m	–52 (150)	–66 (148)	–
Median change from baseline (range) at week 26, m	4 (–448 to 260)	–9 (–438 to 262)	Between-group difference of change: 12.0; 99% CI, 1 to 24
WHO FC Changes			
Absence of worsening from baseline of WHO FC at week 26 compared with baseline, n/N (%)	444/571 (78)	430/574 (75)	OR 1.16; 99% CI, 0.81 to 1.66; *P* = 0.19
Improvement in WHO FC at week 26 compared with baseline, n/N (%)	77/571 (13)	50/574 (9)	
Deaths			
All deaths up to EOT + 7 days	46 (8.0)	37 (6.4)	HR 1.17; 99% CI 0.66 to 2.07[6]
All deaths up to EOT + 30 days	[redacted]	[redacted]	
All deaths up to study closure	100 (17.4)	105 (18.0)	HR 0.97; 99% CI, 0.68 to 1.39

Outcome	GRIPHON Study		
	Selexipag N = 574	Placebo N = 582	
SAE, n (%)	252 (44)	272 (47)	
Stopped treatment due to adverse events, n (%)	182 (32)	214 (37)	

6MWD = six-minute walking distance; CI = confidence interval; EOT = end of treatment (last dose of study drug); FC = functional class; HR = hazard ratio; OR = odds ratio; PAH = pulmonary arterial hypertension; SAE = serious adverse event; SD = standard deviation; WHO = World Health Organization.
Note: Populations in this table are from the full analysis set unless otherwise stated. WHO FC analysis imputed missing data as worsening, and FC IV was excluded for the worsening analysis, because those patients could not worsen to another class.[7]
[a] Counting of deaths as a primary outcome event only included deaths if they occurred as a first event.
Source: Clinical Study Report,[8] Sitbon et al.,[9] with additional information from the manufacturer.[6]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Pulmonary arterial hypertension (PAH) is an uncommon, debilitating, progressive, and life-threatening disease of the pulmonary vasculature, characterized by vascular proliferation and remodelling of small pulmonary arteries. If left untreated, it can lead to right heart failure and premature death. PAH is defined by an increase in mean pulmonary arterial pressure (mPAP) ≥ 25 mm Hg.[1]

The symptoms of PAH include breathlessness, fatigue, weakness, chest pain, light-headedness or fainting, and edema or ascites. Severity of disease is based on symptoms and assessed using the New York Heart Association (NYHA) or World Health Organization (WHO) functional classification of heart failure symptoms, ranging from functional class (FC) I to IV, with FC IV being the most severe (Table 2).

TABLE 2: WORLD HEALTH ORGANIZATION FUNCTIONAL CLASSIFICATION OF PULMONARY HYPERTENSION

Class	Description
I	No limitations of physical activity
II	Slight limitation of physical activity, but no symptoms at rest
III	Marked limitation of physical activity, but no symptoms at rest
IV	Inability to perform any physical activity without discomfort; symptoms may be present at rest; signs of right failure present

Source: European Society of Cardiology/European Respiratory Society Guidelines.[1]

PAH is classified as Group 1 of the pulmonary hypertension (PH) classification, which was recently revised and updated in the Fifth World Symposium on Pulmonary Hypertension, held in Nice, France, in 2013.[2] The four main categories of Group 1 include idiopathic PAH, heritable or familial PAH, drug- and toxin-induced PAH, and PAH associated with other conditions such as connective tissue disease, HIV infection, portal hypertension, congenital heart disease, or schistosomiasis (Table 3).

TABLE 3: 2013 (NICE, FRANCE) PULMONARY ARTERIAL HYPERTENSION CATEGORIES

1 Pulmonary arterial hypertension
1.1 Idiopathic
1.2 Heritable
1.2.1. BMPR2
1.2.2. ALK1, ENG, CAV1, KCNK3, Smad9
1.2.3. Unknown
1.3 Drug- and toxin-induced
1.4 Associated with:
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart disease
1.4.5 Schistosomiasis
1’ Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
1’’. Persistent pulmonary hypertension of the newborn

ALK1 = activin receptor-like kinase type 1; BMPR2 = bone morphogenetic protein receptor type 2; CAV1 = caveolin-1; ENG = endoglin; KCNK3 = potassium channel super family K member-3; Smad 9 = mothers against decapentaplegic 9.
Source: Simonneau 2013.[2]

There are no published data on the incidence or prevalence of PAH in Canada; however, data from US and European registries provide some information.[10-13] The incidence of PAH ranges from 2.3 to 7.6 cases per million based on data from the US, France, Spain, and Scotland. Data on the prevalence of PAH vary from 12.4 (US), 15 to 16 (France, Spain), and 26 to 52 cases per million (Scotland). Based on these figures, and 2014 Canadian population data, the manufacturer estimated there are 434 to 1,820 prevalent cases of PAH, with 81 to 266 new cases developing each year.[14]

1.2 Standards of Therapy

Treatment of PAH is generally categorized as supportive therapy or advanced therapy. Supportive therapy includes use of diuretics, oxygen, anticoagulants, and digoxin. Advanced therapy is targeted at the disease itself. As supportive therapies are generally not effective in PAH, advanced therapy is almost always needed.

Health Canada has approved nine advanced treatment options covering four different classes of drugs for PAH, WHO Group 1:

- Prostacyclin therapies (epoprostenol, treprostinil, selexipag)
- Endothelin receptor antagonist (ERAs) (bosentan, ambrisentan, macitentan)
- Phosphodiesterase type 5 (PDE5) inhibitors (sildenafil, tadalafil)
- Soluble guanylate cyclase (sGC) stimulator (riociguat).

In 2015, CADTH published a Therapeutic Review to assess the comparative efficacy and safety and to determine the cost-effectiveness of pharmacologic treatments for adults with PAH.[3] Results from the systematic review and network meta-analysis suggest that there were no significant differences in clinical worsening and FC worsening between drugs used to treat PAH as monotherapy. For FC improvement and six-minute walk distance (6MWD), epoprostenol appeared to be the most effective treatment option in improving clinical status, while there were no apparent differences among other treatments. Addition of macitentan on PDE5 inhibitor or prostanoids background therapy and addition of riociguat or tadalafil on ERA background therapy produce improvement in clinical worsening, FC improvement, FC worsening, and/or 6MWD versus monotherapy with background therapy. There were no differences between combination therapy of riociguat plus ERA and tadalafil plus ERA in all four clinical outcomes. All drugs showed improvement in pulmonary hemodynamics and health-related quality of life compared with placebo. Adverse events were treatment specific. [3]

Based on the Therapeutic Review and patient group input, the CADTH Canadian Drug Expert Committee (CDEC) recommended the following:

- That sildenafil or tadalafil be the preferred initial therapy for adult patients with FC II and III PAH; and
- Add-on therapy should be used in adult PAH patients who are unable to achieve disease control with a single drug.[4]

CDEC could not make a specific recommendation pertaining to subgroups of patients (based on disease severity or other disease characteristics) who may benefit more from specific drugs of combinations of drugs based on the evidence reviewed. [4]

PAH has a significant impact on the lives of patients and caregivers. Patients with PAH have a day-to-day life that is difficult and exhausting, and they progressively lose the ability to care for themselves. While

therapy may delay progression, reduce the severity of symptoms, and make certain tasks easier, there is still no cure for PAH.

1.3 Drug

Selexipag is an oral, selective, IP receptor agonist, and is structurally and pharmacologically distinct from prostacyclin and its analogues. Selexipag is hydrolyzed by carboxylesterase 1 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 (EP1–EP4, 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 recommended starting dose is 200 mcg given twice daily. The dose is increased in increments of 200 mcg given twice daily, usually at weekly intervals, until adverse pharmacological effects that cannot be tolerated or medically managed are experienced, or until a maximum dose of 1,600 mcg twice daily is reached. The highest tolerated dose reached during dose titration should be maintained. If the therapy over time is less tolerated at a given dose, symptomatic treatment or a dose reduction to the next lower dose should be considered.

Indication under review
Long-term treatment of idiopathic pulmonary arterial hypertension, heritable pulmonary arterial hypertension, pulmonary arterial hypertension (PAH) associated with connective tissue disorders and PAH associated with congenital heart disease, in adult patients with WHO functional class II–III to delay disease progression.[a, b]
Reimbursement criteria requested by sponsor
As per indication

ERA = endothelin receptor antagonist; PAH = pulmonary arterial hypertension; PDE5 = phosphodiesterase type 5; WHO = World Health Organization.

Note: According to the product monograph, selexipag is effective in combination with an ERA or a PDE5 inhibitor, or in triple combination with an ERA and a PDE5 inhibitor, or as monotherapy.

[a] Disease progression included hospitalization for PAH, initiation of intravenous or subcutaneous prostanoids, or other disease progression events (decrease of 6-minute walk distance associated with either worsened PAH symptoms or need for additional PAH-specific treatment).

[b] Selexipag may be used in combination with an ERA or PDE5 inhibitor, or in triple combination with an ERA and a PDE5 inhibitor, or as monotherapy.

TABLE 4: KEY CHARACTERISTICS OF PULMONARY ARTERIAL HYPERTENSION DRUGS AVAILABLE IN CANADA

	Riociguat[15]	Macitentan[16]	Ambrisentan[17]	Bosentan[18]	Sildenafil[19]	Tadalafil[20]	Epoprostenol[21]	Treprostinil[22]	Selexipag[23]
Drug Class	sGC stimulator	ERA			PDE5 inhibitor		Prostacyclin therapies		
Mechanism of Action	Dual mode of action acting in synergy with endogenous nitric oxide and also directly stimulating sGC independently of nitric oxide availability	Decreases mean pulmonary arterial pressure without affecting systemic blood pressure, decreased pulmonary arterial hypertrophy, and right ventricular remodelling	Selective inhibition of the endothelin type A receptor that inhibits C-mediated vasoconstriction	Decreases pulmonary and systemic vascular resistance, resulting in increased cardiac output without increase heart rate	Selective inhibition of PDE5, thereby increasing cGMP, leading to selective vasodilation of the pulmonary vascular bed and systemic circulation	Selective inhibition of PDE5, thereby increasing cGMP, leading to selective vasodilation of the pulmonary vascular bed	Direct vasodilation of pulmonary and systemic arterial beds Inhibition of platelet aggregation	Direct vasodilation of pulmonary and systemic arterial beds Inhibition of platelet aggregation	Prostacyclin receptor agonist; has vasodilatory, anti-proliferative and anti-fibrotic effects
Approved Indications[a]	PAH (WHO Group 1), as monotherapy or in combination with ERAs, in adult patients (≥ 18 years of age) with WHO FC II or III	Idiopathic or heritable PAH of WHO FC II or III, or PAH associated with connective tissue disease or congenital heart disease	Idiopathic ("primary") PAH and PAH associated with connective tissue disease in patients with WHO FC II or III symptoms.	WHO FC III or IV primary PH, or PH secondary to scleroderma or congenital heart disease or HIV in patients who did not respond adequately to conventional therapy	Oral: Primary PH or PH secondary to connective tissue disease in patients with WHO FC II or III who did not respond adequately to conventional therapy Intravenous: Patients who are temporarily unable to take oral medication	Idiopathic primary PAH or PAH associated with connective tissue disease, congenital heart disease, or anorexigen use in patients with WHO FC II or III who have not responded to conventional therapy	The long-term intravenous treatment of idiopathic or heritable PAH or PAH associated with CTDs in patients with WHO FC III-IV symptoms who did not respond adequately to conventional therapy	PAH in NYHA class III and IV patients who did not respond adequately to conventional therapy	Most types of Group 1 PAH in patients with NYHA class II and III Indicated for use as mono, dual or triple therapy

	Riociguat[15]	Macitentan[16]	Ambrisentan[17]	Bosentan[18]	Sildenafil[19]	Tadalafil[20]	Epoprostenol[21]	Treprostinil[22]	Selexipag[23]
Route of Administration	Oral	Oral	Oral	Oral	Oral or intravenous	Oral	Continuous chronic intravenous infusion via central venous catheter	Subcutaneous or intravenous (long-term)	Oral
Recommended Dose	0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg, 2.5 mg three times daily	10 mg once daily	Initial: 5 mg/day Increase: 10 mg/day may be necessary for patients with CTD	Initial: 62.5 mg twice daily for 4 weeks Increase: 125 mg twice daily	Oral: 20 mg three times daily Intravenous: 10 mg three times daily; administered as an intravenous bolus injection	40 mg once daily Patients with mild renal insufficiency: 20 mg once daily, increased to 40 mg once daily based on tolerability Patients with mild or moderate hepatic impairment: 20 mg once daily	Initial: 2 ng/kg/min Incremental increase: 1 to 2 ng/kg/min, with at least 15-minute intervals	Initial: 1.25 ng/kg/min If initial dose cannot be tolerated, rate should be reduced to 0.625 ng/kg/min Dose adjustment: based on PAH signs and symptoms and side effects	Initiate at 200 mcg twice daily; may increase in increments of 200 mcg until toxic effects occur to a maximum of 1,600 mcg twice daily
Contraindications (According to Product Monograph)	PDE5 inhibitors (sildenafil, tadalafil, vardenafil) Nitrates Nitric oxide donors, such as amyl nitrate Patients who are pregnant, or during nursing	Patients who are hypersensitive to drug Patients who are pregnant or may become pregnant	Patients with idiopathic pulmonary fibrosis Patients who are pregnant, breastfeeding, or may become pregnant Patients with severe hepatic impairment or	Patients who are hypersensitive to drug or any excipient in the formulation Patients who are pregnant Patients with moderate or severe liver impairment	Patients on nitrate drug therapy or utilizing short-acting nitrate-containing medications Patients with previous episode of NAION	Patients with previous episode of NAION Patients on nitrate drug therapy	Patients with congestive heart failure due to severe left ventricular systolic dysfunction Patients who develop pulmonary edema during dose initiation	Patients with known hyper-sensitivity to the drug, any of its excipients, or to structurally related compounds	Patients with hyper-sensitivity to the drug or drug formulation

	Riociguat[15]	Macitentan[16]	Ambrisentan[17]	Bosentan[18]	Sildenafil[19]	Tadalafil[20]	Epoprostenol[21]	Treprostinil[22]	Selexipag[23]
			liver enzymes > 3 x ULN	Concomitant use of cyclosporine A or glyburide	In combination with the most potent of the CYP3A4 inhibitors				
Warnings and Precautions (According to Product Monograph)	Risk of hypotension, particularly in patients with concomitant or underlying conditions such as low systemic blood pressure (e.g., systolic blood pressure < 95 mm Hg), coronary artery disease, hypovolemia, severe left ventricular outflow obstruction or autonomic dysfunction, as well as in patients on antihypertensive therapy or with resting hypertension Risk of additive or synergistic effects on systemic blood pressure when concomitantly used with PDE5 inhibitors, nitrates or nitric oxide donors	Potential for hepatic enzyme elevations; therefore, not to be used in patients with moderate-to-severe hepatic impairment Potential for development of decrease in hemoglobin; not recommended for use in patients with severe anemia Patients with moderate or severe renal impairment could experience hypotension and anemia	Patients with clinically significant anemia. Potential development of decreases in hemoglobin and hematocrit Potential for hepatic enzyme elevations; therefore, not to be used in patients with severe hepatic impairment, and used with caution in patients with moderate hepatic impairment Peripheral edema may develop Acute pulmonary edema with the possibility of pulmonary veno-occlusive disease	Reversible increases in liver enzymes; potential for hepatic cirrhosis; liver failure Potential for worsening of chronic heart failure, possibly due to fluid retention Potential for decreases in hemoglobin	Not recommended for patients with pulmonary veno-occlusive disease Patients with abnormal disks or previously diagnosed with NAION, due to potential development of NAION Patients with PH secondary to sickle cell anemia The use of sildenafil with bosentan is not recommended in patients with PAH associated with CTD	Potential to significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease Patients with abnormal disks or previously diagnosed with NAION, due to potential development of NAION Patients with severe renal or hepatic insufficiency	Abrupt withdrawal should be avoided Not to be used in patients having pulmonary edema during dose initiation Acute dose initiation must be performed in hospital with adequate personnel and equipment for physiologic monitoring and emergency care Increased risk for hemorrhagic complications in patients with other risk factors for bleeding	Abrupt withdrawal should be avoided Administration must be performed in hospital with adequate personnel and equipment for physiological monitoring and emergency care Dosage should be adjusted at the first sign of recurrence or worsening of symptoms attributable to PAH or the occurrence of intolerable adverse events	Potential interactions with strong inhibitors or inducers of CYP2C8, UGT1A3, and UGT2B7. Caution in patients with hepatic or renal impairment, patients prone to hypotension. Risk of developing hyper-thyroidism, pulmonary veno-occlusive disease

	Riociguat[15]	Macitentan[16]	Ambrisentan[17]	Bosentan[18]	Sildenafil[19]	Tadalafil[20]	Epoprostenol[21]	Treprostinil[22]	Selexipag[23]
	Risk of bleeding particularly in patients taking anticoagulants. May worsen cardiovascular status of patients with pulmonary veno-occlusive disease				Caution is advised when co-administered with alpha-blockers, as both are vasodilators with blood pressure–lowering effects				

cGMP = cyclic guanosine monophosphate; CTD = connective tissue disease; ERA = endothelin receptor antagonist; FC = functional class; IPAH = idiopathic pulmonary arterial hypertension; NAION = non-arteritic anterior ischemic optic neuropathy; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PDE5 = phosphodiesterase type 5 inhibitor; PH = pulmonary hypertension; sGC = soluble guanylate cyclase; ULN = upper limit of normal; WHO = World Health Organization.

[a] Health Canada indication.

Source: Product monographs.[15-18,18,19,21-23]

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of selexipag for the treatment of PAH in adults.

2.2 Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase III studies were selected for inclusion based on the selection criteria presented in Table 5.

TABLE 5: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adults (≥ 18 years of age) with PAH (idiopathic PAH, heritable PAH, PAH associated with connective tissue disorders and PAH associated with congenital heart disease) in WHO FC II or III pulmonary hypertension **Subpopulations:** • Patients unable to achieve disease control with another PAH therapy • FC • Patients receiving mono or combination PAH therapy, by drug class
Intervention	Selexipag as monotherapy or in combination with ERAs and/or PDE5 inhibitors, at Health Canada–approved doses
Comparators	Medical intervention/pharmacotherapy: • ERAs (bosentan, macitentan, ambrisentan) • PDE5 inhibitors (sildenafil, tadalafil) • Prostacyclin therapies (epoprostenol, treprostinil) • Soluble guanylate cyclase stimulator (riociguat)

Outcomes	**Key efficacy outcomes:**
	• Survival[a]
	• Hospitalization
	• Clinical worsening[a]
	• Change in WHO FC
	• HRQoL[a]
	Other efficacy outcomes:
	• 6MWD
	• Cardiopulmonary exercise testing
	• Change in pulmonary hypertension symptoms
	• Change in:
	  ○ mPAP
	  ○ Cardiac index
	  ○ BNP/NT-pro-BNP
	Harms outcomes:
	• AEs[a]
	• Serious AEs[a]
	• WDAEs
	• AEs of interest: gastrointestinal adverse events, syncope, anemia, headache, jaw pain

Study Design	Published and unpublished phase III RCTs

6MWD = six-minute walk distance; AE = adverse event; BNP = brain natriuretic peptide; ERA = endothelin receptor antagonist; FC = functional class; HRQoL = health-related quality of life; mPAP = mean pulmonary artery pressure; NT-pro-BNP = N-terminal prohormone of brain natriuretic peptide; PDE5 = phosphodiesterase PAH = pulmonary arterial hypertension; RCT = randomized controlled trial; WDAE = withdrawal due to adverse events; WHO = World Health Organization.
[a] These outcomes were identified as important to patients (Appendix 1).

The literature search was performed by an information specialist using a peer-reviewed search strategy. Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates via Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Uptravi (Selexipag).

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on April 28, 2016. Regular alerts were established to update the search until the CDEC meeting on September 21, 2016. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Devices Regulatory Approvals, Advisories and Warnings, Drug Class Review, Databases (free). Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CADTH Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 6; excluded studies (with reasons) are presented in APPENDIX 3: EXCLUDED STUDIES.

3. RESULTS

3.1 Findings From the Literature

One study was identified from the literature for inclusion in the systematic review (Figure 1). The studies are summarized in Table 6 and described in section 3.2. A list of excluded studies is presented in APPENDIX 3: EXCLUDED STUDIES.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

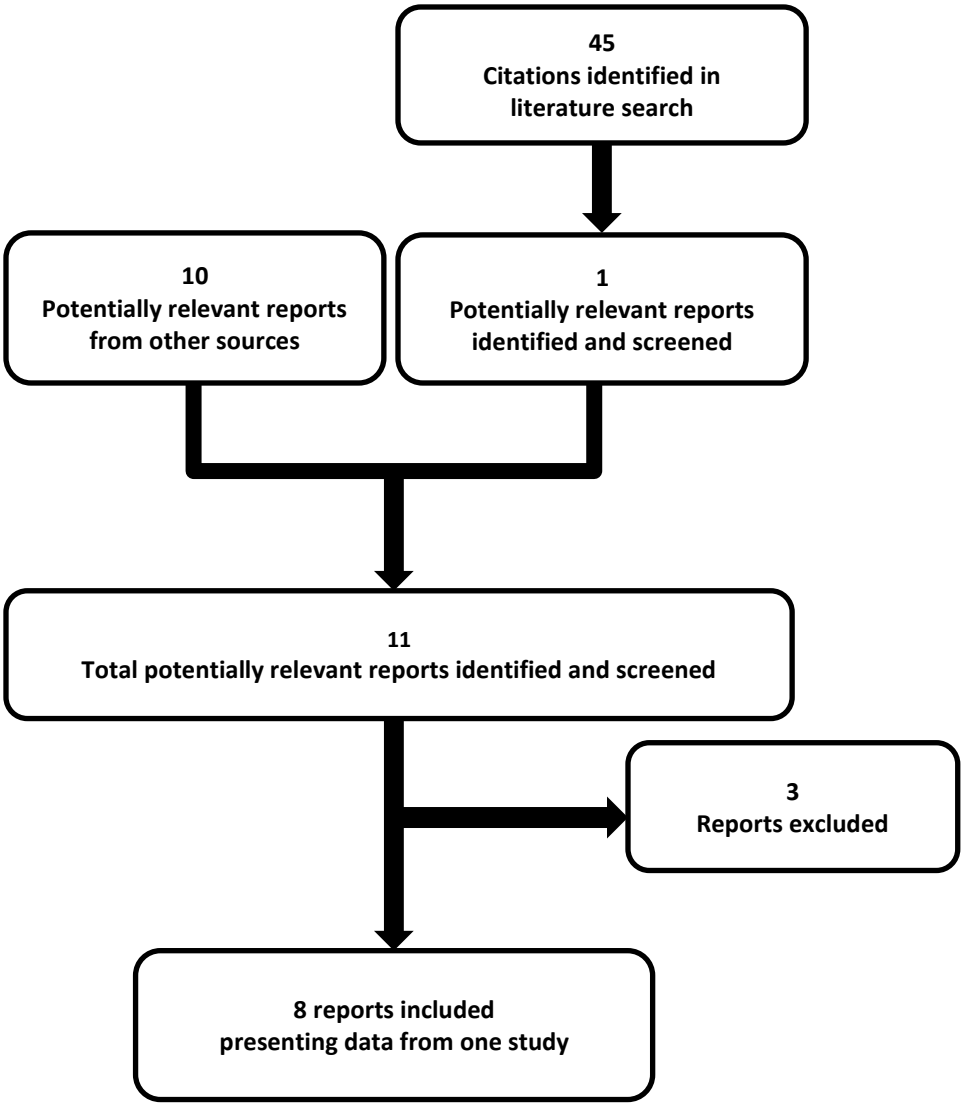


TABLE 6: DETAILS OF INCLUDED STUDY

		GRIPHON Study
DESIGNS & POPULATIONS	**Study Design**	DB RCT, event-driven, placebo-controlled, group-sequential trial with interim analysis
	Locations	181 sites in 39 countries (Asia, Australia, Europe, Latin America, and North America)
	Randomized (N)	1,156 patients were randomized between December 30, 2009, and May 17, 2013. Last patient, last visit was on April 27, 2014.
	Inclusion Criteria	• Patients aged 18 to 75 years with Group 1 symptomatic PAH (idiopathic PAH, heritable PAH, or PAH associated with HIV infection, drug use or toxin exposure, connective tissue disease, or repaired congenital systemic-to-pulmonary shunts at least one year after surgical repair) • Patients without treatment for PAH or patients receiving an ERA or PDE5 drugs • Confirmation of the diagnosis by means of right heart catheterization was required before screening • Resting mean pulmonary arterial pressure ≥ 25 mm Hg • Resting pulmonary vascular resistance ≥ 400 dyn·s·cm^{-5} • Pulmonary capillary wedge pressure or left ventricular end diastolic pressure ≤ 15 mm Hg • 6MWD between 50 m and 450 m
	Exclusion Criteria	• Other forms of Group 1 PAH not included above • Pulmonary hypertension Groups 2 to 5 • Prostacyclin (epoprostenol) or prostacyclin analogues (i.e., treprostinil, iloprost, beraprost) up to 1 month prior to baseline • Moderate or severe obstructive lung disease: FEV_1/FVC < 70% and FEV_1 < 65% of predicted value after bronchodilator administration • Moderate or severe restrictive lung disease: Total lung capacity < 70% of predicted value • Moderate or severe hepatic impairment • Documented left ventricular dysfunction (i.e., ejection fraction < 45%) • Creatinine clearance < 30 mL/min • Recently conducted cardiopulmonary rehabilitation program based on exercise training • Life expectancy less than 12 months
DRUGS	**Intervention**	Starting dose of selexipag was 200 mcg twice daily and was increased weekly in twice-daily increments of 200 mcg until unmanageable adverse effects or 1,600 mcg twice daily was reached
	Comparator	Placebo
	Background Therapy	Concomitant ERAs and PDE5 inhibitors were permitted
DURATION	**Dose Titration and Follow-up**	12 weeks dose titration Duration: This was an event-driven trial. The required number of primary outcome events was 331. Median time in placebo group: 63.7 weeks; median time in selexipag group: 70.7 weeks
OUTCOMES	**Primary End Point**	Composite of death or a morbidity event related to PAH (time to first event). Morbidity events were defined as disease progression or worsening of PAH that resulted in hospitalization, initiation of parenteral prostanoid therapy or long-term oxygen therapy, or the need for lung transplantation or balloon atrial septostomy.

		Disease progression was defined as a decrease from baseline of at least 15% in the 6MWD accompanied by a worsening in WHO FC or the need for additional treatment of PAH
	Other End Points	• Change in 6MWD to week 26 • Absence of worsening from baseline to week 26 in WHO FC • Death due to PAH or hospitalization for worsening of PAH • Change in NT-proBNP level to week 26 • CAMPHOR • Harms
NOTES	**Publications**	Sitbon 2015[9]

6MWD = six-minute walk distance; CAMPHOR = Cambridge Pulmonary Hypertension Outcome Review; DB = double-blind; ERA = endothelin receptor antagonists; FC = functional class; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; NT-proBNP = N-terminal pro-brain natriuretic peptide; PAH = pulmonary arterial hypertension; PDE5 = phosphodiesterase type 5 inhibitors; RCT = randomized controlled trial; WHO = World Health Organization.
Note: Four additional reports were included (CADTH Common Drug Review Submission,[24] FDA Medical and Statistical Reports,[25,26] Health Canada Reviewer report.[27])
Source: Sitbon 2015,[9] Clinical Study Report,[8] Study Protocol,[28] Supplemental Appendix.[7]

1.4 Included Studies

1.4.1 Description of study

The GRIPHON study, a double-blind, event-driven, placebo-controlled, group-sequential trial, met the inclusion criteria and is summarized in Table 6. The primary objective of the study was to demonstrate the effect of selexipag on time to first primary outcome event in patients with PAH. The duration of the study depended on the occurrence of the primary outcome events. Patients were randomized 1:1 to selexipag or placebo via a central randomization system. Randomization was stratified by site. A block size of four was used. Identical placebo was used and the investigator and study staff, patients, monitors, and sponsor were blinded to the treatment.

1.4.2 Population

a) Inclusion and exclusion criteria

The trial included patients who had a diagnosis of PAH consistent with one of the categories of Group 1 PAH (Table 3). A few Group 1 categories were excluded, such as PAH associated with portal hypertension or schistosomiasis. Patients who were not receiving treatment for PAH and those who were receiving an ERA, a PDE5 inhibitor, or both at a dose that had been stable for at least three months were eligible for enrolment; patients who were receiving prostacyclin analogues were not eligible.

Baseline characteristics

The majority of patients were female (80%), had idiopathic PAH (56%), were classified as WHO FC II (46%) or III (53%) and had a mean time since PAH diagnosis slightly greater than two years. Eighty per cent of patients were taking one or two concomitant medications for PAH at baseline. The distribution of patients by geographical region was Eastern Europe (26.3%), Asia (19.7%), Latin America (9.5%), North America (16.7%), and Western Europe and Australia (27.8%). [redacted] of 1,156 patients [redacted] were enrolled in Canada.

Prognostic risk factors were well balanced between selexipag and placebo groups at baseline.

TABLE 7: SUMMARY OF BASELINE CHARACTERISTICS IN THE GRIPHON STUDY

Characteristic	Selexipag N = 574	Placebo N = 582
Female, n (%)	457 (80)	466 (80)
Mean age (SD), years	48 (15)	48 (16)
Ethnicity		
Caucasian or Hispanic	427 (74)	438 (75)
Asian	125 (22)	120 (21)
Mean time since PAH diagnosis (SD), years	2.3 (3.5)	2.5 (3.8)
PAH Classification, n (%)		
Idiopathic	312 (54)	337 (58)
Heritable	13 (2)	13 (2)
Drug or toxin-induced	17 (3)	10 (2)
Connective tissue disease	167 (29)	167 (29)
Congenital heart disease	60 (10)	50 (9)
HIV	5 (1)	5 (1)
WHO Functional Class		
I	4 (1)	5 (1)
II	274 (48)	255 (44)
III	293 (51)	314 (54)
IV	3 (< 1)	8 (1)
Mean 6MWD (SD), m	358 (76)	348 (83)
Mean Borg Dyspnea Index (SD)	[redacted]	[redacted]
PAH medications concomitant at baseline, n (%)		
None	112 (20)	124 (21)
ERA monotherapy	94 (16)	76 (13)
PDE5 inhibitor monotherapy	189 (33)	185 (32)
ERA and PDE5 inhibitor	179 (31)	197 (34)

6MWD = six-minute walk distance; ERA = endothelin receptor antagonists; PAH = pulmonary arterial hypertension; PDE5 = phosphodiesterase 5; SD = standard deviation; WHO = World Health Organization.
Source: Sitbon 2015,[9] Clinical Study Report.[8]

1.4.3 Interventions

The initial dose of selexipag was 200 mcg twice daily. If this was well tolerated, the dose was increased by weekly increments of 200 mcg until 1,600 mcg twice daily was reached at week 12. If the patient experienced adverse events known to be associated with IP receptor agonists, such as headache, diarrhea, jaw pain, myalgia, flushing, and nausea, the dose could be maintained or reduced and the adjusted dose was to be defined as the maximum tolerated dose. At week 12, the maximum tolerated dose for each patient was determined, and this dose was to be kept stable for the next 14 weeks, up to the week 26 assessment of the secondary end point, change in 6MWD. After week 26, for patients with study drug dose < 1,600 mcg twice daily, investigators were allowed to further up-titrate the dose, if needed, by 200 mcg increments up to the maximum of 1,600 mcg twice daily, if the investigator identified a tolerability concern for a patient. The investigators could discontinue study treatment at their discretion.[8]

TABLE 8: MAINTENANCE DOSE OF SELEXIPAG IN THE SELEXIPAG TREATMENT GROUP IN GRIPHON

Twice Daily Dose	Selexipag N = 575 N (%)	Placebo N = 582 N (%)
0 mcg	14 (2)	9 (2)
200 mcg	68 (12)	15 (3)
400 mcg	65 (11)	18 (3)
600 mcg	62 (11)	20 (3)
800 mcg	82 (14)	21 (4)
1,000 mcg	35 (6)	27 (5)
1,200 mcg	42 (7)	20 (3)
1,400 mcg	41 (7)	55(10)
1,600 mcg	163 (28)	393 (68)
Dosing contrary to protocol	2 (< 1)	4 (1)

Source: Clinical Study Report.[8]

Of the selexipag-treated patients, 28% received a selexipag maintenance dose of 1,600 mcg twice daily (Table 8; i.e., the maximum selexipag dose allowed in the study) and in the placebo group, the highest number of tablets corresponding to the 1,600 mcg twice daily dose was achieved by 68% of patients. In 14 patients taking selexipag (2%), the selexipag maintenance dose was set to 0 (i.e., patients who received only the initial selexipag 200 mcg dose during the titration period and discontinued at this dose).

Concomitant therapy protocol rules in the GRIPHON study
Concomitant ERAs and/or PDE5 inhibitors were allowed if patients had been on a stable dose for at least three months prior to baseline. The dose was to remain unchanged during study treatment up to week 26. Diuretics were permitted. Introduction of any new treatment for PAH (or increase in dose) without a morbidity or mortality event confirmed by the Critical Event Committee (CEC) was permitted but discouraged. Concomitant administration of prostacyclin (epoprostenol) or prostacyclin analogues (i.e., treprostinil, iloprost, beraprost) was not permitted according to the study protocol.

Concomitant therapy for pulmonary arterial hypertension at baseline
There were differences in concomitant therapy at baseline across geographical groups. In an analysis by geographical region, [redacted] of patients in the selexipag and placebo groups in the geographical regions of North America, Western Europe, and Australia, including Israel and Latin America, were receiving a PAH-specific medication at baseline compared with approximately [redacted] in Asia and [redacted] in Eastern Europe, including Turkey. Most of the patients in North America ([redacted] and Western Europe and Australia, including Israel ([redacted] were receiving treatment with two PAH-specific therapies. Sildenafil was the most frequently reported PDE5 inhibitor used as monotherapy in [redacted].[8]

Concomitant therapy for pulmonary arterial hypertension while on study drug
In spite of the protocol guidelines, [redacted] of patients in the selexipag group and [redacted] in the placebo group started treatment with a PAH-specific medication *while on study drug*.[8] Treatment with two PAH-specific therapies (an ERA and a PDE5 inhibitor) was initiated for [redacted] of patients in the selexipag and placebo groups, respectively, with bosentan and sildenafil the most frequently reported ERA and PDE5 inhibitor combination ([redacted]).

The proportion of patients who started treatment with a PDE5 inhibitor (monotherapy) *while on study drug* was [redacted] in the selexipag group compared with [redacted] in the placebo group, with sildenafil reported for [redacted] patients in the selexipag group and [redacted] in the placebo group. A total of [redacted] patients in the selexipag group and [redacted] the placebo group started treatment with an ERA (monotherapy) while on study drug, with bosentan reported for [redacted] patients in the selexipag group and [redacted] the placebo group.

Initiation of treatment with a prostacyclin or prostacyclin analogue *while on study drug* was reported for [redacted] patients in the selexipag group and [redacted] the placebo group. The proportion of patients who started treatment with epoprostenol was [redacted] the selexipag group and [redacted] the placebo group.

The proportion of patients who started treatment with at least one PAH-nonspecific medication *while on study drug* was [redacted] in the selexipag and placebo groups, respectively. Diuretics (e.g., furosemide, spironolactone) were the most frequently reported medications in both groups ([redacted]). The proportions of patients who concomitantly received oxygen were [redacted] the selexipag group and [redacted] the placebo group, calcium channel blockers ([redacted]).

PAH medication started after study drug discontinuation
In response to a request for additional information (June 30, 2016), the manufacturer stated that PAH-specific medication that was initiated after study drug discontinuation, before the end of the study, occurred [redacted] patients in the selexipag group and [redacted] patients in the placebo group.

1.4.4 Outcomes

Primary End Point:
An independent CEC adjudicated all reported morbidity or mortality events. The committee was blinded to each patient's study treatment allocation and to the occurrence of typical prostacyclin-associated adverse events. The primary outcome in GRIPHON was time to first CEC-confirmed morbidity or mortality event up to seven days after the last study drug intake. The following morbidity or mortality events were considered:

- Death (all causes)
- Hospitalization for worsening of PAH defined as any non-elective hospital stay (≥ 24 hours) for worsening of PAH
    - Worsening of PAH included signs and symptoms of right heart failure (e.g., syncope or near syncope, cyanosis, increase of breathlessness, clinically relevant deterioration of exercise capacity, decrease of oxygen saturation, increased peripheral edema, hepatomegaly, and ascites)
- Worsening of PAH resulting in need for lung transplantation or balloon atrial septostomy
- Initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH
    - Chronic oxygen therapy was defined as a continuous use (24 hours, seven days per week) of oxygen, with the intention of maintaining the therapy long-term
- Disease progression (patients in modified WHO FC II or III at baseline) confirmed by a decrease in 6MWD from baseline (≥ 15%, confirmed by two tests on different days within two weeks) and worsening of WHO FC
- Disease progression (patients in WHO FC III or IV at baseline) confirmed by a decrease in 6MWD from baseline (≥ 15%, confirmed by two tests on different days within two weeks) and the need for additional PAH-specific therapy

- (Patients in WHO morbidity/mortality III at baseline were qualified for both the above disease progression definitions).

Secondary End Points (Listed in Order of Testing Hierarchy):

- Absolute change from baseline to week 26 in 6MWD measured at dosing trough
- Absence of worsening from baseline to week 26 in WHO FC
- Time from randomization to first CEC-confirmed death due to PAH or a CEC-confirmed hospitalization due to PAH worsening up to seven days after last study drug
    - The following two CEC-confirmed morbidity or mortality events were considered:
        - Hospitalization for worsening of PAH based on predefined criteria
        - Death due to PAH
- Time from randomization to death of all causes up to study closure
- Absolute change from baseline to week 26 in the subscale Breathlessness of Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) Symptoms. The subscale Breathlessness of CAMPHOR Symptoms was defined as the sum of the breathlessness items 11 to 18. It ranged from 0 (good) to 8 (poor)
- Absolute change from baseline to week 26 in CAMPHOR Symptoms score. The CAMPHOR Symptoms score was defined as the sum of the symptoms 1 to 25. It ranged from 0 (good) to 25 (poor).

Other End Points:

- Borg dyspnea index

Safety End Points:

- adverse events, serious adverse events, study drug discontinuation due to adverse events
- electrocardiogram abnormalities
- thyroid markers, bone turnover markers
- fundoscopy.

1.4.5 Statistical Analysis[8,9]

a) Primary outcome

GRIPHON had a group-sequential design for the primary outcome with options to recommend stopping for futility or for compelling efficacy at the interim analysis. Initial estimates were that 202 primary end point events would be needed for the study to have 90% power to detect a hazard ratio (HR) of 0.57 for the primary end point with selexipag, as compared with placebo, over an estimated study duration of 3.5 years, assuming a HR of 0.22 per year in the placebo group, at a one-sided type I error rate of 0.005. Authors assumed that to reach that number of primary end point events, they would need to enrol 670 patients over the course of two years, assuming an annual rate of attrition of 5%. Twenty months after the study was initiated, a blinded review of baseline data from 154 patients indicated that more patients than expected were receiving background therapy for their disease. Therefore, the hypothesized HR was changed from 0.57 to 0.65 to reflect a lower anticipated treatment effect. It was reported that to preserve the type I and type II error rates and the study duration, the required number of primary end point events was increased to 331 and the required number of patients was increased to 1,150. An independent data and safety monitoring committee performed an interim analysis, which had been planned after 202 events had occurred, with stopping rules for futility and efficacy that were based on Haybittle–Peto boundaries. The final analysis used a one-sided significance level of 0.00499.[9]

The primary end point analysis was an on-treatment analysis with follow-up data censored at the time selexipag or placebo was discontinued. No data imputation was used for the primary end point. The primary analysis of the primary outcome was performed on the full analysis set (FAS; see section 3.2.5.1 for description) using a one-sided unstratified log-rank test. Supportive time-to-event analyses of the primary outcome were performed, stratifying for variables including geographical region, PAH etiology, WHO FC at baseline and PAH medication at baseline.

TABLE 9: SUMMARY OF GROUP-SEQUENTIAL DESIGN

Analysis Stage (Anticipated Cumulative Number of Primary Outcome Events)	Guidance to Data Monitoring Committee to Reject Null Hypothesis
Interim (202 events)	$P \leq 0.00005$ (i.e., stopping rule for clear efficacy of selexipag)
Final (331 events)	$P \leq 0.00499$

Note: *P* values are one-sided and based on the log-rank test.
Source: Clinical Study Report.[8]

***Secondary outcomes, analysis procedures and data imputation*[26]**
Secondary outcomes were tested hierarchically to control for multiplicity. In time-to-event analyses, end points were estimated with the use of the Kaplan–Meier method and were analyzed with the use of the log-rank test. HRs with 99% confidence intervals (CIs) (for primary and secondary end points) and 95% CIs (for exploratory end points) were estimated with the use of proportional-hazard models.

In case of rejection of the null hypothesis in the main statistical analysis of the primary efficacy end point, the null hypotheses for the secondary efficacy end points were tested in a conditional hierarchical manner (as listed in section 3.2.4). A null hypothesis was rejected if the main analysis of the end point and all main analyses of preceding secondary efficacy end points resulted in rejection of respective null hypotheses.[26]

Six-minute walk distance
For the secondary outcome of absolute change from baseline in 6MWD at week 26, the main analysis was performed on the FAS (see section 3.2.5.1 for description). The following non-parametric analysis of covariance (ANCOVA) procedure was used:

1. Transformation of baseline and post-baseline values for all patients (regardless of treatment groups) to standardized ranks (i.e., ranks divided by the number of patients ranked plus 1, mean ranks in case of ties)
2. Determination of residuals from the linear regression of the response variable standardized ranks on baseline variable standardized ranks
3. Application of the one-sided Wilcoxon–Mann–Whitney test to these residuals. The standardized test statistic with a continuity correction of 0.5 is an asymptotically standard normally distributed under the null hypothesis. A one-sided significance level of 0.005 is used.

For the main analysis, all available 6MWD data at week 26 were used irrespective of whether the test was performed at trough or not. For patients without any 6MWD data available at week 26, the following main imputation algorithm was applied:

Rule 1: for patients unable to walk at week 26, this included the following:

- Patients who died before study day 271 (upper limit of the week 26 time window) without any visit performed in the week 26 time window
- Patients for whom the week 26 visit corresponded to a clinical worsening event visit and who were unable to walk for PAH reasons (i.e., reason was "Dyspnea/Fatigue" or reason was coded as "Related to Pulmonary Arterial Hypertension"); a value of 0 was imputed for 6MWD at week 26.

Rule 2 (if rule 1 did not apply): the second-lowest observed 6MWD value at week 26 in the same analysis set, irrespective of study treatment group, was imputed. In the FAS, this was 10 m.

Absence of worsening in World Health Organization(WHO) functional class at week 26
The main analysis was performed on the FAS excluding patients in WHO FC IV at baseline. A Cochran–Mantel–Haenszel test stratified by WHO FC at baseline was used. For patients with missing WHO FC at week 26, the WHO FC was considered as having worsened from baseline at week 26 in the main analysis.

Other secondary end points:
The main analyses for the remaining time-to-event and continuous secondary end points were tested similarly as the primary end point and key secondary end point, respectively. (Note: As explained in the Efficacy section [3.6], in the FAS, the statistical significance stopped at absence of worsening from baseline in WHO FC at week 26.)

Summary of major protocol changes affecting statistical analyses, and added after patient enrolment had begun in the GRIPHON study:[26]

- The primary outcome was changed from 6MWD to time to first morbidity or mortality event.
- An interim analysis was added to the protocol and would occur after observing 202 primary outcome events.
- By August 16, 2011, a total of 47 primary outcome events had occurred and the authors increased the target number of primary outcome events from 202 to 332. The sample size was increased from 670 to 1,150. Subsequently, two of these patients experienced a primary outcome event. Therefore, the main analysis of the primary outcome excluded 45 primary outcome events (15 in the selexipag group and 30 in the placebo group). A sensitivity analysis was planned that will include these 45 primary outcome events.[8,26]

b) Analysis populations

The main statistical analyses for the efficacy end points were performed on the FAS, which included all randomized patients and evaluated patients based on the group to which they were randomized. The per-protocol (PP) set included patients from the FAS, but excluded some patients who did not meet certain criteria specified in the protocol. PP set analyses were considered supplemental analyses to the main analyses. The safety analysis set included all randomized patients who had received at least one dose of the study drug.

1.5 Patient Disposition

TABLE 10: PATIENT DISPOSITION

	GRIPHON	
Screened, N	1,351	
Failed screening, n (%)	195 (14)	
Most common reason for screening failure, n (%)		
6MWD not within protocol range	46 (23)	
Moderate or severe obstructive lung disease	19 (10)	
Hemodynamic values not within protocol range	17 (9)	
	Selexipag	**Placebo**
Randomized, N (%)	574 (100)	582 (100)
Treated, n (%)	574 (100)	578 (99)
Full analysis set	574	582
Safety analysis set	575	577
Patients performed end-of-study visit, n (%)	500 (87)	520 (89)
Patient withdrew consent except vital status, n (%)	44 (8)	39 (7)
Patient withdrew consent from all, n (%)	20 (4)	19 (3)
Vital status at study closure		
Missing	0	1
Alive	450 (78)	449 (77)
Died	100 (17)	105 (18)
Not known	24 (4)	27 (5)
Discontinued study drug, n (%)[a]	280 (49)	319 (55)
Discontinued due to clinical worsening event	117 (20)	83 (14)
Discontinued study drug without CEC, n (%)[b]	148 (26)	97 (17)
Patient consented to post-treatment observation period, n (%)	113 (20)	137 (24)

6MWD = six-minute walking distance; CEC = Critical Event Committee.
Source: Clinical Study Report.[8]
[a] Includes patients with or without a CEC-confirmed primary outcome event
[b] In this analysis, patients who discontinued study drug prior to study closure and who did not have a CEC-confirmed primary outcome event with an onset date prior to, or on the date of study drug discontinuation were considered.[8]

During the trial, the investigator was to interrupt or permanently discontinue the study treatment if continued administration was believed to be contrary to the best interests of the patient. Discontinuation of the study drug could be due to the occurrence of a primary outcome event or occur independently of such an event. The number of patients who discontinued the study drug prior to study closure was slightly lower in the selexipag group (49%) compared with placebo (55%). When patients who had a CEC-confirmed primary outcome event were excluded, the reverse pattern was observed, with more patients discontinuing the study drug in the selexipag group (26%) compared with placebo (17%).[8] Further details on patient disposition in the GRIPHON study can be found in Appendix 4.

1.6 Exposure to Study Treatments

The duration of the study was not fixed a priori, but depended on the occurrence of primary outcome events; the median duration on treatment in the selexipag group was 70.7 weeks (range: 0.3 to 217 weeks) and the median in the placebo group was 63.7 weeks (range: 0.7 to 192 weeks).

Treatment period was concluded with an end-of-study visit at the time of study closure announcement (i.e., once the overall target number of 331 CEC-confirmed morbidity or mortality events with onset date up to seven days after last study drug intake was achieved), which was to be performed within four weeks of the study closure announcement. For patients who had a CEC-confirmed morbidity or mortality event or those who prematurely discontinued the study drug prior to study closure, the end-of-study visit occurred following the morbidity event or following premature discontinuation.[8]

1.7 Critical Appraisal

1.7.1 Internal validity

- The GRIPHON study applied adequate methods for blinding, randomization, and allocation concealment via centralized treatment allocation procedures. Baseline prognostic factors were well balanced at the beginning of the trial between the selexipag and placebo groups. Matched placebo, including sham titration for placebo, was used to maintain blinding.
- A blinded CEC adjudicated all reported morbidity or mortality events, which would be expected to reduce bias for the analyses of the primary outcome of the study.
- There were several amendments to the protocol, including a change in the primary outcome and an increase in sample size. These were significant changes that would have potential to bias the results of the study if the reason for the changes was related to the results that were emerging at the time of the amendments. To mitigate this risk, the manufacturer performed analyses on the primary outcome that both included and excluded the 46 events that occurred prior to the sample size increase (August 16, 2011). The time-to-event results were similar when these 46 primary outcome events were included or excluded, reducing concern that the post-hoc sample size adjustments had introduced bias.
- The investigators applied means to reduce the risk of type I error through use of 99% CIs and a hierarchical testing procedure for secondary outcomes. The rationale for the order of the hierarchy was not clearly explained. The 6MWD was the first outcome in the hierarchy, but it is not as clinically relevant to patients as outcomes further down the hierarchy (e.g., time to death from any cause). Additionally, subgroup analyses were not included in the hierarchy and, given the number of comparisons tested, these are potentially subject to inflated type I error.
- Vital status was unknown in approximately 5% of patients at the end of the study. While this represents reasonably complete follow-up for a study of this duration, these missing data would have the potential to impact the analyses of rare outcomes such as death.
- Prognostic factors at baseline were well balanced, but the initiation of concomitant medications for PAH (e.g., PDE5 inhibitors and ERAs) during the study occurred in [redacted] of patients in the selexipag and [redacted] in the placebo groups and this may have introduced treatment bias. The direction of the bias cannot be ascertained with certainty, but if the placebo group received more aggressive concomitant therapy approaches than the selexipag patients, this could bias the results toward the placebo group. The higher rate of PAH-specific therapies in the placebo group could also have resulted in underestimating the difference in adverse event rates between selexipag and placebo because some of the adverse events occurring in the placebo group would have been caused by concomitant PAH therapies.

1.7.2 External validity

- [redacted] patients in the trial were enrolled at Canadian sites. Compared with the overall group of patients in GRIPHON, patients who are candidates to receive selexipag in Canada may be slightly older, with a higher male representation. There were substantial differences in rates of concomitant PAH therapies at baseline across the different geographical regions. In spite of these

potential differences and the small Canadian group in the study, the clinical expert for this review believed that the overall population of the GRIPHON study was reasonably similar to the Canadian population in which selexipag would be used.

- Selexipag is indicated for mono, dual, or triple therapy. Treatment with stable doses of ERAs and/or PDE5 inhibitors was permitted at the study start and new ERAs or PDE5 inhibitors could be added during the study. The overall trial population was heterogeneous with respect to the number and type of concomitant PAH agents and the trial was not specifically designed to compare monotherapy versus dual therapy versus triple therapy. Therefore, there is uncertainty regarding the population to which the results are generalizable, with respect to concomitant therapies.

1.8 Efficacy

Only those efficacy outcomes identified in the review protocol are reported in Table 5, section 2.2. See APPENDIX 4: DETAILED OUTCOME DATA for detailed efficacy data.

Note that the variability for some estimates in the GRIPHON study was expressed as a 99% CI.

1.8.1 Deaths

There were multiple analyses of deaths in the GRIPHON trial. A total of 100 and 105 patients in the selexipag and placebo groups, respectively, died up to study closure (HR 0.97; 99% CI, 0.68 to 1.39). Death was a component of the composite primary outcome of GRIPHON (see section 3.2.4). Death as a first primary outcome event from any cause up to seven days after the last dose of the study drug [redacted] in the selexipag group [redacted] compared with the placebo group [redacted] see first subcomponent of clinical worsening, Table 1). However, these numbers need to be interpreted cautiously because of the competing nature of the primary outcome events; i.e., the CEC-confirmed event with the earliest onset ("first" was considered. For this reason, other analyses of the deaths in GRIPHON were performed, such as analyses in Table 11. These analyses include all deaths that occurred up to the time point specified, including deaths that occurred subsequent to a primary end point morbidity event.[6]

Cumulative incidence of death up to end of study is summarized in Table 12. The incidence of death up to end of study is numerically lower in the selexipag group, relative to placebo at all time points.

TABLE 11: ALL-CAUSE AND PULMONARY ARTERIAL HYPERTENSION–RELATED DEATHS

Analyses of Deaths	GRIPHON Study		
	Selexipag N = 574	Placebo N = 582	HR (99% CI)
All deaths up to study closure[a]	100 (17.4)	105 (18.0)	0.97 (0.68 to 1.39)
Deaths due to PAH up to study closure[a]	70 (12.2)	83 (14.3)	0.86 (0.63 to 1.18)
All deaths up to EOT + 7 days	46 (8.0)	37 (6.4)	1.17 (0.66 to 2.07)[6]
All deaths up to EOT + 30 days	[redacted]	[redacted]	[redacted]

CI = confidence interval; EOT = end of treatment; HR = hazard ratio; PAH = pulmonary arterial hypertension.
[a] The median follow-up times for all deaths to study closure was selexipag 98.3 weeks and placebo 98.0 weeks.[6]
Note: These data are from the full analysis set.
Source: Clinical Study Report;[8] additional information from the manufacturer.[6]

TABLE 12: CUMULATIVE INCIDENCE OF DEATH UP TO END OF STUDY

	All-Cause Deaths		PAH-Related Deaths	
Study Time Point	**Selexipag**	**Placebo**	**Selexipag**	**Placebo**
Month 6	[redacted]	[redacted]	[redacted]	[redacted]
Month 12	[redacted]	[redacted]	[redacted]	[redacted]
Month 18	[redacted]	[redacted]	[redacted]	[redacted]
Month 24	[redacted]	[redacted]	[redacted]	[redacted]
Up to end of study	[redacted]	[redacted]	[redacted]	[redacted]

PAH = pulmonary arterial hypertension.
Source: Additional information from the manufacturer.[6]

1.8.2 Hospitalization

The annualized numbers of PAH hospitalizations up to the end-of-study treatment were 147 for the selexipag group and 167 for the placebo group. The annualized number of hospitalizations per year for all causes was 349 for the selexipag group and 344 for the placebo group. There were no statistically significant differences in overall hospitalization rates or number of days spent in hospital after these rates were adjusted for cumulative time on study at the group level (Table 13).

TABLE 13: HOSPITALIZATION FOR ANY CAUSE DURING GRIPHON

	Selexipag N = 574	Placebo N = 582
PAH-related hospitalizations up to end-of-study visit	[redacted]	[redacted]
Number of hospitalizations for all causes up to end-of-study visit	[redacted]	[redacted]
Cumulative time on study	[redacted]	[redacted]
Group level annualized number of hospitalizations/year	[redacted]	[redacted]
Total number of days spent in hospital	[redacted]	[redacted]
Group level annualized number of days spent in hospital/year	[redacted]	[redacted]

PAH = pulmonary arterial hypertension.
Source: Clinical Study Report.[8]

1.8.3 Clinical worsening

The composite primary outcome of morbidity and mortality event met the review protocol definition for clinical worsening; the results can be found in Table 1. Overall, [redacted] selexipag patients [redacted] patients ([redacted]) had a primary outcome event. The HR for the primary outcome in the selexipag group versus placebo was 0.61 (99% CI, 0.46 to 0.81). The median time to clinical worsening [redacted] for the selexipag group and was [redacted]) in the placebo group.

a) Death

The occurrence of death as a first primary outcome event from any cause up to seven days after the last dose of the study drug [redacted] in the selexipag group [redacted] compared with the placebo [redacted]. This analysis of deaths needs to be considered in the larger context of deaths in the GRIPHON study (see section 3.6.1).

Hospitalization for pulmonary arterial hypertension worsening

The occurrence of hospitalization for PAH worsening when counted as a first primary outcome event was 71 (12.4%) in the selexipag group and 95 (16.5%) in the placebo group. This analysis of PAH

hospitalization needs to be considered in the larger context of PAH hospitalization in the GRIPHON study (see section 3.6.2).

Lung transplantation and atrial septostomy
During the trial, one patient in the selexipag group had a CEC-confirmed primary outcome event of PAH worsening, resulting in the need for lung transplantation, and one patient had a lung transplantation that did not qualify as a primary outcome event.[29] In the placebo group, two patients met the "need" for lung transplantation due to PAH worsening primary outcome event, but only one of these had a transplantation during the study.[29] No patients in the study had a balloon atrial septostomy.[29]

b) Parenteral prostanoid therapy or chronic oxygen therapy

[redacted] in the selexipag group and [redacted] in the placebo group initiated parenteral prostanoid therapy or chronic oxygen therapy.

c) Disease progression

Thirty-two patients (5.6%) met criteria for disease progression in the selexipag group, compared with 84 patients (14.4%) in the placebo group.

Subgroup Analyses

Subpopulations of interest in this review were: 1) patients unable to achieve disease control with another PAH therapy, 2) FC, and 3) patients receiving mono or combination PAH therapy, by drug class. There were no data available for (1). Data for (2) and (3) are presented in Table 14.

There was no evidence of interaction (*P* = 0.95) for study drug by PAH therapy in GRIPHON. The HRs for each concomitant therapy subgroup were similar to one another and were similar to the HR for the overall study population of 0.61 (99% CI, 0.46 to 0.81). There was no evidence of interaction for study drug by WHO FC. The HRs for the two groups (I and II versus III and IV) were similar to each other and to the HR for the overall study population.

TABLE 14: TIME FROM RANDOMIZATION TO FIRST CRITICAL EVENT COMMITTEE–CONFIRMED MORBIDITY OR MORTALITY EVENT UP TO 7 DAYS AFTER LAST STUDY DRUG INTAKE, FULL ANALYSIS SET

Subgroup	Selexipag (n/N)	Placebo (n/N)	Hazard Ratio (99% CI)	*P* Value for Interaction
PAH therapy at baseline				0.95
ERA monotherapy	23/94	29/76	0.66 (0.32 to 1.35)	
PDE5 inhibitor monotherapy	54/189	84/185	0.58 (0.37 to 0.91)	
ERA and PDE5 inhibitor	47/179	80/197	0.63 (0.39 to 1.01)	
No PAH-specific therapy	31/112	49/124	0.57 (0.32 to 1.03)	
WHO FC at baseline				0.78
Class I/II	52/278	74/260	0.63 (0.40 to 1.00)	
Class III/IV	103/296	168/322	0.60 (0.43 to 0.83)	

CEC = Critical Event Committee; CI = confidence interval; ERA = endothelin receptor antagonist; FAS = full analysis set; FC = functional class; MM = morbidity/mortality; PAH = pulmonary arterial hypertension; PDE5 = phosphodiesterase type 5; WHO = World Health Organization.
Note: The data in this table appear to include the events that occurred before the protocol amendment.
Source: Clinical Study Report.[8]

1.8.4 WHO functional class

Absence of worsening from baseline in WHO FC at week 26 was reported for 444 of 571 (77.8%) of patients in the selexipag group and 430 of 574 (74.9%) in the placebo group (OR 1.16; 99% CI, 0.81 to 1.66), *P* = 0.19). Approximately 17% of selexipag patients and 20% of placebo patients had missing data for this analysis and "worsened" was imputed for these patients. Patients with FC IV at baseline were excluded as they could not shift to a worse category.

Relative to baseline, approximately [redacted] of selexipag and placebo patients had improvements in FC at week 26, respectively; this analysis included patients in all FCs at baseline.[8]

1.8.5 Quality of life

The CAMPHOR questionnaires consisting of three sections, symptoms (with subscales related to energy, breathlessness, and mood), activity, and quality of life, were assigned to be completed by [redacted] selexipag and [redacted] placebo patients in the GRIPHON trial.[8] Other than the data from the symptoms and breathlessness scales presented in section 3.6.8, there were no quality of life data reported for the GRIPHON trial.

1.8.6 Six-minute walking distance

The mean baseline (standard deviation [SD]) 6MWD was 358 m (76) in the selexipag group and 348 m (83) in the placebo group. Mean absolute change (SD) from baseline to week 26 in 6MWD measured at trough was –52 m (150) in the selexipag group and –66 m (148) in the placebo group. Median absolute change (range) from baseline to week 26 in 6MWD was +4.0 m (–448, 260) in the selexipag group and –9.0 m (–438, 262) in the placebo group. In the main analysis using a non-parametric ANCOVA with covariate 6MWD at baseline, the difference was [redacted] (one-sided Wilcoxon–Mann–Whitney [redacted]). The treatment effect (location shift using Hodges–Lehmann method) versus placebo in the selexipag group was [redacted]). Missing 6MWD values at week 26 were imputed for 19.9% of patients in the selexipag group and 23.4% in the placebo group.[8]

1.8.7 Cardiopulmonary exercise testing

There were no outcomes reported for cardiopulmonary exercise testing.

1.8.8 Change in pulmonary hypertension symptoms

Baseline median values for the CAMPHOR Symptoms subscale were 10.0 in the selexipag group and 11.0 in the placebo group. Median absolute change from baseline to week 26 for the symptoms score was –1.0 in the selexipag group and 0.0 in the placebo group. Missing values were imputed in approximately [redacted] patients. The CAMPHOR Symptoms score can range from 0 (good) to 25 (poor). The treatment effect of selexipag versus placebo was [redacted][8] The treatment effect was calculated using the Hodges–Lehmann method.

Baseline median values for the breathlessness subscale were 4.0 in both the selexipag and placebo groups. Median absolute change from baseline to week 26 in the breathlessness subscale score was 0.0 in both treatment groups. Missing values were imputed in approximately 22% of patients. The CAMPHOR breathlessness section can range from 0 (good) to 8 (poor). The treatment effect of selexipag versus placebo was 0.0 (99% CI, −0.4 to 0.0; *P* = 0.17). The treatment effect was calculated using the Hodges–Lehmann method.

The Borg dyspnea index rates dyspnea severity on a scale from 0 (no shortness of breath) to 10 (very, very severe shortness of breath). At baseline, median score was [redacted] in both groups. At end of treatment

(corresponding to individual patients' end-of-study visit), the median score was [redacted] in the selexipag group and [redacted] in the placebo group.[8]

1.8.9 N-terminal prohormone of brain natriuretic peptide, mean pulmonary artery pressure, Cardiac index

The mean (SD) baseline plasma N-terminal prohormone of brain natriuretic peptide (NT-pro-BNP) was 504 ng/L (range: 13 to 11,012) in the selexipag group and 507 ng/L (range: 13 to 28,414) in the placebo group. The absolute change from baseline to end of treatment (corresponding to individual patients' end-of-study visit) in median NT pro-BNP was 5.5 ng/L (range: −4790 to 10,873) in the selexipag group compared with 75.0 ng/L (range: −7309 to 41,586) in the placebo group. The difference in median values at the end of study was 70 ng/L.[8]

Cardiac index and mean pulmonary artery pressure were not specified as efficacy end points in the GRIPHON study.

1.9 Harms

Only those harms identified in the review protocol are reported below (see Table 5).

1.9.1 Adverse events

Most patients experienced an adverse event during GRIPHON and the adverse events with at least 1% difference in incidence between selexipag and placebo are summarized in Table 15. The difference in incidence of adverse events between selexipag and placebo was 5% or greater for the following events: headache, diarrhea, pain in jaw, nausea, myalgia, vomiting, pain in extremity, and flushing (Table 15).

Prostacyclin-like adverse events were separately analyzed and the difference between the selexipag and placebo groups was greater during the titration phase, compared with the difference during the maintenance phase for many of these events (headache, diarrhea, nausea, pain in jaw, myalgia, pain in extremity, vomiting, and flushing; Table 15).

TABLE 15: PROSTACYCLIN-LIKE ADVERSE EVENTS IN GRIPHON BY TITRATION AND MAINTENANCE DOSING PHASES

	Selexipag		Placebo	
Adverse event, n (%)	**Titration N = 509**	**Maintenance N = 509**	**Titration N = 508**	**Maintenance N = 508**
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhea	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Pain in jaw	[redacted]	[redacted]	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Flushing	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal pain	[redacted]	[redacted]	[redacted]	[redacted]
Temporomandibular joint syndrome	[redacted]	[redacted]	[redacted]	[redacted]

Source: Clinical Study Report.[8]

1.9.2 Serious adverse events

Serious adverse events were reported in 252 patients (44%) in the selexipag group compared with 272 patients (47%) in the placebo group (Table 17). Other than PAH worsening, the most common serious adverse events were right ventricular failure, pneumonia, dyspnea, syncope and atrial fibrillation, all of which occurred at similar rates in selexipag and placebo groups.

1.9.3 Adverse events that resulted in discontinuation of study drug regimen

Fewer patients discontinued the study drug regimen in the selexipag group (32%) compared with the placebo group (37%). This was mainly due to worsening of PAH (Table 17).

In addition to the common adverse events that resulted in discontinuation of study drug regimen listed in Table 17, adverse events of interest that led to discontinuation of the study regimen included the following: hyperthyroidism (none with placebo and one with selexipag), hypotension (two with placebo and none with selexipag), syncope (two with placebo and one with selexipag), and major bleeding event (four with placebo and two with selexipag). No events of anemia resulted in discontinuation of the study regimen.[9]

1.9.4 Notable harms

Other adverse events of interest identified in the protocol for this review that were not previously mentioned in the preceding sections included gastrointestinal adverse events, syncope, and anemia; they are listed in Table 16.

TABLE 16: NOTABLE HARMS OF INTEREST

	Selexipag N = 575	Placebo N = 577
Gastrointestinal Disorders (System Organ Class)	[redacted]	[redacted]
Syncope	37 (6)	51 (9)
Anemia	48 (8)	31 (5)
Hemoglobin < 8 g/dL	7 (1)	4 (< 1)

Note: Bleeding events were adjudicated by an independent committee according to the criteria of the International Society on Thrombosis and Hemostasis.
Source: Sitbon et al.,[9] Clinical Study Report.[8]

TABLE 17: ADVERSE EVENTS

	Selexipag N = 575	Placebo N = 577
AE, number	4,607	3,937
Patients with ≥ 1 AE, n (%)	565 (98)	559 (97)
SAEs, number	513	515
Patients with ≥ 1 SAE, n (%)	252 (44)	272 (47)
Most common SAE		
PAH worsening	[redacted]	[redacted]
RVF	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Dyspnea	[redacted]	[redacted]
Syncope	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]

	Selexipag N = 575	Placebo N = 577
AEs with ≥ 1% difference between selexipag and placebo		
Headache	375 (65)	189 (33)
Diarrhea	244 (42)	110 (19)
Pain in jaw	148 (26)	36 (6)
Nausea	193 (34)	107 (19)
Myalgia	92 (16)	34 (6)
Vomiting	104 (18)	49 (9)
Pain in extremity	97 (17)	46 (8)
Flushing	70 (12)	29 (5)
Arthralgia	62 (11)	44 (8)
Anemia	48 (8)	31 (5)
Abdominal pain	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Pain	[redacted]	[redacted]
Nasopharyngitis	75 (13)	63 (11)
Hypotension	29 (5)	18 (3)
Dyspepsia	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Weight decreased	[redacted]	[redacted]
Neck pain	[redacted]	[redacted]
Hyperthyroidism	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Abdominal discomfort	[redacted]	[redacted]
Acute renal failure	[redacted]	[redacted]
Bone pain	[redacted]	[redacted]
Eye pain	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Influenza	[redacted]	[redacted]
Musculoskeletal pain	[redacted]	[redacted]
Nasal congestion	[redacted]	[redacted]
Hot flush	[redacted]	[redacted]
Burning sensation	[redacted]	[redacted]
Patients who stopped treatment due to AE, n (%)	182 (32)	214 (37)
Most common reasons		
PAH	[redacted]	[redacted]
Headache	[redacted]	[redacted]
RVF	[redacted]	[redacted]
Diarrhea	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Dyspnea	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]

AE = adverse event; PAH = pulmonary arterial hypertension; RVF = right ventricular failure; SAE = serious adverse event.
Source: Sitbon et al.,[9] Clinical Study Report.[8]

4. DISCUSSION

4.1 Summary of Available Evidence

One randomized, event-driven study in patients with symptomatic PAH met the inclusion criteria for this review. Patients, treating physicians, and investigators who assessed the primary outcome were blinded to treatment. The objective of the trial was to demonstrate the effect of selexipag on time to first morbidity or mortality event (primary composite outcome) in patients with PAH. A total of 1,156 patients, mainly with WHO FC II or III, were randomized to selexipag or placebo (1:1) and titrated to the highest tolerated dose. The median duration on treatment in the selexipag group was 70.7 weeks and 63.7 weeks in the placebo group.

4.2 Interpretation of Results

4.2.1 Efficacy

The GRIPHON trial had some unique features compared with studies of other drugs for PAH. A detailed summary of such studies was published in the CADTH Therapeutic Review of Drugs for PAH.[3] Other than a recent macitentan study with more than 12 months of median follow-up,[30] most PAH drug trials were shorter than GRIPHON, less than 18 weeks in duration. The GRIPHON trial also differed from many other PAH studies in that it did not use the 6MWD as a primary outcome. GRIPHON investigators originally planned to use 6MWD as a primary outcome but replaced it with "clinical worsening" and subsequently renamed it "morbidity/mortality event." The challenges inherent in interpreting the results of composite outcomes whose individual components do not carry equal importance to patients has been extensively discussed in the literature.[31,32] The change in name for this outcome in GRIPHON has the potential to mislead as mortality is only one component of the outcome and was not the main driver of the results. The overall time-to-event analysis of morbidity or mortality events favoured selexipag compared with placebo (HR 0.61; 99% CI, 0.46 to 0.81); it appeared that hospitalization for PAH and disease progression were the main drivers of this finding. The clinical expert consulted for this review believed that the primary outcome of GRIPHON was a clinically relevant outcome and its composition was reasonably similar to the primary outcome of clinical worsening used in other PAH trials.

The results of the primary outcome were clinically meaningful, but the lack of corroborating evidence from the secondary outcomes makes interpretation of the results of GRIPHON challenging. The 6MWD was the first secondary outcome in the hierarchy to be tested. There were statistically significant improvements in the 6MWD favouring selexipag compared with placebo (median difference of change 12 m), but this change is lower than the minimal clinically important change of 33 m (see Appendix 1). There was no statistically significant difference in absence of WHO FC worsening and therefore the hierarchical testing procedure was halted at this stage and no claims of statistical significance were made for subsequent outcomes as listed in section 3.2.4. There were no statistically significant differences in hospitalization rates between selexipag and placebo.

The occurrence of death was higher in the selexipag group compared with placebo in certain analyses in GRIPHON. Concerns about an adverse effect on mortality were alleviated by the analysis that counted all deaths up to study closure, which found approximately the same number of deaths in each treatment group (selexipag 100 [17.4%] and placebo 105 [18.0%]) and no statistically significant difference between groups (HR 0.97; 99% CI, 0.68 to 1.39).[26,27]

CDR reviewers requested details regarding the counting of deaths in the GRIPHON trial and the manufacturer provided some of the data presented in Table 11 and Table 12.[6] The manufacturer stated

that the reason for the apparent difference in analyses of deaths is related to informative censoring and in such cases (e.g., deaths up to end of therapy plus seven days), "deaths are not counted in the analysis as they are 'censored' due to end of treatment, which is triggered by a primary end point event. More (and earlier) primary end point events have occurred in the placebo arm of GRIPHON, therefore this informative censoring occurs in greater proportion in placebo rather than selexipag arm."[6] CDR reviewers agree that these are possible explanations for the observed results for deaths in GRIPHON, and conclude that selexipag did not appear to have an effect on mortality compared with placebo in the trial. However, it is noted that the manufacturer's conclusions regarding the data are based upon several assumptions, such as the assumption that patients who experience a morbidity event and discontinue study medication are at an increased risk of mortality, and the assumption that prognostic factors remained balanced in the selexipag and placebo groups after study treatment was discontinued, until the end of the study.

Patient input indicated that patients are concerned with the impact of PAH on daily activities, travel, mood, social relationships, and impact on caregivers. They are also concerned about their reduced ability to work and earn income (see Patient Input in Appendix 1). There were no data to assess the impact of selexipag on these outcomes. Quality-of-life data were collected in the GRIPHON trial, but were not reported. No statistically significant differences between selexipag and placebo were reported for symptom scores (CAMPHOR and the Borg dyspnea scale).

In 2015, CADTH conducted a Therapeutic Review to assess the comparative efficacy and safety and to determine the cost-effectiveness of pharmacological treatments for adults with PAH.[3] Based on the Therapeutic Review and patient group input, CDEC recommended that sildenafil or tadalafil be the preferred initial therapy for adult patients with FC II and III PAH; and that add-on therapy should be used in adult PAH patients who are unable to achieve disease control with a single drug. The CADTH review did not include selexipag because GRIPHON was ongoing at the time the review was conducted. No indirect treatment comparisons were identified in the literature that included selexipag; therefore, the relative effectiveness of selexipag compared with other PAH therapies is unknown. The GRIPHON trial provides no information regarding the relative effectiveness of selexipag compared with other prostacyclin agents (e.g., epoprostenol and treprostinil).

Selexipag is indicated for mono, dual, or triple therapy. Treatment with stable doses of ERAs and/or PDE5s were permitted at the study start and new ERAs or PDE5s could be added during the study. This is a common feature of trials for PAH therapies. The overall study population thus includes subgroups with different stages of disease, including incident cases (e.g., treatment-naive patients) and prevalent cases (e.g., patients who are already receiving drug therapy for PAH). The trial was not specifically designed to compare monotherapy versus dual therapy versus triple therapy. Therefore, there is uncertainty regarding the population to which the results are generalizable, with respect to concomitant therapies. While there were some subgroup analyses that suggested the effect of selexipag is similar across monotherapy, dual therapy, and triple therapy populations, the primary and secondary outcomes for the GRIPHON study were analyzed in the overall population, which was heterogeneous with respect to concomitant therapies. The subgroup analyses for the 6MWD results suggested that there may be some differences in selexipag's effect on outcomes in the group not taking concomitant therapy, compared with those taking concomitant therapy (Figure 6, Appendix 4). From these data, a reasonable hypothesis could be made that selexipag may not be as effective in patients taking concomitant therapies, compared with patients not taking concomitant therapies. This has also been observed in other trials of drugs for PAH.[4,33]

4.2.2 Harms

Selexipag dosing is determined by tolerability and adverse effects. Therefore, it is possible that the rates of prostacyclin-related adverse effects would vary with the maintenance dose achieved. The subjective nature of deciding on an appropriate maintenance dose may result in different rates of adverse effects between different clinical practice sites.

Overall, 182 patients (32%) in the selexipag group and 214 patients (37%) in the placebo group discontinued their study regimen prematurely because of an adverse event (Table 17). The most frequent adverse events leading to discontinuation in the selexipag group (events for which there was a > 1% difference between the selexipag and placebo groups) were headache (3%), diarrhea (2%), and nausea (2%). Hyperthyroidism occurred in eight patients in the selexipag group and led to treatment discontinuation in one patient.

Overall serious adverse event rates were similar between the selexipag (44%) and placebo (47%) groups. No serious adverse events were reported more frequently (i.e., at a rate > 1% higher) in the selexipag group than in the placebo group.

The most frequent adverse events associated with prostacyclin use that were reported during the dose-adjustment and maintenance phases included headache, diarrhea, nausea, pain in jaw, myalgia, pain in extremity, vomiting, and flushing (Table 17). Adverse events associated with prostacyclin occurred more frequently during the dose-adjustment phase.

Patient input indicated that patients commonly report experiencing adverse effects, such as headaches, digestive problems, sleeping difficulties, nausea and/or stomach pain, stuffy nose, flushing, fainting, and dizziness, with other drug treatments for PAH. Patients stated that they are willing to accept adverse events associated with an oral prostacyclin therapy for PAH if there are advantages compared with parenteral administration. There were no data available to compare adverse event rates of selexipag with parenteral prostacyclin therapies.

The median exposure to study drug was approximately one year, which represents a reasonable duration of follow-up time to assess outcomes in PAH. It is possible that patients would use selexipag for longer periods of time and therefore it will be important to quantify risk of harms with greater accuracy subsequent to longer follow-up in future research.

No new safety signals were identified based on interim safety data from 218 patients who enrolled in the open-label extension study (study 303) after a morbidity event in the GRIPHON trial (Appendix 6).

4.3 Potential Place in Therapy

This information is based on that provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

The clinical expert consulted by CDR discussed the unmet needs in this patent population, including:

- Persistent symptoms and significant morbidity and mortality in patients despite aggressive combination therapy, and
- Lack of therapeutic options for patients with persistent symptoms who are not candidates for intravenous prostacyclin therapy.[5]

According to the clinical expert, selexipag has the potential to address both unmet needs, and it has a place in the pharmacotherapy of PAH. The data from the GRIPHON study suggest that selexipag delays clinical worsening in a population of patients that would be very similar to those whom PAH specialists treat in Canada. There is no way to make conclusions with respect to the comparative benefits and safety with selexipag versus other drugs, as no head-to-head studies or indirect treatment comparisons have been done.

In practice, selexipag would not be a replacement for intravenous prostacyclins in patients who require and are candidates for such therapy, according to the clinical expert consulted. In addition, given the complexity of the drug with respect to administration and monitoring, relative to others available, it would likely not be used as a first-line agent.

The place in therapy rests on patients who fail to meet treatment goals despite background mono or dual therapy. This might include an NYHA II or early NYHA III patient who does not yet require escalation to intravenous prostacyclins; selexipag can be an option in this population, similar to all other oral agents when making this decision. The other potential use for this drug would be in patients who are not candidates for intravenous prostacyclin therapies, such as those with advanced WHO FC III (IIIB) or IV, and/or those with cognitive, physical, or medical contraindications that would preclude safe use of a chronic indwelling intravenous catheter. This represents a very small percentage of patients; however, there is no evidence from the reviewed trial on outcomes for this specific subpopulation.

There are no additional specific diagnostic tests required to prescribe this drug beyond what is routinely done. The monitoring and titration is more complex, but with patient support programs, much of this could be done remotely.

The barriers to prescribing will largely involve tolerance as the adverse effect profile is considerable and in line with other drugs targeting the prostacyclin pathway.

5. CONCLUSIONS

Results of one randomized controlled trial indicated that selexipag is associated with clinically and statistically significant improvements in time to clinical worsening (composite outcome) compared with placebo in patients with PAH on a heterogeneous background of PAH therapies or no PAH therapy. There were no clinically significant improvements observed in the 6MWD test for selexipag compared with placebo. There was no clear evidence of improvement observed for selexipag compared with placebo for overall deaths, PAH-related deaths, hospitalization rates, WHO FC changes, quality of life, symptoms of PAH, breathlessness, or dyspnea.

Based on the results of GRIPHON, some patients would be expected to discontinue selexipag due to headache, diarrhea, or nausea. Adverse events associated with prostacyclin use are more likely to occur during the dose-adjustment phase compared with the maintenance phase. These include headache, diarrhea, nausea, pain in jaw, myalgia, pain in extremity, vomiting, and flushing.

A number of important gaps in information remain. The presence of different background PAH therapies, or no PAH therapy, in the trial population creates uncertainty regarding the generalizability of the data from the GRIPHON study. There was no evidence identified that allowed an assessment of the relative effects of selexipag to other oral PAH therapies or prostacyclin therapies.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input
Input was received from two patient groups. The submission was developed jointly by both organizations.

The Pulmonary Hypertension Association of Canada (PHA Canada) is a federally registered charity established by patients, caregivers, and health care professionals whose goal is to empower the Canadian pulmonary hypertension (PH) community through awareness, advocacy, education, research, and patient support. PHA Canada receives funding from members of its Standing Corporate Committee, which consists of pharmaceutical companies (including Actelion). Funding is provided through membership dues and grants. The Board Chair, who helped prepare the submission, has received consulting and speaking fees, research grants, and investigator fees from pharmaceutical companies, including Actelion.

The Scleroderma Society of Canada (SSC) is the national organization representing all scleroderma organizations and groups in Canada. The SSC works to improve the quality of life of those with scleroderma through promoting public awareness, supporting those affected by scleroderma, and funding research to find a cure. The SSC has received unrestricted funding from pharmaceutical companies, including Actelion. The SSC made no statement with regard to potential conflicts of interest for the individuals who prepared the submission.

2. Condition-Related Information
Information for the submission was gathered through telephone interviews with three patients who had experience with Uptravi as part of the GRIPHON clinical trial, and an online survey of pulmonary arterial hypertension (PAH) patients and caregivers (available March 21 to April 6, 2016), which was completed by 94 PAH patients, 21 caregivers, and three parents of pediatric PAH patients. Additional information was obtained from PHA Canada's 2013 Burden of Illness Survey, the Canadian Scleroderma Research Group's patient registry, previous CADTH submissions, and stories collected through each organization's work.

PAH is a form of PH caused by a narrowing of the pulmonary arteries of the lungs. PAH is a common complication of scleroderma and can be very severe in patients affected by this progressive connective tissue disease. PAH has a significant impact on the lives of patients and caregivers, and can affect patients' ability to work, raise a family, and participate in everyday activities. Of the patients surveyed, 87% to 90% reported fatigue and difficulty breathing upon exertion, while one-third of patients reported swelling of feet, ankles, or belly; chest pain; fainting or light-headedness; heart palpitations; and coughing.

One patient remarked:

> "I have always been an active person; it was hard for me to sit down. Now I have to space out my activities. If I do too much on one day, I pay for it the next. I am still able to take care of myself, to do laundry, go grocery shopping, and take care of the cooking, but I am not able to clean my house anymore.... It's hard to stay positive. It's difficult because you don't know how much longer you have to live."

Most patients surveyed reported limitations to recreational activities (88%), household chores (76%), and travel (74%). More than half of patients reported decreased income as a result of PAH, and 43% were no longer able to work. Half of the patients reported social isolation. Patients commonly experience depressed mood, anxiety, feelings of helplessness and hopelessness, and may also face social stigma because they do not appear sick when resting or seated. Women have to give up their dreams of becoming pregnant, as pregnancy is contraindicated in those with PH.

Caregivers are often the main support for patients, taking on the brunt of the work around the home (including caring for any children), often while being sole financial providers. They attend medical appointments, help to administer medication and manage side effects, and give much of their personal time. Many caregivers also feel isolated from society and face "burnout." Relationships may be strained and the prospect of losing a loved one places a heavy burden on everyone.

3. Current Therapy-Related Information

There are currently nine Health Canada–approved therapies available in Canada to treat PAH, including six oral drugs: ambrisentan (Volibris), bosentan (Tracleer), macitentan (Opsumit), sildenafil (Revatio, Viagra), tadalafil (Adcirca, Cialis), and riociguat (Adempas); and three infusion therapies: epoprostenol (Flolan), treprostinil (Remodulin), and thermostable epoprostenol (Caripul). Responses to PH monotherapy are often limited, such that many patients require two or more PH medications used concurrently. This is especially true for patients with more advanced, moderate-to-severe PH. For patients with pre-existing and ongoing damage to the vascular system and fibrosis (i.e., scleroderma), PAH treatment is especially complicated and quality of life is profoundly affected.

Among the survey respondents, the most common treatments (alone or in combination) were bosentan (35%), sildenafil (35%), or tadalafil (31%), macitentan (22%), or an infusion therapy (approximately 30%). Most patients reported some benefit from current therapies, including improving breathing on exertion (somewhat effective: 60%, highly effective: 20%), improving fatigue (somewhat effective: 56%, highly effective: 8%), or improving breathlessness at rest (highly effective: 31%). In terms of disease progression, 35% felt current treatments were somewhat effective, while 25% reported high effectiveness and another 22% reported no effectiveness.

The available treatments are associated with a number of adverse effects than can affect patients' quality of life. The adverse events most frequently cited by the PAH patients surveyed included headaches (52%), digestive problems (45%), sleeping difficulties (44%), nausea and/or stomach pain (42%), and stuffy/runny nose (42%), flushing, fainting, or dizziness (33%).

Barriers to accessing treatments also exist, and one-quarter of patients surveyed reported difficulties in accessing their current PAH therapies due to lack of access to a PH specialist close to home; paying out of pocket for supplies necessary to administer treatment; and relying solely on a manufacturer's compassionate access program. Initial approval for combination and/or dual therapies can be difficult to obtain, which adds additional stress on patients and their families. Co-payments may not be affordable due to the high cost of treatments. Treatments to manage adverse effects of therapy may be expensive and may not be covered by government programs.

While treatments may help control symptoms and stabilize their condition, they are not a cure, and patients face the prospect of more complex and invasive medications, possible lung transplantation, and shortened life expectancy. One-third of respondents identified both disease progression and the physical impacts of PAH as areas not being addressed by current treatments, and at least half stated that

their symptoms (breathing difficulties, fatigue) or social or psychological needs are not being adequately addressed by treatments.

4. Expectations About the Drug Being Reviewed

Patients and caregivers stated that oral therapy with selexipag offers advantages over injectable treatments in terms of treatment burden, and they are willing to tolerate serious adverse effects (especially scleroderma patients) if selexipag slows disease progression or improves quality of life.

Of the four patients with prior experience with selexipag (three telephone interviews, one survey respondent), all reported positive experiences with the drug. This included reduced shortness of breath and fatigue, more stamina, and improved ability to be active. One patient reported substantial improvements that allowed her to resume many activities, while another patient stated that her symptoms stabilized for one year, but she later needed to switch to treprostinil and then underwent a double-lung transplant. Another patient reported having to persevere through serious adverse effects at the start of therapy but thought the benefits outweighed the negative effects.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	April 28, 2016
Alerts:	Bi-weekly search updates until September 21, 2016
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj	Requires words are adjacent to each other (in any order)
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.po	Population group [PsycInfo only]
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
*selexipag/	37
(uptravi or selexipag or NS-304 or NS304 or ACT293987 or ACT-293987 or UNII5EXC0E384L or 5EXC0E384L).ti,ab,kw.	101
1 or 2	103
"[4 [(5,6 diphenyl 2 pyrazinyl)(isopropyl)amino]butoxy]acetic acid"/	9
(ACT 333679 or ACT333679 or MRE 269 or MRE269).ti,ab,kw.	59
4 or 5	62
3 or 6	122
conference abstract.pt.	2223614
7 not 8	84
9 use oemezd	46
(uptravi or selexipag or NS-304 or NS304 or ACT293987 or ACT-293987 or UNII5EXC0E384L or 5EXC0E384L).ti,ab,ot,hw,kf,rn,nm.	203
(ACT 333679 or ACT333679 or MRE 269 or MRE269 or 475085-57-5).ti,ab,ot,hw,kf,rn,nm.	65
11 or 12	222
13 use pmez	39
10 or 14	85
exp animals/	41734467
exp animal experimentation/ or exp animal experiment/	1937285
exp models animal/	1365015
nonhuman/	4740733
exp vertebrate/ or exp vertebrates/	40546416
or/16-20	43185163
exp humans/	33041467
exp human experimentation/ or exp human experiment/	363950
or/22-23	33043565
21 not 24	10143200
15 not 25	72
remove duplicates from 26	40

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	April 22, 2016
Keywords:	Uptravi (Selexipag)/Pulmonary Arterial Hypertension (PAH)
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for searching health-related grey literature" (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

APPENDIX 3: EXCLUDED STUDIES

Phase II trial
Simonneau G, Torbicki A, Hoeper MM, Delcroix M, Karlocai K, Galie N, et al. Selexipag: an oral, selective prostacyclin receptor agonist for the treatment of pulmonary arterial hypertension. Eur Respir J. 2012 Oct;40(4):874-80.

Not a randomized controlled trial
Sharma K. Selexipag for the treatment of pulmonary arterial hypertension. Expert Rev Respir Med. 2016 Jan;10(1):1-3.

Skoro-Sajer N, Lang IM. Selexipag for the treatment of pulmonary arterial hypertension. Expert Opin Pharmacother. 2014 Feb;15(3):429-36.

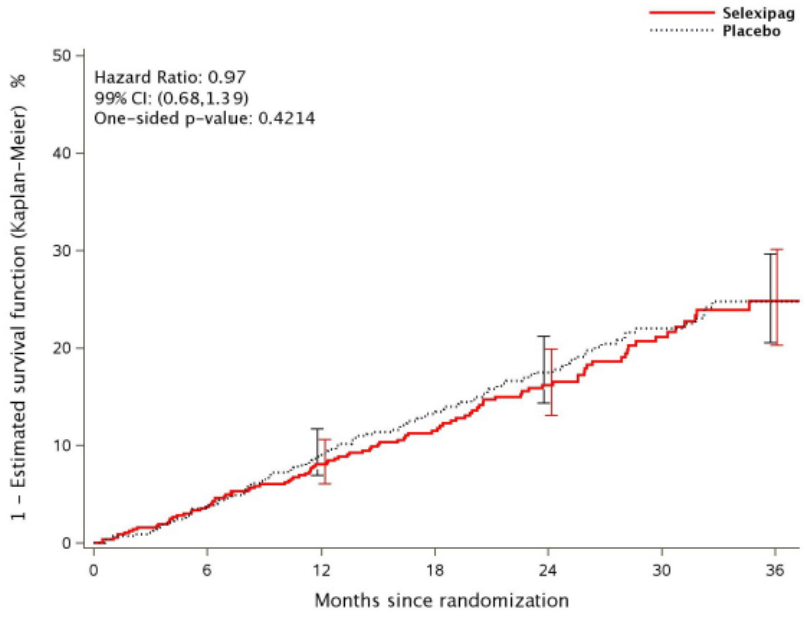
APPENDIX 4: DETAILED OUTCOME DATA

FIGURE 2: DISPOSITION OF PATIENTS IN GRIPHON

Redacted at the request of the manufacturer.

Source: Clinical Study Report.[8]

FIGURE 3: TIME TO DEATH UP TO STUDY CLOSURE



Selexipag patients:							
at risk	574	543	473	350	257	161	64
event(s)	0	21	45	61	78	91	97
censored	0	10	56	163	239	322	413

Placebo patients:							
at risk	582	546	491	356	273	168	70
event(s)	0	22	51	71	87	100	105
censored	0	14	40	155	222	314	407

Note: Bars on the graph show 95% confidence intervals of the estimates.
Death with onset date up to 16 Aug 2011 are included as death.

CI = confidence interval.
Source: Clinical Study Report.[8]

FIGURE 4: ABSENCE OF WORSENING IN FUNCTIONAL CLASS FROM BASELINE TO WEEK 26

Table S3. Patients With and With No Worsening in WHO Functional Class (FC) from Baseline to Week 26. All patients.

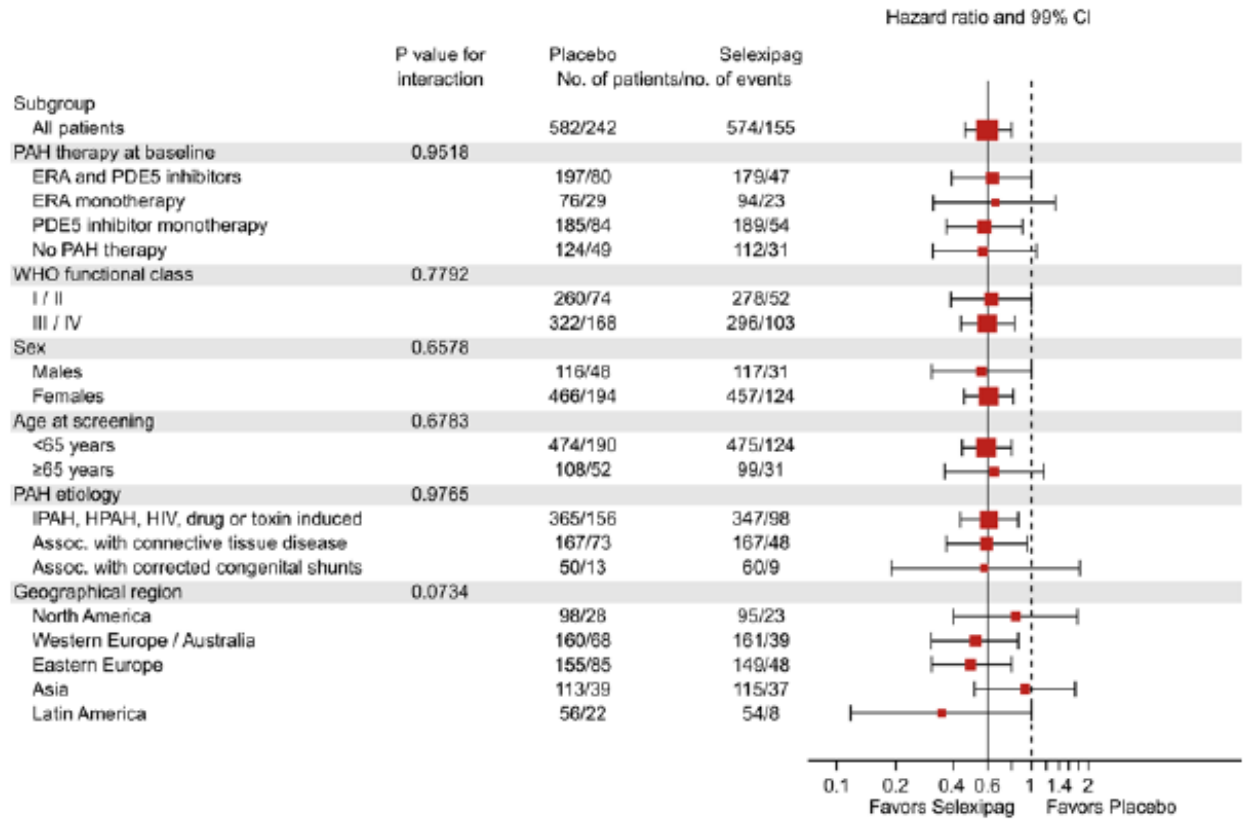
Baseline			Week 26					No worsening N (%)	Selexipag vs. Placebo Point estimate odds ratio (99% CI)	P value
			FC I N	FC II N	FC III N	FC IV N	Missing* N			
Selexipag N=571	FC I	4	**4**	-	-	-	-	**444 (77.8)**	**1.16 (0.81–1.66)**	**0.28**
	FC II	274	**7**	**207**	21	-	39			
	FC III	293	**1**	**67**	**158**	10	57			
Placebo N=574	FC I	5	**4**	-	-	-	1	**430 (74.9)**		
	FC II	255	**7**	**197**	16	-	35			
	FC III	314	**4**	**37**	**181**	14	78			

FC denotes WHO functional class.

* Missing data at week 26 were included in the analysis as worsening.

CI = confidence interval; FC = functional class; vs. = versus; WHO = World Health Organization.
Source: From N Engl J Med. Sitbon O, Channick R, Chin KM, Frey A, Gaine S, Galie N, et al. Selexipag for the treatment of pulmonary arterial hypertension. 373(26), p.2522-33 Copyright © (2015) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

FIGURE 5: PRIMARY COMPOSITE END POINT BY SUBGROUP



CI = confidence interval; ERA = endothelin receptor agonist; HPAH = heritable pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; PAH = pulmonary arterial hypertension; PDE5 = phosphodiesterase type 5; WHO = World Health Organization.

Source: From N Engl J Med. Sitbon O, Channick R, Chin KM, Frey A, Gaine S, Galie N, et al. Selexipag for the treatment of pulmonary arterial hypertension. Supplementary appendix. 373(26), p.2522-33 Copyright © (2015) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

FIGURE 6: ABSOLUTE CHANGE FROM BASELINE TO WEEK 26 IN SIX-MINUTE WALK DISTANCE AT DRUG TROUGH: EXPLORATORY SUBGROUP ANALYSES FROM THE GRIPHON TRIAL

Redacted at the request of the manufacturer.

Source: Clinical Study Report.[8]

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Aim

To summarize the validity of the following outcome measures:

- Clinical worsening
- Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR)
- World Health Organization (WHO) functional class (FC)
- Six-minute walk distance (6MWD).

Findings

TABLE 18: TABLE VALIDITY AND MINIMAL CLINICALLY IMPORTANT DIFFERENCE OF OUTCOME MEASURES

Instrument	Type	Evidence of Validity	MCID	References
Clinical worsening	Composite outcome includes various components designed to measure PH morbidity and mortality. May also be reported as time to clinical worsening	No	Unknown	Ventetuolo 2008[34] Frost 2013[35]
CAMPHOR	PH-specific instrument that includes 3 scales assessing symptoms, functioning, and quality of life	Yes	Utility index 0.09	McKenna 2006[36] Meads 2008[37]
WHO FC	PH severity classification system. Based on NYHA functional classification system for heart failure	No	Unknown	Galie 2009[1] Taichman 2009[38]
6MWD	Total distance walked in 6 minutes Submaximal test to assess exercise capacity Widely used in studies and clinical practice; accepted by regulatory agencies	Yes	33.0 m (range: 25.1 to 38.6 m)	Gabler 2012[39] Fritz 2013[40] Savarese 2012[41] Mathai 2012[42]

6MWD = six-minute walk distance; CAMPHOR = Cambridge Pulmonary Hypertension Outcome Review; FC = functional class; MCID = minimal clinically important difference; NYHA = New York Health Association; PH = pulmonary hypertension; WHO = World Health Organization.

Clinical Worsening

The composite outcome of clinical worsening — combining the events of death, heart or lung transplantation, atrial septostomy, initiation of new pulmonary hypertension (PH) medications, hospitalization, persistent decrease of > 15 % from baseline or > 30% compared with the last measurement in 6MWD due to worsening PH, and persistent worsening of WHO FC due to deterioration of PH as a single outcome — may improve precision (increased statistical power would make it easier to detect a therapeutic benefit) and offer a more global assessment of the patient and his/her clinical state by including nonfatal but important morbid events in the course of disease.[34] Therefore, it is likely a clinically relevant outcome. However, there are limitations using composite outcomes in PH studies:[34]

- Confounding may occur if a component outcome occurs at a different rate versus others in the composite outcome, especially during a trial of short duration
- Including outcomes such as hospitalization in a composite outcome may be a problem because they may, at least partially, be driven by social or nonmedical factors, which may disproportionately influence a composite also containing more direct measures of disease progression (death)
- A composite outcome driven by individual outcomes with centre-specific availability (lung transplantation and atrial septostomy) may pose difficulty in multicenter trials
- In a composite outcome, each of the components has equal clinical implications
- There is no standardized definition for clinical worsening and the component end points vary across pulmonary arterial hypertension (PAH) trials.

A recent assessment of survival in an observational study suggested that clinical worsening was highly predictive of subsequent mortality and was meaningful as a primary end point in clinical trials of PAH.[35]

Clinical worsening is recommended as a key outcome for use in PAH studies by the European Medicines Agency, the World Symposium on Pulmonary Hypertension 2008 Dana Point, and 2013 Nice clinical trial design task forces.[43-45]

Cambridge Pulmonary Hypertension Outcome Review

CAMPHOR is a self-administered, disease-specific instrument designed to assess symptoms, activity limitations, and quality of life in patients with PH.[36] It includes a 25-item overall symptom scale based on three subscales (energy [10 items], breathlessness [eight items] and mood [seven items]), a 15-item function scale, and a 25-item quality of life scale.[36] The questions for the symptom and quality of life scales have dichotomous (true or false) response options, whereas the functioning scale has a three-point response option (able to do on own without difficulty, able to do on own with difficulty, unable to do on own). The scoring of the scales range from 0 to 25 for symptoms, 0 to 30 for functioning, and 0 for 24 for quality of life, with higher scores indicating more severe symptoms or functional impairment, and worse quality of life.[36]

The CAMPHOR symptom, functioning, and quality of life scales showed good construct validity, test–retest reliability, and internal consistency in UK,[36] US,[46] and Australian and New Zealand[47,48] PAH patients. Known group validity was also demonstrated.[36,46-48] No information was found on the responsiveness or minimal clinically important difference (MCID) of the symptom, functioning, or quality-of-life scales of the CAMPHOR questionnaire.

A preference-based utility index (score 1 = perfect health; 0 = death) was developed based on the health state determined by six items from the CAMPHOR quality-of-life scale.[49] The index showed good test–retest reliability, construct validity, and known group validity.[37,49] Using anchor and distribution-based

methods, estimates of the utility index MCID ranged from 0.05 to 0.13, with 0.09 selected as the most reasonable estimate of the within-group MCID.[37]

World Health Organization Functional Classification

The WHO FC system for PH was adapted from the New York Heart Association (NYHA) functional classification system for heart failure.[1] The WHO functional class system is used widely in clinical practice and as an outcome in clinical trials. One study reported clinicians' assessment of FC varied widely in PAH, especially when classifying patients as FC II or III.[38] The intra-class correlation coefficient was low (approximately 0.6). In one instance, 53% of clinicians classified a patient as FC II and 47% classified the patient as FC III. Thus, despite wide use of the WHO classification system, inter-rater agreement may be poor. FC may also be less responsive to changes perceived by patients as clinically important, than other measures, such as the CAMPHOR functional scale or utility index.[37]

Six-Minute Walk Distance

The 6MWD measures the distance a patient can walk in six minutes. Change in 6MWD is the most widely used test to assess exercise capacity in PAH and is used in most PAH trials as a primary outcome.[50-54] 6MWD is also used in clinical practice and is widely accepted by regulatory agencies.[55] The main advantage of the 6MWD is its ease of administration; it is a submaximal exercise test that can be performed by a patient who is unable to tolerate maximal cardiopulmonary exercise testing.[53] Baseline 6MWD in PAH treatment studies has been shown to correlate with long-term outcomes such as morbidity and mortality, as has the absolute 6MWD during treatment for PAH.[40,56] The change in 6MWD is a surrogate outcome and has demonstrated moderate to poor correlation with key clinical outcomes in PAH.[39-41,56,57] However, some studies have shown that a decline in 6MWD may be more strongly associated with prognosis than stable or increased 6MWD.[56,57] Performance on the 6MWD may be influenced by patient age, sex, height, weight, lung function, and ethnicity, and it may be susceptible to motivational factors and a training effect.[58-60] Furthermore, in multi-centre trials, experience and technical skills may vary between sites, and the correlations between the 6MWD and cardiopulmonary exercise testing might improve over time with increasing experience.[61] There is also evidence of a ceiling effect on the 6MWD, whereby the effect of the treatment on the test is diminished due to the inclusion of patients with milder disease (NYHA/WHO FC II, baseline 6MWD > 450 m) who demonstrate a smaller improvement with treatment given the relatively higher baseline 6MWD value versus patients with more severe PAH.[62] Despite these limitations, improvement in function, as reflected by 6MWD, remains clinically valuable in PAH. Mathai et al., using distributional and anchor-based methods of estimating an MCID, reported a change of 33.0 m (range 25.1 to 38.6 m) for patients with PAH compared with placebo.[42]

Conclusion

Of the four reviewed outcome measures — 6MWD, CAMPHOR, WHO FC, clinical worsening — used in the GRIPHON trial, only the 6MWD and CAMPHOR have been validated in PAH. In patients with PAH, an MCID of 33.0 m (range: 25.1 m to 38.6 m) has been reported for the 6MWD, and 0.09 for the CAMPHOR utility index. Clinical worsening is recommended as a key outcome for use in PAH studies.

APPENDIX 6: SUMMARY OF OTHER STUDIES

Aim

To review the available safety data for the GRIPHON open-label, uncontrolled extension study (Study 303).

Summary

[redacted]

TABLE 19: BASELINE PATIENT CHARACTERISTICS (STUDY 303)

Characteristic[a]	Study 303	
	Selexipag/selexipag [redacted]	Placebo/selexipag [redacted]
Female	[redacted]	[redacted]
Age, years, mean (SD)	[redacted]	[redacted]
6MWD, m, mean (SD)	[redacted]	[redacted]
NYHA/WHO functional class, n (%)		
I	[redacted]	[redacted]
II	[redacted]	[redacted]
III	[redacted]	[redacted]
IV	[redacted]	[redacted]

6MWD = six-minute walk distance; NYHA = New York Heart Association; SD = standard deviation; WHO = World Health Organization.
[a] Baseline visit for GRIPHON study.
Source: Clinical Study Report.[8]

[redacted]

TABLE 20: DISPOSITION OF PATIENTS IN STUDY 303

	Study 303	
	Selexipag/selexipag	**Placebo/selexipag**
Randomized in GRIPHON trial, N	[redacted]	[redacted]
Enrolled in Study 303, n (%)	[redacted]	[redacted]
Discontinued study and performed EOS visit, n (%)	[redacted]	[redacted]
Discontinued study and did not perform EOS visit, n (%)	[redacted]	[redacted]
Died	[redacted]	[redacted]
Withdrawal of consent	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
Administrative reason	[redacted]	[redacted]
Total duration of follow-up, weeks, median (range)	[redacted]	[redacted]

EOS = end of study.
Source: Clinical Study Report,[8] with additional data from the manufacturer.[29]

[redacted]

TABLE 21: HARMS IN STUDY 303

	Study 303		
	Selexipag/selexipag [redacted]	**Placebo/selexipag**	**All patients**
Any adverse event, n (%)	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]
Diarrhea	[redacted]	[redacted]	[redacted]
PAH	[redacted]	[redacted]	[redacted]
Pain in jaw	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]
Right ventricular failure	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]
Peripheral edema	[redacted]	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]
Flushing	[redacted]	[redacted]	[redacted]
Notable harms, n (%)			
Syncope	[redacted]	[redacted]	[redacted]
Presyncope	[redacted]	[redacted]	[redacted]
Anemia[a]	[redacted]	[redacted]	[redacted]
Hemorrhage	[redacted]	[redacted]	[redacted]

	Study 303		
	Selexipag/selexipag [redacted]	**Placebo/selexipag**	**All patients**
Decrease in hemoglobin to < 100 and/or < 80 g/L	[redacted]	[redacted]	[redacted]
Gastrointestinal disorder (SOC)	[redacted]	[redacted]	[redacted]
SAE, n (%)	[redacted]	[redacted]	[redacted]
Worsening of PAH	[redacted]	[redacted]	[redacted]
Right ventricular failure	[redacted]	[redacted]	[redacted]
Adverse event leading to treatment discontinuation, n (%)	[redacted]	[redacted]	[redacted]
PAH	[redacted]	[redacted]	[redacted]
Right ventricular failure	[redacted]	8 (5)	10 (5)

NR = not reported; PAH = pulmonary arterial hypertension; SAE = serious adverse event; SOC = system organ classification.
[a] Includes anemia, iron deficiency anemia, pancytopenia and decreased hemoglobin.
Source: Clinical Study Report.[8]

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