

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**207947Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

<b>Date</b>	19 November 2015
<b>From</b>	Shari L. Targum, M.D., M.P.H.
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA #</b>	207947
<b>Supplement#</b>	
<b>Applicant</b>	Actelion
<b>Date of Submission</b>	22 December 2014
<b>PDUFA Goal Date</b>	22 December 2015
<b>Proprietary Name / Non-Proprietary Name</b>	Uptravi/Selexipag
<b>Dosage form(s) / Strength(s)</b>	Tablet
<b>Applicant Proposed Indication(s)/Population(s)</b>	Treatment of pulmonary arterial hypertension to delay disease progression and reduce the risk of hospitalization for pulmonary arterial hypertension (PAH)/ PAH, WHO Group I
<b>Recommendation on Regulatory Action</b>	<i>Approval</i>

**Overview**

This review conveys the Cross-Discipline Team Leader's assessment of the major issues pertinent to approvability of the application, providing a summary of the clinical evidence (efficacy trials, safety database, critical pharmacology data) and key review issues from other disciplines (e.g., pharmaceutical quality, microbiology, non-clinical pharmacology/toxicology).

**1. Benefit-Risk Assessment**

**Benefit-Risk Summary and Assessment**

I recommend approval of selexipag to delay disease progression and reduce the risk of hospitalization due [REDACTED] (b) (4) [REDACTED] in [REDACTED] (b) (4) patients with pulmonary arterial hypertension (PAH), WHO Group 1.

In a single, multicenter, multinational, randomized, double-blind, placebo-controlled, event-driven outcome study (GRIPHON), selexipag met its primary endpoint with a highly statistically significant ( $p < 0.0001$ ) 39% reduction in the time to the first morbidity-mortality (MM) event, driven by a delay in disease progression and PAH hospitalization, endpoints that have been clinically meaningful in PAH, a serious, progressive condition. Selexipag has not been shown to improve survival.

While the GRIPHON protocol underwent several significant changes (including changes to the primary endpoint and sample size), the applicant appears to have adequately addressed study design and statistical concerns posed by the Agency; several sensitivity analyses supported the results of the primary endpoint. The primary outcome was also consistent whether or not background therapy was present, and across a representative PAH population, except for a “post-hoc” subgroup analysis in Asia (a finding not replicated at this point). There were few Black or African-American study subjects, and even fewer MM events, in the GRIPHON study population, limiting generalizability to Black or African-American patients. Of note, the available pharmacokinetic/pharmacodynamic results of selexipag, as well as its safety profile, did not seem to be affected by race.

The observed adverse events in subjects treated with selexipag (e.g., headache, diarrhea, nausea, jaw pain) appear to be similar to those observed with other prostacyclin receptor agonists (e.g., treprostinil, epoprostanol, iloprost). There appear to be no major safety findings that outweigh the benefits of selexipag in its target population.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
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Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p><a href="#">Analysis of Condition</a></p>	<ul style="list-style-type: none"> <li>• Pulmonary arterial hypertension (PAH) is a progressive condition characterized by elevated pulmonary arterial pressures leading to right ventricular failure (Chin KM and Rubin LJ 2008).<sup>1</sup> The current classification groups forms of pulmonary hypertension based on similar pathophysiology and response to treatment. Group 1 PAH is composed of diseases in which the primary abnormality is localized to the small pulmonary arteries.<sup>1</sup></li> <li>• PAH is considered to be a rare disease, with an estimated prevalence of 15-50 cases per million.<sup>2</sup> Registry data indicate a greater incidence in females.</li> <li>• The symptoms of pulmonary hypertension are often nonspecific and variable. Most symptomatic patients will present with shortness of breath and/or fatigue.<sup>3</sup></li> <li>• Reduced prostacyclin synthase activity, variably reduced IP receptor expression, up-regulated endothelin system, and abnormalities of nitric oxide pathways are considered important mediators for pathologic changes (Chin 2008, McGoon 2009)<sup>1,4</sup></li> </ul>	<p>PAH can be characterized as a rare, serious, debilitating, chronic and progressive condition.</p> <p>Selexipag has received orphan drug designation and is exempt from the requirement for pediatric studies.</p>

<sup>1</sup> Chin KM and Rubin LJ. Pulmonary arterial hypertension. JACC 2008; 51 (16): 1527-38.

<sup>2</sup> Source: [www.pah-info.com/How\\_common\\_is\\_PAH](http://www.pah-info.com/How_common_is_PAH)

<sup>3</sup> Waxman AB and Loscalzo J. Pulmonary hypertension. In: Harrison's Principles of Internal Medicine, 19<sup>th</sup> edition.

<sup>4</sup> McGoon MD and Kane GC. Pulmonary hypertension: Diagnosis and management. Mayo Clin Proc 2009; 84 (2): 191-207.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p><u>Current Treatment Options</u></p>	<ul style="list-style-type: none"> <li>• Available therapies for PAH address one of four target pathways:</li> <li>• Endothelin-receptor antagonists</li> <li>• Prostacyclin/IP receptor agonists (such as treprostinil, iloprost, epoprostanol)</li> <li>• PDE-5 inhibitors</li> <li>• Soluble guanylate cyclase stimulators</li> </ul>	<p>Of the IP receptor agonists, only treprostinil (recommended administration three times daily) is available in an oral formulation. If approved, selexipag, administered twice daily, would be the second oral IP receptor agonist.</p>
<p><u>Benefit</u></p>	<ul style="list-style-type: none"> <li>• GRIPHON was a single, randomized, double-blind, multinational study comparing selexipag to placebo in the time to first morbidity-mortality event in symptomatic patients with PAH, WHO Group 1.</li> <li>• GRIPHON demonstrated a statistically significant reduction, versus placebo, in the risk of MM events; results were driven by hospitalization for PAH worsening and disease progression.</li> <li>• More placebo subjects, compared to selexipag subjects, reported PAH worsening and right ventricular failure as serious adverse events (supporting a benefit of selexipag)</li> <li>• Results of the primary endpoint were consistent whether or not subjects were on background therapy</li> <li>• Uncertainties: Favorable primary endpoint result not consistent in Asian region subgroup. There were insufficient data in African-American or Black subjects to draw conclusions. The benefit was studied in symptomatic (WHO/NYHA Functional Class</li> </ul>	<p>The submitted evidence has met the evidentiary standard for benefit. According to FDA Guidance<sup>5</sup>, "reliance on only a single study will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible."</p> <ol style="list-style-type: none"> <li>1. In a serious, progressive disease such as PAH, delaying disease progression and reducing the risk of PAH hospitalization can be considered clinically meaningful effects on irreversible morbidity and prevention of potentially serious outcomes; therefore, confirmation of the result in a second trial could prove to be ethically difficult.</li> <li>2. The primary analysis of GRIPHON was statistically persuasive (low p-value, making the null hypothesis improbable).</li> <li>3. GRIPHON was a multicenter study where no site provided an unusually large fraction of the patients and no single investigator/site was disproportionately responsible for the favorable effect.</li> <li>4. Except for results of the primary outcome in Asia, there was consistency across study subsets.</li> <li>5. In a Phase 2 hemodynamic study, the decrease in pulmonary vascular resistance with selexipag treatment supports evidence of effectiveness.</li> </ol>

<sup>5</sup> Food and Drug Administration (May 1998): Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>II-III patients) and there are insufficient data in patients with functional class I or IV.</p>	<p>Results by race, region, or disease severity can be communicated in the label.</p>
<p><u>Risk</u></p>	<ul style="list-style-type: none"> <li>• Excluding MM events, more subjects randomized to selexipag prematurely discontinued treatment compared to subjects randomized to placebo; the most frequent reason for discontinuation was adverse events (Table 9, clinical review).</li> <li>• The most frequently reported adverse events with selexipag were typical prostacyclin-associated adverse events (headache, diarrhea, and nausea, jaw pain).</li> <li>• Uncommon adverse events included hyperthyroidism (also reported in postmarketing safety of epoprostenol) and eye pain.</li> </ul>	<p>Because there is no direct comparison of selexipag to the other IP receptor agonists, it is impossible to predict whether selexipag will be more or less tolerated than the other IP receptor agonists.</p> <p>Based on the current database, the safety profile of selexipag appears to be consistent with prostacyclin-associated adverse events observed with other IP receptor agonists.</p> <p>Adverse events can be communicated via labeling.</p>
<p><u>Risk Management</u></p>	<ul style="list-style-type: none"> <li>• The risks and safety of selexipag can be communicated in labeling.</li> </ul>	

## 2. Background

- *The product information and the applicant's proposals.*
  - Selexipag is an oral selective IP prostacyclin receptor agonist that is structurally distinct from prostacyclin and its analogs (e.g., epoprostenol, iloprost). The proposed indication for selexipag is to delay disease progression and reduce the risk of hospitalization for patients with pulmonary arterial hypertension (PAH) WHO Group I. The proposed dosing is 200 to 1600 µg oral tablets twice daily, with up-titration to the highest tolerated dose.
- *Therapeutic context*
  - PAH (WHO Group 1) is characterized by an increase in pulmonary arterial pressure (PAP) and pulmonary vascular resistance (PVR), which limits the ability of the right ventricle to pump blood through the lungs, causing shortness of breath and reduced physical performance. PAH is a rare, progressive disease that ultimately leads to right heart failure and death. PAH may be idiopathic, inherited, or associated with connective tissue diseases, congenital systemic-to-pulmonary shunts, drugs or toxins, HIV infection, and other conditions.
  - Other than heart-lung transplantation, there is no cure for PAH. In the past, approvals of PAH drugs have relied on an improvement in 6-minute walk distance. More recent approvals of PAH drugs such as macitentan and riociguat have relied on a single outcome study demonstrating a decrease in the risk of disease progression and PAH hospitalization.
  - The pathophysiology of PAH is poorly understood, but thought to involve abnormal interactions between endothelial and smooth muscle cells. Available pharmacologic therapies have addressed three target pathways:
    - Prostacyclin and analogs: relax and reduce proliferation of vascular smooth muscle cells;
    - ERAs: inhibit effects of elevated ET-1 levels, reduce vasoconstriction, smooth muscle proliferation, pulmonary vessel fibrosis;
    - PDE-5 inhibitors and the guanylate cyclase agonist, riociguat, potentiate the anti-platelet, antiproliferative, and vasodilatory effects of nitric oxide.

Of the available IP receptor agonists, only treprostinil is marketed in an oral formulation (Orenitram) and labeled for administration three times daily. Selexipag, if approved, is proposed for twice daily administration, a potential advantage for patients taking an oral IP receptor agonist.

- *Regulatory background and marketing history*
  - Selexipag was granted orphan drug designation, [REDACTED] (b) (4)

- The Division reviewed the protocol for the GRIPHON study through a Special Protocol Assessment and issued an agreement letter.
- Selexipag is not yet marketed in any country.

### 3. Product Quality

The product quality reviewers recommended approval of Uptravi® (selexipag) tablets (200, 400, 600, 800, 1000, 1200, 1400, and 1600 mcg).

The reviewers recommended storage at room temperature and a 36-month drug product expiry for all tablet strengths stored in the 60-count high-density polyethylene (HDPE) bottles and a 24-month drug product expiry for the 200 mcg tablet strength stored in the 140-ct HDPE bottle.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments

The reviewers did not recommend any Phase 4 (post-marketing) commitments. There are no unresolved product quality issues.

#### A. Selexipag Drug Substance Quality Summary

- Selexipag is known to have (b) (4)  
[Redacted]
- The drug substance is manufactured via a (b) (4)  
[Redacted]

#### B. Selexipag tablet Drug Product Quality Summary

UPTRAVI® (selexipag) is manufactured as round film-coated immediate release tablets in eight different strengths: 200, 400, 600, 800, 1000, 1200, 1400 and 1600 mcg. Although the amount of the active ingredient differs between the tablet strengths, the total weight and size of the tablets remain the same. (b) (4)

[Redacted] the colorants used for the film coat. The tablets are visually distinguished by the numbers debossed on the tablets and the colors of the film coats, which are unique for each strength.

Excipients: All the excipients are compendial and there are no novel excipients. However, the (b) (4)

[Redacted] (b) (4)

(b) (4)

Up to (b) (4)% of (b) (4) was observed in the drug substance batches that were used for the clinical studies. Because of the (b) (4) in the drug product (between (b) (4)% and (b) (4)%), the current analytical method does not have adequate sensitivity to assure the (b) (4) of tablets. However, the product quality and clinical pharmacology reviewers felt that (b) (4) was not likely to affect the clinical safety and efficacy.

Manufacturing: The product quality reviewers note that the drug substance and its synthesis appear to be well characterized and controlled based on the in-process, release, and stability testing controls. The drug product design and formulation appear to be robust and provide for a commercially viable product. The drug product control strategy, including dissolution testing, and the container closure appear to ensure the quality and integrity of the drug product over the shelf life. The applicant provided adequate information to describe the manufacturing process, its control and the associated (b) (4) tests.

A post-approval inspection was recommended for (b) (4) (responsible for drug substance manufacture and drug substance release testing). The manufacturing facilities identified to support commercialization were found to be in good standing.

## 4. Nonclinical Pharmacology/Toxicology

According to the pharmacology-toxicology reviewer, Dr. James Willard, selexipag is approvable from a nonclinical pharmacology/toxicology perspective. There are no outstanding issues or additional nonclinical recommendations.

Selexipag is scheduled to be discussed at an upcoming (1 December 2015) Carcinogenicity Assessment Committee (CAC) meeting.

Selexipag, a non-prostanoid, is active at the prostacyclin receptor and is rapidly converted to an active metabolite, ACT-333679, a more potent prostacyclin IP receptor agonist with a much longer half-life, allowing selexipag to be administered twice daily. Stimulation of the IP receptor leads to vasodilation of the pulmonary and systemic arterial vascular beds.

Although no “head to head” comparisons have been made, findings suggest that selexipag is pharmacologically and toxicologically similar to other prostacyclin agonists. Most of the adverse effects are believed to be related to the pharmacology of the drug, with severe gastrointestinal effects at high doses, skin flushing at all dose levels, and scaly skin, alopecia, piloerection and hair clumping at high doses.

High dosages of selexipag (safety margin >10-fold the human exposure) caused lethal intussusception in the adult and juvenile animal studies.

In the 2 year carcinogenicity studies, chronic dietary administration of selexipag revealed no evidence of carcinogenic potential in rats and mice at exposures that more than 25-fold above human exposures.

1. In the mouse carcinogenicity study, the applicant observed a small, insignificant trend in thyroid follicular cell tumors (adenoma + carcinoma); there were no statistically significant differences in either trend analysis or pairwise comparison between the control and any dose group. The number of thyroid tumors was lower than historical controls. The pharmacology reviewer noted that a primary issue was the dosage-dependent hyperplasia/hypertrophy of the follicular cells.
  - The high dosage caused lethal gastric erosion in 24/60 females, the adverse gastrointestinal effects perhaps reflecting the prominence of prostacyclin receptors in the gastrointestinal tract.
  - The skin was also affected in the high-dose carcinogenicity studies, with flushing, scaling, piloerection, alopecia and hair clumping.
  - Additional effects included adrenal gland hypertrophy and increased ossification of the periosteum and trabeculae.
2. In the rat carcinogenicity study, flushing was observed at all dosages. Some other symptoms (flaccidity, lacrimation, salivation, alopecia) were observed at higher dosages.
  - A marginally increased incidence of Leydig cell tumors was observed in the 100 mg/kg group, and a statistically significant positive trend was noted (rare tumor,  $p < 0.025$ ); however, there was no statistical significance in pairwise comparison between control and 100 mg/kg groups. The pharmacology reviewer felt that the tumors are within historical controls and that there is no increase in tumor incidence.
  - Tortuosity and dilatation of retinal arterioles in the 2-year rat carcinogenicity study were observed by the applicant. Meandering (tortuosity) of the retinal arterioles with dilatation of the arterioles was observed in both sexes in the 30 and 100 mg/kg groups. Examination conducted before dosing (that is, next morning of the previous dosing) revealed tortuosity of the retinal arterioles, but dilatation of the arterioles disappeared, and dilatation of arterioles was judged to be a pharmacological effect of NS-304. Histopathology revealed no treatment-related lesions in the retina or blood vessels of any other organ/tissue. Therefore, this ophthalmological finding was felt by the applicant to be of low toxicological significance (the pharmacology-toxicology reviewer concurred with the applicant). Even so, the applicant instituted an ophthalmology sub-study in the Phase 3 GRIPHON study to further evaluate the preclinical eye findings.

Mutagenesis: Selexipag and ACT-333679 were negative in a battery of genotoxicity tests.

Reproductive toxicology: In a rat study, the high-dose group was delayed in time to copulation, and all the treated animals had reduced litter size; however, the reduction was not statistically significant and there was no effect on the number of corpora lutea or pre/post-implantation loss.

Safety pharmacology studies showed no effects on hERG channels.

## 5. Clinical Pharmacology

According to the clinical pharmacology reviewer, selexipag can be approved from a clinical pharmacology perspective pending agreement on labeling. There are no outstanding issues or recommended post-marketing commitments or requirements.

The clinical pharmacology reviewer recommended that the following instructions are included in labeling:

- Once-a-day regimen in patients with moderate hepatic impairment
- Avoid use in severe hepatic impairment
- Avoid use in patients with concomitant use of strong CYP2C8 inhibitor

The applicant has developed an oral immediate release tablet, with a proposed dose range of 200 to 1600 mcg in increments of 200 mcg. The proposed starting dose is 200 mcg twice daily, titrated in 200 mcg increments based on tolerability.

The clinical pharmacology program included 11 *in vivo* studies in healthy subjects and special populations; in addition, the applicant submitted *in vitro* studies that evaluated plasma protein binding, blood to plasma partitioning, isozyme characterization, and metabolic enzyme and transporter interaction of selexipag and ACT-333679.

### Pharmacokinetics (PK):

Following oral administration, selexipag is absorbed with a median  $T_{max}$  of 1 hour (h) and a mean terminal elimination half-life of 0.8 to 2.5 h across studies. The oral bioavailability of selexipag is not known. Selexipag is hydrolyzed by CES-1 to a pharmacologically active metabolite, ACT-333679. Peak plasma concentration of ACT-333679 is achieved by 3 to 4 h [median] with a terminal elimination half-life of 6 to 13 h [mean] across studies.

The systemic exposure to ACT-333679 at steady state is 3- to 4-fold higher than that of selexipag. In addition, ACT-333679 is 37-fold more potent than selexipag. There is no significant accumulation of selexipag or ACT-333679 upon twice-daily dosing. The steady state exposures of selexipag and ACT-333679 are achieved within 3 days following repeat administration. The PK measures of selexipag are dose-proportional in the range of 100 µg to 1800 µg. For ACT-333679, the increase in PK measures is slightly less than dose-proportional in this range. For every 2-fold increase in dose, there is approximately 85% increase in exposure.

Selexipag is eliminated mainly by metabolism followed by excretion of the metabolites predominantly in the feces. No unchanged selexipag or ACT-333679 is excreted in the urine.

Pharmacodynamics:

In a Phase 2 study (NS-304-02), subjects on selexipag (N=33), titrated up to 800 µg twice-daily based on maximum tolerated dose, were observed to have a 33 % reduction (95% CI: 47% to 15% reduction) in mean percent change from baseline to Week 17 in pulmonary vascular resistance (PVR) compared to placebo (N=10). This decrease in PVR is consistent with the expected pharmacologic effect of the drug and is supportive of effectiveness. Other effects consistent with a vasodilator include the Week 17 decrease (vs. placebo) in systemic vascular resistance (median treatment effect -427 dyn\*sec/cm<sup>5</sup> [95% CI: -668, -135]) and increase in cardiac index (median treatment effect: 0.41 L/min/m<sup>2</sup> [95% CI: 0.10, 0.71]).

There were observed trends in decreased systolic, diastolic and mean pulmonary arterial pressure and an increase in pulmonary capillary wedge pressure following treatment with selexipag, compared to placebo, that were not statistically significant.

No significant inhibition of platelet aggregation [measured *ex vivo* with ADP as agonist] was observed following administration of selexipag up to 1600 µg twice-daily.

Impact of Intrinsic Factors:

Because of the relative higher potency of ACT-333679 compared to selexipag, dosing recommendations are made based on the exposure to the metabolite.

No dose adjustment is recommended in patients with mild hepatic impairment. Subjects with moderate hepatic impairment developed 2-fold higher exposure to ACT-333679 following twice daily administration. Based on pharmacokinetic modeling and simulation, a once daily regimen is expected to result in a similar exposure to ACT-333679 when compared to healthy subjects. Therefore, the clinical pharmacologist recommended a once daily dosing in patients with moderate hepatic impairment. Because of limited PK data in severe hepatic impaired group (N=2), the clinical pharmacologist recommended avoiding the use of selexipag in patients with severe hepatic impairment.

No dose adjustment is required in patients with renal impairment.

While body weight was found to be a covariate affecting selexipag and ACT-333679 plasma exposures [30% increase in 50 kg vs 75 kg subject], the reviewers did not recommend adjusting dose based on weight, since patients will undergo up-titration based on tolerability. Other covariates such as age, gender and ethnicity do not significantly impact the PK of selexipag or ACT-333679.

Impact of extrinsic factors:

Selexipag is hydrolyzed to ACT-333679 by carboxylesterase 1 (CES-1). Potential for CES-1 inhibition *in vivo* is minimal because of its ubiquitous expression in many tissues. Cytochromes

(CYP) 3A4 and CYP2C8 are other CYP isoforms involved in the metabolism of selexipag to minor metabolites. Importantly, metabolism of ACT-333679 to P10, one of the major metabolite in feces is mediated by CYP2C8. To mitigate the risk of higher exposures of ACT-333679, selexipag should be avoided when administered with a concomitant strong CYP2C8 inhibitor, as recommended by the clinical pharmacology reviewer.

Co-administration of Kaletra® [CYP3A, P-gp and OATP1B1/1B3 inhibitor] with selexipag resulted in approximately 2-fold increase in the exposure to selexipag, but not ACT-333679;

(b) (4)

Co-administration with a high fat meal did not significantly impact the PK of selexipag or ACT-333679, but improved tolerability. Selexipag should be administered with a meal for better tolerability.

Biopharmaceutics: The final, to-be-marketed formulation was used in GRIPHON. Therefore, no pivotal bioequivalence study was conducted. A bioequivalence study conducted showed that selexipag and ACT-333679 PK from 1 x 1600 µg tablet and 8 x 200 µg tablets are bioequivalent.

QT/QTc effects:

No significant QTcI prolongation effect of selexipag (800 mcg and 1600 mcg twice daily) was detected in a thorough QT study. However, the highest tested dose of 1600 mcg twice daily was felt unlikely to cover patients with hepatic impairment who receive the maximum dose of 1600 mcg twice daily. Since we are recommending once daily dosing in patients with moderate hepatic impairment, and avoiding use in patients with severe hepatic impairment, I do not have concerns about higher exposures not covered by the thorough QT study.

Selexipag did not show an effect on the PR or QRS interval and had a mild accelerating heart rate effect.

## 6. Clinical Microbiology

Not applicable.

## 7. Clinical/Statistical- Efficacy

The efficacy of selexipag is based on the results of a single Phase 3 outcome study, GRIPHON,<sup>6</sup> a multicenter, randomized, placebo-controlled, double-blind, event-driven study that randomized 1156 PAH patients (1:1 ratio) to selexipag or placebo.

The primary objective was to demonstrate the effect of selexipag on the time to first morbidity/mortality (MM) event up to 7 days after the last study drug intake in the treatment period.

Secondary objectives included the effects of selexipag on exercise capacity and other endpoints.

Eligible subjects were 18-75 years with symptomatic PAH. The PAH etiology was within groups 1.1 to 1.4 of the updated Dana Point 2008 clinical classification, i.e., idiopathic (IPAH), heritable (HPAH), or PAH association with connective tissue disease, congenital systemic-to-pulmonary shunt, HIV infection, or PAH induced by drug or toxin. Subjects were also required to have a 6-minute walk distance (6MWD) between 50 and 450 m at screening (different day than baseline).

The MM events were:

- Death (all-causes)
- Hospitalization for worsening of PAH based on predefined criteria
- 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
- Disease progression (patients in modified NYHA/WHO Functional Class (FC) II/III at baseline) confirmed by:
  - Decrease in 6MWD from Baseline ( $\geq 15\%$ , confirmed by 2 tests on different days) **and** Worsening of NYHA/WHO FC
- Disease progression (patients in NYHA/WHO FC III/IV at baseline) confirmed by:
  - Decrease in 6MWD from Baseline ( $\geq 15\%$ , confirmed by 2 tests on different days) **and** Need for additional PAH-specific therapy.

Patients in NYHA/WHO FC III at baseline qualified for both disease progression definitions.

The secondary endpoints were:

- Absolute change from Baseline to Week 26 in 6MWD measured at trough. Prior to Amendment 1, this was the primary endpoint.
- Absence of worsening from Baseline to Week 26 in NYHA/WHO FC.
- Time from randomization to first of clinical events committee (CEC)-confirmed death due to PAH or CEC-confirmed hospitalization due to PAH worsening up to 7 days after last study drug intake.
- Time from randomization to death of all causes up to study closure.

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<sup>6</sup>The acronym GRIPHON is based on the title of the study: Prostacyclin (PGI<sub>2</sub>) receptor agonist in pulmonary arterial hypertension

- Absolute change from baseline to Week 26 in the sub-scale ‘Breathlessness’ of CAMPHOR (Cambridge Pulmonary Hypertension Outcome Review) ‘Symptoms’ (at selected centers).
- Absolute change from Baseline to Week 26 in CAMPHOR ‘Symptoms’ score (at selected centers).

MM events were adjudicated by an independent clinical events committee (CEC) that was blinded to study treatment.

There were no dedicated dose/concentration-effect studies to guide dosing for GRIPHON. Study drug (200 mcg selexipag or matching placebo) was initiated and up-titrated to each individual subject’s maximum tolerated dose in the range of 200-1600 mcg bid. If intolerable effects typical of IP receptor agonists (e.g., headache, diarrhea, jaw pain, myalgia, flushing, and nausea) occurred, the investigator was to reduce the dose by 200 mcg bid. At Week 12, the maximum tolerated dose (MTD) was determined, and this dose was to be kept stable for the next 14 weeks, up to the Week 26 assessment of the secondary endpoint, change in 6MWD. After Week 26, investigators were allowed to up-titrate the dose or down-titrate in the event of a tolerability issue.

Subjects were allowed to take concomitant approved ERAs or PDE5 inhibitors, but concomitant prostacyclin (epoprostenol) or prostacyclin analogs were forbidden from 1 month prior to baseline to end of study (EOS), with the exception of a single administration of IV/inhaled prostacyclin or analog during a right heart catheterization procedure.

There were six protocol amendments. Key changes included: 1. Changing the primary endpoint; 2. Increasing the number of primary endpoint events and addition of an interim analysis in Amendment 4; 3. Censoring events until 16 August 2011 in the primary analysis in order to eliminate concerns that Amendment 4 could be considered to be informative; 4. Altering the scope of adjudication and re-adjudicating MM events.

The original protocol (17 September, 2009) planned for the primary endpoint of “change from baseline to Week 16 in 6MWD.”

Amendment 1 (11 March, 2010) changed the primary endpoint to “time to first clinical worsening” and made 6MWD a secondary endpoint, assessed at Week 26. Subjects without a clinical worsening event were to be censored seven days after study treatment discontinuation. Amendment 1 also merged study AC065A301 into AC-06A302 and renamed the study AC-065A302/GRIPHON.

Amendment 4 (10 August 2011) increased the initial target hazard ratio from 0.5729 to 0.65, increased the number of primary events from 202 to 332, and increased the sample size from 670 to 1150 subjects. Amendment 4 also added an interim analysis after 202 primary events.

Amendment 5 (14 December 2011) attempted to eliminate any concern that Amendment 4 could be considered “informed,” by censoring the events observed until 16 August 2011 in the primary

endpoint analysis and including these censored events in a sensitivity analysis of the primary endpoint.

Amendment 6 (23 January 2013) renamed the primary “clinical worsening event” to “morbidity and mortality (MM) event” (without changing the definition) and added a “post treatment observation period” to collect data up to study closure on all subjects who prematurely discontinued the study. Since Amendment 6 broadened the scope of the adjudication process, all events adjudicated prior to the amendment were submitted to the CEC for re-adjudication; all MM events were readjudicated by the CEC prior to unblinding.

All main statistical analyses of all efficacy endpoints were based on the Full Analysis Set (FAS), which included all randomized subjects in GRIPHON. GRIPHON employed a group-sequential design for the primary efficacy endpoint with options to stop for futility or for compelling and robust efficacy at the interim analysis. The primary analysis used a one-sided unstratified log-rank test.

No imputation method was applied to the primary endpoint. If the study met its primary endpoint (i.e., the primary null hypothesis was rejected), the secondary efficacy endpoints were tested in a hierarchical manner.

### Results:

A total of 1351 subjects at 181 sites in 39 countries were screened, with 195 screening failures, 1156 subjects were randomized, and 1152 subjects received study drug. A total of 87% of selexipag subjects and 89% of placebo subjects underwent an end-of-study visit. About 4% of selexipag subjects (N=24) and 5% of placebo subjects (N=27) had unknown vital status at study closure. The numbers and percentage of subjects with missing or unknown vital status seem comparable across treatment groups and unlikely to change the primary result.

The top enrolling countries were the US (13%), China (12%) and Russia (8%).

There was a higher premature discontinuation rate in subjects randomized to selexipag (148/575, 26%) compared to those randomized to placebo (97/577, 17%) in subjects that did not experience an adjudicated MM event; the most frequently reported reason for discontinuation was an adverse event. Only 28% of selexipag subjects, compared to 68% of placebo subjects, achieved an individual maintenance dose (IMD), the dose to which the subject was exposed for the longest duration, of 1600 mcg bid; over half of the selexipag subjects were exposed to IMD of 1000 mg bid.

Treatment compliance, assessed by study drug accountability, was < 80% at end of study (EOS) for 7% of selexipag subjects versus 3% of placebo subjects.

Taken together, the higher premature discontinuation rate and lower treatment compliance rate in subjects randomized to selexipag and the lower percentage of selexipag subjects achieving the highest IMD are consistent with tolerability issues.

Protocol violations and deviations appeared to be balanced across treatment groups.

The study population was mostly female (about 80%) and mostly in WHO Functional Class (FC) II and III (Table 3-4, statistical review). Median age was 49 years; about 17% of the study population was 65 years and older. About 80% of subjects were receiving at least one background PAH-specific medication and about 1/3 of subjects were receiving two PAH drugs. Mean baseline 6MWD was 10 m longer for subjects randomized to selexipag, compared to those on placebo. Otherwise, no imbalances were observed between treatment groups.

GRIPHON met its primary endpoint, with a statistically significant 39% risk reduction for the occurrence of a first MM event up to EOT + 7 days. Results were similar whether or not CEC-confirmed MM events up to 16 August 2011 were censored. PAH hospitalization was the most frequently reported first adjudicated event; according to the statistical reviewer, disease progression was the most influential component of the MM event (see clinical and statistical reviews).

**Table 1. Summary of first CEC-confirmed MM event and components up to 7 days after last study drug intake (FAS)**

Event	Selexipag N=574		Placebo N=582		Hazard Ratio (99% CI)	p-value
	n	%	n	%		
<b>Final Analysis</b>					0.61	
First morbidity/mortality event	140	24.4	212	36.4	[0.46,0.81]	<0.0001
<b>Decomposition of the first MM event</b>						
• <b>Death</b>	25	4.4	16	2.7		
• <b>Hospitalization</b> for PAH worsening	71	12.4	96	16.5		
• <b>PAH</b> worsening resulting in need for lung transplantation or balloon atrial septostomy	1	0.2	2	0.3		
• <b>Parenteral</b> prostanoid therapy or chronic oxygen therapy	11	1.9	14	2.4		
• <b>Disease</b> progression	32	5.6	84	14.4		
<b>First Occurrence of each component of MM event</b>						
• <b>Death</b>	40	7.0	34	5.8	1.10 [0.61,2.01]	
• <b>Hospitalization</b> for PAH worsening	77	13.4	111	19.1	0.65 [0.44,0.95]	
• <b>PAH</b> worsening resulting in need for lung transplantation or balloon atrial septostomy	2	0.3	3	0.5	0.63 [0.06,6.67]	
• <b>Parenteral</b> prostanoid therapy or chronic oxygen therapy	30	5.2	45	7.7	0.62 [0.34, 1.14]	
• <b>Disease</b> progression	58	10.1	127	21.8	0.43 [0.29,0.65]	

Source: statistical review (Table 3-5). First occurrence of each component of MM event refers to events occurring up to 7 days after the last study drug intake; an event that occurred outside this window would not be counted in this table.

Effects of adjudication:

A total of 82 events in the selexipag group and 124 events in the placebo group were submitted for adjudication in both CEC adjudication processes. A high percentage of agreement was recorded between the two CEC adjudication processes in 80/82 (98%) of events in the selexipag group and 116/124 (94%) events in the placebo group.

Of 203 MM investigator-reported events in the selexipag group and 303 in the placebo group, an agreement between the investigator and the new CEC process was recorded for 166 events (82%) in the selexipag group and 260 events (86%) in the placebo group.

The two treatment groups appear comparable in the adjudication process (investigator vs. new CEC, old vs new CEC).

Based on the Kaplan-Meier graph of the time from randomization to the first CEC-adjudicated MM event up to 7 days after the last study drug intake (Figure 1), the selexipag and placebo curves appear to separate as early as 2.5-3 months after randomization, remaining separated until the end of study.

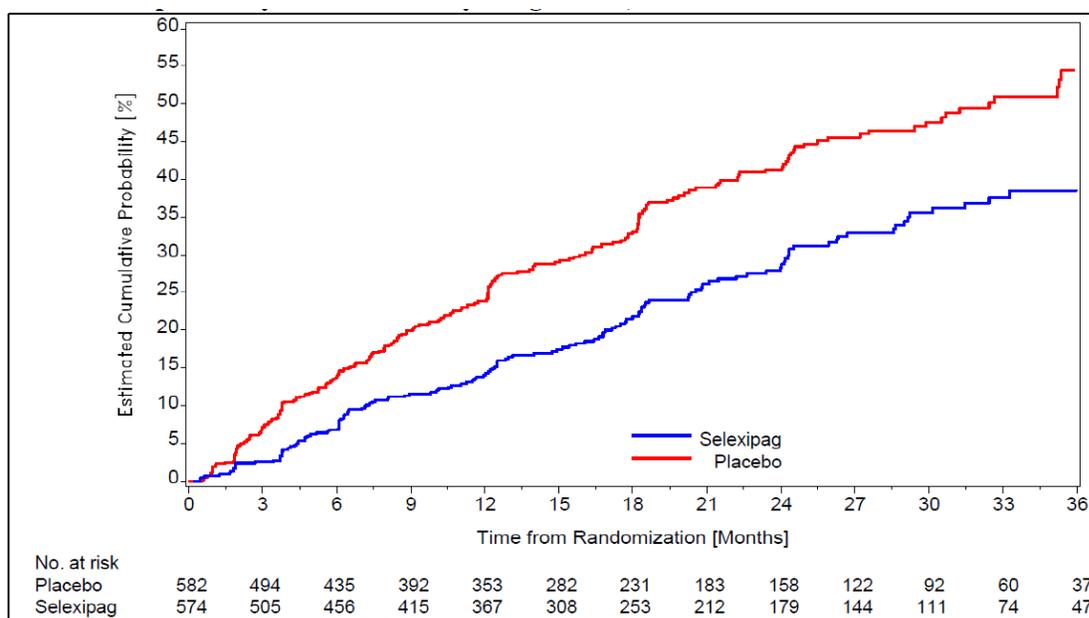


Figure 1. Kaplan-Meier estimate of time from randomization to first CEC-confirmed MM event up to 7 days after last study drug intake, FAS. Source: statistical review (Figure 3-1)

One can observe a higher number and percentage of deaths as the first MM event in subjects randomized to selexipag compared to those randomized to placebo (Table 1). However, in an analysis of the time to all-cause death up to study closure (study end date), the mortality hazard ratio for selexipag versus placebo was 0.97 (99% CI: 0.68, 1.39); a total of 100 and 105 subjects in the selexipag and placebo groups, respectively, died up to study closure. If one had a concern about increased mortality with selexipag, these results seem reassuring.

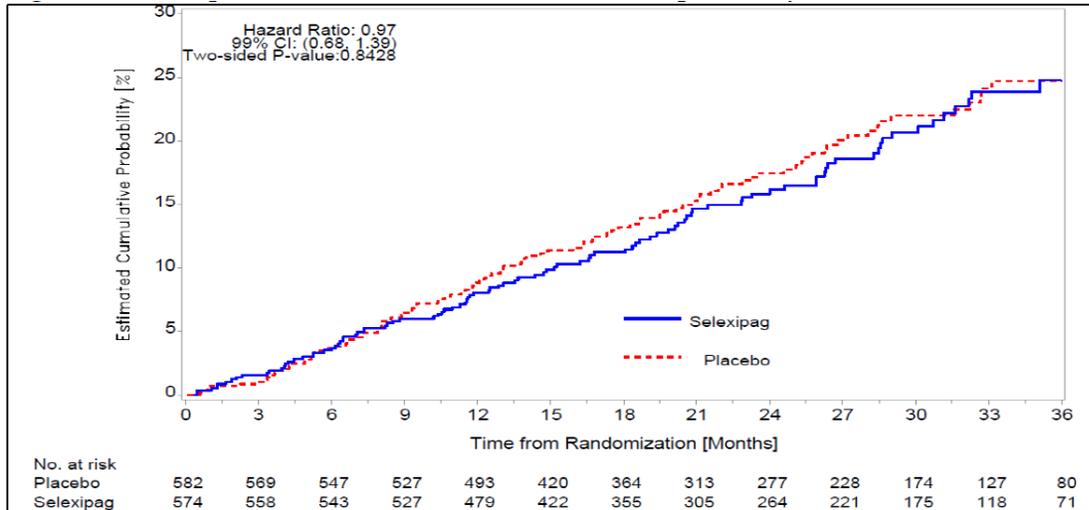
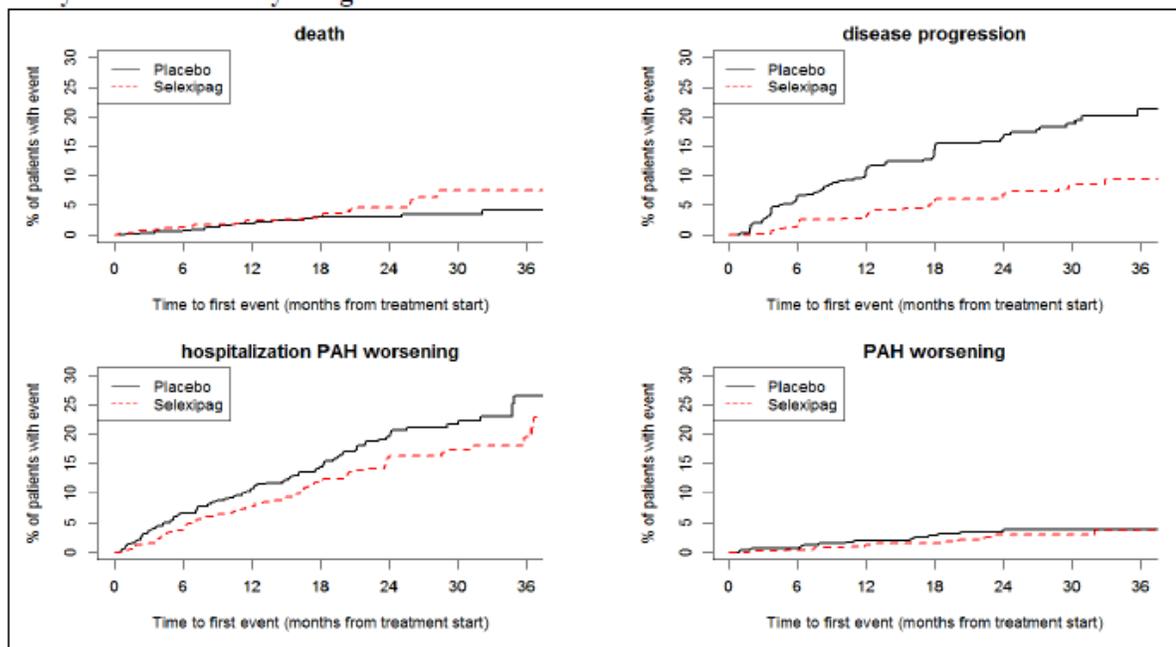


Figure 2. Kaplan-Meier estimate of time to death up to study closure, FAS (source: statistical review, Figure 3-2).

Results of a sensitivity analysis including events prior to 16 August 2011, as well as a supportive analysis in the first 670 randomized subjects up to the occurrence of 202 first CEC-confirmed MM events, were consistent with the primary analysis. The results of the planned interim analysis came close to, but did not meet, the statistical stopping criterion for efficacy. As sensitivity analyses, results of Gray’s competing risk analysis and cumulative incidence functions were consistent with the primary analysis, where the MM results appear primarily driven by the components of disease progression and hospitalization for PAH worsening.



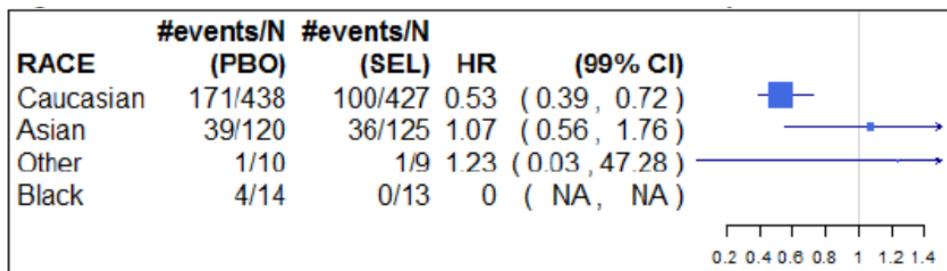
[Source: Reviewer Results]

Figure 3. Cumulative incidence function for the first CEC-confirmed MM event up to 7 days after last study drug intake (source: statistical review, Figure 3-3).

Analysis of the primary endpoint by subpopulations:

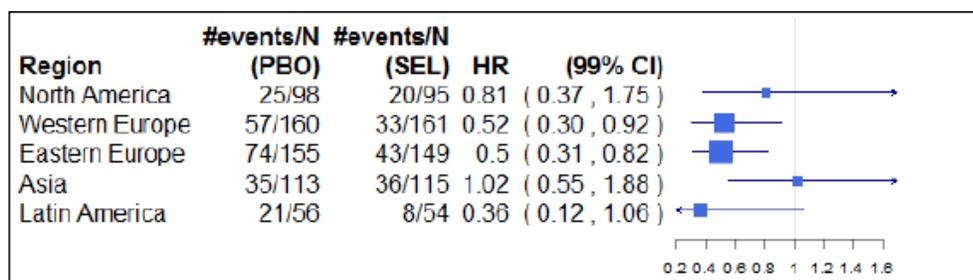
1. Age: Most (82%) of subjects in GRIPHON were under 65 years-old. The treatment effect in the elderly appeared consistent with the overall effect.
2. Gender: Effects within each gender group were consistent with the primary efficacy result.
3. Race: The majority of subjects were Caucasian (65%) or Asian (21%). There were too few Black/African-American subjects to draw conclusions. Results were not consistent in the Asian population, with wide confidence intervals (Table 2). The number of events and the denominators (n/N) in the Asian subgroup and the Asia region were similar, suggesting that most of the Asians were located in Asia (rather than other regions such as the US).
4. Geographic area: With the exception of Asia, results for North America, Latin America, and Western and Eastern Europe were consistent with the primary efficacy results (Table 3).
5. Background PAH-specific therapy: Results appeared consistent with the overall results whether subjects were taking ERAs, PDE5 inhibitors, both ERAs and PDE5 inhibitors, or no background PAH therapy.
6. Baseline WHO functional class: The study population was mostly classified as WHO functional class II or III. Results were consistent with the overall primary efficacy results regardless of baseline WHO functional class (I/II or III/IV).

Table 2. Results of the primary endpoint by race (Source: statistical review).



[Source: Reviewer's Results]

Table 3. Results of the primary endpoint by region (Source: statistical review)



[Source: Reviewer's Results]

Number Needed to Treat (NNT):

As provided by the applicant, this analysis suggests that 8 and 7 patients, respectively, need to be treated with selexipag to prevent one MM event in up to 1 or 2 years, respectively.

**Table 4. Number needed to treat to prevent one additional adjudicated MM event (source: applicant)**

**Table 3-25 Number needed to treat to prevent one additional CEC-confirmed MM event up to AC-065A302 EOT + 7 days, FAS**

Time from Treatment start	Number of patients still at risk	Number needed to treat Estimate 95% C.I.
CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period		
12 months	708	8.0 ( 5.7,13.6)
18 months	466	7.1 ( 5.0,12.1)
24 months	320	7.1 ( 4.8,13.5)
30 months	189	8.0 ( 5.0,19.3)

CEC = Critical Event Committee.  
Source: modified from Appendix 2, Table 1-37

Secondary endpoints:

6MWD:

The main analysis of 6MWD used a non-parametric ANCOVA with baseline 6MWD as covariate. The difference in median absolute change from Baseline to Week 26 in 6MWD measured at trough was statistically significant between selexipag and placebo, with a treatment effect of 12 meters (99% CI: 1, 24, 1-sided Wilcoxon-Mann-Whitney p = 0.0027, source: statistical review). Both selexipag and placebo groups deteriorated from baseline 6MWD, a result that seemed unusual to some; one would expect and hope for a treatment-related improvement from baseline. The selexipag group deteriorated less than placebo, thus the result was favorable for selexipag.

A review of other IP receptor agonists shows 6MWD results that were measured at shorter time points. It does not seem appropriate to compare results at Week 12 to those at Week 26 in a progressive disease.

**Table 5. Summary of 6MWD results from package inserts of other IP receptor agonists**

Drug	Total N	change from baseline(drug)	change from baseline (placebo)	Time point	Analysis
Ventavis® (iloprost solution)	203	+31 meters	-9 meters	12 weeks	p <0.01
Orenitram™ (oral treprostinil)	228	+23 meters	-5 meters	12 weeks	p=0.013

Remodulin® (treprostinil injection)	470	+10 meters	0	12 weeks	p=NS
Flolan® (epoprostenol injection)	107	Not stated	Not stated	12 weeks	“Statistically significant improvement compared with those receiving conventional therapy alone...improvements were apparent in some patients at the end of the first week of therapy.”

Source: package inserts

Missing data:

One might also expect more missing data (e.g., dropouts or MM events) when measuring 6MWD at a more distant time point. In GRIPHON, missing Week 26 6MWD values were imputed for 20% of selexipag subjects and 23% of placebo subjects (including deaths). A “0” was imputed for the Week 26 6MWD for subjects who died before Study Day 271 or for subjects unable to walk at Week 26 due to PAH (Rule 1). Otherwise, the second lowest observed 6MWD value at Week 26 was imputed; in the FAS, this was 10 m (Rule 2).

In a sensitivity analysis, where only Rule 1 was imputed, there was a median increase in the absolute change from baseline in 6MWD of 14.0 m for selexipag subjects and 2.5 m for placebo subjects.

**Table 6. Reasons for missing 6MWD (source: applicant)**

**Table 15-76 Reason for missing 6MWD, FAS**

ACT-293987, Protocols AC-065A302/AC-065A303  
Reason for missing 6-Minute-Walk-Distance  
Set: Full analysis set

	Selexipag N=574		Placebo N=562	
	n	%	n	%
Total patients with at least one reason	114	19.9%	136	23.4%
Reasons:				
Death before Week 26	25	21.9%	26	19.1%
Study drug discontinuation before Week 26 with CEC-confirmed M/M event	16	14.0%	56	41.2%
Study drug discontinuation before Week 26 with no CEC-confirmed M/M event	61	53.5%	37	27.2%
Withdrawal of consent or loss to follow up before Week 26	32	28.1%	23	16.9%
Visit done, Assessment not performed	11	9.6%	13	9.6%
Assessment not performed for other reasons	1	0.9%	4	2.9%

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(Page 1/1)

In the Phase 2 study, the Week 17 6MWD results, while not statistically significant, also show a favorable trend for selexipag (see clinical review).

The statistical reviewer stated that the 6MWD result has “little or no clinical meaning” without further explanation in his review. I acknowledge the limitations of the Week 26 6MWD in GRIPHON (deterioration in both treatment groups, small median treatment effect, missing data) but note that the 6MWD results (from the Phase 2 study and GRIPHON) show small but consistent favorable results for selexipag, supporting the primary endpoint.

Worsening in NYHA/WHO FC: All subjects in the study were NYHA functional class II or III at baseline, and selexipag had a higher proportion of subjects in class II (44%) than placebo (20%). There was no difference between selexipag and placebo in the proportion that worsened from baseline; the common odds ratio was 1.161 (99% CI 0.811, 1.664). Because this analysis was not statistically significant, the other secondary endpoints in the hierarchy become “exploratory.”

The time from randomization to first CEC-confirmed death due to PAH or CEC-confirmed PAH hospitalization up to 7 days after the last study drug intake was favorable for selexipag (HR 0.70, 99% CI 0.50, 0.98, one-sided unstratified log-rank p-value =0.0031). Please see the clinical review for further details.

The time from randomization to all-cause mortality up to study closure analysis resulted in a hazard ratio of 0.97 (99% CI: 0.68, 1.39, one-sided unstratified log-rank p=0.42) (Figure 2, above).

There was no difference between selexipag and placebo in the change from baseline to Week 26 CAMPHOR symptom and breathlessness subscale.

In the phase 2 study, there was no effect on pulmonary vascular resistance (PVR) measured 4 hours after a single selexipag oral dose; however, at Week 17, there was a statistically significant 30% decrease in the geometric mean PVR vs. placebo. There was also a decrease in systemic vascular resistance (SVR) at Week 17, consistent with the expected pharmacology of selexipag.

#### Review Issues:

1. GRIPHON was modified a number of times throughout its course, including modifications of the primary endpoint (finally becoming MM event in Amendment 6) and an increase in sample size, along with the addition of an interim analysis in Amendment 4. Because of concerns that Amendment 4 could be informative, the primary events observed prior to 16 August 2011 were censored in the primary analysis. These changes occurred before any version of Statistical Analysis Plan. However, the primary endpoint analyses appear consistent, whether or not the earlier events are censored.
2. In the decomposition of the primary endpoint, there are more mortality first events in subjects randomized to selexipag, compared to those randomized to placebo. However, a Kaplan-Meier curve of all-cause mortality to the end-of study provides reassurance against a concern of increase in mortality.
3. The 6MWD results at Week 26, while favorable for selexipag vs. placebo, show deterioration in both groups, with more deterioration in the placebo group (if one

uses the main analysis) and a small treatment effect. Interpretation of these results is limited by the amount of missing Week 26 data.

The statistical reviewer (Dr. Bai) concluded that GRIPHON was adequately designed as a morbidity/mortality event-driven clinical outcome trial with strict statistical specifications. The primary objective of the study was met with a statistically highly significant 39% risk reduction for the occurrence of a first MM event up to the end of treatment (+7 days) with selexipag, a “clinically relevant treatment effect in a progressive and ultimately fatal cardiovascular disease” (statistical review).

The clinical reviewer (Dr. Gordon) observed that hospitalizations for PAH worsening and disease progression were the most frequently adjudicated first morbidity/mortality events. More placebo than selexipag patients reported PAH worsening and right ventricular failure as serious adverse events and/or discontinued therapy for these reasons, supporting effectiveness of selexipag. The clinical reviewer concluded that evidence of benefit has met the statutory evidentiary standard. The statistical reviewer concluded that GRIPHON was adequately designed as a morbidity/mortality event-driven clinical outcome trial with strict statistical specification. I concur.

The evidence of effectiveness for selexipag relies on a single study which met its primary endpoint, driven by a decrease in the risk of PAH hospitalization and disease progression, endpoints that have been considered to be important clinical outcomes in past PAH drug applications. While there were several amendments to the protocol, I concur with the clinical and statistical reviewers that adequate controls were in place to preserve study integrity.

The FDA 1998 Guidance “Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products” addresses situations in which “a single multicenter study, without supporting information from other adequate and well-controlled studies, may provide evidence that a use is effective.” Such approvals have relied on particularly persuasive results from an internally consistent, multicenter study that demonstrated a major effect on mortality and/or significant morbidity (e.g., myocardial infarction, heart failure hospitalization, PAH hospitalization).

GRIPHON was a multicenter study that met its primary endpoint with highly persuasive results, a 39% reduction in MM events and low p-value ( $< 0.0001$ ); no single site was responsible for the primary result. Results were consistent whether or not early MM events were censored, following sensitivity analyses and, with the exception of the Asian region, results were consistent across subsets (e.g., age, functional class, gender, concomitant therapy). In a serious, progressive disease, the risk reduction in GRIPHON was driven by PAH hospitalization and disease progression, clinically meaningful endpoints; it might therefore prove practically or ethically difficult to conduct a confirmatory trial.

Furthermore, the IP receptor agonist activity of selexipag, along with the statistically significant decrease in PVR at Week 17 in subjects treated with selexipag, provides a mechanistic rationale to support effectiveness.

While reliance on a single adequate and well-controlled study may ultimately be a matter of judgment, I conclude that the GRIPHON results are persuasive and internally consistent, and supported by the effects of selexipag in decreasing pulmonary vascular resistance; it would likely be ethically difficult to repeat such a study. I therefore conclude that the evidence of benefit has met the statutory evidentiary standard for effectiveness.

## 8. Safety

Christine Garnett, Pharm.D. conducted the safety review of selexipag.

The primary source of safety data is the GRIPHON study, which exposed 575 subjects to selexipag; the median duration of selexipag exposure was 71 weeks, with 367 (64%) subjects receiving treatment for at least one year and 180 (31%) receiving treatment for at least two years. The total selexipag exposure was 842 patient-years and the total placebo exposure was 786 patient-years.

The safety database seems acceptable, considering that PAH is a rare disease. The number of subjects exposed to selexipag in GRIPHON seems comparable to (in fact, larger than) the number exposed to macitentan (N=498) in SERAPHIN. Selexipag is proposed for (b) (4) use, and over 100 subjects were exposed to selexipag for at least 2 years.

About 24% of selexipag-treated subjects were down-titrated at least once from their individual maximum tolerated dose (IMD) compared to 11% of placebo-treated subjects. In both groups, the main reason for down-titration was adverse events.

Since prostacyclin inhibits platelet aggregation, bleeding was a concern; treprostinil and epoprostenol labeling carries precautionary language about the risk of bleeding. During GRIPHON, adverse events associated with bleeding were independently adjudicated by two external expert reviewers who were blinded to treatment assignment. A major bleeding event was defined as either fatal bleeding; symptomatic bleeding in a critical area or organ; or bleeding causing a fall in hemoglobin level of at least 20 g/L (1.24 mmol/L) leading to transfusion of at least 2 units of whole blood or red cells.

Since there was a preclinical retinal finding, an Ophthalmology Safety Board, blinded to treatment assignment, was established to assess the nature and relevance of treatment-emergent retinal abnormalities. In addition, an ophthalmology sub-study collected additional funduscopy/fundus assessment in 54 selexipag-treated and 48 placebo-treated subjects.

Key safety results from GRIPHON were as follows:

3. Excluding subjects with MM events, there was a higher premature discontinuation rate (overall and AE-related) in subjects randomized to selexipag compared to those randomized to placebo (Table 9, clinical review).

4. Prostacyclin-like events were the most frequently reported AEs with selexipag and were associated with dose reduction and treatment discontinuation. Examples of prostacyclin-like AEs included: headache, diarrhea, nausea/vomiting, jaw pain, extremity pain, flushing, myalgia (Figure 5, Figure 7, Table 10, Table 11, clinical review). Subgroup analysis by gender, age, BMI, race/ethnicity and background medications did not detect a population that was more sensitive to these AEs; however, some subgroups were too small to render such analyses as conclusive.
5. The prostacyclin-associated AE appeared to occur early, mostly within the first 2 weeks of administration. The median time to the first prostacyclin-associated AE was 11 days (95% CI: 9, 14 days) in the selexipag group and 57 days (95% CI: 45, 93 days) in the placebo group (Figure 6, clinical review).
6. Since selexipag, an IP receptor agonist, decreased SVR in the Phase 2 hemodynamic study, one might have expected decreases in systemic BP in the Phase 3 program. Vital signs, as collected during GRIPHON, were similar between the selexipag and placebo groups (Figures 16 and 17, clinical review) and there appears to be no “signal” for notable decreases in SBP or hypotension AE (Tables 21, 22, clinical review). There was no selexipag-related increase in the incidence of orthostatic hypotension, dizziness, postural dizziness, or syncope.
7. Numerical imbalances were observed in the frequencies of subjects reporting eye and retinal disorders in the selexipag group (N=63, 11%) compared to those on placebo (N=45, 8%). Eye pain (n=9 on selexipag vs. N=2 on placebo) was the most frequently reported eye disorder; otherwise, the difference between groups is small (Table 13, clinical review). An ophthalmology sub-study, including fundoscopy and digital photography, was conducted in 54 selexipag and 48 placebo subjects at 33 sites in 22 countries; Dr. Wiley Chambers reviewed the ophthalmology safety findings and noted that the clinical relevance of the ocular AE cannot be determined due to the small number of events; the sub-study did not include measures of visual function or ascertainment of other ocular abnormalities. Dr. Chambers recommended describing eye pain in the label; and that any future ocular evaluation includes a measurement of visual function.
8. The overall frequency of bleeding events and adjudicated major bleeding events were similar across treatment groups (Tables 14, clinical review). There were 6 cases of cerebrovascular hemorrhage in subjects treated with selexipag (4 in GRIPHON and 2 in study NS-304/-03), which appear to be confounded (e.g., car accident, alcohol, concomitant anticoagulants). One cannot exclude an increase in bleeding associated with selexipag when this medication is used in a broader population. There was a slight imbalance in anemia AEs in selexipag-treated subjects (8%) vs. placebo (5%) and small decreases in hemoglobin, but no imbalances in discontinuation due to anemia or increased rate of transfusion.

9. There was an apparent difference in the incidence of cerebral ischemic events in selexipag-treated subjects vs. those on placebo (6 selexipag vs. 1 placebo subject); however, the numbers are too small to draw conclusions about causality.
10. The applicant noted a small reduction in median TSH levels (up to -0.3 MU/L from baseline) in the selexipag group at some visits. No thyroid “signal” based on laboratory testing was observed (Figure 12, clinical review). Eight selexipag-treated subjects reported hyperthyroidism (including 1 SAE), 2 subjects reported autoimmune thyroiditis and one subjects reported an SAE of Basedow’s disease, compared to 0 thyroid reports in placebo subjects. Of note, IP receptors can be found in thyroid tissue, and hyperthyroidism has been observed during post-approval use of epoprostenol.

In clinical trials, hyperthyroidism was detected from scheduled thyroid function testing, which was included in GRIPHON after increases in thyroid hyperplasia were observed in 24-month carcinogenicity studies. Nine of the 10 subjects who developed hyperthyroidism continued taking selexipag without dose adjustments or discontinuations.

11. The safety reviewer observed a slight imbalance in the incidence of malignancy events in selexipag-treated subjects. However, according to the pharmacology reviewer, the 2-year carcinogenicity studies did not show a signal; the incidence of thyroid adenomas in mice and Leydig cell adenomas in rats are not higher than historical controls.

In summary, the safety profile of selexipag appears to be consistent with its pharmacologic activity; adverse events related to selexipag should be communicated in the label.

## **9. Advisory Committee Meeting**

This application was not presented to an advisory committee.

## **10. Pediatrics**

Since PAH is an orphan indication, this application is exempt from PREA requirements.

## 11. Other Relevant Regulatory Issues

- Financial disclosures: In a 70-page list, the applicant certified that no financial arrangement was made whereby the value of compensation to the investigator could be affected by the outcome of the study (Form 3454). A total of 45 investigators had disclosable interests, but do not appear to have had sufficient influence or independent ability to influence to the overall study conduct or outcomes.
- Office of Scientific Investigations (OSI) audits: The applicant underwent inspection by OSI. In addition, three GRIPHON international sites were chosen for inspection based on high enrollment and favorable treatment effect for selexipag. Based on their findings, OSI recommended that the data be considered acceptable for this study.

## 12. Labeling

### Prescribing Information

At the time of this review, final labeling is under discussion by the reviewers and the applicant.

Recommendations by the reviewers include:

- Inclusion of the primary analysis (with censoring of events prior to Amendment 2)
- Clinical pharmacology recommendations:
  - Once-a-day regimen in patients with moderate hepatic impairment
  - Avoid use in severe hepatic impairment
  - Avoid use in patients with concomitant use of strong CYP2C8 inhibitor

Section 5 (Warnings and Precautions) includes a (b)(4) warning for pulmonary edema in patients with pulmonary veno-occlusive disease.

### Other Labeling

- According to the Division of Medication Error Prevention and Analysis (DMEPA review 19 February 2015): the proposed proprietary name, Uptravi, was acceptable.
- Patient labeling (i.e., Medication Guide, Patient Information, Instructions for Use): The Division of Medical Policy Programs (3 September 2015) reviewed the patient labeling and made several recommendations to simplify wording, ensure that the PPI is consistent with prescribing information, and ensure that the PPI meets criteria per the 2006 FDA guidance. These proposed labeling changes seem reasonable and should be communicated to the applicant.
- Carton and container labeling: In response to recommendations by DMEPA, the applicant submitted revised carton labeling, which was felt to be acceptable from a medication error perspective (Gao review, 3 April 2015).

### **13. Postmarketing Recommendations**

Risk Evaluation and Management Strategies (REMS): The applicant did not propose a REMS, and the clinical and DRISK reviewers felt that risk mitigation measures beyond labeling are not warranted (Gordon review, 2 September 2015; Fitzgerald review, 29 September 2015). I concur.

Postmarketing Requirements (PMRs) and Commitments (PMCs): None recommended.

### **14. Recommended Comments to the Applicant**

There are no deficiencies to be communicated.



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11/19/2015