CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Office of Drug Evaluation-I: Decisional Memo

Date	December 21, 2015
From	Ellis F. Unger, M.D., Director Office of Drug Evaluation-I, Office of New Drugs, CDER
Subject	Office Director Decisional Memo
NDA #	207947
Applicant Name	Actelion Pharmaceuticals US, Inc.
Date of Submission	December 22, 2014
PDUFA Goal Date	December 22, 2015
Proprietary Name	Uptravi
Established (USAN) Name	selexipag
Dosage Forms/ Strengths	200, 400, 600, 800, 1000, 1200, 1400, and 1600 mcg Tablets
Indication	…for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression…. (*See Section 7 for full text.*)
Action:	*Approval*

Material Reviewed/Consulted - Action Package, including:	
Project Manager	Wayne Amchin
Medical Officer Clinical Review	Maryann Gordon (efficacy); Christine Garnett (safety)
Clinical Pharmacology Review	Sudharshan Hariharan; Luning (Ada) Zhuang
Statistical Review	Steve Bai; James Hung
Pharmacology Toxicology	James M. Willard; Albert De Felice
Executive Cancer Assessment Committee	Karen Davis Bruno; Abby Jacobs; Paul Brown; Tim McGovern; John Leighton; Adele Seifried
Chemistry Manufacturing and Controls	Wendy Wilson-Lee; Katherine Windsor; Mariappan Chelliah; Akm Khairuzzaman; Ruth Moore; Maryam Kord Bacheh Changi; Sharon Thoma; James Laurenson; Tanya Clayton; Olga Simakova
ONDQA Biopharmaceutics Review	Om Anand
Method Validation	Laura Pogue; David Keire
Statistical Review - Carcinogenicity Study	Steven Thompson
Office of Scientific Investigation	Sharon Gershon; Susan Thompson; Kassa Ayalew
Division of Medication Error Prevention and Analysis	Tingting Gao; Chi-Ming (Alice) Tu; Todd Bridges
Risk Evaluation and Mitigation Strategy (REMS) Review	Donella Fitzgerald; Reema Mehta
Office of Prescription Drug Promotion	Puja Shah
QT/IRT	Moh Jee Ng; Qianyu Dang; Kevin Krudys; Michael Li; Jiang Liu
Ophthamology Consult Review	Wiley Chambers
OSE PMs	Darrell Lyons; Louis Flowers; Tri Bui Nguyen
Epidemiology Reviewer	Efe Eworuke
Pharmacovigilance	Amy Chen; Thou Tran, Susan Lu
Cross-Discipline Team Leader	Shari Targum
Director, Division of Cardiovascular and Renal Products	Norman Stockbridge

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Selexipag is a non-prostanoid prostacyclin agonist. A number of prostacyclin agonists are approved for pulmonary arterial hypertension (PAH), but selexipag is the only non-prostanoid agonist. Approval of selexipag is supported by a double-blind trial in which subjects with PAH WHO Group I were randomized to placebo or selexipag (titrated as tolerated) and followed for disease progression, PAH hospitalization, and death. The study showed a highly statistically significant ($p<0.0001$) delay in time-to-first event, with a 39% relative reduction in risk. The primary outcome results were consistent across most subsets of the population, including background therapies, baseline WHO Functional Class II or III, sex, age, PAH etiology, and geographic location (US vs. non-US).

There were few Black or African-American study subjects, limiting generalizability on race. Of note, however, selexipag's pharmacokinetics and pharmacodynamics did not seem to be affected by race.

The safety profile appears similar to the prostacyclins (e.g., treprostinil, epoprostanol, iloprost), with excess adverse drug reactions of headache, diarrhea, jaw pain, and nausea.

Although the study was positive on the 1° composite endpoint, deaths trended unfavorably, with a hazard ratio of 1.6, an obvious concern for the review team. Analyses of mortality were difficult to interpret. The deaths were largely the result of PAH progression, the very cause selexipag mitigated so strongly; that is, few reflected a plausible "off target" effect, such as pro-arrhythmia, that could have led to death.

Unfortunately, many patients in the placebo group switched to selexipag after experiencing a non-fatal endpoint event, confounding the analyses of mortality.

Ultimately, we concluded that the nominal increase in mortality in the selexipag group is most consistent with play of chance: 1) the difference was small; 2) the difference didn't appear until 18 months into the trial; 3) there was no corresponding non-fatal safety signal; and 4) death did not appear to have a unique cause.

Our view is that even if the excess deaths are attributable to the drug, the excess is 10 deaths per 1,000 patient-years, and most patients would trade this small reduction in longevity for the benefits: ~90 fewer disease progressions per 1,000 patient-years; ~48 fewer hospitalizations for PAH events per 1,000 patient-years. Section 14 of labeling will include the Kaplan-Meier plot for efficacy, as well as the plot showing the mortality findings. But given the likelihood that these are chance findings, there will be no warning with respect to mortality, and no post-marketing cardiovascular outcome study is desired. Study 302 was already the largest study of its kind to date.

Most importantly, weighing the magnitude of the benefit here against the small size of the risk – and the *uncertainty* of that risk – most would not have the equipoise that would permit a placebo-controlled cardiovascular outcome study, even if it were feasible.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Pulmonary arterial hypertension (PAH) is a progressive condition characterized by elevated pulmonary arterial pressures leading to right ventricular failure and death. PAH is a rare disease, with an estimated prevalence of 15-50 cases per million. The incidence is higher in females, reflecting the underlying etiologies of the disease. Common symptoms of PAH include shortness of breath, exertional dyspnea, and fatigue.	PAH is a rare, serious, debilitating condition, which generally progresses to death from right heart failure. Selexipag has received orphan drug designation and is exempt from the requirement for pediatric studies.
Current Treatment Options	Available therapies for PAH address one of 4 target pathways: 1) endothelin-receptor antagonists; 2) prostacyclin/IP receptor agonists; 3) PDE-5 inhibitors; and 4) soluble guanylate cyclase stimulators	Drug effects are generally small. Of the IP receptor agonists, only treprostinil is available in an oral formulation. Selexipag will be the only non-prostacyclin IP receptor agonist, and the second approved IP receptor agonist that is dosed orally.
Benefit	GRIPHON was a single, randomized, double-blind, multinational study comparing selexipag to placebo in the time-to-first event in symptomatic patients with PAH, WHO Group 1. There was a statistically significant reduction, versus placebo, in the composite endpoint of time-to-first hospitalization for PAH worsening, disease progression, or need for parenteral prostanoid therapy. Although there was only one trial, the study has most of the characteristics of a single adequate and well-controlled trial that can support efficacy (with supportive information). Results of the primary endpoint were consistent, whether or not subjects were on background therapy, and consistent with respect to sex, age, geographic location, baseline Functional Class, and disease etiology. More placebo subjects, compared to selexipag subjects, reported PAH	The submitted evidence has met the evidentiary standard for benefit. According to FDA Guidance,"…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." 1. For a serious, progressive disease such as PAH, delaying disease progression and 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 be difficult from an ethical standpoint. 2. The primary analysis of GRIPHON was statistically persuasive (low p-value, making the null hypothesis improbable). 3. GRIPHON was a multinational study where no site provided an unusually large

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	worsening and right ventricular failure as serious adverse events (supporting a benefit of selexipag) Uncertainties: A favorable 1° endpoint result was not present in Asians. There were insufficient data in African-American or Black subjects to draw conclusions. The benefit was studied in symptomatic (WHO/NYHA Functional Class II-III patients) and there are insufficient data in patients who are Functional Class I or IV.	fraction of the patients and no single investigator/site was disproportionately responsible for the favorable effect. 4. Except for results of the 1° outcome in Asians, there was good consistency across study subsets. 5. In a phase 2 hemodynamic study, the decrease in pulmonary vascular resistance with selexipag supports the evidence of effectiveness.
Risk	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). The most frequently reported adverse events with selexipag were typical prostacyclin-associated adverse events (headache, diarrhea, and nausea, jaw pain). Uncommon adverse events included hyperthyroidism (also reported in postmarketing safety of epoprostenol) and eye pain.	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. 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. Adverse events can be communicated via labeling.
Risk Management	The risks and safety of selexipag can be communicated in labeling.	

2. Background

Selexipag is a non-prostanoid prostacyclin agonist. A number of prostacyclin agonists are approved for pulmonary arterial hypertension (PAH), but selexipag is the only agonist that is not a prostanoid. The proposed dosing is 200 to 1600 µg PO BID, with titration to the highest tolerated dose. With changes to the label and indication statement, the NDA can be approved.

Pulmonary arterial hypertension is a rare, progressive disease, characterized by elevated pulmonary vascular resistance (PVR) and pulmonary arterial pressure (PAP), ultimately leading to right heart failure and death. Cardinal symptoms include effort dyspnea, reduced physical performance, and cough. PAH may be idiopathic, inherited, associated with connective tissue diseases, secondary to congenital systemic-to-pulmonary shunts, drugs, toxins, HIV infection, and other conditions.

Available pharmacologic therapies are based on 4 mechanisms of action, although all are pulmonary vasodilators. Of note, none of these drugs are selective (i.e., non-systemic) pulmonary vasodilators:

- Prostacyclin/prostacyclin analogs (epoprostenol [IV route], treprostinil [IV, SQ, inhaled, or oral routes]) relax vascular smooth muscle cells.
- Endothelin receptor antagonists (bosentan, ambrisentan, macitentan [PO route]) inhibit effects of endothelin-1 (a vasoconstrictor).
- Phosphodiesterase type 5 inhibitors (sildenafil, tadalafil [oral route]) potentiate the vasodilatory effects of nitric oxide.
- The soluble guanylate cyclase agonist riociguat [oral route] sensitizes soluble guanylate cyclase to endogenous nitric oxide and directly stimulates soluble guanylate cyclase.

Of the available prostacyclin receptor agonists, only treprostinil is marketed in an oral formulation (marketed as Orenitram).

Approvals of most PAH drugs have generally been based on improvement in exercise capacity, as assessed by 6-minute walk distance. More recent approvals of PAH drugs such as macitentan and riociguat have relied on a single study demonstrating a decrease in the risk of disease progression and PAH hospitalization, as part of a composite endpoint.

3. Product Quality

There are no unresolved product quality issues. The Office of Pharmaceutical Quality (OPQ) granted a 36-month expiry for all tablet strengths stored in 60-count bottles and a 24-month expiry for the 200 mcg tablet strength stored in 140-count bottles.

Selexipag is considered a narrow therapeutic index drug. (b) (4), the drug product is (b) (4) offered over eight tablet strengths from 200 to 1600 mcg to allow for titration.

OPQ viewed the drug substance and its synthesis to be well characterized and controlled based on the in-process, release, and stability testing controls. The applicant provided adequate information to describe the manufacturing process, its control, and the in-process tests. Manufacturing facilities identified to support commercialization were found to be in good standing. Facility inspections have been completed. No post-marketing commitments are sought.

4. Nonclinical Pharmacology/Toxicology

Selexipag is toxicologically similar to other prostacyclin agonists. Most adverse effects are believed to be related to the pharmacology of the drug, with severe gastrointestinal effects at high doses (i.e. gastric erosion and intussusception), some degree of skin flushing at all dose levels, and scaly skin, alopecia, piloerection, and hair clumping at high dosages.

Reversible effects on retinal vessels in one of the non-clinical studies prompted additional clinical work-up and a consultative review by Dr. Wiley Chambers, and there does not appear to be cause for concern.

Selexipag was found to be negative in genotoxicity assays in bacteria, eukaryotic cell cultures, and *in vivo*. The requisite 2-year mouse and rat carcinogenicity studies were deemed acceptable and negative by the CDER Executive Carcinogenicity Assessment Committee.

No post-marketing commitments are sought.

5. Clinical Pharmacology

There are no clinical pharmacology issues that should prevent approval. There are no outstanding issues or recommended post-marketing commitments or requirements.

The applicant developed oral immediate-release tablets with a range of doses from 200 to 1600 mcg. The recommended starting dose is 200 mcg BID, with the dose to be increased in 200-mcg increments as tolerated.

Following oral administration, selexipag is absorbed with a median T_{max} of 1 h and a mean terminal elimination half-life of ~0.8 to 2.5 h. The oral bioavailability of selexipag is not known.

Selexipag is essentially a pro-drug, hydrolyzed by carboxylesterase-1 to a pharmacologically active metabolite, ACT-333679. Steady state exposure to ACT-333679 is 3- to 4-fold higher than selexipag, and the metabolite has 37 times the potency of selexipag. Peak plasma ACT-333679 concentration is reached by ~3 to 4 h with a terminal elimination half-life of ~6 to 13 h. Following hydrolysis to ACT-333679, there is additional metabolism to minor metabolites by CYP3A4 and particularly CYP2C8, with excretion predominantly in the feces.

There is no significant accumulation of selexipag or ACT-333679 with BID dosing; steady state exposures are achieved within 3 days. Pharmacokinetics of selexipag are dose-proportional over the range of 100 to 1800 mcg, whereas pharmacokinetic measures are slightly less than dose-proportional for the active metabolite.

Impact of Intrinsic Factors:
Because of the higher potency of ACT-333679 compared to selexipag, dosing recommendations are based on the exposure to the metabolite. No dose adjustment is recommended for patients with mild hepatic impairment. Patients with moderate hepatic impairment developed 2-fold higher exposure to ACT-333679; based on pharmacokinetic modeling and simulation, once daily dosing is recommended for such patients. Because only limited PK data were available in patients with severe hepatic impairment (n=2), use of selexipag should be avoided in such patients.

No dose adjustment is required for age, gender, ethnicity, or renal impairment. Body mass affects selexipag and ACT-333679 exposure, but dose adjustment was not recommended, given that the dose is titrated based on tolerability.

As noted above, selexipag is hydrolyzed to ACT-333679 by CES-1. The potential for CES-1 inhibition is minimal because of its ubiquitous expression in many tissues. Of note, however, metabolism of the active metabolite is by CYP2C8, and use of selexipag should be avoided in patients receiving a strong CYP2C8 inhibitor.

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

The clinical pharmacology reviewer had the following recommendations for labeling:

- daily (instead of BID) regimen in patients with moderate hepatic impairment
- avoid use in patients with severe hepatic impairment
- avoid use in patients using strong CYP2C8 inhibitors
- no dose adjustments for renal dysfunction, age, sex, or weight
- administer with meals for better tolerability

Hemodynamics:
In a phase 2 study, PAH patients (WHO Functional Class II-III on a background of ERA and/or PDE5 inhibitors) were up-titrated to selexipag 800 mcg twice-daily as tolerated. Compared to baseline, patients (n=33) had a 33% reduction (95% CI: -47% to -15%) in PVR at Week 17 compared to placebo (n=10). At Week 17, there was also a decrease in systemic vascular resistance (median change vs. placebo -427 dyn*sec/cm^5 [95% CI: -668 to -135]) and an increase in cardiac index (median change: 0.41 L/min/m^2 [95% CI: 0.10 to 0.71]).

Biopharmaceutics: The to-be-marketed formulation was used in the phase 3 study; therefore, a pivotal bioequivalence study was not needed or conducted. A single 1600-mcg tablet and eight 200-mcg tablets were shown to be bioequivalent.

QT/QTc effects:
No significant QTc prolongation was detected in a thorough QT study at doses of 800 mcg and 1600 mcg twice daily. Although the highest dose tested (1600 mcg BID) was deemed inadequate to provide exposure similar to that predicted in patients with hepatic impairment, patients with moderate hepatic impairment are to take a reduced dose ($\leq$ 1600 mcg QD), and patients with severe hepatic impairment should not use the drug. Thus, the higher exposures not covered by the thorough QT study were not deemed to constitute an issue. Selexipag had a mild chronotropic effect, presumably secondary to blood pressure-lowering effects, and did not affect the PR or QRS intervals.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

The indication statement originally sought by the applicant was:

The study supporting approval is study 302 ("GRIPHON"), in which 1156 subjects with PAH WHO Group I and WHO Functional Class II-III were randomized to placebo or selexipag. Patients were titrated to a dose between 200 and 1600 mcg BID, as tolerated. Endothelin receptor antagonists and PDE5 inhibitors were allowed, but other prostacyclin agonists were not. The 1° endpoint, assessed over 26 weeks, was time-to-first event of:

- all-cause mortality
- hospitalization for worsening PAH
- initiation of parental prostanoid or chronic oxygen, or
- confirmed 15% decrease in 6MWD plus worsened Functional Class or need for additional PAH therapy (see clinical review for details).

Events were adjudicated by a clinical events committee (CEC).

Alpha was set at 0.01, because this single study was intended to support approval. Secondary endpoints included 6-minute walk distance, various components of the 1° endpoint, and various symptom scales of dyspnea.

After enrollment began, the 1° endpoint was changed by dropping 6-minute walk distance, which had been a 1° endpoint. Some analyses were conducted that excluded events before the change in the 1° endpoint on August 16, 2011, but all analyses provided similar results, and the label will include all of the data.

The study was event-driven, so that participants were followed for various lengths of time, depending on when they were enrolled relative to study closure. Patients who had non-fatal events had the option of entering a post-treatment observational period within Study 302, and/or enrolling in an open-label extension study.

Study 302 was conducted from December, 2009 to May, 2013. Patients were enrolled at 181 sites in 39 countries.

The population was 80% female, 65% Caucasian, 21% Asian, 10% Hispanic, and 2% Black. Thirteen percent (13%) of patients were from the US. Median age was 49 years. Patients were fairly equally divided between Functional Class II and III, with negligible numbers of

Functional Class I and IV patients. Mean time from PAH diagnosis was 2.4 years. Mean 6-minute walk distance was 353 meters at study entry.

Some 80% of patients were taking PAH-specific concomitant therapies at baseline. Approximately 15% of patients were taking endothelin receptor antagonists as monotherapy, 32% were taking phosphodiesterase type-5 inhibitors as monotherapy, and 33% were taking both classes of drugs. Most patients were on a diuretic, with ~25% using calcium channel blockers, and 15% using digoxin. Approximately 15% of patients were using oxygen.

Over 26 weeks, 26% of subjects in the selexipag group discontinued their study drug, mostly for adverse events, vs. 17% of subjects on placebo.

Results for the primary endpoint, its decomposition, and time-to-event for each component of the 1° endpoint (shown independently) are shown in Table 1, and the Kaplan-Meier plot for the 1° endpoint is shown in Figure 1, both as analyzed by Dr. Bai, the statistical reviewer. These results are from the full analysis set, excluding patients who were Functional Class IV at baseline, and counting only events occurring within 7 days after last study drug intake. They do not include events that occurred before the 1° endpoint was changed on August 16, 2011, but results here are (b) (4):

Figure 1: Study 302, Primary Endpoint

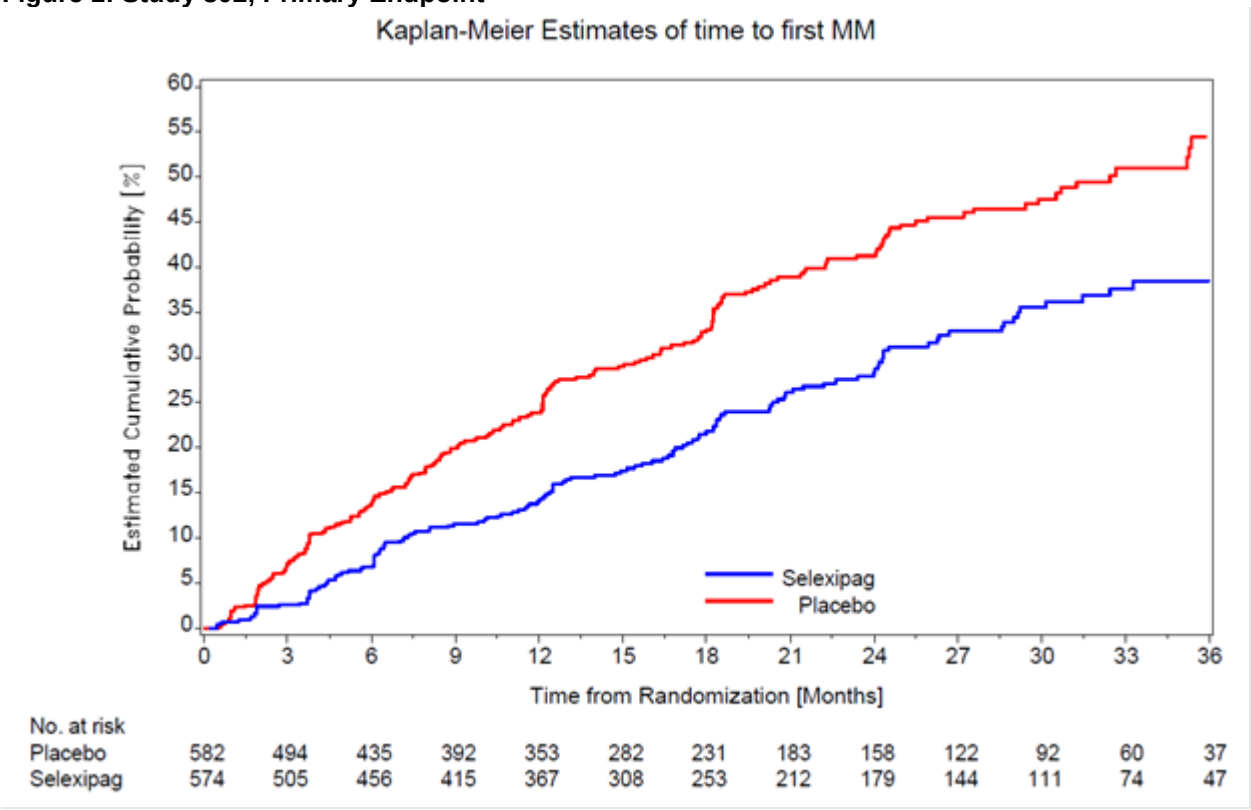


Table 1: Study 302, 1° Endpoint, Endpoint Events as Decomposition of the 1° Endpoint, and Time-to-First Occurrence of Each (Events before August 16, 2011 are excluded here.)
Event

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

Overall, there is a 39% relative risk reduction on the 1° endpoint in the selexipag group relative to the placebo group (hazard ratio 0.61, 95% confidence interval 0.46 to 0.81; $p<0.0001$). The top portion of the table shows the "decomposition" of the primary endpoint, i.e., each of the events listed is a first event, such that the numbers of events add to the total for both the selexipag and placebo groups. The bottom portion of the table shows the time to the first occurrence for each component of the composite endpoint, evaluated independently of the others, and including events that followed the first event.

Across both treatment groups, approximately 50% of the first events are hospitalizations for PAH worsening, ~30% represent disease progression, ~13% are deaths, and ~7% represent the need for parenteral prostanoid or chronic oxygen therapy. The numbers of patients who underwent balloon atrial septostomy or lung transplantation are negligible. (In retrospect, perhaps, it was not useful to have included this category in the composite endpoint, because all such patients would have contributed to the composite endpoint as a hospitalization for PAH.)

The treatment effect was similar in most subsets of the population, including patients who, at baseline, were on endothelin receptor antagonists, phosphodiesterase type-5 inhibitors, both,

or neither, baseline WHO Functional Class II or III, sex, age, PAH etiology, and geographic location (US vs. non-US).

Asians comprised 21% of the population and accounted for 27% of the events. The results in this population are neutral, but as Dr. Stockbridge points out, the point estimate of the overall study treatment effect lies within the 99% CI for Asians. I agree that this finding should not be over-interpreted. Subgroup analyses will be shown in Section 14 of the label with appropriate language to caution the reader with respect to over-interpretation of differences (as well as over-interpretation of apparent consistencies).

FDA has described in guidance the characteristics of a single adequate and well-controlled study that, along with supporting data, could support an effectiveness claim. These factors include: 1) large multicenter study; 2) consistency across study subsets; 3) multiple studies within a study (e.g., properly designed factorial study analyzed as a series of pairwise comparisons); 4) multiple endpoints involving different events; and 5) statistically very persuasive findings. Study 302 has all of these characteristics; with the exception of #3 (multiple studies study within a study). Given the results of Study 302, along with supportive evidence showing that selexipag reduces pulmonary vascular resistance (as would be expected), approval based on a single adequate and well-controlled study is possible.

Selexipag had a 12-meter mean effect on 6-minute walk distance, which, though highly statistically significant, represented a change of only 3% (mean baseline distance was 353 meters). (The effect size was also small compared with other therapies for PAH, but statistically significant because of the large size of the study.) The analysis was problematic for a number of reasons, and the reader is referred to the statistical and medical reviews. The Division concluded (b) (4) and I agree, although we are allowing display of the results in Section 14 of the label.

Mortality

Despite the marked reduction in overall events in the selexipag group in Study 302 (hazard ratio 0.61), deaths trended unfavorably, with a hazard ratio of 1.6. This trend has obviously been a concern of the review team.

The composite endpoint includes a number of events with competing risks. Thus, one could posit that because there were fewer non-fatal events in the selexipag group, more patients remained at risk to experience death as a first event. (b) (4) (b) (4)

To examine this possibility, a simple analysis of time-to-death for the entire study (not just time to *first* event) is salient, because such an analysis disregards the competing risks of non-fatal events in the composite endpoint. As seen in the bottom section of Table 1, however, this analysis shows mortality rates of 7.0% and 5.8% in the selexipag and placebo groups, respectively, with a hazard ratio of 1.1. Although this represents an exploratory analysis, it has some validity given that patients are analyzed as randomized. Recognizing that a hazard ratio of 1.1 represents less of a concern than the hazard ratio from the decomposition of the 1° endpoint (1.6), it is nevertheless disconcerting. Given selexipag's clear effects in decreasing hospitalization for PAH and disease worsening, one would expect the drug to decrease

mortality as well. Thus, in the face of an expected trend that would favor *decreased* mortality, the trend for *increased* mortality is problematic.

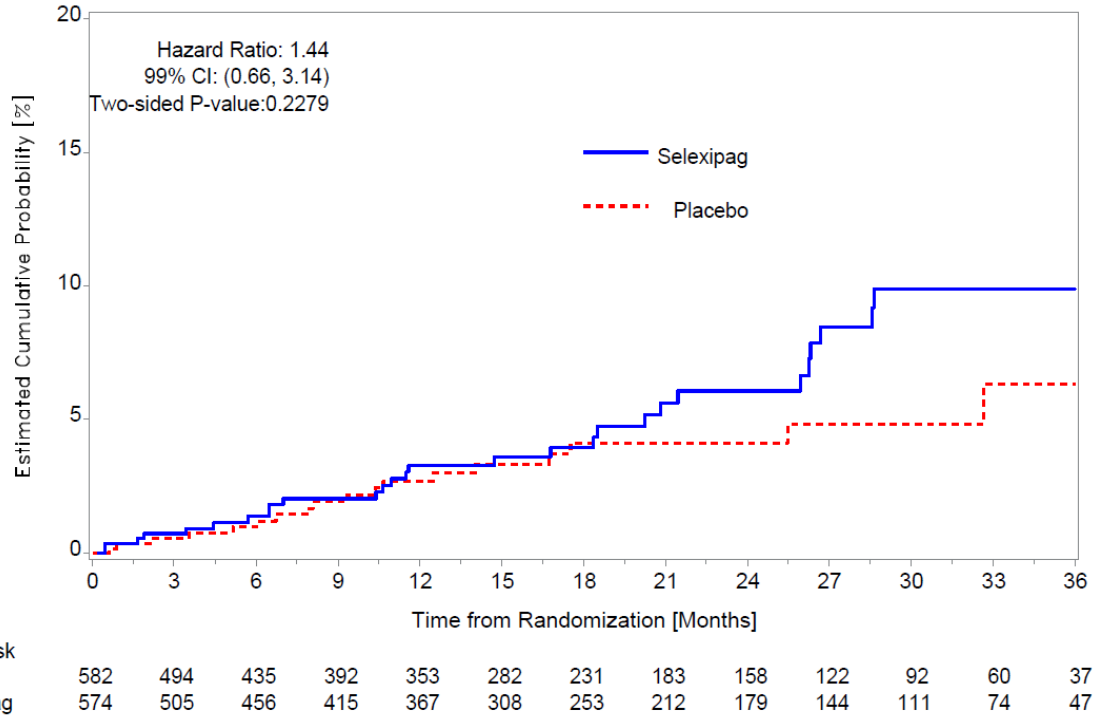
Initially, it appeared reassuring that, through study closure, the hazard ratio for death was close to unity, with 100 deaths (17%) in the selexipag group and 105 in the placebo group (18%). (See Division's review documents.) But the handling of patients who had experienced non-fatal events in Study 302 was quite complex. When the Division performed its initial reviews, it was not obvious that the majority of patients who had experienced a non-fatal endpoint event in Study 302 were transitioned to Study 303, and those who had been assigned to the placebo group were switched to selexipag. Specifically, from the placebo group of Study 302, 155 of 582 patients (27%) were switched to selexipag. Almost all of these patients (149, 96%) had a prior non-fatal endpoint event, and among these patients, the mortality rate after switching to selexipag was 30%.

For the patients in the placebo group who did not switch to selexipag, 18% experienced a non-fatal event, and 14% died.

In summary, patients in the placebo group of Study 302 who had done poorly, i.e., those who had experienced a non-fatal endpoint event, were preferentially switched to selexipag, and subsequent mortality in this selected group was high. Any analysis that the review team contemplated that would take this information into consideration was confounded – influenced by post-randomization events; interpretation of such analyses would be difficult at best. Moreover, selexipag's unfavorable trend on mortality was observed despite its large treatment effect on non-fatal events.

I agree with the Division and Dr. Bai (the statistician), as described in their review addendum of 12/21/15, that given the uncertainties of the condition of patients who crossed over after an event, the most reasonable analysis of mortality is death as the first event through the end-of-treatment + 7 days. Based on this analysis, there are 28 deaths in the selexipag group vs. 18 in the placebo group, with a hazard ratio of 1.44. The absolute difference in deaths is approximately 10 per 1,000 patient-years. The Kaplan-Meier plot is shown in Figure 2.

Figure 2: Study 302, Kaplan-Meier Plot of Time to First Occurrence of Death



No. at risk													
Placebo	582	494	435	392	353	282	231	183	158	122	92	60	37
Selexipag	574	505	456	415	367	308	253	212	179	144	111	74	47

Analysis:

Study 302 was that largest study ever conducted for a drug for treatment of pulmonary HTN, and the study showed an effect size of 39% (95% confidence interval, 19% to 54%) as a relative reduction in a composite endpoint that included hospitalizations for PAH worsening, disease progression, death, or need for parenteral prostanoid therapy. Results were consistent across subgroups and robust to exploration. This treatment effect was shown in patients who were presumably well-managed at baseline, with some 80% of patients taking an endothelin receptor antagonist, phosphodiesterase type-5 inhibitor, or both.

Despite the considerable treatment effect, there was an unfavorable trend on death, as noted above, with 28 deaths in the selexipag group and 18 in the placebo group as a first event. The critical question is whether this difference represents a drug effect or play of chance.

To be clear, this is not a question that can be answered with certainty. Nevertheless, it is worth considering factors that would seem to make causality more likely – or less likely – and to reach the most sensible conclusion in light of the limitations of the data. Moreover, if one were to reach the conclusion that the excess deaths in the selexipag group represent a drug effect, it is incumbent upon us to consider how the mortality difference would affect the estimation of the drug's benefit-risk profile, as well as the drug's approvability and labeling.

The estimates of the cumulative probability of death as a first event are identical for the drug and placebo through the first 18 months following randomization (i.e., the lines in Figure 2 are superimposable through 18 months). Thus, the shape of the Kaplan-Meier plot shows that the excess deaths in the selexipag group occur relatively late.

With the delayed difference in mortality, most factors that have been known to increase mortality *early* seem implausible. Such factors might have included hemodynamic effects, pro-arrhythmic effects, pro-thrombotic effects (effects on platelets or on the coagulation cascade), and adverse effects on the immune system. Factors that might have contributed to later deaths include hepatic and renal toxicities, valvulopathies, deleterious effects on cholesterol or hematocrit, and acceleration of tumor growth and/or metastasis. Importantly, the profile of adverse events in Study 302 fails to provide support for *any* of these factors, such that drug causality is not supported by the adverse event profile.

The Division further considered the causes of death in Study 302, and found that some 60% were related to PAH; this was true in both treatment groups. For the ~40% of deaths that were not considered to be related to underlying PAH, there was no signal suggesting a particular etiology or toxicity that could be responsible for late effects. Moreover, as noted by the Division, for the other components of the 1° endpoint, selexipag's treatment effects are large, appear rapidly, and persist throughout the period of follow-up.

Thus, I agree with the position of the Division, that the nominal increase in mortality in the selexipag group is most consistent with play of chance: 1) the difference is small; 2) the difference doesn't appear until 18 months into the trial; 3) there is no corresponding safety signal; and 4) death does not appear to have a unique cause.

We all recognize, however, that this interpretation could be incorrect: the excess deaths in the selexipag group could represent a true drug effect. If so, the best-estimate on the mortality effect would be about 10 excess deaths per 1,000 patient-years (of course, the 95% confidence interval straddles both sides of zero).

In terms of benefit, the best-estimate of the effect on disease progression is a reduction of approximately 90 events per 1,000 patient-years; with respect to hospitalization, the best-estimate is a reduction of some 48 events per 1,000 patient-years.

The Division concludes that selexipag's benefit remains positive, even if the excess deaths are attributed to the drug, and I agree with this view.

The labeling will provide (b) (4) time-to-event curves for hospitalizations for PAH, other disease progression events, and death.

Although some in the Division proposed that the label be silent on the question of whether excess deaths were drug-related (because this is unknown), I believe that the conclusions of the lines of reasoning discussed above must be conveyed to the public in labeling. We have proposed the following statement for the package insert, to be displayed with the table showing excess deaths in the selexipag group:

It is not known whether the excess number of deaths in the selexipag group is drug-related, as there were relatively few deaths, and the imbalance was not observed until 18 months into GRIPHON.

The indication statement that will be granted is:

"UPTRAVI® is a prostacylin receptor agonist indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression and reduce the risk of hospitalization for PAH."

8. Safety

The safety database exceeds ICH standards for a chronically administered drug; this has not been the case for all approved drugs for PAH.

Overall, the safety database attests to tolerability issues—higher rate of withdrawal on selexipag than on placebo, failure of many subjects to titrate to the highest dose of 1600 mcg—generally consistent with other vasodilators with respect to adverse events observed—headache, nausea, flushing, etc., observed mostly in the first few months of treatment. Of note, it took about 8 weeks to get subjects onto the 1600-mcg dose, and that distribution of doses remained quite stable thereafter.

There is a small, dose-dependent, but not progressive, decrease in hemoglobin on selexipag—as there is for all PAH drugs. Cerebral ischemic events occurred in 6 subjects on selexipag (including 2 strokes) vs. 1 stroke on placebo.

9. Advisory Committee Meeting

Although selexipag is a new molecular entity, its approval raised no issues that would justify an Advisory Committee meeting, and none was held. The drug is not the first in its class, and the safety profile is similar to that of other drugs approved for this indication.

We might have considered convening an advisory committee meeting had we better understood the mortality findings at the beginning of our review, but the crossover of patients from placebo to selexipag was not appreciated until late. Given the balance of benefit and risk (see Benefit Risk Summary and Assessment, page 2), we believe it would be counterproductive to delay approval because of the small imbalance in mortal events.

10. Pediatrics

Selexipag has orphan exclusivity; no pediatric obligations exist.

11. Other Relevant Regulatory Issues

The Office of Scientific Investigations inspected three clinical sites (Prague, Shanghai, Santiago) and concluded that their data were fit for use. The review team had no concerns regarding the adequacy of financial disclosure information. The proprietary name UPTRAVI was deemed to be acceptable.

12. Labeling

The major discussion had to do with Section 14. As above, the following statement is included to highlight and explain the uncertainty around the mortality imbalance:

> "It is not known if the excess number of deaths in the selexipag group is drug-related, because there were so few deaths and the imbalance was not observed until 18 months into GRIPHON."

The approved labeling is included in the letter of approval.

13. Postmarketing

No REMS has been proposed. No PMR or PMC is necessary.

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/s/

ELLIS F UNGER
12/21/2015