CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207947Orig1s000

SUMMARY REVIEW

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Divisional Memo Addendum

NDA: 207947 UPTRAVI (selexipag for PAH.

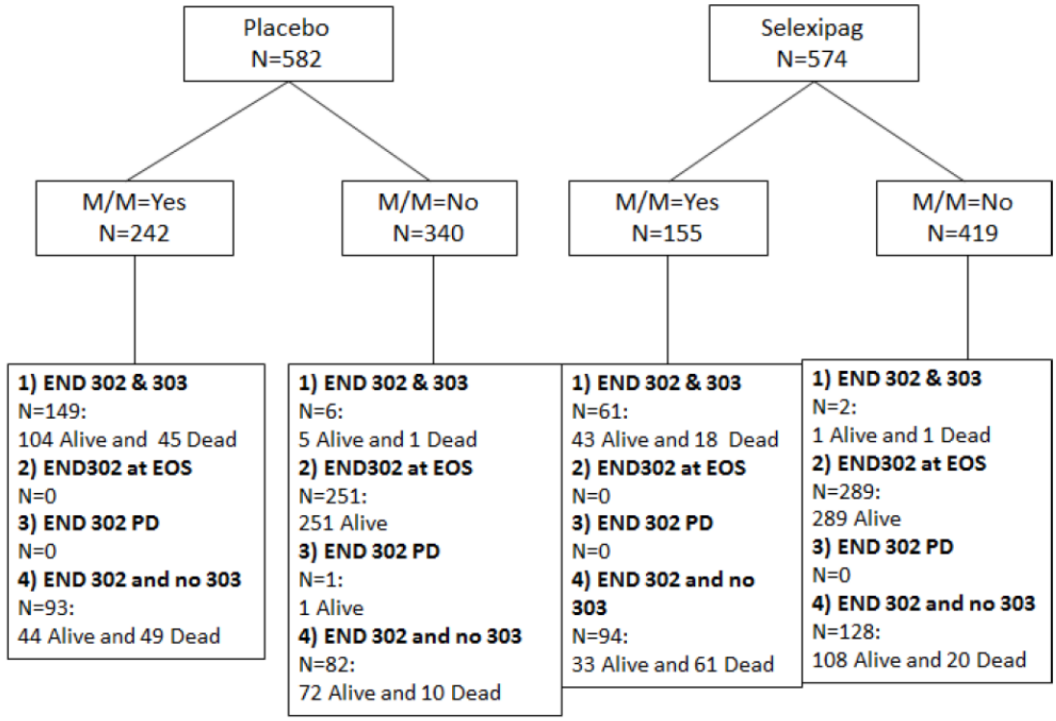
Sponsor: Actelion

Review date: 18 December 2015

Reviewers: Maryann Gordon, MD
Stephen Bai, PhD
Christine Garnett, PharmD
Shari Targum, MD
N. Stockbridge, M.D., Ph.D.

We all noted the increased mortality on selexipag in the GRIPHON study, but our concerns were assuaged by more nearly equal mortality when one included events after a non-fatal primary end point event. At the time, we were unaware of how many subjects on placebo transitioned to active drug for open-label follow-up after experiencing a non-fatal end point, as shown in the figure below.

Figure 1 Patient disposition flow-chart

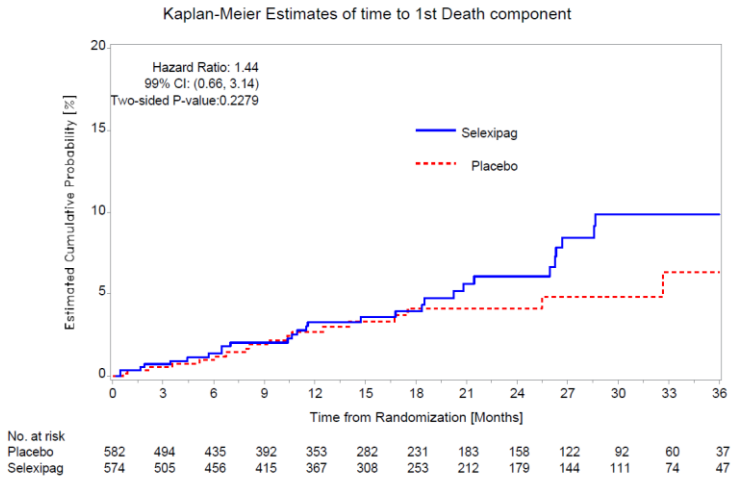


The category "Alive" includes 55 (4.8%) patients (25 on Selexipag, 30 on placebo) that did not have vital status available at study closure.

EOS = End of Study;; M/M = morbidity/mortality; PD = protocol deviation

After much internal discussion with the signatory authority, we conclude that analyses of mortality after subjects crossover is complicated by unverifiable assumptions, so the best estimate of the effect of selexipag on mortality comes from the analysis censoring

at the time of the first event (*EOT*+ 7 days). The K-M analysis of mortality so censored is shown below.



Note that no difference between the groups appears until some 18 months.

We next looked at causes of death and its relationship to PAH per adjudication, acknowledging that it is unreliable to classify further than "cardiovascular". These data are shown in the table below.

Table: Summary of Deaths in Study 302 Using the Efficacy Population

Event		**Selexipag (N=574)**		**Placebo (N=582)**		**Risk Difference**
		n	%	n	%	
EOT+7	First MM event (event>16AUG2011)	140	24%	212	36%	-12.0%
EOT+7	First Death event (event>16AUG2011)	25	4.4%	16	2.7%	1.6%
EOT+7	First MM event (inclusive)	155	27%	242	42%	-14.6%
EOT+7	First death event (inclusive)	28	4.9%	18	3.1%	1.8%
	Due to PAH[a]	16	2.8%	11	2.1%	0.7%
EOT+7	*All Deaths*	*46*	*8.0%*	*37*	*6.4%*	*1.7%*
	Due to PAH[a]	33	5.7%	27	4.6%	1.1%
	Not due to PAH[b]	13	2.3%	10	1.7%	0.5%
	Unexplained death[c]	3	0.5%	1	0.2%	0.4%
	CV death[d]	3	0.5%	1	0.2%	0.4%
	Sepsis	2	0.3%	0	0.0%	0.3%
	Respiratory failure	2	0.3%	3	0.5%	-0.2%
	Other[e]	3	0.5%	5	0.9%	-0.3%
EOT+30	All Deaths	53	9.2%	43	7.4%	1.8%
Study Closure	All Deaths (excludes deaths from study -303)	81	14.1%	59	10.1%	4.0%

	Study -303 (open label selexipag treatment)	Selexipag/Selexipag (N=63)		Placebo/Selexipag (N=155)		
Study Closure	Deaths	19	30%	46	30%	0%

Notes: [a]CEC-adjudication; [b]all other deaths were reported by investigator; [c] sudden death; [d]includes MI, coronary occlusion/insuff; [e]includes hypovolemic shock, acute right ventricular failure, deep vein thrombosis, road traffic accident, renal failure acute, systemic sclerosis, subdural hematoma.

Cross-reference: Table 11-2, Table 11-4, Table 12-7

Table: Causes of Death (First Event) for Selexipag

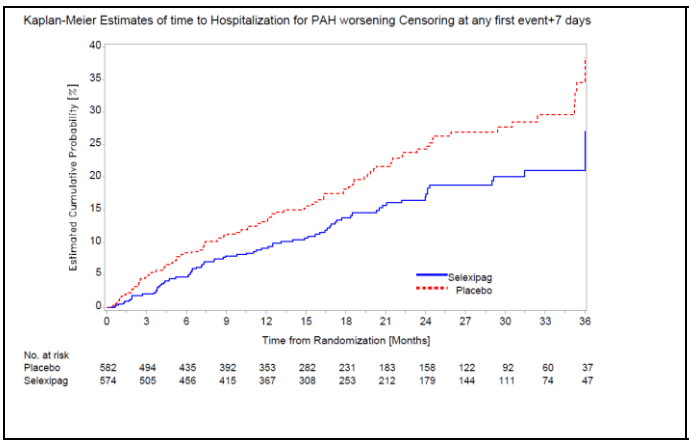
		Selexipag (N=574)	
	Death Term	n	%
DEATH RELATED TO PAH		16	2.8%
	Pulmonary arterial hypertension	8	1.4%
	Disease progression	6	1.0%
	Right heart failure	3	0.5%
	Sudden death	2	0.3%
	Acute right ventricular failure	1	0.2%
	Bradycardia	1	0.2%
	Hypoglycemia	1	0.2%
	Hypotension	1	0.2%
	Sudden cardiac death	1	0.2%
	Unknown cause of death	1	0.2%
	Ventricular fibrillation	1	0.2%
	Viral infection	1	0.2%
DEATH NOT RELATED TO PAH		12	2.1%
	Acute calculous cholecystitis	1	0.2%
	Acute renal failure	1	0.2%
	Cardio-respiratory failure	1	0.2%
	Coronary insufficiency	1	0.2%
	Coronary occlusion	1	0.2%
	Death from natural causes	1	0.2%
	Deep vein thrombosis	1	0.2%
	Myocardial infarction	1	0.2%
	Post procedural sepsis	1	0.2%
	Septic shock	1	0.2%
	Subdural haematoma	1	0.2%
	Sudden death	1	0.2%
	Sudden death, cause unknown	1	0.2%

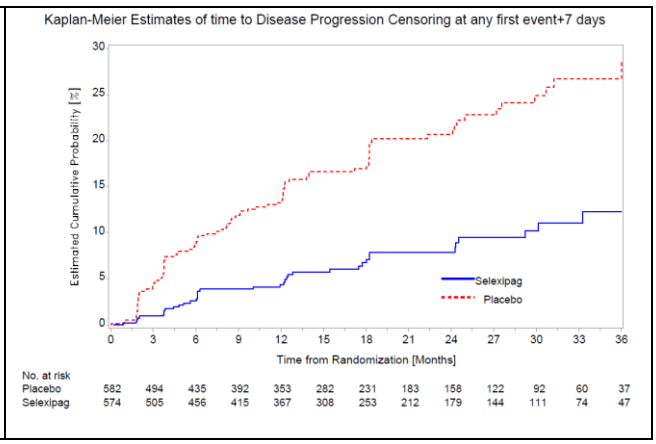
Table: Causes of Death (First Event) for Placebo

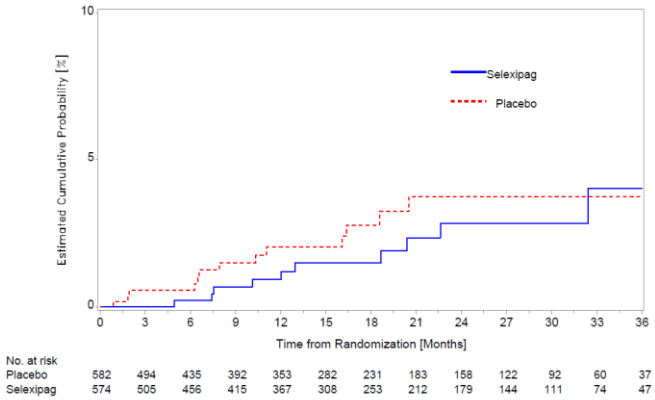
		Placebo (N=582)	
	Death Term	n	%
DEATH RELATED TO PAH		11	1.9%
	Pulmonary arterial hypertension	3	0.5%
	Acute right ventricular failure	2	0.3%
	Sudden death	2	0.3%
	Unknown cause of death	2	0.3%
	Acute renal failure	1	0.2%
	Cardiogenic shock	1	0.2%
	Cardiopulmonary failure	1	0.2%
	Chronic right ventricular failure	1	0.2%
	Disease progression	1	0.2%
DEATH NOT RELATED TO PAH		7	1.2%
	Acute right ventricular failure	1	0.2%
	Bilateral pneumonia	1	0.2%
	Hypovolemic shock	1	0.2%
	Lung abscess	1	0.2%
	Motor vehicle accident	1	0.2%
	Pneumonia	1	0.2%
	Respiratory failure	1	0.2%
	Sudden death	1	0.2%

Note that most deaths appear to be related to the underlying disease and that no obvious candidate emerges as a plausible explanation of a late toxicity of selexipag. Indeed, despite this being the largest PAH development program to date, there appear to be no adverse effects of selexipag other than ones attributable to its systemic vasodilatory properties.

In contrast, the benefits of selexipag on other components of the primary end point are large, appear early, and appear to continue unabated throughout follow-up, as shown in the figures below.







We conclude that the nominally increased mortality on selexipag is likely to be a chance finding, because it appears late with no corresponding safety findings, and it does not appear to have some unique cause.

We recognize that this chance-finding interpretation may be incorrect. If so, selexipag's best-estimated effect on mortality is about 10 more events per thousand patient-years. The corresponding best-estimated effect on hospitalization is a reduction of about 48 events per thousand patient-years and for other diseases progression it is a reduction of about 90 events per thousand patient-years. We conclude that selexipag's benefit remains positive.

We propose labeling that gives the decomposition of primary end point events only as first events and inclusion of time to event curves for hospitalizations for PAH, other disease progression events, and for death. Other than describing the censoring for these analyses, we propose no further interpretation.

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Division Director Summary Review for Regulatory Action

Date	(electronic stamp)
From	Norman Stockbridge
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	207947
Applicant	Actelion
Date of Submission	22 Dec 2014
PDUFA Goal Date	22 Dec 2015
Proprietary Name / **Non-Proprietary Name**	UPTRAVI / selexipag
Dosage Form(s) / Strength(s)	Oral tablets / 200/400/600/800/1000/1200/1400/1600 mcg
Applicant Proposed Indication(s)/Population(s)	Delay disease progression and reduce risk of hospitalization for PAH / PAH WHO Group I
Action/Recommended Action for NME:	Approval
Approved/Recommended Indication/Population(s) (if applicable)	As above.

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Gordon/Garnett; 2 Sep 2015
Statistical Review	Bai; 29 Jul 2015. Thompson (Carc); 19 Nov 2015
Pharmacology Toxicology Review	Willard; 27 Sep 2015
OPQ	Windsor/Chelliah/Khairuzzaman/Moore/Anand/Laurenson; 25 Aug 2015
Microbiology Review	n/a
Clinical Pharmacology Review	Hariharan/Zhuang; 6 Nov 2015
OPDP	Shah; 2 Sep 2015
OSI	Gershon; 3 Sep 2015
CDTL Review	Targum; 19 Nov 2015
OSE/DEPI	
OSE/DMEPA	Gao; 3 Apr 2015
OSE/DRISK	
Other	Chambers; 27 July 2015

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

DRISK=Division of Risk Management

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Approval is supported by a single 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 and PAH hospitalization events. The 39% reduction in the risk of a first event was highly statistically significant ($p<0.0001$). The safety profile is that of other systemic vasodilators, and is easily compatible with the demonstrated benefit.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Pulmonary arterial hypertension (PAH) is an orphan progressive disease resulting in death from right heart failure. Symptoms are primarily related to shortness of breath. • The pulmonary vascular changes are both proliferative and vasoconstrictive.	PAH is a serious, symptomatic and life-threatening condition.
Current Treatment Options	• Various non-specific vasodilators, some with only exercise claims, others with similar disease progression claims • Only one other oral prostacyclin inhibitor • Lung transplant	Drug effects are generally small because none of the available treatments address occlusive/proliferative aspects of the disease
Benefit	• Reduced risk of disease progression • Reduced risk of hospitalizations for PAH • Favorable effects on exercise capacity • Question whether results apply to Asians	Benefits were clinically important and of clinically relevant magnitude. Difference seen in Asian population is plausibly a chance finding.
Risk	• Headache, nausea, and jaw pain are all common among the non-specific vasodilators. • These effects limit the dose	Symptomatic, dose-limiting adverse effects did not prevent observation of clinical benefits and do not prevent approval.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk Management	• Labeling can adequately communicate the risks of treatment.	

2. Background

Selexipag is an agonist at the prostacyclin PGI2 receptor, but it is not a prostacyclin analog. The only other orally available prostacyclin agonist is treprostinil. The design of the study supporting approval was subject of a Special Protocol Agreement.

3. Product Quality

There are no unresolved product quality issues. All tablet strengths have a 24- or 36-month stability recommendation. Facility inspections have been completed.

No post-marketing commitments are sought.

4. Nonclinical Pharmacology/Toxicology

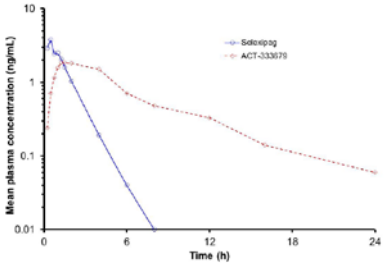
Reversible effects on retinal vessels prompted additional clinical work-up and a consultative review by Dr. Chambers; there does not appear to be any cause for concern clinically.

The carcinogenicity assessment committee has not met.

No post-marketing commitments are sought.

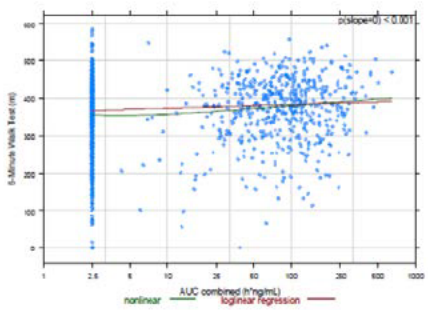
5. Clinical Pharmacology

Selexipag is mostly a pro-drug for ACT-333679. Plasma levels of selexipag are slightly less than proportional to dose. Conversion to the active metabolite is by ubiquitous CES-1. Further metabolism is by CYP 2C8, 3A4, and others, with products appearing in feces through biliary excretion.



The half-life[1] of the parent is pretty short, but the active metabolite is more reasonable for twice-daily dosing.

[1] Figure 2, page 12 of the clinical pharmacology review.



There are dose-response relationships for pulmonary vascular resistance and for 6MWD. The effect on the latter is small[2] (as it is for most vasodilators). This is further discussed below.

There are no known important extrinsic factors for metabolism. Minor effects will result in titration as tolerated.

Selexipag does not inhibit ADP-dependent platelet aggregation, at least at pharmacologically relevant doses.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

The study supporting approval is GRIPHON, in which 1156 subjects with PAH WHO Group I and WHO Functional Class II-III were randomized to placebo or selexipag, titrated between 200 and 1600 mcg. Endothelin receptor antagonists and PDE5 inhibitors were allowed, but other prostacyclin agonists were not. The primary end point, assessed over 26 weeks, was time to first event of (a) all-cause mortality, (b) hospitalization for worsening PAH, (c) initiation of parental prostanoid or chronic oxygen, (d) confirmed 15% decrease in 6MWD plus worsened Functional Class or need for additional PAH therapy. Alpha was set at 0.01, because this was a single study supporting approval and the distribution of events could not be predicted. Secondaries included components of the primary end point and symptoms.

The primary end point was amended after enrollment began, but any analysis that excludes early events gives similar results, and this review and the label include the full data.

The population was 80% female, 13% from US, and had a median age of 49 years. Over 26 weeks, 26% of subjects on selexipag discontinued, mostly for adverse events, vs. 17% on placebo. Results for the primary end point and components thereof at any time were as follows:

	Placebo N=582	**Selexipag N=574**	**RR (99% CI)**
Composite	36.4%	24.4%	0.61 (0.46, 0.81)
Death	5.8%	7.0%	1.10 (0.61, 2.01)
Hospitalization for worsening PAH	19.1%	13.4%	0.65 (0.44, 0.95)
Parenteral prostanoid/chronic oxygen	7.7%	5.2%	0.62 (0.34, 1.14)
Disease progression	21.8%	10.1%	0.43 (0.29, 0.65)

[2] Figure 1, page 11 of the clinical pharmacology review.

Although death trends adversely in this analysis, the primary analysis included events within 7 days of treatment. The total mortality up to study closure was 100 on selexipag vs. 105 on placebo, and cause-specific death trends lower on selexipag as well. I and the review team are reassured by these.

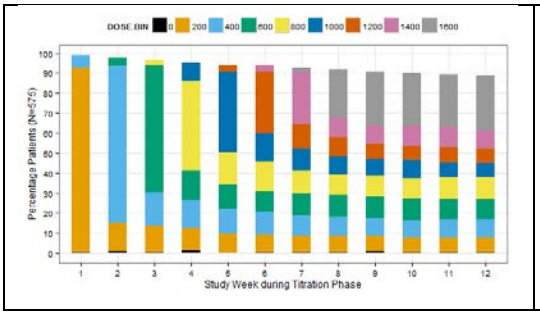
Similar effects are seen among patients who, at baseline, were on an endothelin receptor antagonist, a phosphodiesterase type 5 inhibitor, both, or neither.

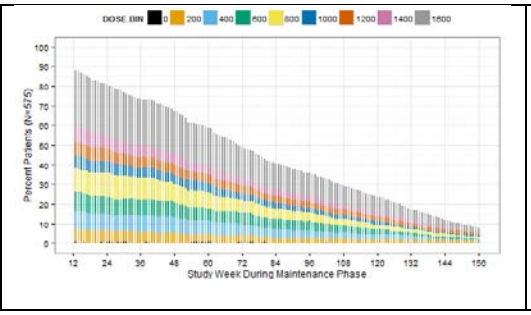
Asians comprised about 20% of the population and accounted for about 20% of the events. The results in this population trend adversely, but the overall study treatment effect lies within the 99% CI for Asians. I do not think that much can be made of this.

The effect of selexipag on 6MWD was a mean of 12 m, highly statistically significant, but miniscule, compared with other therapies, with baseline deficits, and with intra-subject variability in 6MWD. It was also somewhat attributable to imputation rules. (b) (4) .

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.





Figures 2 and 3 from the clinical review show distribution of doses of selexipag by time during the titration and maintenance phases of GRIPHON.

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.

A few observations warrant attention during post-marketing surveillance. Cerebral ischemic events occurred in 6 subjects on selexipag (including 2 strokes) vs. 1 on placebo (stroke). There were 8 cases of hyperthyroidism on selexipag vs. none on placebo.

9. Advisory Committee Meeting

Although selexipag was a new molecular entity, its approval raised no issues that would justify an Advisory Committee meeting, and none was held.

10. Pediatrics

Selexipag has orphan exclusivity; no pediatric obligations exist.

11. Other Relevant Regulatory Issues

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 acceptable.

12. Labeling

There are no major labeling issues, but there are numerous small matters still in negotiation (after several iterations) and for which the signatory authority will need to decide.

13. Postmarketing

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

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/s/

NORMAN L STOCKBRIDGE
11/25/2015