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APPLICATION NUMBER:

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MEDICAL REVIEW(S)

CLINICAL REVIEW

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Division/Office	ODE1/DCRDP
Reviewer Name(s)	Maryann Gordon, M.D. Christine Garnett, Pharm.D. (safety)
Review Completion Date	September 2, 2015
Established Name	Selexipag
(Proposed) Trade Name	Uptravi®
Applicant	Actelion
Formulation(s)	Tablets
Dosing Regimen	Twice daily
Proposed Indication(s)	Pulmonary arterial hypertension (PAH)
Intended Population(s)	PAH, WHO Group 1
Recommendation on Regulatory Action	approval

Reference ID: 3814728

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List of Abbreviations and Acronyms

6MWD	6 minute walk distance
6MWT	6 minute walk test
AC	advisory committee
AE	adverse event
ALT	alanine aminotransferase
APAH	Pulmonary arterial hypertension associated with other diseases, e.g., scleroderma
AST	aspartate aminotransferase
BID	twice daily
BL	baseline
BMI	body mass index
BP	blood pressure
bpm	beats per minute
CAMPHOR	Cambridge Pulmonary Hypertension Outcome Review
CEC	clinical events committee
CES1	carboxylesterase 1
CHD	congenital heart disease
CI	confidence interval
CL	confidence limit
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CT	computed tomography
CTEPH	Chronic thromboembolic pulmonary hypertension
CV	coefficient of variation
CWE	clinical worsening event
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
EOS	end of study
EOTE	end of treatment extension
ERA	endothelin receptor antagonist
FAS	full analysis set
FC	functional class
FDA	Food and Drug Administration
FVC	forced vital capacity

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GCP	good clinical practice
GI	gastrointestinal
GRMP	good review management practice
HIV	human immunodeficiency virus
HPAH	heritable pulmonary arterial hypertension
HR	heart rate
ICF	informed consent form
IMD	individual maintenance dose
IND	Investigational New Drug
INR	international normalization ratio
IP	prostacyclin receptor
IPAH	idiopathic pulmonary arterial hypertension
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
iv	intravenous
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MM	morbidity/mortality
mPAP	mean pulmonary arterial pressure
MTD	maximum tolerated dose
NDA	new drug application
NME	new molecular entity
NYHA	New York Heart Association
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PAP	pulmonary arterial pressure
PCWP	pulmonary capillary wedge pressure
PD	pharmacodynamic
PDE-5	phosphodiesterase type-5
PGI_2	prostacyclin (prostaglandin I_2
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PSUR	Periodic Safety Update report
PVR	pulmonary vascular resistance
QoL	quality of life
REMS	risk evaluation and mitigation strategy

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RHC	right heart catheterization
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SD	standard deviation
SOC	standard of care
SOP	standard operating procedures
T_3	triiodothyronine
T_4	thyroxine
Tmax	time to reach maximum concentration
TSH	thyroid stimulating hormone
TEAE	treatment emergent adverse event
ULN	Upper limit of the normal range
UV	Ultraviolet
WBC	White blood cell
WHO	World Health Organization
WHODRUG	WHO Drug Dictionary

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1 Executive Summary

1.1. Product Introduction

Selexipag (Uptravi®) is being proposed for the (b) (4) treatment of pulmonary arterial hypertension (PAH), WHO Group I, (b) (4). Safety and efficacy conclusions are based primarily on the outcome of the GRIPHON trial for which the study design, endpoints, and analysis strategy were discussed with the Division of Cardiovascular Drug Products at the US FDA. The protocol for this study was based on an agreement between the FDA and the sponsor within a Special Protocol Assessment (SPA).

PHARMACOLOGIC CLASS
Selexipag (ACT-293987) is a non-prostanoid agonist active at the prostacyclin receptor (IP). Enzymatic hydrolysis of selexipag by carboxylesterase 1 (CES1) in the liver yields ACT-333679, the active metabolite of selexipag. Both selexipag and ACT-333679 bind to the IP receptor with high affinities *in vitro*. ACT-333679 is up to 37-fold more potent than selexipag in cellular systems. It is present at 3- to 4-fold higher levels than the parent drug at steady-state in humans.

Selexipag appears to be similar to other approved prostacyclin receptor agonists. The current list of approved prostacyclin receptor agonists includes treprostinil, iloprost, and epoprostenol.

MODE OF ACTION
Stimulation of the IP receptor by selexipag and the active metabolite leads to vasodilatory as well as anti-proliferative and anti-fibrotic effects. Selexipag improves hemodynamic variables and prevents cardiac and pulmonary remodeling in a rat model of PAH46. In these PAH rats, pulmonary and peripheral vasodilation in response to selexipag correlate, indicating that peripheral vasodilation reflects pulmonary pharmacodynamic efficacy. Selexipag does not cause IP receptor desensitization *in vitro* nor tachyphylaxis in a rat model.

The proposed dosing regimen is starting oral dose 200 mcg twice daily (bid) with titration of 200 mcg bid at weekly intervals up to 1600 mcg bid. Maintenance dose is determined by tolerability.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The sponsor has demonstrated that selexipag 200ug to 1600ug twice daily has been shown to delay disease progression in patients with PAH, WHO Group 1. Disease progression is defined as death, hospitalization, initiation of intravenous or subcutaneous prostanoids or other disease progression events (decreased 6-minute walk distance [6MWD] associated with either worsened PAH symptoms or need for additional PAH-specific treatment). As stated in the statistical review by Dr. Bai, “a statistically highly significant 39% risk-reduction for the

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occurrence of a first [mortality/morbidity] event up to the end of treatment + 7 days was demonstrated with selexipag treatment."(see page 24-25 of his review). Dr. Bai also concluded that he "does not consider the statistically significant difference between selexipag and placebo in the 6-minute walk distance, secondary symptomatic variable, [to have] any clinical relevance. (Page 25 of his review)

In addition, selexipag was shown to reduce hospitalizations for PAH.

1.3. Benefit-Risk Assessment

Selexipag has shown to be effective in the slowing of clinical worsening in patients with PAH. The one major study, GRIPHON, demonstrated that compared to placebo selexipag is of benefit in reducing the risk of adjudicated morbidity/mortality events. These events included the time to the first death (all causes), hospitalization for worsening PAH, lung transplantation, atrial septostomy, initiation of parenteral prostanoids or chronic oxygen therapy, or disease progression. The primary objective was met.

AC-065A302/GRIPHON was a long-term study assessing the benefit-risk of an individualized selexipag dose, titrated according to tolerability. The trial was randomized, placebo-controlled, and event-driven and enrolled subjects receiving standard treatment (ongoing PAH-specific therapy, ERA and/or PDE-5 inhibitors) or treatment naïve. This pivotal study was conducted under the US FDA Special Protocol Assessment.

Patients with symptomatic PAH and etiology within groups 1.1 to 1.4 of the updated Dana Point 2008 clinical classification, i.e., idiopathic or heritable, or PAH associated with CTD, CHD with simple systemic-to-pulmonary shunts at least 1 year after surgical repair, HIV infection, or drug or toxin induced, were included. Concomitant treatment with PAH-specific medications (approved ERAs and/or PDE-5i) was allowed if patients had been on a stable dose for at least 3 months prior to the Baseline visit. Most patients (80%) were receiving were receiving one or more PAH-specific medications at baseline.

At baseline, the majority of study patients were NYHA/WHO FC II and III. Selexipag was up-titrated to each individual patient's maximum tolerated dose in the range of 200–1600 µg bid. The majority of patients did not receive the maximum dose.

Hospitalization for PAH worsening and disease progression were the most frequently adjudicated first MM events. Hospitalization for PAH worsening was reported in 12% and 17% patients in the selexipag and placebo groups, respectively. Disease progression, defined as a decrease in 6MWD from baseline with either worsening of NYHA/WHO FC o**r a** need for additional PAH-specific therapy, was reported in 6% and 14% of patients in the selexipag and placebo groups, respectively. Death as first MM event was noted in 4% and 3% of patients in the selexipag and placebo groups, respectively.

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Regarding safety, more placebo patients than selexipag patients reported PAH worsening and right ventricular failure as serious adverse events, indicating the effectiveness of selexipag in treating PAH, Also, more placebo patients discontinued study drug because of PAH worsening and/or right ventricular failure than did selexipag patients.

The safety profile of selexipag is predominantly characterized by typical prostacyclin associated adverse events including headache, diarrhea, nausea, jaw pain, vomiting, and myalgia. While usually not serious, these adverse events resulted in some patients discontinuing use of selexipag or lowering the dose. Additional, although uncommon, adverse events included hyperthyroidism (also reported in the postmarketing safety of epropostenol) and eye pain (could be referred pain from the jaw). These events are not thought to alter the risk-benefit ratio of selexipag.

Selexipag, up-titrated to 1600 µg b.i.d. or to an individualized highest tolerated dose, significantly reduced the risk for a morbidity/mortality event during treatment, compared to placebo, irrespective of background PAH therapy. The observed treatment effect was consistent across a representative PAH population. The safety profile was predominantly characterized by the adverse events associated with other IP prostacylin receptor agonists. There are no major safety findings that outweigh the benefits of selexipag in its target patient population.

2 Therapeutic Context

2.1. Analysis of Condition

PAH is characterized by vasculopathy with extensive remodeling of the pulmonary circulation that results in narrowing of the arterial lumen and impaired flow-mediated vasodilation. The consequent increase in pulmonary arterial pressure (PAP) and pulmonary vascular resistance (PVR) limits the ability of the right ventricle to pump blood through the lungs, causing shortness of breath and reduced physical performance. PAH is a progressive disease, and ultimately leads to right heart failure and death. The pathophysiology of PAH is not fully understood, but is thought to involve abnormal interactions between endothelial and smooth muscle cells, leading to vasoconstriction, vascular smooth muscle cell proliferation, vascular endothelial proliferation, and *in situ* thrombosis. Reduced prostacyclin synthase activity and variably reduced IP receptor expression, an up-regulated endothelin (ET-1) system, and abnormalities of the nitric oxide pathway are considered important mediators of these pathological changes, and form the therapeutic targets for currently available PAH-specific therapies [Chin 2008, McGoon 2009].

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The accepted hemodynamic definition of PAH is the finding of a mean pulmonary arterial pressure (mPAP) > 25 mmHg at rest in the presence of a pulmonary capillary wedge pressure (PCWP) < 15 mmHg and pulmonary vascular resistance greater than 3 Wood units, as assessed by right heart catheterization (RHC) [Badesch 2009]. PAH is a rare disease affecting fewer than 200,000 people in the US, around 90,000 in Europe [Gomberg-Maitland 2009], and under 50,000 in Japan. The etiologies of PAH include idiopathic (most common), inherited, or associated with connective tissue diseases, congenital systemic-to-pulmonary shunts, drugs or toxins, HIV infection.

2.2. Analysis of Current Treatment Options

Recent data indicate an average survival of 4 to 5 years after diagnosis in PAH patients with access to current general medical care and the pharmacological treatment options. There is no cure and PAH remains a progressive and ultimately fatal disorder.

Approvals of most PAH medications have been based on their symptom benefits, evaluated mainly as improvement in exercise capacity in relatively short-term, placebo-controlled studies in selected populations. Macitentan is a recent exception in that clinical worsening as well as hospitalizations for PAH were shown to be improved. As with selexipag, there is no known improvement in survival by the available treatment options (and, in fact, there are possible mortality effects of sildenafil in children).

Available pharmacological therapies for PAH address one of four target pathways:
- Prostacyclin (epoprostenol) and its analogs relax and reduce proliferation of vascular smooth muscle cells.

- Endothelin receptor antagonists (ERAs), by inhibiting the effects of elevated ET-1 levels, reduce vasoconstriction, smooth muscle cell proliferation and pulmonary vessel fibrosis.

- Phosphodiesterase type-5 inhibitor (PDE-5 inhibitor) increases cGMP within pulmonary vascular smooth muscle cells resulting in relaxation. This can lead to vasodilation of the pulmonary vascular bed and, to a lesser degree, vasodilatation in the systemic circulation.

-Soluble guanylate cyclase agonist potentiates the anti-platelet, antiproliferative, and vasodilatory effects of nitric oxide.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

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Selexipag is a new molecular entity that is currently not marketed in the U.S. or any other country. The sponsor is seeking approval only for the PAH, WHO group 1 indication.

3.2. Summary of Presubmission/Submission Regulatory Activity

Selexipag, granted orphan drug designation, is being proposed for the (b) (4) treatment of pulmonary arterial hypertension (PAH, WHO Group I) in patients (b) (4) The safety and efficacy of this application is based mainly on the outcome of the GRIPHON trial for which the study design, endpoints, and analysis strategy were discussed with the Division of Cardiovascular Drug Products at the US FDA. The protocol for this study was based on an agreement between the FDA and the sponsor within Special Protocol Assessment (SPA).

Selexipag is not considered to be breakthrough therapy. It received neither fast track nor priority review designation.

See section 1.6.3 in the NDA for complete submissions and communications with FDA regarding the development of selexipag.

3.3. Foreign Regulatory Actions and Marketing History

Selexipag is neither marketed in the U.S. nor any other country.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The inspection audited protocol AC-065A302 (GRIPHON). Dr. Liu has (b) (4) no prior inspections. This site was chosen to inspect because of high enrollment (32 subjects) and high treatment effect size in favor of study drug. Only minor discrepancies were observed and there was no under-reporting. Although the minor deficiencies were observed, they are unlikely to importantly impact the efficacy analysis for this NDA or impact the safety or integrity of human subjects involved in clinical trials. The study appears to have been conducted adequately and the data have been deemed usable in the NDA review.

4.2. Clinical Microbiology

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Not applicable

4.3. Nonclinical Pharmacology/Toxicology

Please see review

4.4. Clinical Pharmacology

4.4.1. Mechanism of Action

The vasculo-protective effects of prostacyclin (PGI2) are mediated by the prostacyclin receptor (IP receptor). Decreased expression of IP receptors and decreased synthesis of prostacyclin contribute to the pathophysiology of PAH.

Selexipag is an oral, selective, IP receptor agonist, and is structurally and pharmacologically distinct from prostacyclin and its analogs. Selexipag is hydrolyzed by carboxylesterase 1 to yield its active metabolite, which is approximately 37-fold more potent than selexipag.
Selexipag and the active metabolite are high affinity IP receptor agonists with a high selectivity for the IP receptor versus other prostanoid receptors (EP1-EP4, DP, FP and TP).

Stimulation of the IP receptor by selexipag and the active metabolite leads to vasodilatory as well as anti-proliferative and anti-fibrotic effects. Selexipag improves hemodynamic variables and prevents cardiac and pulmonary remodeling in a rat model of PAH46. In these PAH rats, pulmonary and peripheral vasodilation in response to selexipag correlate, indicating that peripheral vasodilation reflects pulmonary pharmacodynamic efficacy. Selexipag causes neither IP receptor desensitization *in vitro* nor tachyphylaxis in a rat model.

4.4.2. Pharmacodynamics

Cardiac electrophysiology:
At the maximum tolerated dose of 1600 mcg twice daily, selexipag does not prolong the QT interval to any clinically relevant extent.
Platelet Aggregation:
Multiple-dose administrations of selexipag in healthy subjects had no relevant effect on platelet aggregation test parameters across doses from 400 mcg up to 1800 mcg twice daily.
Pulmonary hemodynamics:
A Phase 2 clinical study assessed hemodynamic variables after 17 weeks of treatment in patients with PAH WHO FC II–III and concomitantly receiving ERAs and/or PDE-5 inhibitor. Patients titrating selexipag to an individually tolerated dose (200 mcg twice daily increments up to 800 mcg twice daily) (N=33) achieved a mean reduction in pulmonary vascular resistance of 30.3% (95% confidence interval [CI] −44.7%, −12.2%; P = 0.0045) and an increase in cardiac index (median treatment effect) of 0.41 L/min/m^2 compared to placebo (N=10).

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4.4.3. Pharmacokinetics

The pharmacokinetics of selexipag and its active metabolite have been studied primarily in healthy subjects. The pharmacokinetics of selexipag and the active metabolite, both after single and multiple-dose administration were dose-proportional up to a single dose of 800 mcg and multiple doses of up to 1800 mcg twice daily. After multiple-dose administration, steady-state conditions of selexipag and the active metabolite were reached within 3 days. No accumulation in plasma, either of parent compound or active metabolite, occurred after multiple-dose administration.

4.1. Devices and Companion Diagnostic Issues

Not applicable

4.2. Consumer Study Reviews

Not applicable.

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5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

This NDA consists of clinical data from:
-eleven clinical pharmacology studies,
-one study in PAH patients evaluating pulmonary hemodynamics and 6MWD (NS--304-02),
-one study in PAH patients that is event driven (AC-065A302/GRIPHON)
-one study in PAH patients that is long term, open label and uncontrolled (AC-065A201).

Details of these studies as well as two studies conducted in patients with CTEPH are shown in the table below.

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Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Comparative bioanalytical and bioequivalence study	AC-065-108	5.3.1.2	To demonstrate bioequivalence in the rate ($C_{max,ss}$) and extent (AUC_τ) of absorption between 1600 µg selexipag test and reference drugs at steady state following a multiple-dose up-titration scheme. To investigate safety, tolerability, and PK of selexipag and its active metabolite, ACT-333679, at doses of selexipag up to 1600 µg b.i.d.	Randomized, two-period, two-treatment, crossover, multiple-dose, up-titration, uncontrolled Phase 1 study.	**Selexipag** Selexipag tablet (strengths: 200 and 1600 µg) Randomization (1:1): treatment sequence AB or BA **Up-titration scheme (200 µg strength tablet for both treatments):** Day 1–3: 400 µg b.i.d. Day 4–6: 600 µg b.i.d. Day 7–9: 800 µg b.i.d. Day 10–12: 1000 µg b.i.d. Day 13–15: 1200 µg b.i.d. Day 16–18: 1400 µg b.i.d. **Treatment A (reference drug: strength 200 µg) only:** Day 19–22: 1600 µg (8 × 200 µg tablets) b.i.d. Day 23: 1600 µg (8 × 200 µg tablets) o.d **Treatment B (test drug: strength 1600 µg) only:** Day 19–22: 1600 µg (1 × 1600 µg tablet) b.i.d. Day 23: 1600 µg (1 × 1600 µg tablet) o.d Washout period between Periods 1 and 2 at least 6 days Oral	80	Healthy male subjects	2 × 22.5 days

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Healthy subject PK and initial tolerability study	PS003	5.3.3.1	Investigation of PK, safety, and tolerability of selexipag and its active metabolite, ACT 333679.	Single dose, non randomized, uncontrolled Phase 1 study.	Selexipag Single dose of selexipag (100 µg in 10 mL solution) Oral	5	Healthy male subjects	Single dose
Healthy subject PK and initial tolerability study	186933	5.3.3.1	Investigation of the mass balance PK, metabolism and tolerability of [^{14}C] selexipag.	Single dose, non randomized, uncontrolled Phase 1 study.	[^{14}C] Selexipag Single dose of [^{14}C] selexipag liquid suspension (400 µg in 40 mL) Oral	6	Healthy male subjects	Single dose
Healthy subject PK and initial tolerability study	QGUY/2006/NS 304/ 01	5.3.3.1	**Part A**: Investigation of the safety, tolerability, and PK of selexipag. **Part B**: Investigation of the safety and tolerability, and food effect on PK of selexipag. **Part C**: Investigation of the PK, safety and tolerability of selexipag. **Part D**: Investigation of safety and tolerability, and the potential PD and PK interactions of selexipag and warfarin.	**Part A**: Single ascending dose, randomized, double blind, placebo controlled. **Part B**: Single doses, randomized, 2 period, cross over, uncontrolled. **Part C**: Multiple ascending dose, randomized, double blind, placebo controlled. **Part D**: Multiple dose, randomized, double blind, 2	**Part A** Selexipag Placebo Selexipag tablet (strengths: 100, 200, 400, or 800 µg) Placebo tablet 5 dose groups: 6 subjects on selexipag and 2 on placebo/group Single dose of selexipag 100, 200, 400, 600, or 800 µg Oral **Part B**: Selexipag Selexipag tablet (strength: 400 µg) Randomization (1:1): treatment sequence fasted fed or fed fasted.	**Part A**: 40 (30 selexipag, 10 placebo) **Part B**: 12 **Part C**: 25 (19 selexipag, 6 placebo) **Part D**: 19 (18 selexipag, 19 placebo)	Healthy male subjects	**Part A**: Single dose **Part B**: Two single doses **Part C**: 6 days **Part D**: 11.5 days

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Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
				period, cross-over, placebo-controlled. Phase 1 study.	Single dose of selexipag 400µg in the fasted or in the fed state. Washout period between Period 1 and Period 2: 7 days Oral **Part C** Selexipag Placebo Selexipag tablet (strengths: 200 and 400 µg) Placebo tablet 3 dose groups: 6 subjects on selexipag and 2 on placebo/group **Treatment regimen (200 µg dose group):** Day 1: 200 µg single dose Day 2: no study drug Day 3–7: 200 µg b.i.d. Day 8: 200 µg single dose **Treatment regimen (400 µg dose group):** Day 1: 400 µg single dose Day 2: no study drug Day 3–7: 400 µg b.i.d. Day 8: 400 µg single dose **Treatment regimen (400-600 µg dose group):** Day 1: 400 µg single dose			

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
					Day 2: no study drug Day 3–4: 400 µg b.i.d. Day 5–7: 600 µg b.i.d. Day 8: 600 µg single dose Oral **Part D:** Selexipag Placebo Selexipag tablet (strength: 400 µg) Placebo tablet Randomization (1:1): treatment sequence active or placebo Period 1 Day 1: 400µg single dose or placebo Days 2-12: 400µg selexipag b.i.d. or placebo Day 8: concomitant administration of a single dose of warfarin 20 mg Period 2 the alternative selexipag or placebo combination to that received in Period 1. Washout period between Period 1 and Period 2: at least 8 days. Oral			

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Healthy subject PK and initial tolerability study	NS304/P1/01	5.3.3.1	Part I: Investigation of the safety, tolerability, and PK of selexipag in healthy adult and elderly subjects. Investigation of the food effect on the PK of selexipag **Part II:** Investigation of the safety, tolerability, and PK of selexi after meal in healthy adult and elderly subjects (effect of dose on PK).	**Part I:** Single-ascending dose, randomized, double-blind, nested one-way cross-over, placebo-controlled. **Part II:** Multiple-ascending dose, randomized, double-blind placebo-controlled. Phase 1 study.	Selexipag Placebo **Part I:** Selexipag tablet (strength: 200 µg) Placebo tablet 4 dose groups: 6 subjects on selexipag and 2 on placebo/group **Treatment regimen for adult 200 µg and 600 µg and elderly 200 µg dose groups:** Single dose in the fasted state **Treatment regimen for adult 400 µg dose group (food effect group):** Single dose of selexipag 400µg (once in the fasted state and once in the fed state) Washout period: at least 7 days **Part II:** Selexipag tablet (strength: 200 µg) Placebo tablet 4 dose groups: 6 subjects on selexipag and 2 on placebo/group **Treatment regimen for adult 200 µg dose group (in the fed state):** Day 1: 200 µg single dose Day 2: no study drug Day 3–9: 200 µg b i d Day 10: 200 µg single dose **Treatment regimen for adult 400 µg**	**Part I:** 32 (24 selexipag, 8 placebo) **Part II:** 32 (24 selexipag, 8 placebo)	Healthy male subjects (48) Elderly male subjects (16)	**Part I:** single dose or two single doses **Part II:** 8 or 10 days pag

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Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
					and elderly 400 µg dose groups (in the fed state): Day 1: 400 µg single dose Day 2: no study drug Day 3–9: 400 µg b.i.d. Day 10: 400 µg single dose. **Treatment regimen for adult 400–600 µg dose group (in the fed state):** Day 1: 400 µg single dose Day 2: no study drug Day 3–4: 400 µg b.i.d. Day 5–11: 600 µg b.i.d. Day 12: 600 µg single dose Oral			
Healthy subject PK and initial tolerability study	AC 065 101	5.3.3.1	Investigation of the PK, PD, safety, and tolerability of selexipag and its active metabolite, ACT 333679.	Multiple ascending dose, randomized, double blind, multiple period, parallel group, placebo controlled Phase 1 study.	Selexipag Placebo Selexipag tablet (strength: 200 µg) Placebo tablet **Up titration scheme:** Day 1–3: 400 µg b.i.d. Day 4–6: 600 µg b.i.d. Day 7–9: 800 µg b.i.d. Day 10–12: 1000 µg b.i.d. Day 13–15: 1200 µg b.i.d. Day 16–18: 1400 µg b.i.d. Day 19–21: 1600 µg b.i.d. Day 22–23.5 (2.5 days) 1800 µg b.i.d. Oral	16 (12 selexipag, 4 placebo)	Healthy male subjects	23.5 days

Reference ID: 3814728

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s): Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Healthy subject PK and initial tolerability study	AC-065-102	5.3.3.1	Investigation of the phototoxic potential, safety and tolerability, of selexipag. Investigation of the PK of selexipag and its active metabolite, ACT 333679.	Randomized, double-blind (selexipag), assessor-blind (all treatments), multiple period, parallel group, placebo- and positive-controlled Phase 1 study.	Selexipag Placebo Ciprofloxacin Selexipag tablet (strength: 200 µg) Placebo Ciprofloxacin tablet (strength: 500 mg) **Group A treatment (up to 800 µg selexipag) regimen:** Day 1–3: placebo 400 µg b.i.d. Day 4–6: placebo 600 µg b.i.d. Day 7–9: selexipag 400 µg b.i.d. + placebo 400 µg b.i.d. Day 10–12: selexipag 600 µg b.i.d. + placebo 400 µg b.i.d. Day 13–17: selexipag 800 µg b.i.d. + placebo 400 µg b.i.d. **Group B treatment (up to 1200 µg selexipag) regimen:** Day 1–3: selexipag 400 µg b.i.d. Day 4–6: selexipag 600 µg b.i.d. Day 7–9: selexipag 800 µg b.i.d. Day 10–12: selexipag 1000 µg b.i.d Day 13–17: selexipag 1200 µg b.i.d **Group C treatment (placebo) regimen:** Day 1–3: placebo 400 µg b.i.d. Day 4–6: placebo 600 µg b.i.d. Day 7–9: placebo 800 µg b.i.d. Day 10–12: placebo 1000 µg b.i.d. Day 13–17: placebo 1200 µg b.i.d. **Group D treatment (ciprofloxacin) regimen:**	52 (Groups A, C, D: 12 per Group. Group B: 16)	Healthy male subjects	17 days for each Group. Treatment with selexipag only: Group A: 11 days. Group B: 17 days.

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
					Day 1–3: placebo 400 µg b.i.d. Day 4–6: placebo 600 µg b.i.d. Day 7–9: placebo 800 µg b.i.d. Day 10–12: ciprofloxacin 500 mg b.i.d. + placebo 1000 µg b.i.d Day 13–17: ciprofloxacin 500 mg b.i.d + placebo 1200 µg b.i.d Oral			
Healthy subject PK and initial tolerability study	AC-065-106	5.3.3.1	Investigation of the effect of two dose levels (800 µg and 1600 µg b.i.d.) of selexipag on the QT/QTc interval. Investigation of safety and tolerability the PK of selexipag and its active metabolite, ACT 333679.	Double-blind, randomized, parallel group with nested crossover, multiple-dose, up-titration, placebo- and positive-controlled Phase 1 study.	Selexipag Placebo Moxifloxacin Selexipag tablet (strength: 200 µg) Placebo tablet/capsule Moxifloxacin over-encapsulated tablet (strength: 400 mg) Randomization (4 3): Treatment A or B Within Treatment B (1:1): B1 or B2 **Treatment A:** Day 1: placebo matching selexipag o.d. Day 2: placebo matching moxifloxacin o.d. Day 3–5: selexipag 400 µg b.i.d. Day 6–8: selexipag 600 µg b.i.d. Day 9–11: selexipag 800 µg b.i.d. Day 12–14: selexipag 1000 µg b.i.d. Day 15–17: selexipag 1200 µg b.i.d. Day 18–20: selexipag 1400 µg b.i.d. Day 21–22: selexipag 1600 µg b.i.d. Day 23: selexipag 1600 µg o.d. Day 24: placebo matching moxifloxacin o.d.	159 (103 male, 56 female) Treatment A: 91 (60 males, 31 females) Treatment B1: 34, (21 males, 13 females) Treatment B2: 34 (22 males, 12 females)	Healthy male and female subjects	20.5 days

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
					Treatment B1: Day 1: placebo matching selexipag o.d. Day 2: moxifloxacin 400 mg o.d. Day 3–23: placebo matching selexipag b.i.d. Day 24: placebo matching moxifloxacin o.d. **Treatment B2:** Day 1: placebo matching selexipag o.d. Day 2: placebo matching moxifloxacin o.d. Day 3–23: placebo matching selexipag b.i.d. Day 24: moxifloxacin 400 mg o.d. Oral			

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Intrinsic factor PK study	AC-065-104	5.3.3.3	Investigation of the PK, safety, and tolerability of selexipag and its active metabolite, ACT-333679, in subjects with mild, moderate, or severe hepatic impairment.	Single dose, parallel group, uncontrolled Phase 1 study.	Selexipag Selexipag tablet (strength: 200 µg) Single dose of selexipag 400 µg: subjects with mild and moderate hepatic impairment and healthy subjects Single dose of selexipag 200 µg: subjects with severe hepatic impairment Oral	26 (17 males, 9 females) Mild hepatic impairment [Child-Pugh A]: 8 (6 males, 2 females) Moderate hepatic impairment [Child-Pugh B]: 8 (5 males, 3 females) Severe hepatic impairment [Child-Pugh C]: 2 (1 male, 1 female) Healthy subjects: 8 (5 males, 3 females).	Mild, moderate, or severe hepatic impairment Healthy subjects	Single dose

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Intrinsic factor PK study	AC-065-105	5.3.3.3	Investigation of the PK, safety, and tolerability of selexipag and its active metabolite, ACT-333679, in subjects with renal function impairment.	Single dose, parallel group, uncontrolled Phase 1 study.	Selexipag Selexipag tablet (strength: 200 µg) Single dose of selexipag 400 µg Oral	16 (8 males, 8 females). Severe renal impairment [creatinine clearance range: 15.0–37.0 mL/min]: 8 (4 males , 4 females) Healthy subjects [creatinine clearance range: 73.0–107.0 mL/min]: 8 (4 males, 4 females)	Severe renal function impairment Healthy subjects	Single dose

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Extrinsic factor PK study	AC-065-109	5.3.3.4	Evaluation of PK interactions between selexipag and Kaletra® (lopinavir/retonavir). Investigation of safety, tolerability and PK of selexipag and its active metabolite, ACT-333679, when administered concomitantly with Kaletra®.	Randomized, two-period, two-treatment, crossover, uncontrolled Phase 1 study.	Selexipag Kaletra® Placebo Selexipag tablet (strength: 200 µg) Kaletra® tablet (strength: lopinavir 200 mg/ritonavir 50 mg) Placebo tablet Randomization (1:1): treatment sequence: AB or BA **Treatment A:** Day 1: single oral selexipag 400 µg **Treatment B:** Day 1–12: Kaletra® b.i.d. in the fasted or fed state. Day 10: concomitant administration of a single dose of selexipag 400 µg Washout period between Period 1 and Period 2: 14 –22 days Oral	20	Healthy male subjects	**Treatment A:** single dose **Treatment B:** 12 days including a single dose of selexipag

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Population PK study	AC-065A302 PK/GRIPHON	5.3.3.5	Description of the population PK characteristics of selexipag and its active metabolite, ACT-333679. Evaluation of the PK/PD relationship between selexipag/ACT-333679 plasma levels and selected clinical safety and efficacy endpoints and plasma N-terminal pro-brain natriuretic peptide (NT pro-BNP) levels. Assessment of the relationship between different subject-specific factors and model parameters. Performing simulations based on PopPK/PD results to assess the goodness of fit of the model and to visualize results.	Double-blind, randomized, placebo-controlled, parallel group Phase 3 study (PK/PD report).	Selexipag Placebo Selexipag tablet (strength: 200 µg) Placebo tablet **Up-titration scheme*:** Day 1 p.m.: 200 µg Day 2 a.m.–Day 8 a.m.: 200 µg b.i.d. Day 8 p.m.–Day 15 a.m.: 400 µg b.i.d. Day 15 p.m.–Day 22 a.m.: 600 µg b.i.d. Day 22 p.m.–Week 4 a.m.: 800 µg b.i.d. Week 4 p.m.–Week 5 a.m.: 1000 µg b.i.d. Week 5 p.m.–Week 6 a.m.: 1200 µg b.i.d. Week 6 p.m.–Week 7 a.m.: 1400 µg b.i.d. Week 7 p.m.–Week 12 a.m.: 1600 µg b.i.d. Determination of the individual MTD: Week 12 From Week 12 onwards: maintenance dose * Dose titration was based on individual patient's tolerability to selexipag. Oral	PK/PD report: 1156 patients randomized in the main study (574 selexipag, 582 placebo)	Symptomatic PAH	PK/PD report: at least 52 weeks

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Controlled clinical studies pertinent to the claimed indication	NS-304-02	5.3.5.1	**Period A:** to evaluate the effect of single, oral dose of selexipag on hemodynamic variables, safety, and tolerability. **Period B:** to assess the efficacy of selexipag as measured by the change in PVR from baseline to Week 17 in PAH patients. Other objectives: 6MWT, RHC parameters other than PVR, NYHA functional class, Borg dyspnea score, NT-proBNP, echocardiography parameters, safety and tolerability, and PK.	**Period A:** open-label, uncontrolled. **Period B:** Randomized, double-blind, placebo-controlled, parallel group. Phase 2a study.	Selexipag Placebo Selexipag tablet (strength: 200 µg) Placebo tablet **Period A:** Day 0: single dose of selexipag 200 µg (12 patients) or 400 µg (31 patients). Observation period: up to 4 h after dosing **Period B (up-titration scheme*):** Day 1–2: selexipag 200 µg b.i.d. Day 3–6: selexipag 400 µg b.i.d. Day 7–20: selexipag 600 µg b.i.d. Day 21-35: selexipag 800 µg b.i.d. Determination of the maintenance dose: Day 35 ± 3 days (Week 5) Maintenance period: from Week 5 onwards up to the end of the study, i.e., Week 17-21 Transition to the OL extension study: Week 17–21 * Dose titration was based on individual patient's tolerability to selexipag. Oral	**Period A:** 43 **Period B:** 43 (33 selexipag, 10 placebo) (8 male, 35 female)	Symptomatic PAH	**Period A:** single dose **Period B:** Median treatment duration: Selexipag: 149.0 days (range: 17.0-176.0 days) Placebo: 146.0 days (range: 61.0-152.0 days)

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Controlled clinical studies pertinent to the claimed indication	AC-065A302 (GRIPHON)	5.3.5.1	To assess the safety and efficacy of selexipag on morbidity and mortality in patients with PAH.	Double-blind, randomized, placebo-controlled, parallel group Phase 3 study.	Selexipag Placebo Selexipag tablet (strength: 200 µg) Placebo tablet **Up-titration scheme*:** Day 1 p.m.: 200 µg Day 2 a.m.–Day 8 a.m.: 200 µg b.i.d. Day 8 p.m.–Day 15 a.m.: 400 µg b.i.d. Day 15 p.m.–Day 22 a.m.: 600 µg b.i.d. Day 22 p.m.–Week 4 a.m.: 800 µg b.i.d. Week 4 p.m.–Week 5 a.m.: 1000 µg b.i.d. Week 5 p.m.–Week 6 a.m.: 1200 µg b.i.d. Week 6 p.m.–Week 7 a.m.: 1400 µg b.i.d. Week 7 p.m.–Week 12 a.m.: 1600 µg b.i.d. Determination of the individual MTD: Week 12 From Week 12 onwards: maintenance dose * Dose titration was based on individual patient's tolerability to selexipag. Oral	1156 (574 selexipag, 582 placebo)	Symptomatic PAH	Median treatment duration: selexipag: 70.7 weeks (range: 0.3–216.7 weeks) placebo: 63.7 weeks (range: 0.7–192.0 weeks)

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	
Uncontrolled clinical studies	AC-065A201	5.3.5.2	To assess the efficacy, safety, and PK of selexipag in patients with PAH.	Uncontrolled, open-label, one treatment arm Phase 2 study.	Selexipag Selexipag tablet (strength: 200 µg) Up-titration scheme*: Day 1–3: selexipag 200 µg b.i.d. Day 4–6: selexipag 400 µg b.i.d. Day 7–9: selexipag 600 µg b.i.d. Day 10–12: selexipag 800 µg b.i.d. Day 13–19: selexipag 1000 µg b.i.d. Day 20–26: selexipag 1200 µg b.i.d. Day 27–33: selexipag 1400 µg b.i.d. Day 34 up to Week 12: selexipag 1600 µg b.i.d. Determination of the maintenance dose: Week 12 ± 1 week Maintenance dose period: for at least 4 weeks, from Week 12 (± 1 week) to Week 16 (± 1 week) Long-term treatment period: from Week 16 up to Week 144. Patients without clinically significant adverse events at Week 144 may be treated further if the investigator requests to do so. * Dose titration was based on individual patient's tolerability to selexipag. Oral	37 (11 male, 26 female)	Symptomatic PAH	As described in interim report: Median treatment duration: Selexipag 16.29 weeks (range: 0.1-20.0 weeks)	C I r \ e

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Other	AC-065B201	5.3.5.4	To evaluate the effect of selexipag on PVR, other pulmonary hemodynamic variables, exercise tolerability (6MWD/Borg dyspnea index), WHO functional class, NT-proBNP, and PK, safety and tolerability in CTEPH patients.	Randomized, double-blind, placebo-controlled, parallel group Phase 2 study.	Selexipag Placebo Selexipag tablet (strength: 100 µg) Placebo tablet **Up-titration scheme*:** Day 1–3: selexipag 100 µg b.i.d. Day 4–6: selexipag 200 µg b.i.d. Day 7–9: selexipag 300 µg b.i.d. Day 10–12: selexipag 400 µg b.i.d. Day 13–15: selexipag 600 µg b.i.d. Day 16–35 (± 7 days) (i.e., Week 5 ± 1 week): selexipag 800 µg b.i.d. Determination of the maintenance dose: Week 5 ± 1 week Maintenance dose period: for 12 weeks after Week 5 (± 1 week) Transition to the OL extension study: Week 17–21 * Dose titration was based on individual patient's tolerability to selexipag. Oral	34 (25 selexipag, 9 placebo) (10 male, 24 female)	CTEPH	Median treatment duration: Selexipag: 120 days (range: 114–127 days) Placebo: 119 days (range: 1–125 days)
Other	AC-065B202	5.3.5.4	Long-term safety of selexipag in patients with CTEPH.	Single-arm, open-label treatment, extension Phase 2 study.	Selexipag Selexipag tablet (strength: 100 µg) Selexipag 100 µg b.i.d. up to 800 µg b.i.d. Oral	27 (26 selexipag)	CTEPH	Median treatment duration: 105.9 weeks (range: 24.4–166.4 weeks)

6MWD =6-minute walk distance; 6MWT =6-minute walk test; b.i.d. = twice daily; CTEPH = chronic thromboembolic pulmonary hypertension; NT-proBNP = N-terminal pro-B type natriuretic peptide; NYHA = New York Heart Association; o.d. = once daily; OL = open-label; PAH = pulmonary arterial hypertension; PD = pharmacodynamics; PK = pharmacokinetics; PVR = pulmonary vascular resistance; QTc = corrected QT interval; RHC =right heart catheterization; WHO = World Health Organization

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5.2. Review Strategy

This is a primary review prepared by a medical officer and a safety reviewer with the support of a statistical reviewer. The focus of the review was on the large GRIPHON trial. The other trials were reviewed and included in this document as deemed appropriate by the medical officer. All necessary safety discussions are included as well.

Selexipag is being proposed for the (b) (4) treatment of pulmonary arterial hypertension (PAH), WHO Group I, in patients (b) (4) The safety and efficacy of this application is based primarily on the outcome of the GRIPHON trial for which the study design, endpoints, and analysis strategy were discussed with the Division of Cardiovascular Drug Products at the US FDA. The protocol for this study was based on an agreement between the FDA and the sponsor within Special Protocol Assessment (SPA).

6 Review of Relevant Individual Trials Used to Support Efficacy

The clinical evidence for the efficacy and safety of selexipag in the treatment of patients with PAH is derived from the double blind, randomized, placebo controlled, event driven studyAC-065A302/GRIPHON. The other controlled study in PAH subjects include NS-304/-02.

The long-term safety data in patients with PAH are derived from the open label studies AC-065A303, NS-304/-03 (ongoing), and AC-065A201 (Japanese patients with PAH, ongoing).

6.1. Study AC-065A302/GRIPHON

6.1.1. Study Design

Overview and Objective

This was a multicenter, double-blind, placebo-controlled, event driven study assessing the efficacy and safety of selexipag on morbidity and mortality in patients with PAH.

Trial Design

This was a multicenter, randomized, double-blind, parallel group, placebo-controlled, event-driven study to compare the effects (efficacy, safety, tolerability, pharmacokinetics/ pharmacodynamics [PK/PD]) of selexipag (administered orally at an individualized dose in the range of 200–1600 µg b.i.d.) versus placebo in patients with symptomatic PAH.

The study design is shown in the figure below.

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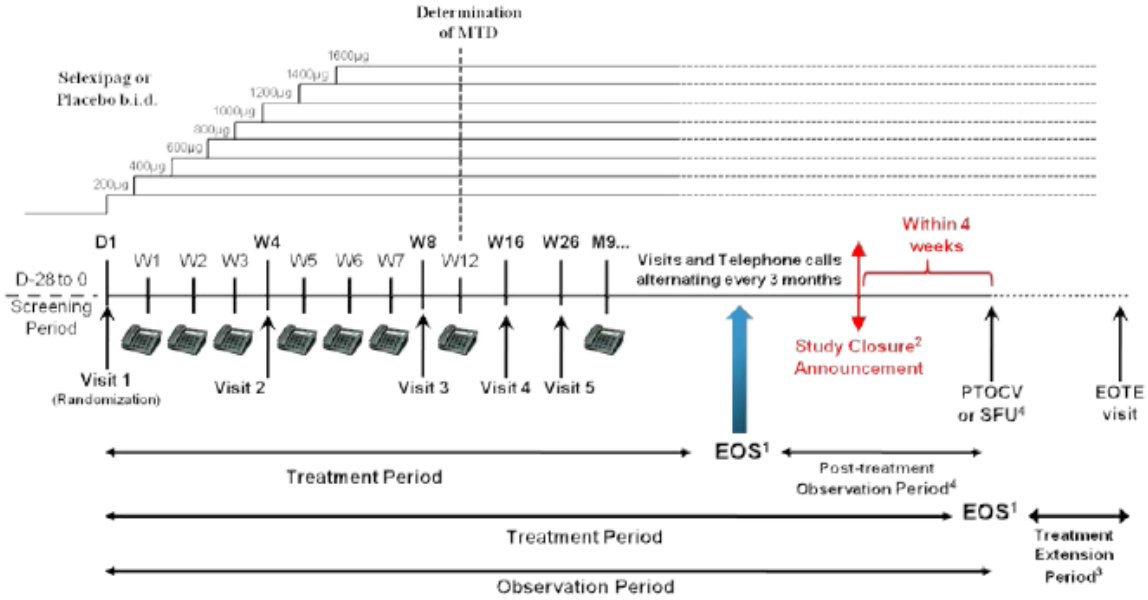
Figure 9-1 AC-065A302/GRIPHON study design



1. EOS Visit was to be performed within 4 weeks of Study closure announcement. For patients who had a CEC-confirmed MM event or discontinued study drug before Study closure, the EOS Visit was performed following the morbidity event or following premature discontinuation. A Post-treatment safety follow-up phone call was performed for all patients who discontinued treatment.
2. Study closure was announced when the target number of CEC-confirmed MM events was achieved.
3. If study AC-065A303/GRIPHON OL was approved by the National Health Authority, patients who were on study drug at Study closure and who wished to enter study AC-065A303/GRIPHON OL once the GRIPHON study results confirmed a positive benefit-risk for selexipag were required to enter the Treatment Extension period.
4. Patients who discontinued study drug in AC-065A302/GRIPHON before Study closure had an option to enter the post-treatment observation period, irrespective of whether they were enrolled into AC-065A303/GRIPHON OL. A post-treatment observation closure visit (PTOCV) was to be performed within 4 weeks of Study closure announcement. All patients (except those who had withdrawn consent from all study components) were contacted (phone call) at the time of Study closure to ascertain their vital status.

The study phases were screening (days -28 to 0), randomization (visit 1), treatment phase, end of study (EOS) visit. Determination of maximum tolerated dose (MTD) was made at week 12.

Patient selection

Eligible patients were randomized using a centralized randomization system. Randomization was performed by an independent Contract Research Organization. A unique randomization number was assigned to each patient (patient randomization number).

Inclusion criteria

Eligible patients were required to have fulfilled all of the following inclusion criteria:

- Signed informed consent prior to initiation of any study-mandated procedure.
- Male and female[d,e] patients aged from 18 to 75 years inclusive with symptomatic PAH (*following Protocol Amendment 1, an upper age limit of 75 years was defined [Amendment 1, Table 9-10]*).
- Patients with PAH belonging to one of the following subgroups of the Updated Dana Point 2008 Clinical Classification Group 1:
  - Idiopathic (IPAH)[f]
  - Heritable (HPAH)[f]
  - Drug or toxin induced
  - Associated (APAH) with one of the following:
    - Connective tissue disease
    - Congenital heart disease with simple systemic-to-pulmonary shunt at least 1 year after surgical repair

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    - HIV infection
- Documented hemodynamic diagnosis of PAH by right heart catheterization - performed at any time prior to Screening that showed (*this criterion was clarified following Protocol Amendment 5 [Amendment 5, Table 9-10]*):
  - Resting mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg,
    and
  - Resting pulmonary vascular resistance (PVR) ≥ 400 dyn·s·cm^{-5} (*following Protocol Amendment 1, the lower limit of resting PVR was increased, from 240 to ≥ 400 dyn·s·cm^{-5} [Amendment 1, Table 9-10]*)
    and
  - Pulmonary capillary wedge pressure (PCWP) or left ventricular end diastolic pressure (LVEDP) ≤ 15 mmHg.
- 6-MWD between 50 and 450 m (inclusive) at Screening (up to 2 weeks prior to the Baseline Visit and on a different day than the Baseline visit) (*prior to Protocol Amendment 1, inclusion criterion on 6MWT was '6-MWD between 50 and 450 m [inclusive] within 2 weeks prior to the baseline visit, confirmed by a second 6-MWT at the baseline visit. The value of the second 6MWT to be within ± 10% of the first assessment'*).

Following Protocol Amendment 2, inclusion criterion to refrain from prolonged exposure to sun during the study was removed [Amendment 2, Table 9-10].

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[d] Women of childbearing potential were required to use a reliable method of contraception (failure rate less than 1% per year) from screening until 1 month after study drug discontinuation.

[e] A woman was considered to be of childbearing potential unless she met at least one of the following criteria:

- previous bilateral salpingecto-oophorectomy or hysterectomy
- premature ovarian failure confirmed by a specialist gynecologist
- pre-pubescence, XY genotype, Turner syndrome, uterine agenesis
- age > 50 years with amenorrhea for at least 24 consecutive months prior to screening.

[f] Other forms of PH were to be excluded and appropriately documented in the patient chart (e.g., results of pulmonary function tests, ventilation/perfusion lung scan, echocardiogram/or cardiac MRI, hospital summary from referred patients) [clarified in Amendment 5, Table 9-10].

Exclusion criteria

Eligible patients were required to have had none of the following exclusion criteria:

• Patients with pulmonary hypertension (PH) in the Updated Dana Point 2008 Clinical Classification Groups 2-5, and PAH Group 1 subgroups that were not covered by the inclusion criterion.

• Patients who had received prostacyclin (epoprostenol) or prostacyclin analogsg (i.e., treprostinil, iloprost, beraprost) up to 1 month prior to the Baseline visit, or were scheduled to receive any of these compounds during the study.

• Patients with moderate or severe obstructive lung disease: FEV1/FVC < 70% and FEV1 < 65% of predicted value after bronchodilator administration (*this criterion was modified following Protocol Amendment 1* .

• Patients with moderate or severe restrictive lung disease: Total Lung Capacity < 70% of predicted value (*this criterion was clarified following Protocol Amendment 1*.

• Patients with moderate or severe hepatic impairment (Child-Pugh B and C).

• Patients with documented left ventricular dysfunction (i.e., ejection fraction < 45%) (*this criterion was clarified following Protocol Amendment 1),*

• Patients with severe renal insufficiency (estimated creatinine clearance < 30 mL/min, or serum creatinine > 2.5 mg/dL).

• Patients with BMI < 18.5 kg/m2 (*this criterion replaced the body weight criterion following Protocol Amendment 1)*

• Patients who had received any investigational drugs within 1 month prior to the Baseline visit.

• Acute or chronic impairment (other than dyspnea), which would limit the ability to comply with study requirements, in particular with 6MWT (e.g., angina pectoris, claudication, musculoskeletal disorder, need for walking aids).

• Recently conducted (the program should have been completed at least 8 weeks prior to screening) or planned cardio-pulmonary rehabilitation program based on exercise training (*this criterion was added in Protocol Amendment 1)*

• Psychotic, addictive or any other disorder which would limit the ability to provide informed consent or to comply with study requirements.

• Life expectancy less than 12 months.

• Lactating or pregnant (positive pre-randomization serum pregnancy test) women or those who planned to become pregnant during the study.

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• Known hypersensitivity to any of the excipients of the drug formulations.
Following Protocol Amendment 1, exclusion criterion on hypotensive patients was removed.

Study treatment
The study drug was up-titrated to each individual patient's maximum tolerated dose (MTD) in the range of 200–1600 mcg bid.

The first dose of the study drug (one tablet of selexipag 200 mcg or matching placebo) was administered orally in the evening of Day 1 (Visit 1). From Day 2 onwards, a bid dose regimen was followed. If this dose (selexipag 200 mcg bid) was well-tolerated, the investigator informed the patient to up-titrate dose with weekly increments of 200 mcg during scheduled telephone calls or visits until the MTD (up to a maximum of 1600 mcg bid) for an individual patient was achieved up to Week 12.

If the patient could not tolerate the occurrence and severity of typical pharmacological effects of IP receptor agonists (including headache, diarrhea, jaw pain, myalgia, flushing, and nausea), the investigator was to reduce the dose by 200 mcg bid, and the adjusted dose was to be defined as the MTD.

At Week 12 (scheduled phone call), the MTD for each patient was determined, and this dose was to be kept stable for the next 14 weeks (i.e., from Week 12 onwards) up to the Week 26 assessment of the secondary endpoint which was change in six minute walk distance (6MWD).

After Week 26, for patients with study drug dose < 1600 mcg bid, investigators were allowed to further up-titrate the dose, if needed, by 200 mcg increments up to the maximum of 1600 mcg bid. Dose reduction was allowed at any time if the investigator identified a tolerability concern for a patient.

Allowed concomitant therapy
• Approved ERAs and/or PDE-5i for PAH treatment were allowed if patients had been on a stable dose for at least 3 months prior to the Baseline visit. The dose was to remain unchanged during study treatment up to Week 26 (Month 6).
• Treatment with diuretics was allowed if patients had been on a stable dose for at least 1 month prior to Baseline visit. The dose was to remain unchanged during study treatment up to Week 26 (Month 6).
• A single administration of medication used for acute vasodilator testing during a right heart catheterization (RHC) procedure was allowed.

Forbidden concomitant therapy
• Concomitant administration of prostacyclin (epoprostenol) or prostacyclin analogs (i.e., treprostinil, iloprost, beraprost) was forbidden from 1 month prior to Baseline up to EOS

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Visit, with the exception of a single administration of i.v./inhaled prostacyclin or analogs during a RHC procedure.
• Any investigational drug other than the study drug from 1 month prior to Baseline up to EOS or EOTE (end of treatment extension).

Study Endpoints

Primary efficacy endpoint
The primary efficacy endpoint in AC-065A302 was time to first critical event committee (CEC)-confirmed morbidity/mortality (MM) event up to 7 days after the last study drug intake in the AC-065A302 treatment period (i.e., end of treatment [EOT] + 7 days).

The included MM events were:
• Death (all-causes) **or**
• Hospitalization for worsening of PAH based on predefined criteria defined as any non-elective hospital stay (≥ 24 h) for worsening of PAH. Worsening of PAH included signs and symptoms of right heart failure (e.g., syncope or near syncope, cyanosis, increase of breathlessness, clinically relevant deterioration of exercise capacity, decrease of oxygen saturation, increased peripheral edema, hepatomegaly, and ascites) **or**
• Worsening of PAH resulting in need for lung transplantation or balloon atrial septostomy **or**
• Initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH **or**
• Disease progression (patients in modified NYHA/WHO FC II or III[1] at baseline) confirmed by:
– Decrease in 6MWD from Baseline (≥ 15%, confirmed by 2 tests on different days within 2 weeks) **and**
– Worsening of NYHA/WHO FC
or

• Disease progression (patients in NYHA/WHO FC III or IV at baseline) confirmed by:
– Decrease in 6MWD from Baseline (≥ 15%, confirmed by 2 tests on different days within 2 weeks) **and**
– Need for additional PAH-specific therapy.

MM events were adjudicated by the independent CEC blinded to study treatment. The CEC comprised three clinical experts who were not study investigators.

[1] Patients in NYHA/WHO FC III at baseline were qualified for both disease progression definitions. For patients in NYHA/WHO FC I (total of 9 patients) at baseline, the disease progression component was not defined in the protocol. Sites which had enrolled patients with baseline NYHA/WHO FC I and the CEC was informed and instructed to respectively report and adjudicate disease progression events for these patients as per criteria applicable for NYHA/WHO FC II.

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Initially, event-adjudication was only performed to confirm the occurrence of an MM event. Following Global Protocol Amendment 6, the process was adjusted to adjudicate the following details:
i) presence of an MM event,
ii) type of endpoint component,
iii) MM event onset date, and
iv) PAH-association with a fatal outcome.

Information regarding typical prostacyclin-associated adverse events was removed from documentation made available to the CEC to maintain the blind.

Imputation
No imputation method was applied. For a patient without a CEC-confirmed MM event up to 7 days after last study drug intake in the AC-065A302 treatment period, time to first CEC-confirmed MM event (up to 7 days after last study drug intake in the AC-065A302 treatment period) was defined using the following censoring rules.

Censoring rules
• For randomized patients who received at least one intake of study drug and who did not consent to the AC-065A302 post-treatment observation period: minimum (date of last study drug intake in the AC-065A302 treatment period plus seven, EOS visit date, date of last contact, analysis cut-off date of AC-065A302, i.e., April 27, 2014) minus date of randomization plus one.
• For randomized patients who received at least one intake of study drug and who did consent to the AC-065A302 post-treatment observation period: minimum (date of last study drug intake in the AC-065A302 treatment period plus seven, date of last contact, April 27, 2014) minus date of randomization plus one.
• For randomized patients who did not receive any study drug: minimum (maximum [EOS visit date, randomization date], date of last contact, April 27, 2014) minus date of randomization plus one.

Following Global Amendment 5, CEC-confirmed MM events with onset date (as per CEC) up to August 16, 2011 were considered as censored at the event onset date for the primary statistical analysis. In the event that a patient with a CEC-confirmed MM event with onset date up to August 16, 2011 had a subsequent CEC confirmed MM event with onset date after August 16, 2011, then the first event was disregarded and the second event was counted as an event in the statistical analysis.

Secondary efficacy endpoints
Following Amendment 1, all the secondary endpoints were to be assessed at Week 26 instead of Week 16

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• Absolute change from Baseline to Week 26 in 6MWD measured at trough. Prior to implementation of 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 CEC-confirmed death due to PAH or CEC confirmed hospitalization due to PAH worsening up to 7 days after last study drug intake in the AC-065A302 treatment period.
• Time from randomization to death of all causes up to Study closure.
• Absolute change from Baseline to Week 26 in the sub-scale 'Breathlessness' of CAMPHOR (Cambridge Pulmonary Hypertension Outcome Review) 'Symptoms' (at selected centers). The sub-scale 'Breathlessness' of CAMPHOR 'Symptoms' was defined as the sum of the 'Breathlessness' items 11 to 18. It ranged from 0 (good) to 8 (poor).
• Absolute change from Baseline to Week 26 in CAMPHOR 'Symptoms' score (at selected centers). The CAMPHOR 'Symptoms' score was defined as the sum of the 'Symptoms' items 1 to 25. It ranged from 0 (good) to 25 (poor). The 2 endpoints on CAMPHOR were only analyzed for patients in the Quality of Life (QoL) analysis set.

Statistical Analysis Plan

See Dr. Bai's statistical review page 8.

Protocol Amendments

The recommendations of the Scientific Advisory Board to refine certain inclusion/exclusion criteria (e.g., age limitation to ≤ 75 years, lower limit of PVR increased to 400 dyn·s·cm−5) and to request a stable dose of allowed PAH background medication for 3 months prior to baseline were implemented in Global Protocol Amendment 1.

The ophthalmology experts recommended that the sponsor conduct an exploratory ophthalmology sub-study in order to collect retinal photographs at baseline and at specific time points during the study, and to use a Central Reading Center. This was implemented with Global Protocol Amendment 3.

CEC-confirmed MM events with onset date (as per CEC) up to 16 August 16, 2011 were not considered as events in the primary statistical analysis. This was implemented with Local Protocol Amendment 5.

Recommendations made by the Steering Committee and Scientific Advisory Board, i.e., to collect data up to Study closure in all patients who prematurely discontinued study drug and to reinforce that the best available PAH treatment was offered to each study participant, were implemented with Global Protocol Amendment 6.

Data Quality and Integrity: Sponsor's Assurance

Reference ID: 3814728

The study AC-065A302 (and the extension AC-065A303) was performed in compliance with GCP guidelines, including the archiving of essential documents. The overall procedures for quality assurance of clinical study data are described in the Actelion Standard Operating Procedures (SOPs). All investigators were trained to comply with GCP and to conduct both studies in accordance with their study protocols. The review statistician Dr. Bai stated that he had no questions about data or analysis quality (statistical review page 5).

Study AC-065A302 and the extension AC-065A303 were monitored by appropriately trained staff of Actelion Pharmaceuticals Ltd or CROs. An initiation visit was performed before the first patient was included in each study. The monitor contacted and visited the investigator at regular intervals thereafter, according to the frequency defined in the study-specific monitoring plan. It was the monitor's responsibility to inspect the CRFs at regular intervals throughout the study, to verify adherence to the protocol and the completeness, consistency and accuracy of the data being entered on the CRFs. Actelion monitoring standards required full verification of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of the main efficacy, safety and tolerability endpoints, and study assessments.

The investigator was required to ensure that patient anonymity was maintained. On CRFs or other documents submitted to Actelion, patients were identified only by number, and never by name. The investigator was required to keep a patient identification code list with the randomization number, the patient's name, date of birth and address or any other locally accepted identifiers. Documents identifying the patients were not sent to Actelion, and were kept in strict confidence by the investigator. The Patient Identification Log and signed Informed Consent document for the study were maintained in the investigator site file and were not collected by, or on behalf of Actelion.

The investigator and co-investigators agreed to cooperate with the monitor(s) to ensure that any issues detected in the course of the monitoring visits were resolved. If the patient had to be hospitalized or died in a hospital other than the study center, the investigator was responsible for contacting that hospital in order to document the SAE.

The investigator was to supply Actelion with any required background data from the study documentation or clinical records. This was particularly important when CRFs were illegible or when errors in data transcription were suspected. In the case of special problems and/or governmental queries, it was also necessary to have access to the complete study records, provided that patient confidentiality was protected.

6.1.2. Study Results

Compliance with Good Clinical Practices

Reference ID: 3814728

Prior to the start of the Griphon study, each study site consulted an Independent Ethics Committee (IEC) or Institutional Review Board (IRB), a review panel that was responsible for

ensuring the protection of the rights, safety and well-being of human subjects involved in a clinical investigation. The sponsor ensured that each IEC/IRB consulted was adequately constituted to provide assurance of that protection.

Patient Disposition

A total of 1156 patients were randomized in a ratio of 1:1 selexipag (n=574) and placebo (n=582), with stratification by study site and a block size of 4.

Study duration/centers
Study dates: December 30, 2009 to May 17, 2013
Centers: 181 sites in 39 countries with the number of subjects by country and treatment group shown below.

Reference ID: 3814728

Table 15-21 Summary of country at screening, FAS

ACT-293987, Protocols AC-065A302/AC-065A303
Summary of country at screening
Set: Full analysis set

	Selexipag N=574 n	%	Placebo N=582 n	%
Country [n (%)]				
Non-missing	574		582	
United States	74	12.9%	81	13.9%
China	70	12.2%	70	12.0%
Russian Federation	46	8.0%	45	7.7%
Australia	30	5.2%	32	5.5%
Germany	32	5.6%	29	5.0%
Belarus	25	4.4%	26	4.5%
Ukraine	26	4.5%	24	4.1%
France	24	4.2%	23	4.0%
Canada	21	3.7%	17	2.9%
Chile	19	3.3%	19	3.3%
Israel	16	2.8%	16	2.7%
Korea, Republic of	16	2.8%	15	2.6%
Mexico	15	2.6%	15	2.6%
Argentina	10	1.7%	14	2.4%
Czech Republic	12	2.1%	11	1.9%
Hungary	9	1.6%	14	2.4%
India	12	2.1%	11	1.9%
Belgium	12	2.1%	10	1.7%
Turkey	10	1.7%	12	2.1%
Poland	8	1.4%	11	1.9%
United Kingdom	9	1.6%	9	1.5%
Peru	7	1.2%	8	1.4%
Sweden	7	1.2%	8	1.4%
Spain	6	1.0%	7	1.2%
Netherlands	6	1.0%	7	1.2%
Taiwan, Province of China	6	1.0%	6	1.0%
Romania	6	1.0%	5	0.9%
Serbia	5	0.9%	6	1.0%
Singapore	5	0.9%	5	0.9%
Greece	5	0.9%	4	0.7%
Italy	4	0.7%	4	0.7%
Thailand	4	0.7%	4	0.7%
Austria	3	0.5%	3	0.5%
Ireland	3	0.5%	3	0.5%
Denmark	2	0.3%	3	0.5%
Switzerland	2	0.3%	2	0.3%
Malaysia	2	0.3%	2	0.3%
Colombia	3	0.5%	-	
Slovakia	2	0.3%	1	0.2%

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

Disposition

Of the 1351 screened patients, a total of 1156 were randomized in a 1:1 ratio to selexipag (n=574) or placebo (n = 582). There were 374 selexipag and 582 placebo patients who received study drug. There were four placebo patients who did not receive drug (one patient had a CEC confirmed event on day 1, two patients withdrew consent, one patient was withdrawn for administrative reasons).

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The disposition of the randomized patients is shown below and includes patients who enrolled into the open label extension (AC-065A303). (A total of 289 selexipag patients and 252 placebo patients completed the study with no CEC-confirmed MM event. Table 15-44).

Table 15-1 Disposition of patients in studies AC-065A302 and AC-065A303, FAS

ACT-293987, Protocols AC-065A302/AC-065A303
Disposition of patients in studies AC-065A302 and AC-065A303
Set: Full analysis set

	Selexipag N=574 n	%	Placebo N=582 n	%
AC-065A302 Treatment Period				
Patients randomized	574	100%	582	100%
Patients treated	574	100%	578	99.3%
Patients performed end of study visit	500	87.1%	520	89.3%
Patients withdrew consent from all study components except vital status at study closure	44	7.7%	39	6.7%
Patients withdrew consent from all study components	20	3.5%	19	3.3%
AC-065A302 Post-Treatment Observation Period *				
Patients consented	113		137	
Patients completed PTOP	98	86.7%	118	86.1%
Patients did not complete PTOP	15	13.3%	19	13.9%
Reason: Death	11	9.7%	17	12.4%
Withdrawal of consent	2	1.8%	2	1.5%
Administrative reason	2	1.8%	0	
AC-065A302 Vital status at study closure				
Missing	0		1	
Alive	450	78.4%	449	77.1%
Deceased	100	17.4%	105	18.0%
Not known	24	4.2%	27	4.6%
AC-065A303 **				
Patients enrolled	63		155	
Patients treated	63	100%	155	100%
Patients did not discontinue the study	36	57.1%	84	54.2%
Patients discontinued the study and performed end of study visit	4	6.3%	32	20.6%
Patients discontinued the study and did not perform end of study visit	23	36.5%	39	25.2%
Reason: Death	19	30.2%	36	23.2%
Withdrawal of consent	3	4.8%	1	0.6%
Lost to follow-up	0		1	0.6%
Administrative reason	1	1.6%	1	0.6%

PTOP=post-treatment observation period.
* denominator is number of patients who consented to AC-065A302 PTOP.
** denominator is number of patients enrolled in AC-065A303. Patients summarized under "placebo" were
randomized to placebo in AC-065A302 and treated with selexipag in AC-065A303.

There were nearly equal percentages of subjects who performed the end of study visit (87% selexipag, 89% placebo). The follow up of vital status (alive or dead) at study closure was similar for both study groups (96% selexipag, 95% placebo) with approximately 4% in each treatment group having unknown status.

The table below shows the number and percent of patients who had a primary efficacy endpoint.

Reference ID: 3814728

Table 15-3 Patient flow up to Study closure, FAS

ACT-293987, Protocols AC-065A302/AC-065A303
Patient flow up to Study Closure
Set: Full analysis set

	Selexipag N=574 n	%	Placebo N=582 n	%
Patient had a primary endpoint	155	27.0%	242	41.6%

There were 155 selexipag patients (27%) and 242 placebo patients (42%) who had a primary endpoint (i.e., a CEC-confirmed MM event up to EOT + 7 days).

The table and figure below show the numbers and percentages of patients with premature discontinuation prior to study closure and no CEC-confirmed MM event.

Table 10-2 Reasons for premature discontinuation of study drug in AC-065A302, SAF

	Selexipag N=575 n	%	Placebo N=577 n	%
Patients prematurely discontinued study drug	148	25.7%	97	16.8%
ADVERSE EVENT *	82	14.3%	41	7.1%
PATIENT/LEGAL REPRESENTATIVE DECISION TO STOP STUDY TREATMENT	36	6.3%	32	5.5%
CLINICAL WORSENING EVENT *	11	1.9%	11	1.9%
WITHDRAWAL OF CONSENT FOR ALL STUDY COMPONENTS	8	1.4%	3	0.5%
ADMINISTRATIVE/OTHER	3	0.5%	3	0.5%
PHYSICIAN'S DECISION	3	0.5%	0	
LOST TO FOLLOW UP	2	0.3%	3	0.5%
DEATH *	2	0.3%	2	0.3%
ADMINISTRATIVE/OTHER - LOST TO FOLLOW UP	1	0.2%	0	
ADMINISTRATIVE/OTHER - PHYSICIAN'S DECISION	0		2	0.3%

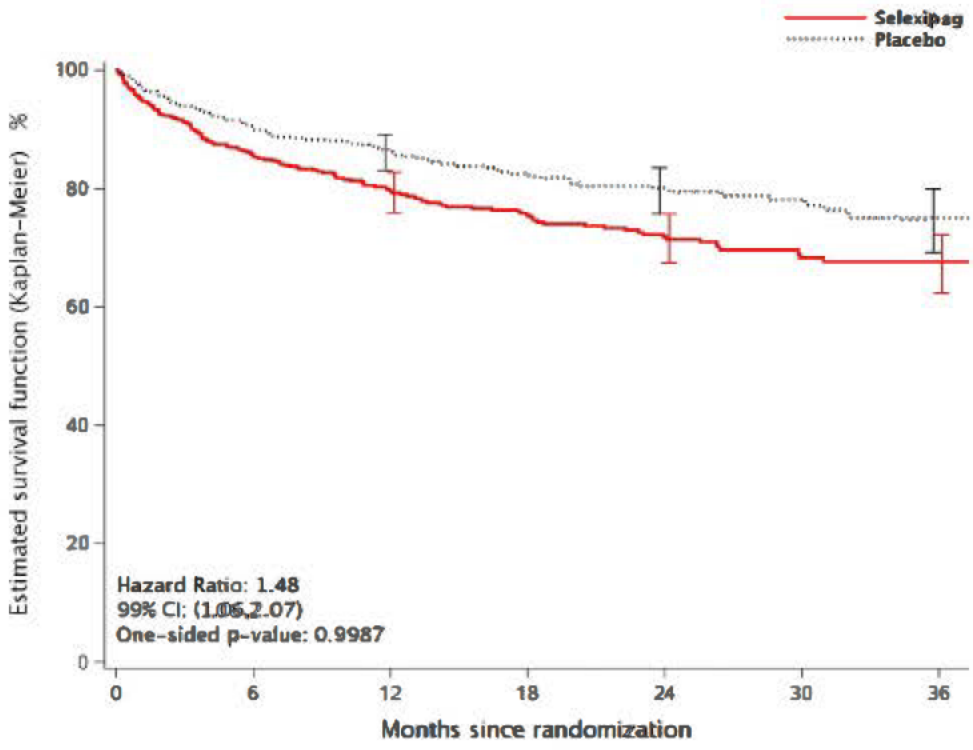
* An AE / death /clinical worsening event may be the reported reason for discontinuation of study drug, but the event may subsequently have been adjudicated by the CEC as a morbidity/mortality event.
Premature discontinuations are study drug discontinuation prior to Study Closure with no CEC-confirmed morbidity/mortality event with onset date prior to or on study drug end date.

The incidence rates of patients who prematurely discontinued study drug any time but no CEC-confirmed MM event were 26% for the selexipag group (148/575) and 17% for the placebo group (97/577). The majority of the selexipag patients withdrew because of an adverse event (55%, 82/148). This is a higher rate compared to the placebo patients (41%, 41/97).

Reference ID: 3814728

Figure 15-1 Time from study drug start to premature discontinuation of study drug in study AC-065A302 - Kaplan-Meier estimates, SAF

ACT-293987, Protocols AC-065A302/AC-065A303
Time from study drug start to premature discontinuation of study drug in study AC-065A302
Kaplan-Meier estimates
Set: Safety analysis set



Selexipag patients:							
at risk	575	456	364	256	177	103	42
event(s)	0	81	111	128	139	146	147
censored	0	38	100	191	259	326	386

Placebo patients:							
at risk	577	443	358	229	154	90	29
event(s)	0	53	71	86	91	94	97
censored	0	81	148	262	332	393	451

Note: Bars on the graph show 95% confidence intervals of the estimates.
Figure FPDT2_S – Produced by (b) (4) on 23JUL14 – Data dump of 12JUN2014

The table below shows the 148 selexipag subjects who prematurely discontinued study drug, by dose.

Table 15-7 Reason for premature discontinuation of study drug in study AC-065A302 by last dose, SAF

ACT-293987, Protocols AC-065A302/AC-065A303
Reason for premature discontinuation of study drug in study AC-065A302 by last dose
Set: Safety analysis set

	Selexipag								
Dose b.i.d. in mcg dosing	200	400	600	800	1000	1200	1400	1600	Other regimen
	N=87	N=68	N=59	N=74	N=40	N=39	N=40	N=161	N=7
	n %	n %	n %	n %	n %	n %	n %	n %	n %
Patients prematurely discontinued study drug	48 55.2%	21 30.9%	20 33.9%	12 16.2%	7 17.5%	5 12.8%	6 15.0%	24 14.9%	5 71.4%
ADVERSE EVENT *	34 39.1%	11 16.2%	9 15.3%	6 8.1%	3 7.5%	2 5.1%	3 7.5%	11 6.8%	3 42.9%
PATIENT/LEGAL REPRESENTATIVE DECISION TO STOP STUDY TREATMENT	11 12.6%	7 10.3%	4 6.8%	5 6.8%	1 2.5%	2 5.1%	3 7.5%	3 1.9%	-
CLINICAL WORSENING EVENT *	-	1 1.5%	3 5.1%	-	2 5.0%	-	-	5 3.1%	-
WITHDRAWAL OF CONSENT FOR ALL STUDY COMPONENTS	2 2.3%	-	2 3.4%	-	1 2.5%	-	-	3 1.9%	-
ADMINISTRATIVE/OTHER	-	1 1.5%	1 1.7%	-	-	-	-	-	1 14.3%
PHYSICIAN'S DECISION	1 1.1%	-	-	-	-	-	-	1 0.6%	1 14.3%
LOST TO FOLLOW UP	-	1 1.5%	-	-	-	-	-	1 0.6%	-
DEATH *	-	-	1 1.7%	1 1.4%	-	-	-	-	-
ADMINISTRATIVE/OTHER - LOST TO FOLLOW UP	-	-	-	-	-	1 2.6%	-	-	-

* AE / Death / Clinical Worsening Event may be the reason for discontinuation of study drug in a patient who experienced morbidity/mortality event.
Premature discontinuation are study drug discontinuation prior to Study Closure with no CEC-confirmed morbidity/mortality event with onset date prior to [redacted] drug end date.
Table TPDTD2_S - Produced by (b) (4) on 10JUL14 - Data dump of 12JUN2014

Protocol Violations/Deviations

In study AC-065A302, any procedure performed outside protocol boundaries was considered a protocol deviation, e.g., missing assessments at baseline, laboratory (local or central) results not available before randomization, inappropriate PK sampling/storage/shipment conditions, and non-specified deviations.

A total of 96% and 95% of randomized patients in the selexipag and placebo groups, respectively, reported at least 1 protocol deviation. Significant protocol deviations were reported for 6% of patients in the selexipag group and 7% in the placebo group. Significant protocol deviations associated with inclusion/exclusion criteria were reported for 5% of patients in the selexipag group and 5% in the placebo group. The most frequently reported such significant protocol deviation was RHC parameter criterion not met at study entry (2% in both groups). The proportion of patients who had at least 1 significant deviation associated with GCP was the same (1%) in both groups. This included performing some study-mandated procedures prior to signing of ICF by patient (1% in both groups).

Table of Demographic Characteristics

Demographics at screening

Many of the demographic characteristics of the subjects at screening are shown below by treatment group.

Reference ID: 3814728

Table 10-5 Demographic characteristics at screening, FAS

	Selexipag N=574	Placebo N=582	Total N=1156
Sex [n (%)]			
Non-missing	574	582	1156
Males	117 20.4%	116 19.9%	233 20.2%
Females	457 79.6%	466 80.1%	923 79.8%
Age at screening (years)			
Non-missing	574	582	1156
Mean	48.2	47.9	48.1
Standard deviation	15.19	15.55	15.37
Min, Q1	18.0 , 37.0	18.0 , 35.0	18.0 , 36.0
Median	49.0	49.0	49.0
Q3 , Max	61.0 , 78.0	60.0 , 80.0	61.0 , 80.0
Age [n (%)]			
Non-missing	574	582	1156
< 65 years old	475 82.8%	474 81.4%	949 82.1%
65 - 74 years old	91 15.9%	103 17.7%	194 16.8%
>= 75 years old	8 1.4%	5 0.9%	13 1.1%
BMI (kg/m2)			
Non-missing	573	582	1155
Missing	1	0	1
Mean	26.9	26.7	26.8
Standard deviation	6.40	6.13	6.26
Min, Q1	17.2 , 21.9	17.5 , 21.9	17.2 , 21.9
Median	25.6	25.5	25.5
Q3 , Max	30.5 , 56.1	30.1 , 50.4	30.3 , 56.1
Race/ethnicity [n (%)]			
Non-missing	574	582	1156
Caucasian/white or Hispanic	427 74.4%	438 75.3%	865 74.8%
Caucasian/white	376 65.5%	375 64.4%	751 65.0%
Asian	125 21.8%	120 20.6%	245 21.2%
Black	13 2.3%	14 2.4%	27 2.3%
Hispanic	51 8.9%	63 10.8%	114 9.9%
Other	9 1.6%	10 1.7%	19 1.6%
Geographical region [n (%)]			
Non-missing	574	582	1156
Asia	115 20.0%	113 19.4%	228 19.7%
Eastern Europe	149 26.0%	155 26.6%	304 26.3%
Latin America	54 9.4%	56 9.6%	110 9.5%
North America	95 16.6%	98 16.8%	193 16.7%
Western Europe / Australia	161 28.0%	160 27.5%	321 27.8%

The majority of subjects were female (80%), < 65 years of age (82%), and white (65%). The study was conducted in Western Europe/ Australia (28%), Eastern Europe (26%), Asia (20%), North America (17%) and Latin America (10%). The treatment groups were well balanced which indicates that randomization was successful in patient distribution.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The disease characteristics of the randomized patients are shown below by treatment group.

Reference ID: 3814728

Table 10-6 Baseline disease characteristics, FAS

	Selexipag N=574	Placebo N=582	Total N=1156
Time since PAH diagnosis* (years)			
Non-missing	574	582	1156
Mean	2.3	2.5	2.4
Standard deviation	3.49	3.75	3.62
Min, Q1	0.0 , 0.3	0.0 , 0.3	0.0 , 0.3
Median	0.9	1.1	1.0
Q3 , Max	2.9 , 37.3	3.0 , 38.9	3.0 , 38.9
Etiology of PAH [n (%)]			
Non-missing	574	582	1156
Idiopathic	312 54.4%	337 57.9%	649 56.1%
Heritable	13 2.3%	13 2.2%	26 2.2%
Drug or toxin induced	17 3.0%	10 1.7%	27 2.3%
Connective tissue disease	167 29.1%	167 28.7%	334 28.9%
Congenital heart disease	60 10.5%	50 8.6%	110 9.5%
HIV infection	5 0.9%	5 0.9%	10 0.9%
NYHA /WHO functional class [n (%)]			
Non-missing	574	582	1156
I	4 0.7%	5 0.9%	9 0.8%
II	274 47.7%	255 43.8%	529 45.8%
III	293 51.0%	314 54.0%	607 52.5%
IV	3 0.5%	8 1.4%	11 1.0%
6-Minutes-Walking-Distance (m)			
Non-missing	574	582	1156
Mean	358.5	348.0	353.2
Standard deviation	76.31	83.23	80.01
Min, Q1	90.0 , 318.0	50.0 , 299.0	50.0 , 307.0
Median	376.0	369.0	372.0
Q3 , Max	418.0 , 482.0	415.0 , 515.0	416.0 , 515.0
Borg Dispnea Index			
Non-missing	574	582	1156
Mean	3.6	3.7	3.7
Standard deviation	2.12	2.11	2.11
Min, Q1	0.0 , 2.0	0.0 , 2.0	0.0 , 2.0
Median	3.0	3.0	3.0
Q3 , Max	5.0 , 10.0	5.0 , 10.0	5.0 , 10.0
Systolic blood pressure (mmHg)			
Non-missing	574	582	1156
Mean	115.0	114.1	114.5
Standard deviation	16.19	15.41	15.80
Min, Q1	85.0 , 103.0	80.0 , 103.0	80.0 , 103.0
Median	112.0	110.0	112.0
Q3 , Max	124.0 , 186.0	123.0 , 170.0	124.0 , 186.0
Diastolic blood pressure (mmHg)			
Non-missing	574	582	1156
Mean	72.3	71.9	72.1
Standard deviation	10.67	10.40	10.53
Min, Q1	45.0 , 64.0	38.0 , 65.0	38.0 , 64.5
Median	70.0	70.0	70.0
Q3 , Max	80.0 , 110.0	80.0 , 106.0	80.0 , 110.0
Heart rate (beats/min)			
Non-missing	574	582	1156
Mean	77.3	77.1	77.2
Standard deviation	12.30	11.83	12.06
Min, Q1	46.0 , 68.0	50.0 , 68.0	46.0 , 68.0
Median	76.0	78.0	77.0
Q3 , Max	85.0 , 115.0	85.0 , 120.0	85.0 , 120.0

* confirmed by Right Heart Catheterization

APPEARS THIS WAY ON ORIGINAL

The mean time since PAH diagnosis was 2.4 years. The PAH etiologies included idiopathic (56%), connective tissue disease (30%), congenital heart disease (10%), heritable (2%), drug or toxin induced (2%), and HIV infection (1%). Most patients were NYHA/WHO functional class II (46%) or III (53%). The remaining 2% was either class I or class IV.

Mean 6 minute walk distance at baseline was 353 m, mean Borg dyspnea index was 3.7, mean blood pressure was 114/72 mmHg, and mean heart rate was 77 beats/min.

The treatment groups were reasonably well balanced for these disease characteristics and it is unlikely that one group was different than the other at baseline.

Concomitant diseases at baseline

Frequently reported medical conditions included cardiac disorders (44% selexipag, 44% placebo), gastrointestinal (GI) disorders (38% selexipag, 38% placebo), and hypertension (32% selexipag, 29% placebo). Systemic sclerosis was the most common CTD (13% selexipag, 16.2% placebo) followed by systemic lupus erythematosus (9% selexipag, 7% placebo). Atrial fibrillation was reported by 6% of patients in the selexipag group and 5% in the placebo group. Atrial flutter was reported by 2% and 1% of patients in the selexipag and placebo groups, respectively.

PAH concomitant medications at baseline

The PAH medications subjects were taking at baseline are shown below by treatment group.

Reference ID: 3814728

Table 15-36 PAH specific medications concomitant at Baseline, FAS

ACT-293987, Protocols AC-065A302/AC-065A303
PAH specific medications concomitant at Baseline
Set: Full analysis set

	Selexipag N=574 n	%	Placebo N=582 n	%
No PAH specific medication concomitant at baseline	112	19.5%	124	21.3%
PAH specific medication concomitant at baseline	462	80.5%	458	78.7%
ERAs monotherapy	94	16.4%	76	13.1%
AMBRISENTAN	26	4.5%	20	3.4%
BOSENTAN	67	11.7%	56	9.6%
SITAXENTAN	1	0.2%	0	0.0%
PDE5-Inhibitors monotherapy	189	32.9%	185	31.8%
SILDENAFIL	164	28.6%	169	29.0%
TADALAFIL	23	4.0%	14	2.4%
VARDENAFIL	2	0.3%	2	0.3%
ERAs and PDE5 - Inhibitors	179	31.2%	197	33.8%
AMBRISENTAN-SILDENAFIL	44	7.7%	40	6.9%
AMBRISENTAN-TADALAFIL	13	2.3%	12	2.1%
BOSENTAN-SILDENAFIL	101	17.6%	115	19.8%
BOSENTAN-TADALAFIL	17	3.0%	22	3.8%
BOSENTAN-VARDENAFIL	2	0.3%	4	0.7%
SITAXENTAN-SILDENAFIL	2	0.3%	4	0.7%

ERA= Endothelin Receptor Antagonists, PDE5= phosphodiesterase type 5.
Table TCBPAH F - Produced by milotiel on 19JUN14 - Data dump of 12JUN2014

Overall, similar percentages of subjects in both treatment groups were receiving at least one PAH drug (81% selexipag and 79% placebo) and roughly 32% of subjects were receiving two PAH drugs. The treatment groups were reasonably well balanced.

Greater than 90% of patients in North America, Western Europe and Australia, including Israel, and Latin America were receiving a PAH-specific medication at baseline. This compares to approximately 70% in Asia and 55% in Eastern Europe, including Turkey, receiving such drugs at baseline

Most patients in North America (51–60%), Western Europe, Australia, and Israel (57–67%) were receiving treatment with 2 PAH-specific therapies.

Sildenafil was the most frequently reported PDE-5i used as monotherapy in Eastern Europe, including Turkey (36%), Asia (35–42%), and Latin America (66–69%).

Other PAH medications included drugs prescribed for supportive treatment of right heart failure. Approximately 78% of patients in both groups were receiving at least 1 PAH non-specific medication at baseline. The non-specific medications included oxygen (16% selexipag, 14% placebo), calcium channel blockers (24% selexipag, 22% placebo), digoxin (15% selexipag, 15% placebo), and diuretics (66% selexipag, 66% placebo).

Reference ID: 3814728

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance was evaluated by study drug accountability. Compliance < 80% at EOS visit was reported for 7% of patients in the selexipag group compared to 3% in the placebo group. In 2% of patients in the selexipag group and 2% in the placebo group study drug interruption for 3 days or more was not followed by a new up-titration.

In 8% of patients in the selexipag group and 5% in the placebo group, study drug was up-titrated between Week 12 and Week 26.

Efficacy Results – Primary Endpoint

Maintenance doses of selexipag

On the evening of Visit 1, patients were instructed to take the first dose of study drug (selexipag 200 µg or placebo). Study drug was to be up-titrated in weekly increments of 200 mcg bid and adjusted until the individual maximum tolerated dose was achieved for each patient up to Week 12. It was then continued at the individualized dose.

The individual maintenance dose (IMD), defined as the dose to which each patient was exposed for the longest duration, are shown in the table below by treatment group.

Table 15-38 Individual maintenance dose of selexipag and placebo in AC-065A302, FAS

ACT-293987, Protocols AC-065A302/AC-065A303
Individual maintenance dose of selexipag and placebo in AC-065A302
Set: Full analysis set

	Selexipag N=574 n	%	Placebo N=582 n	%
b.i.d. dose (or placebo equivalent)	572	99.7%	578	99.3%
0 mcg	14	2.4%	9	1.5%
200 mcg	68	11.8%	15	2.6%
400 mcg	65	11.3%	18	3.1%
600 mcg	62	10.8%	20	3.4%
800 mcg	82	14.3%	21	3.6%
1000 mcg	35	6.1%	27	4.6%
1200 mcg	42	7.3%	20	3.4%
1400 mcg	41	7.1%	55	9.5%
1600 mcg	163	28.4%	393	67.5%
Other than per protocol dosing regimen	2	0.3%	4	0.7%

IMD is defined as the selexipag or placebo b.i.d. dose to which each patient was exposed for the longest duration in the maintenance period, or, for patients who did not enter maintenance, as the highest tolerated selexipag or placebo b.i.d. dose to which each patient was exposed during the titration period.

Reference ID: 3814728

Only 28 % of the selexipag group had an IMD at the maximum dose compared to 67% of the placebo group. Many of the study patients could only tolerate doses of selexipag up 800ug.

Main analysis results
Primary objective was to demonstrate the effect of selexipag on time to first morbidity and/or mortality (MM) event in patients with PAH.

The table below shows the number and percent of subjects who were censored from baseline to up to 7 days after last drug intake by treatment arm.

Table 15-44 Reason for censoring time from randomization to first CEC-confirmed MM event up to 7 days after last study drug intake in AC-065A302 treatment period, FAS

ACT-293987, Protocols AC-065A302/AC-065A303
Reason for censoring Time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period
Set: Full analysis set

	Selexipag N=574 n	%	Placebo N=582 n	%
Censored observation	434	75.6%	370	63.6%
Reasons:				
Study completion with no CEC-confirmed M/M event	289	66.6%	252	68.1%
Patient discontinued (other reasons) with no CEC-confirmed M/M event	120	27.6%	80	21.6%
Patient had an event before 16AUG2011	15	3.5%	30	8.1%
Withdrawal of consent with no CEC-confirmed M/M event	8	1.8%	5	1.4%
Lost to follow up with no CEC-confirmed M/M event	2	0.5%	3	0.8%

CEC=Critical Event Committee.

A total of 45 patients (15 selexipag and 30 placebo) were censored for the main analysis because of an occurrence of an MM event up to August 16, 2011 (see amendment 4). The results for the primary endpoint with and without censoring of CEC-confirmed MM events up to August 16, 2011 were very similar.

The table below shows the number and percent of patients with a CEC-confirmed MM event up to 7 days after last study drug intake in the AC-065A302 treatment period (EOT + 7 days) by treatment group taking into account all patients.

Reference ID: 3814728

Table 11-4 Summary of type of first CEC-confirmed MM event up to 7 days after last study drug intake in AC-065A302 treatment period, analysis including CEC-confirmed MM events up to 16 August 2011, FAS

	Selexipag N=574 n	%	Placebo N=582 n	%
Patients with morbidity/mortality event	155	27.0%	242	41.6%
First morbidity/mortality event:				
Death	28	4.9%	18	3.1%
DEATH	28	4.9%	17	2.9%
HOSPITALIZATION-PAH / DEATH	0		1	0.2%
Hospitalization for PAH worsening	78	13.6%	109	18.7%
HOSPITALIZATION-PAH	54	9.4%	78	13.4%
DIS. PROGR. / HOSPITALIZATION-PAH	16	2.8%	21	3.6%
INIT. OF CHRONIC OXY. THERAPY / HOSPITALIZATION-PAH	4	0.7%	5	0.9%
DIS. PROGR. / INIT. OF CHRONIC OXY. THERAPY / HOSPITALIZATION-PAH	2	0.3%	2	0.3%
INIT. OF PARENTERAL PROST. THERAPY / HOSPITALIZATION-PAH	2	0.3%	3	0.5%
PAH worsening resulting in need for lung transplantation or balloon atrial septostomy	1	0.2%	2	0.3%
NEED FOR LUNG TX.	1	0.2%	2	0.3%
Parenteral prostanoid therapy or chronic oxygen therapy	10	1.7%	13	2.2%
INIT. OF PARENTERAL PROST. THERAPY	6	1.0%	7	1.2%
INIT. OF CHRONIC OXY. THERAPY	4	0.7%	4	0.7%
DIS. PROGR. / INIT. OF CHRONIC OXY. THERAPY	0		2	0.3%
Disease Progression	38	6.6%	100	17.2%
DIS. PROGR.	38	6.6%	100	17.2%

When more than one event have the same onset date, all event components are displayed.
CEC=Critical Event Committee.
Events with CEC-confirmed onset date up to 16 Aug 2011 are included as events.

There were 155 patients in the selexipag group and 242 patients in the placebo group who had a CEC-confirmed MM event up to EOT + seven days. In the time-to-event analysis, the hazard ratio for selexipag versus placebo for the occurrence of an MM event was 0.60 (99% CI: 0.46, 0.78, 1-sided unstratified log-rank $p < 0.0001$).

Compared to placebo, there were more deaths reported in the selexipag group (28, 5% compared to placebo 18, 3%) but fewer hospitalizations for worsening PAH (78, 14% selexipag versus 109, 19% placebo) and fewer with disease progression (38, 7% selexipag versus 100, 17%).

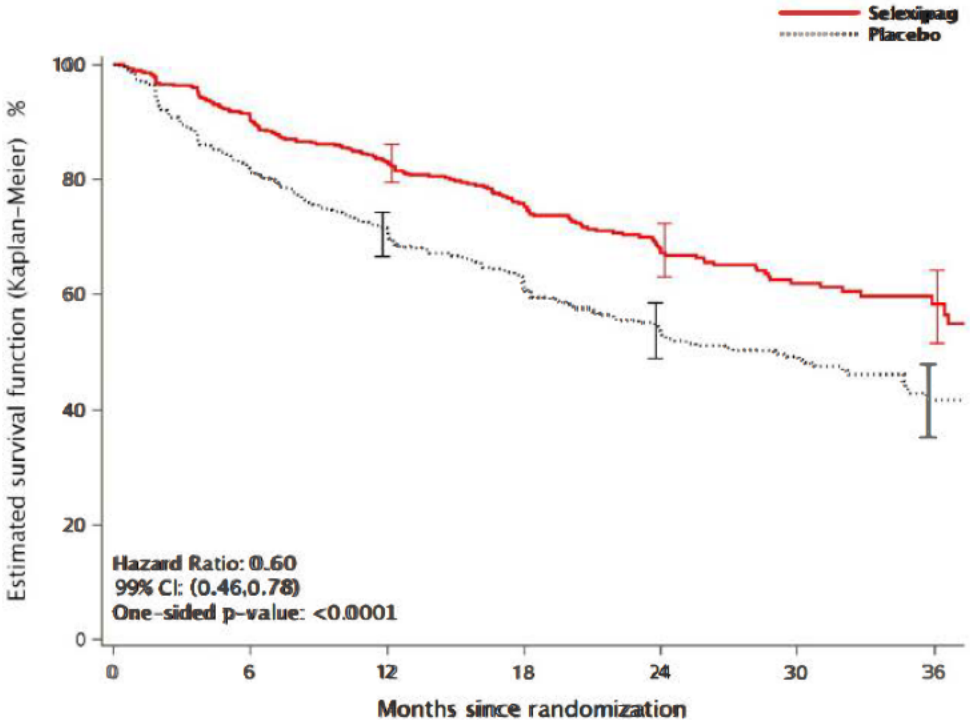
There were nearly similar number of events reported as 1) worsening PAH resulting in need for lung transplantation or atrial septostomy and 2) need for parenteral prostanoids therapy/chronic oxygen therapy.

The Kaplan-Meier estimates are shown below.

Reference ID: 3814728

Figure 11-3 Kaplan-Meier estimates of time from randomization to first CEC-confirmed MM event up to 7 days after last study drug intake in AC-065A302 treatment period, analysis including CEC-confirmed MM events up to 16 August 2011, FAS

ACT-293987, Protocols AC-065A302/AC-065A303
Time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period – Kaplan-Meier estimates
Set: Full Analysis Set



Selexipag patients:

at risk	574	455	361	246	171	101	40
event(s)	0	46	85	114	136	149	153
censored	0	73	128	214	267	324	381

Placebo patients:

at risk	582	433	347	220	149	88	28
event(s)	0	101	158	197	221	232	241
censored	0	48	77	165	212	262	313

Note: Bars on the graph show 95% confidence intervals of the estimates.
Events with CEC-confirmed onset date up to 16 Aug 2011 are included as events.

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The two curves start separating around month one.

A competing risk analysis using Gray's method is shown below.

Table 11-6 Competing risk analysis: first CEC-confirmed MM event up to 7 days after last study intake in AC-065A302 treatment period, supportive analysis counting CEC-confirmed events with onset date up to 16 August 2011 as events, FAS

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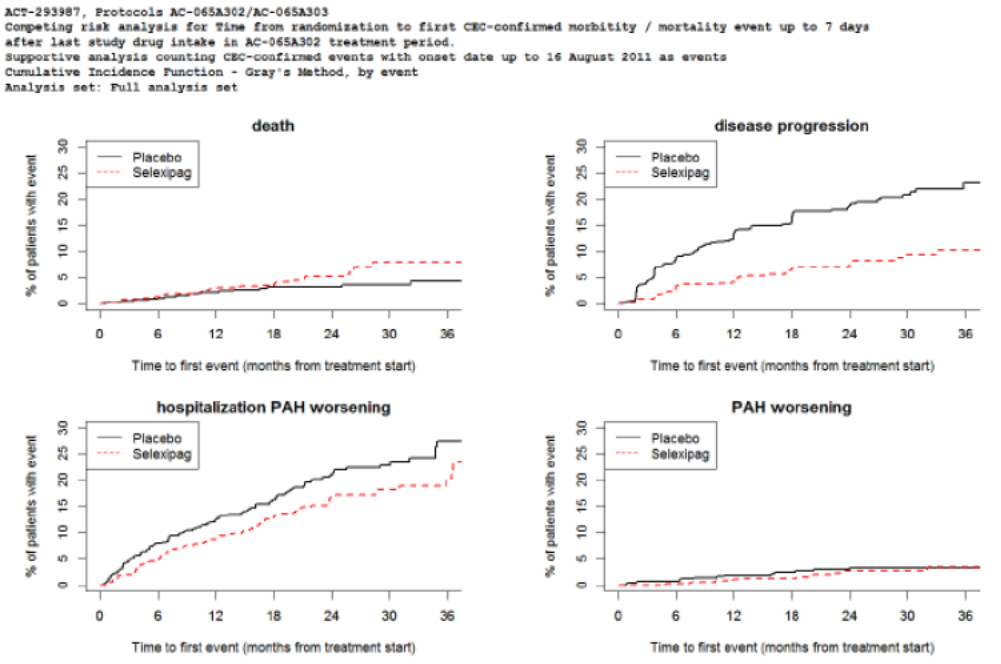
	Selexipag N=574	Placebo N=582	
Treatment differences (Gray's test)	chi-square	DF	p-value
Selexipag vs Placebo:			
death	3.0112	1	0.0827
hospitalization PAH worsening	4.2076	1	0.0402
PAH worsening	0.3864	1	0.5342
disease progression	27.8940	1	0.0000

Events with CEC-confirmed onset date up to 16 Aug 2011 are included as events.

The figures for the different types of MM events are shown below.

Figure 11-8 Cumulative incidence function for the first CEC-confirmed MM event up to 7 days after last study drug intake in AC-065A302 treatment period, supportive analysis counting CEC-confirmed events with onset date up to 16 August 2011 as events, FAS



Only disease progression and hospitalization for PAH worsening show a convincing superiority of selexipag compared to placebo.

Adjudication

Critical Event Committee (CEC)

The CEC adjudicated in a blinded manner all reported morbidity/mortality (MM) events. The committee was composed of 3 clinical experts who were not involved as investigators in the study.

Initially, event-adjudication was only performed to confirm the occurrence of an MM event. Following Global Protocol Amendment 6, the process was adjusted to adjudicate the following details:
i) the presence of an MM event,
ii) the type of endpoint component,
iii) the MM event onset date, and
iv) any PAH-association with a fatal outcome.

Information pertaining to typical prostacyclin-associated adverse events, if any, was removed from documentation made available to the CEC.

All events adjudicated prior to amendment 6 were submitted to the CEC for re-assessment according to the revised criteria and were re-adjudicated.

If there was a missing assessment the CEC was responsible for confirming or not confirming the event and the associated date for the analysis of the primary endpoint, using all available clinical data.

All MM events were re-adjudicated by the CEC prior to unblinding. The table below shows the results of the old and new CEC systems.

Reference ID: 3814728

Table 15-70 Event adjudication in old and new CEC system: agreement/ disagreement - all MM events reported by the investigator and submitted in both CEC systems

ACT-293987, Protocols AC-065A302/AC-065A303
Event adjudication in old and new CEC system: agreement/disagreement
Set: All morbidity/mortality events reported by the investigator and submitted in both CEC systems in study AC-065A302

Old versus new CEC system	Selexipag n	Selexipag %	Placebo n	Placebo %	Total n	Total %
Number of events	82		124		206	
Agreement	80	97.6%	116	93.5%	196	95.1%
As confirmed event	69	84.1%	107	86.3%	176	85.4%
As non-confirmed event	11	13.4%	9	7.3%	20	9.7%
Disagreement	2	2.4%	8	6.5%	10	4.9%
Confirmed as event in old CEC system but not confirmed in the new CEC system	0		2	1.6%	2	1.0%
Not confirmed as event in old CEC system but confirmed in the new CEC system	2	2.4%	6	4.8%	8	3.9%

CEC= Critical Event Committee. The original CEC system was replaced in November 2012 by a new CEC system recording more information. All events adjudicated in the old CEC system were re-adjudicated in the new CEC system.

For the total 206 events, 80/82 events (98%) in the selexipag group and 116/124 (94%) in the placebo group had an agreement recorded between the two CEC adjudication processes. A disagreement was recorded for the remaining 2 events in the selexipag and 8 events in the placebo group.

Investigator assessment versus CEC adjudication is shown in the table below.

Table 15-71 Agreement/disagreement between investigator and CEC (new CEC system) in assessing MM events, all MM events reported by the investigator in study AC-065A302

ACT-293987, Protocols AC-065A302/AC-065A303
Agreement/disagreement between investigator and CEC (new CEC system) in assessing morbidity/mortality events
Set: All morbidity/mortality events reported by the investigator in study AC-065A302

	Selexipag n	Selexipag %	Placebo n	Placebo %	Total n	Total %
Investigator vs. CEC assessment						
Number of events	203		303		506	
Agreement	166	81.8%	260	85.8%	426	84.2%
Disagreement	37	18.2%	43	14.2%	80	15.8%

CEC= Critical Event Committee.
Agreements include all CEC confirmed events, plus one case which was reported by the investigator as not being an event.

Reference ID: 3814728

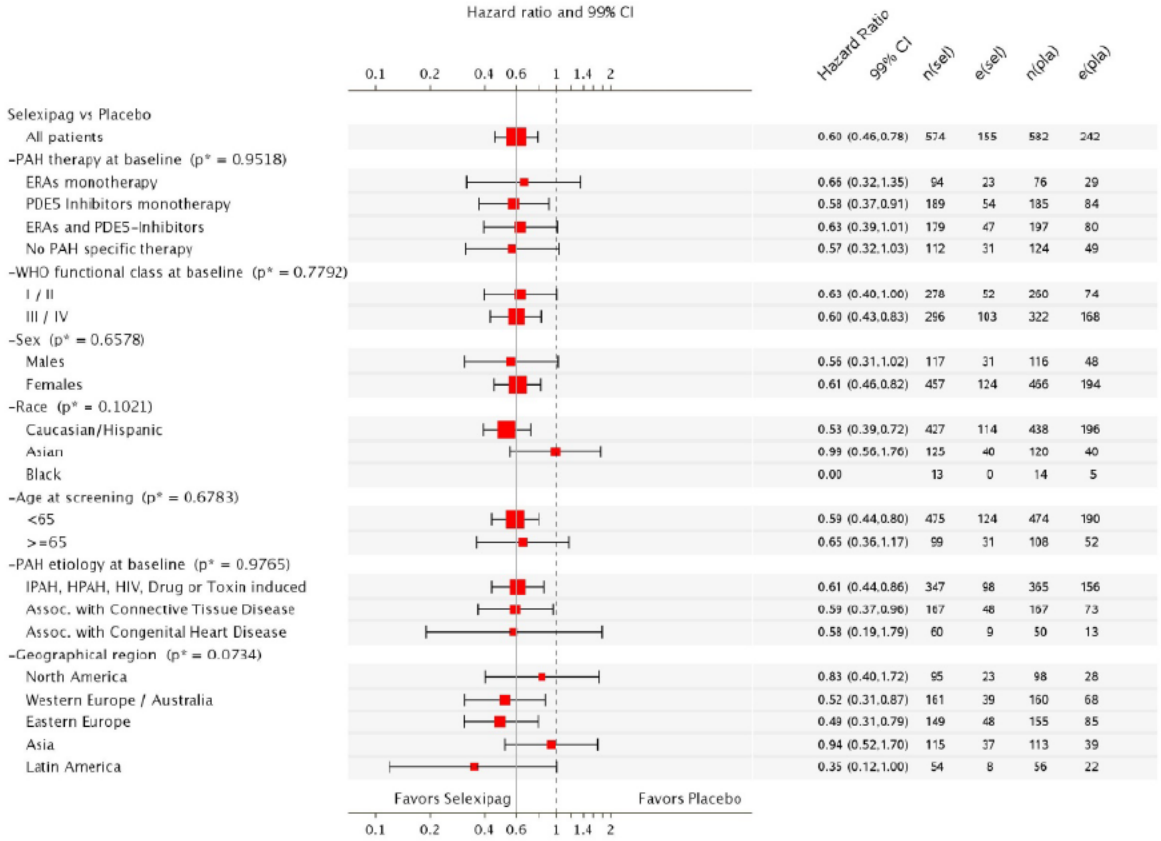
Of the 506 events, 426 (84%) were in agreement and 80 (16%) in disagreement between the investigator and CEC (using the new CEC process).

Subgroups

The figure below shows a forest plot for selected subgroups (PAH therapy at baseline, WHO functional class, sex, race, age at screening, PAH etiology, geographical region) regarding the primary endpoint.

Figure 11-7 Time from randomization to first CEC-confirmed MM event up to 7 days after last study intake in AC-065A302 treatment period - forest plot for subgroup analyses, FAS

ACT-293987, Protocols AC-065A302/AC-065A303
Time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period - forest plot for subgroup analyses
Set: Full Analysis Set



* = Interaction p-value. n(sel) = No. patients in Selexipag. e(sel) = No. patients with event in Selexipag. n(pla) = Number of patients in Placebo e(pla) = No. patients with event in Placebo.
Note: Race group Other is not displayed in analysis, as the population is less than 20. The vertical solid line references the overall treatment effect
Events with CEC-confirmed onset date up to 16 Aug 2011 are included as events.
Figure FMMTGRP_F - Produced by (b) (4) on 28JUL14 - Data dump of 12JUN2014

In none of these subgroups does selexipag appear to be worse than placebo. The effect of selexipag on several subgroups appears to be similar to placebo (ERAs monotherapy at

baseline, Asian population, ages ≥ 65years, etiology of PAH being congenital heart disease, populations in North America and China). Some of this could be attributed to small sample size.

By dose

The figure below shows the primary endpoint by IMD dose category (200-500 mcg bid, 600-1100 mcg bid, 1200-1600 mcg bid) of selexipag.

Reference ID: 3814728

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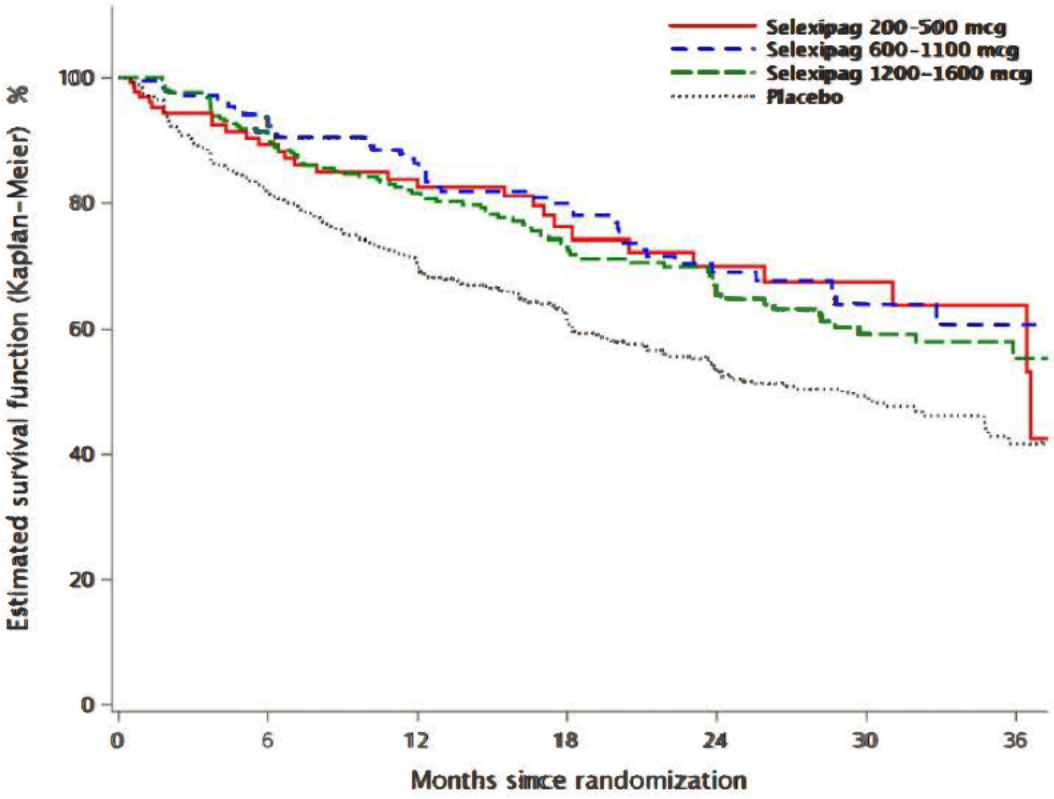
Figure 15-71 Time from randomization to first CEC-confirmed MM event up t 7 days after last study drug intake in AC-065A302 treatment peri by selexipag IMD, FAS (excluding patients randomized to selexip with IMD=0 or 'other')

ACT-293987, Protocols AC-065A302/AC-065A303
Time from randomization to first CEC-confirmed morbidity/mortality event up to 7 days after last study drug intake in AC-065A302 Treatment Period by selexipag individual maintenance dose (IMD)
Set: Full Analysis Set, excluding patients randomized to selexipag with IMD=0 or other



Selexipag IMD 200–500 mcg patients:							
at risk	133	84	68	41	29	19	9
event(s)	0	12	17	22	25	26	27
Selexipag IMD 600–1100 mcg patients:							
at risk	180	152	116	84	52	28	12
event(s)	0	11	22	30	40	43	44
Selexipag IMD 1200–1600 mcg patients:							
at risk	246	219	177	121	90	54	19
event(s)	0	21	44	60	69	78	80
Placebo patients:							
at risk	582	433	347	220	149	88	28
event(s)	0	101	158	197	221	232	241

Events with CEC-confirmed onset date up to 16 Aug 2011 are included as events.

Regardless of dose, selexipag patients were less likely to have a CEC-confirmed MM event compared to placebo patients.

Secondary endpoints

Walk distance

The absolute change from baseline at week 26 in 6MWD measured at trough is shown below by treatment group.

Table 11-7 Absolute change from Baseline to Week 26 in 6MWD at trough - main imputation algorithm for missing data, FAS

6-Minutes-Walking-Distance (m)	Selexipag N=574	Placebo N=582
Baseline		
Non-missing/imputed	574	582
Mean	358.5	348.0
Standard deviation	76.3	83.2
Min , Q1	90 , 318	50 , 299
Median	376.0	369.0
Q3 , Max	418 , 482	415 , 515
Week 26		
Non-missing/imputed	574	582
Mean	306.5	281.7
Standard deviation	170.0	173.8
Min , Q1	0 , 221	0 , 131
Median	370.0	346.0
Q3 , Max	432 , 617	413 , 650
Week 26 done but not at trough ^		
Total	29 5.1%	-
Missing value at Week 26		
Total imputed	114 19.9%	136 23.4%
Reason death*	25 4.4%	26 4.5%
Reason not death:		
Week 26 Visit done		
6MWT not done (reason not PAH related**)	11 1.9%	13 2.2%
6MWT not done for PAH reason*	0	0
Week 26 Visit not done**	78 13.6%	97 16.7%
Absolute change from baseline at Week 26		
Non-missing/imputed	574	582
Mean	-52.00	-66.26
Standard deviation	150.24	148.23
Min , Q1	-448.0 , -66.0	-438.0 , -120.0
Median	4.00	-9.00
Q3 , Max	35.0 , 260.0	25.0 , 262.0

Point estimate and two-sided 99% CI for location shift (1)	12.0 (1 , 24)	
Point estimate and two-sided 99% CI probability to obtain larger change for a patient treated with Selexipag (2)	0.549 (0.547 , 0.551)	
Non-parametric ANCOVA with covariate 6MWD at Baseline One-sided Wilcoxon-Mann-Whitney test statistic and p-value	2.786	0.0027

^ For patients with 6MWT performed not at trough, the value not at trough is used.
* imputed with 0 m. ** imputed with second worst rank value at Week 26.
For patients with 6MWT at Week 26 Visit not performed for PAH reasons, 0 m was entered in the CRF.
(1) Hodges-Lehmann method (2) based on the Mann-Whitney statistic

The mean baseline walk distance was slightly higher for selexipag (358.5 m) compared to placebo (348.0m). At week 26, both treatment groups had a decrease in mean walk distance from baseline, but it was somewhat less for selexipag.

Mean changes from baseline at week 26 were -52m for selexipag compared to -66m for placebo. If week 26 6MWD was not performed, the 6MWD was imputed from the second worst rank value. This was done for 14% of selexipag patients and 17% of placebo patients.

Reference ID: 3814728

Although 6MWD at week 26 was to be recorded at trough drug concentrations (12 hours after last dose), this did not occur for 29 selexipag subjects. The value for the walk test used for the 29 patients was one that was obtained at trough even though it was not at week 26.

Reasons for missing 6MWD

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 n	%	Placebo N=582 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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The incidence rates for missing walk data at week 26 were roughly the same for both treatment groups (20% for selexipag and 23% for placebo). Reasons for the missing data included death (similar for both groups), study drug discontinued with CEC-confirmed MM event (14% selexipag, 41% placebo), study drug discontinued with no CEC-confirmed MM event (54% selexipag, 27% placebo), withdrawal of consent or lost to follow up (28% selexipag, 17%). There were a few subjects who fell into other categories.

Evaluating 6MWD for dose relationship

The table below shows the walk distance data by selexipag dose group (low: 200-500 ug bid, mid: 600-1100 ug bid, high: 1200-1600 ug bid) and placebo.

Reference ID: 3814728

Table 15-159 Absolute change from Baseline to Week 26 in 6MWD at trough by categorical selexipag IMD in AC-065A302 - main imputation algorithm for missing data, FAS (excluding patients randomized to selexipag with IMD=0 or 'other')

ACT-293987, Protocols AC-065A302/AC-065A303
Absolute change from Baseline to Week 26 in 6MWD at trough by categorical selexipag IMD in AC-065A302.
Main imputation algorithm for missing data
Set: Full Analysis Set, excluding patients randomized to selexipag with IMD=0 or other

6-Minute-Walking-Distance (m)	Selexipag IMD 200 - 500 mcg N=133	Selexipag IMD 600 - 1100 mcg N=180	Selexipag IMD 1200 - 1600 mcg N=246	Placebo N=582
Baseline				
Non-missing/imputed	133	180	246	582
Mean	351.8	361.3	362.3	348.0
Standard deviation	81.1	73.7	74.1	83.2
Min , Q1	156 , 300	90 , 327	105 , 325	50 , 299
Median	369.0	378.5	379.0	369.0
Q3 , Max	420 , 471	420 , 463	415 , 482	415 , 515
Week 26				
Non-missing/imputed	133	180	246	582
Mean	236.1	317.7	354.5	281.7
Standard deviation	193.0	162.4	133.2	173.8
Min , Q1	0 , 10	0 , 243	0 , 312	0 , 131
Median	297.0	381.0	391.0	346.0
Q3 , Max	405 , 617	431 , 553	444 , 540	413 , 650
6MWT at Week 26 done not at trough ^				
Total	5 3.8%	11 6.1%	13 5.3%	-
Missing value at Week 26				
Total imputed	48 36.1%	31 17.2%	20 8.1%	136 23.4%
Reason death*	9 6.8%	8 4.4%	6 2.4%	26 4.5%
Reason not death:				
Week 26 Visit done				
6MWT not done (reason not PAH related**)	2 1.5%	7 3.9%	2 0.8%	13 2.2%
6MWT not done for PAH reason*	0	0	0	0
Week 26 Visit not done**	37 27.8%	16 8.9%	12 4.9%	97 16.7%

6-Minute-Walking-Distance (m)	Selexipag IMD 200 - 500 mcg N=133	Selexipag IMD 600 - 1100 mcg N=180	Selexipag IMD 1200 - 1600 mcg N=246	Placebo N=582
Absolute change from baseline at Week 26				
Non-missing/imputed	133	180	246	582
Mean	-115.68	-43.66	-7.75	-66.26
Standard deviation	178.06	146.28	105.79	148.23
Min , Q1	-440.0 , -275.0	-441.0 , -42.0	-448.0 , -16.0	-438.0 , -120.0
Median	-20.00	8.50	15.00	-9.00
Q3 , Max	20.0 , 176.0	35.0 , 222.0	43.0 , 260.0	25.0 , 262.0

^ For patients with 6MWT performed not at trough, the value not at trough is used.
* imputed with 0 m. ** imputed with second worst rank value at Week 26 in the Full Analysis Set.
For patients with 6MWT at Week 26 Visit not performed for PAH reasons, 0 m was entered in the CRF.
IMD = individual maintenance dose. IMD is defined as the selexipag b.i.d. dose to which patient was exposed for the longest duration in the maintenance period or as the highest tolerated selexipag b.i.d. dose to which patient was exposed during the titration period.
Table TWISDSE2_F - Produced by (b) (4) on 25JUL14 - Data dump of 12JUN2014
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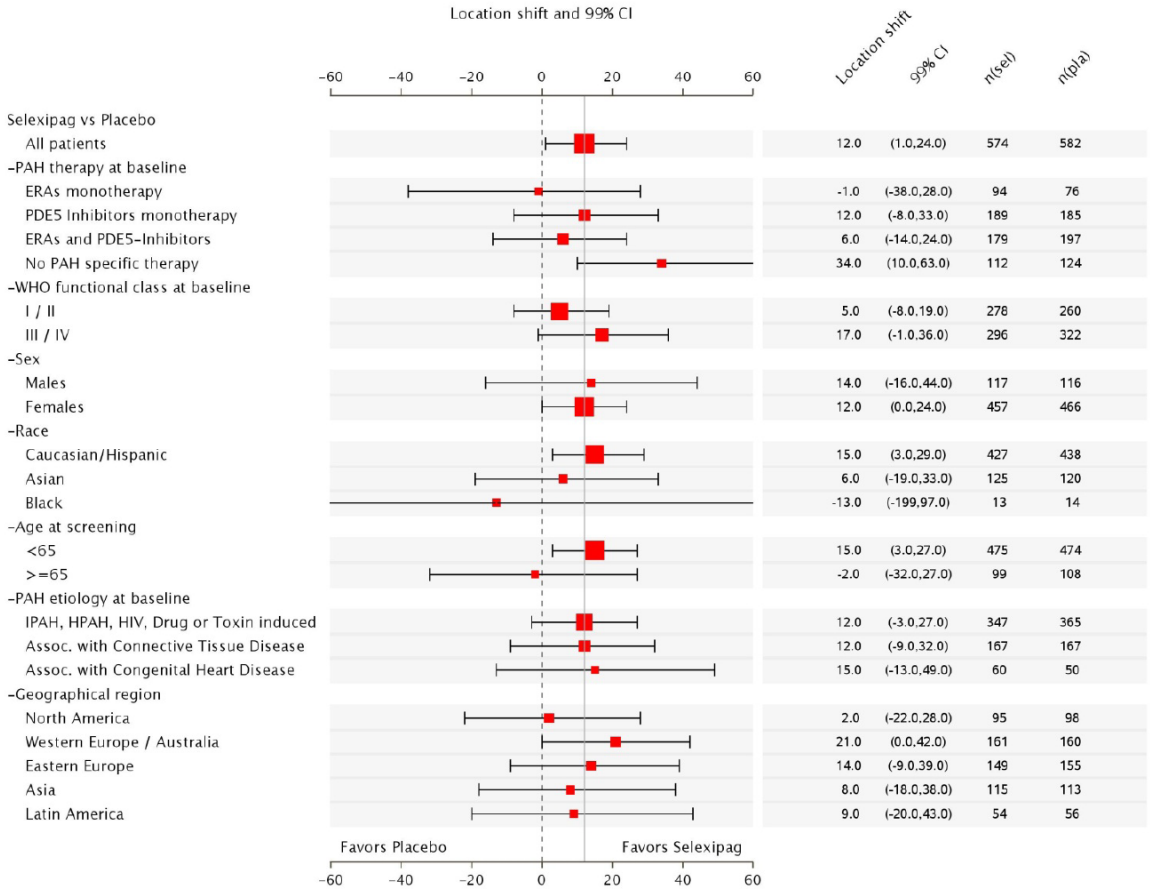
The mean baseline walk distances were similar across the dose groups and somewhat lower than that for placebo. The absolute changes from baseline at week 26 were all negative (meaning patients walked less) but there was less of a drop off as the dose increased (-116 m, -44m, -8m for low, mid. and high selexipag doses, respectively).

Walk distance and subgroups

The walk distance results by selected subgroups are shown in the figure below.

Figure 15-39 Absolute change from Baseline to Week 26 in 6MWD at trough - forest plot for subgroup analyses, FAS

ACT-293987, Protocols AC-065A302/AC-065A303
Absolute change from Baseline to Week 26 in 6-Minute-Walk-Distance at trough - forest plot for subgroup analyses
Set: Full Analysis Set



n(sel) = No. patients in Selexipag. n(pla) = Number of patients in Placebo
Note: Race group Other is not displayed in analysis, as the population is less than 20. The vertical solid line references the overall treatment effect

Most of the groups had results that tended to favor selexipag, most markedly for patients not on PAH background therapy. The effect in North America was nearly zero, reflecting what was found for the primary endpoint.

Absence of worsening from Baseline in NYHA/WHO FC at Week 26

The results are shown in the table below.

Reference ID: 3814728

Table 11-8 Absence of worsening from Baseline in NYHA/WHO functional class at Week 26 - main imputation algorithm for missing data, FAS (excluding patients with baseline FC IV)

		Week 26													
Baseline	n	I		II		III		IV		*missing		Absence of Worsening		Worsening	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%
Selexipag (N=571)															
I	4	4	100.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	4	100.0%	0	0.0%
II	274	7	2.6%	207	75.5%	21	7.7%	0	0.0%	39	14.2%	214	78.1%	60	21.9%
III	293	1	0.3%	67	22.9%	158	53.9%	10	3.4%	57	19.5%	226	77.1%	67	22.9%
All	571	12	2.1%	274	48.0%	179	31.3%	10	1.8%	96	16.8%	444	77.8%	127	22.2%
Placebo (N=574)															
I	5	4	80.0%	0	0.0%	0	0.0%	0	0.0%	1	20.0%	4	80.0%	1	20.0%
II	255	7	2.7%	197	77.3%	16	6.3%	0	0.0%	35	13.7%	204	80.0%	51	20.0%
III	314	4	1.3%	37	11.8%	181	57.6%	14	4.5%	78	24.8%	222	70.7%	92	29.3%
All	574	15	2.6%	234	40.8%	197	34.3%	14	2.4%	114	19.9%	430	74.9%	144	25.1%

Statistic		
Two-sided Cochran-Mantel-Haenszel test statistic stratified by modified NYHA/WHO functional class at Baseline and p-value	1.147	0.2843
Two-sided Breslow-Day test statistic and p-value	3.304	0.1916
Point estimate and two-sided 99% CI for the common odds ratio	1.161	(0.811 , 1.664)

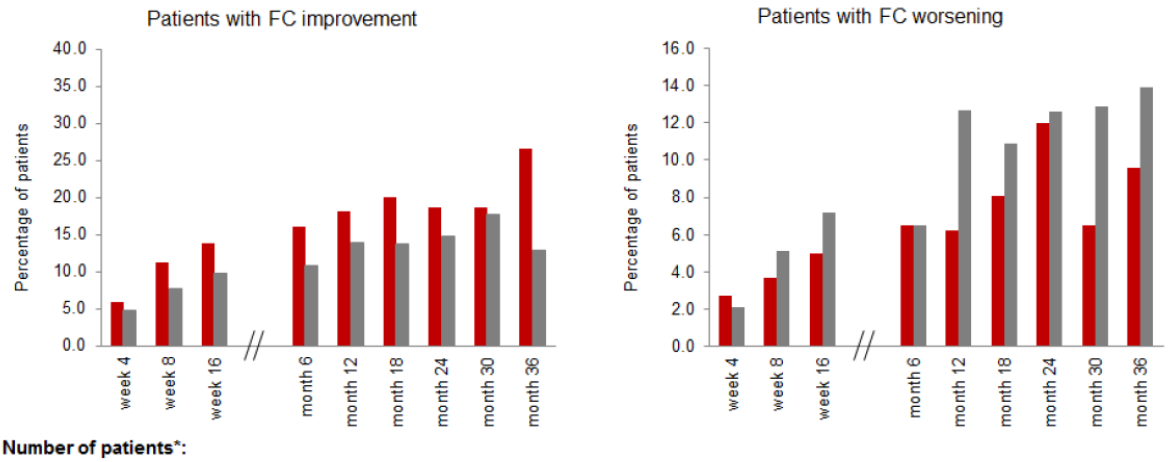
* Missing data at Week 26 are classified as "Worsening", and included into the analysis.

Similar percentages of patients had absence of worsening of NYHA/WHO class at week 26 regardless of treatment group.

The figure below shows the change from baseline in modified NYHA/WHO functional class (FC) by visit and treatment class.

Figure 11-10 Change from Baseline in modified NYHA/WHO FC at regular visits, FAS (excluding patients with baseline FC IV)

Set: AC065A302 full analysis set



Number of patients*:

	week 4	week 8	week 16	month 6	month 12	month 18	month 24	month 30	month 36
Selexipag	562	539	504	478	435	334	241	170	94
Placebo	566	554	512	464	416	311	215	163	101

*Patients with non-missing values;

The left sided figure shows the percentage of patients with improvement in FC. There is a higher percentage of patients randomized to selexipag with improvement compared to placebo at each visit for which FC was recorded.

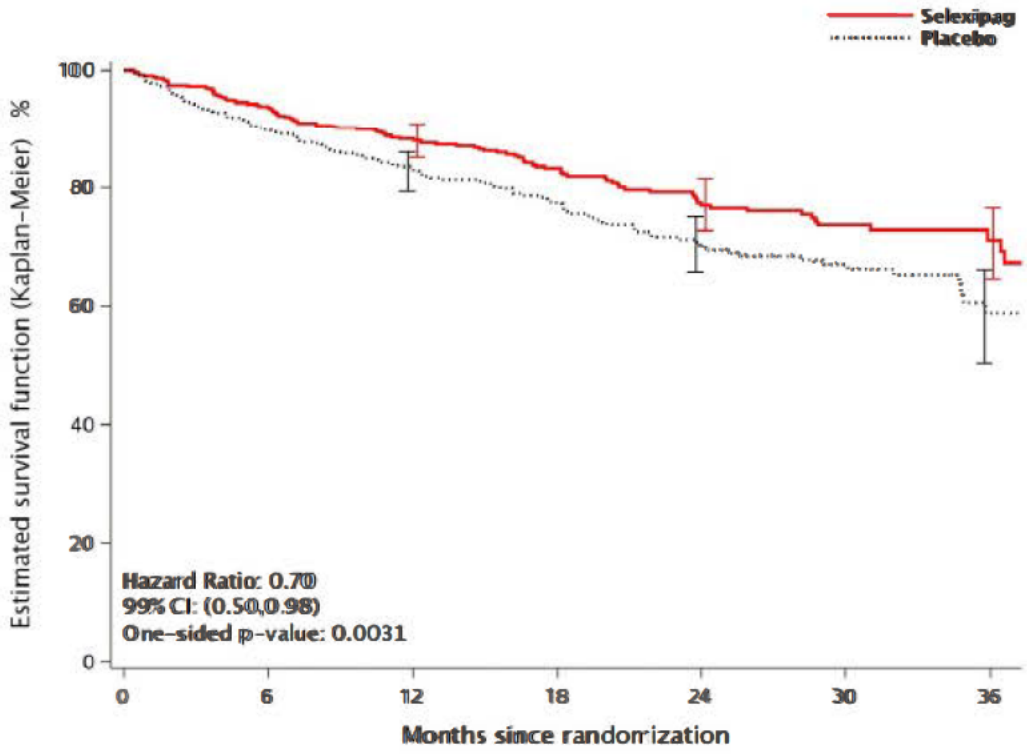
The right sided figure shows the percentage of patients with FC worsening. There is a lower percentage of patients randomized to selexipag with worsening compared to placebo at each visit for which FC was recorded.

Time from randomization to first of CEC-confirmed death due to PAH or CEC-confirmed hospitalization due to PAH worsening up to 7 days after last study drug intake in AC-065A302 treatment period

The figure below shows the results of this secondary endpoint.

Figure 15-42 Time from randomization to first CEC-confirmed death due to PAH or CEC-confirmed hospitalization due to PAH worsening up to 7 days after last study drug intake in AC-065A302 treatment period - Kaplan-Meier estimates, FAS

ACT-293987, Protocols AC-065A302/AC-065A303
Time from randomization to CEC-confirmed death due to PAH or first CEC-confirmed hospitalization due to PAH worsening up to 7 days after last study drug intake in the AC-065A302 Treatment Period.
Kaplan-Meier estimates
Set: Full Analysis Set



Selexipag patients:							
at risk	574	457	364	250	172	102	40
event(s)	0	32	58	76	91	98	100
censored	0	85	152	248	311	374	434

Placebo patients:							
at risk	582	437	351	227	152	89	28
event(s)	0	56	86	106	123	130	136
censored	0	89	145	249	307	363	418

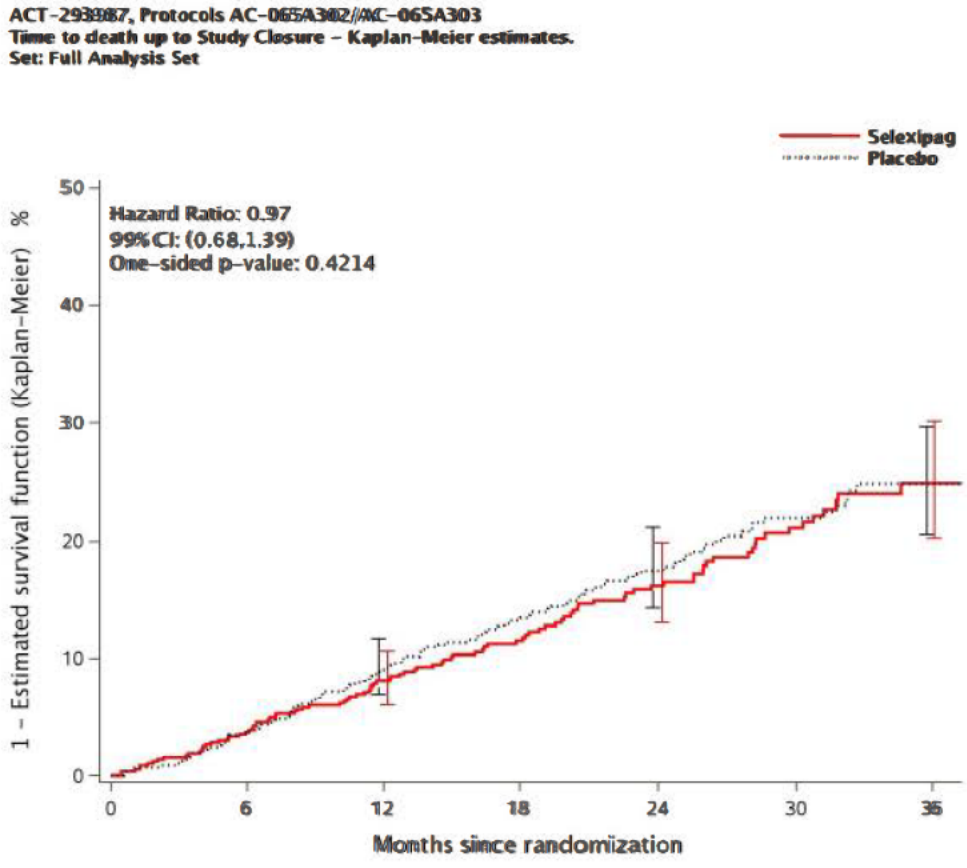
Note: Bars on the graph show 95% confidence intervals of the estimates.

The hazard ratio for selexipag versus placebo for the first occurrence of death due to PAH or hospitalization due to PAH worsening up to 7 days after the last intake of study drug was 0.70 (99% CI: 0.50, 0.98, 1-sided unstratified log-rank p = 0.0031).

Time from randomization to death of all causes up to study closure

This secondary endpoint is shown in the figure below.

Figure 11-13 Kaplan-Meier estimates of time to death up to Study closure, FAS



Selexipag patients:

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

Placebo patients:

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

Note: Bars on the graph show 95% confidence intervals of the estimates.
Death with onset date up to 16 Aug 2011 are included as death.
Figure FTDSTI_F – Produced by (b) (4) *on 29SEP14 - Data dump of 12JUN2014*

In the main analysis in the FAS, the hazard ratio for selexipag versus placebo for the time to death up to Study closure was 0.97 (99% CI: 0.68, 1.39, 1-sided unstratified log-rank p = 0.4214). Selexipag does not appear to have an impact on mortality.

Absolute change from Baseline to Week 26 in CAMPHOR 'Symptoms' and sub-scale 'Breathlessness'

To assess PH-specific Quality of Life (QoL), the CAMPHOR (Cambridge Pulmonary Hypertension Outcome Review) questionnaire consisting of 3 sections: Symptoms (with sub-scales related to Energy, Breathlessness, and Mood), Activity, and QoL, was completed by patients in countries where a validated translation of the questionnaire was available. The CAMPHOR 'Symptoms' score can range from 0 (good) to 25 (poor). Non-missing/imputed values were available for a total of 239 patients in the selexipag group and 240 patients in the placebo group. There was no difference between selexipag and placebo for either one of these endpoints.

Data Quality and Integrity – Reviewers' Assessment

The quality of this submission and the studies conducted in support of the NDA are as expected. A routine DSI inspection was requested for study AC-065A302. No major violations were discovered.

6.2 Study NS-304/-02

Title

A multicenter, multinational, open-label, single-dose, acute hemodynamic study followed by a multicenter, multinational, randomized, double-blind, parallel-group, placebo-controlled study to assess the safety, tolerability, pharmacokinetics, and preliminary efficacy (proof-of-concept) of ACT-293987(selexipag) in the treatment of pulmonary arterial hypertension in subjects aged 18 years and over

Investigators/Center

This study was conducted at seven centers in Europe (one center per country in Austria, Belgium, France, Germany, Hungary, Italy, and Poland).

Objectives

Acute hemodynamic period: The primary objective was to evaluate the effect of the drug on right heart catheterization parameters (pulmonary vascular resistance [PVR], systemic vascular resistance [SVR], and PVR/SVR) after a single oral dose of selexipag.

Double-blind treatment period: The primary objective was a proof-of-concept assessment of the efficacy (change in PVR from baseline at Week 17) of selexipag as add-on therapy in PAH patients compared with placebo. The secondary objective was to assess efficacy using the 6-min walk test (6MWT), proportion of patients with aggravation of PAH, and right heart catheterization parameters other than PVR. The tertiary objective was to assess efficacy using New York Heart Association (NYHA) functional class, Borg dyspnea score, plasma NT pro-brain natriuretic peptide (NT pro-BNP) concentration, and echocardiographic parameters.

Reference ID: 3814728

Exploratory analyses were to include preliminary assessment of the dose-effect relationship in the changes in the primary, secondary, and tertiary efficacy variables, the safety and tolerability of selexipag, and plasma concentrations of selexipag and ACT-333679 at Weeks 5 and 17 in PAH patients.

Study Design

A multicenter, multinational, Phase 2a study consisting of two periods: an open-label, single-dose, acute hemodynamic testing period followed by a randomized, double-blind, placebo-controlled, parallel-group treatment period. The study consisted of a screening visit, acute hemodynamic testing following a single dose of selexipag, and a 21-week double-blind treatment period. Patients had the option to continue in a following open-label extension study, and those who did not continue were followed-up 30 days after the last visit.

Number of Patients

44 patients were planned and 43 patients were randomized (33 were treated with selexipag and 10 patients received placebo).

Main Criteria for Inclusion

-Male or female,
-18 years of age with symptomatic PAH despite treatment with anticoagulants, calcium channel blockers, diuretics, cardiac glycosides, supplemental oxygen, endothelin-receptor antagonists, and/or phosphodiesterase type-5 inhibitors and having a PVR > 400 dyn·s/cm^5 and two 6-min walk tests between150 and 500 m (inclusive) and within ± 15%.

Trial Drug Dose / Route /Regimen / Duration

Acute hemodynamic period: single dose of selexipag (200 ug for the first 12 patients and 400 ug for remaining patients, based on safety assessment of the first 12 patients)

Double-blind treatment period: Each patient was started at 200 ug b.i.d. and up-titrated in 200 ug increments to the final optimized dose by Day 35 with a maximum dose of 800 ug b.i.d. (i.e., up-titration to 400 ug b.i.d. on Day 3, 600 ug b.i.d. on Day 7, and 800 ug b.i.d. on Day 21 if well tolerated)

Efficacy

Primary endpoints:
Acute hemodynamic period – Change in PVR from baseline to 4 hours after the single selexipag dose
Double-blind treatment period – Change in PVR from baseline to Week 17

Secondary endpoints:
Change in 6-min walk test from baseline to Week 17
Patients (proportion) with aggravation of PAH

Reference ID: 3814728

Changes in right heart catheterization parameters other than PVR from baseline to Week 17

Tertiary endpoints:
Changes from baseline to Week 17 in
– NYHA functional class
– Borg dyspnea score
– plasma NT pro-BNP concentration
– echocardiography parameters

Patient Disposition:
The study population was 81% female and 88% Caucasian, with a median age of 57 years (range 19 to 80 years).

Reference ID: 3814728

Table 5 Summary of demographic characteristics, all-treated DB set

ACT-293987, Protocol: NS-304/-02
Summary of demographic characteristics
Set: All-treated DB

	Placebo N=10	ACT-293987 N=33	Total N=43
SEX [n (%)]			
n	10	33	43
Males	2 20.0%	6 18.2%	8 18.6%
Females	8 80.0%	27 81.8%	35 81.4%
AGE (years)			
n	10	33	43
Mean	53.8	54.8	54.6
Standard deviation	16.3	16.8	16.5
Median	54.0	58.0	57.0
Q1 , Q3	46.0 , 61.0	43.0 , 70.0	43.0 , 70.0
Min , Max	25.0 , 80.0	19.0 , 80.0	19.0 , 80.0
WEIGHT (kg)			
n	10	33	43
Mean	70.6	68.7	69.1
Standard deviation	13.9	12.4	12.6
Median	69.2	65.0	66.8
Q1 , Q3	58.5 , 86.0	60.0 , 78.0	60.0 , 79.0
Min , Max	51.6 , 90.0	51.0 , 100.0	51.0 , 100.0
HEIGHT (cm)			
n	10	33	43
Mean	161.5	162.5	162.3
Standard deviation	7.9	9.1	8.7
Median	161.0	162.0	162.0
Q1 , Q3	155.0 , 167.0	158.0 , 168.0	157.0 , 168.0
Min , Max	150.0 , 176.0	144.0 , 183.0	144.0 , 183.0
BMI (kg/cm2)			
n	10	33	43
Mean	27.1	26.0	26.2
Standard deviation	5.6	4.0	4.4
Median	24.7	25.3	25.2
Q1 , Q3	22.7 , 31.6	23.2 , 27.2	23.1 , 29.8
Min , Max	21.0 , 37.9	19.9 , 36.0	19.9 , 37.9
ETHNIC ORIGIN [n (%)]			
n	10	33	43
Caucasian	9 90.0%	29 87.9%	38 88.4%
Hispanic	-	2 6.1%	2 4.7%
Asian	-	2 6.1%	2 4.7%
Other	1 10.0%	-	1 2.3%

PAH etiology was idiopathic in 72% of patients and related to collagen vascular disease in 14%.

Reference ID: 3814728

Table 6 Summary of etiology of PAH, all-treated DB set

ACT-293987, Protocol: NS-304/-02
Summary of etiology of pulmonary arterial hypertension
Set: All-treated DB

	Placebo N=10	ACT-293987 N=33
Time from PAH diagnosis in years		
n	10	33
Mean	4.0	5.5
Standard deviation	3.1	6.1
Median	2.7	3.2
Q1 , Q3	1.3 , 6.8	1.3 , 8.0
Min , Max	0.5 , 8.8	0.3 , 27.1
Number of pts with type of pulmonary arterial hypertension		
n	10	33
IDIOPATHIC PULMONARY ARTERIAL HYPERTENSION	7 70.0%	24 72.7%
COLLAGEN-VASCULAR DISEASE	2 20.0%	4 12.1%
ANOREXIGEN USE	-	2 6.1%
CORRECTED CONGENITAL VITIUM	-	2 6.1%
FAMILIAL PULMONARY ARTERIAL HYPERTENSION	1 10.0%	1 3.0%

pts=patients

All patients completed the acute hemodynamic period, with 12 receiving 200 ug and 31 receiving 400 ug selexipag.

All patients started double-blind treatment; 2 (6%) patients on active treatment were discontinued prematurely (1 (3%) because of hospitalization for worsening of PAH and 1 (3%) because of adverse event) and 1 (10%) on placebo due to hospitalization for worsening of PAH. All patients were included in the all-treated and safety analysis sets.

Table 3 Summary of the reasons for premature discontinuation of study treatment, all-treated DB set

ACT-293987, Protocol: NS-304/-02
Summary of reasons for premature discontinuation of study treatment
Set: All-treated DB

Reason for premature discontinuation	Placebo N=10 n	%	ACT-293987 N=33 n	%
Total pts with at least one reason	1	10.0%	2	6.1%
HOSPITALISATION	1	10.0%	1	3.0%
ADVERSE EVENT	-		1	3.0%

DB = double-blind, pts = patients.

All patients in the study were NYHA functional class II or III at baseline, with the selexipag group having a higher proportion of patients in class II than the placebo group (44% vs 20%).

Reference ID: 3814728

Efficacy Results

Final dose and duration of treatment

Among patients receiving selexipag, the final dosage was:
-800 ug b.i.d. for 14 patients (42%),
-600 ug b.i.d for seven patients (21%),
-400 ug b.i.d. for six patients (18%),
-200 µg b.i.d. for four patients (12.1%), and
-missing for the two patients who were discontinued prematurely.

Among patients on placebo, the final optimized dosage was 800 ug b.i.d. for all except for one patient who was discontinued on Day 61 and had a missing final optimized dosage.

The mean treatment exposure was longer for the selexipag group (143.3 days) compare to placebo group (135.1 days).

Table 14 Summary of double-blind treatment exposure, all-treated DB set

ACT-293987, Protocol: NS-304/-02
Summary of double-blind treatment exposure
Set: All-treated DB

	Placebo N=10	ACT-293987 N=33
Total Exposure (days)		
n	10	33
Mean	135.1	143.3
Standard deviation	27.4	28.6
Median	146.0	149.0
Q1 , Q3	131.0 , 149.0	145.0 , 155.0
Min , Max	61.0 , 152.0	17.0 , 176.0

Table TEXPS_TDB - Produced by petratd on 03JUL09 - Data dump of 03JUL09
(Page 1/1)

Concomitant PAH medications

The most common previous and/or concomitant treatments were bosentan and sildenafil (65% and 63% of patients, respectively).

Results

Cardiac hemodynamics

The single oral dose of selexipag administered during acute hemodynamic testing was not associated with an effect on PVR, whether the patient received a 200- or 400-ug dose, and there were no relevant treatment effects on other right heart catheterization parameters, including SVR.

Reference ID: 3814728

After 17 weeks of twice-daily treatment up-titrated to the patient's optimized dose, a 30% geometric mean decrease in PVR (95% CL -44.7%, -12.2%; P = 0.0045, Wilcoxon rank-sum test) was observed in patients treated with selexipag compared with placebo (main analysis). Similar results were obtained in the supportive analysis on the all-treated DB set -33.0%, 95% CL -47.0, -15.2; P = 0.0022, Wilcoxon rank-sum test).

Table 28 PVR: Change from baseline to Week 17 during the double-blind treatment period, all-treated DB set

ACT-293987, Protocol: NS-304/-02
Change from baseline to Week 17 in Pulmonary Vascular Resistance during the double-blind study
Set: All-treated DB

PVR (dyn*s/cm^5)

	Placebo N=10	ACT-293987 N=33
Baseline		
n	10	32
Mean	867.2	948.6
Standard deviation	379.3	428.0
Standard error	120.0	75.7
95% CL of mean	595.8 , 1138.6	794.3 , 1102.9
Median	771.5	829.0
95% CL of median	606.0 , 1080.0	719.0 , 971.5
Q1 , Q3	638.0 , 967.0	677.0 , 1225.0
Min , Max	524.0 , 1827.0	394.0 , 2167.0
WEEK 17		
n	10	32
Mean	1090.8	818.8
Standard deviation	421.3	416.9
Standard error	133.2	73.7
95% CL of mean	789.4 , 1392.2	668.5 , 969.1
Median	1042.0	719.5
95% CL of median	560.0 , 1741.0	591.0 , 926.0
Q1 , Q3	868.0 , 1290.0	521.0 , 953.0
Min , Max	558.0 , 1788.0	304.0 , 1788.0
Change from Baseline to WEEK 17		
n	10	32
Mean	223.6	-129.8
Standard deviation	355.4	309.7
Standard error	112.4	54.8
95% CL of mean	-30.7 , 477.9	-241.4 , -18.1
Median	124.0	-156.5
95% CL of median	-46.0 , 395.0	-208.0 , -17.0
Q1 , Q3	34.0 , 251.0	-274.5 , 23.0
Min , Max	-86.0 , 1150.0	-806.0 , 962.0
Percent ratio WEEK 17/Baseline		
n	10	32
Geometric Mean	125.5	84.1
95% CL of geometric mean	99.5 , 158.3	75.0 , 94.4
TREATMENT EFFECT		
Percent change (*)		-33.0
95% CL of percent change (*)		-47.0 , -15.2
p-value WIlcoxon rank sum test		0.0022
p-value t-test (†)		0.0014

CL=confidence limits.
(*) Percent change over Placebo = (ratio of geometric means - 1) * 100
(†) on log-transformed data.

Reference ID: 3814728

At Week 17, PVR (geometric mean and 95% CL) in the active and placebo groups, respectively, was 80.7% (72.8, 89.6; n = 29) and 115.9% (106.5, 126.1; n = 6) of baseline values. The decrease in PVR with selexipag was associated with an increase in cardiac index (median treatment effect 0.41 L/min/m2, 95% CL 0.10, 0.71), a decrease in SVR (median treatment effect -427 dyn·s/cm5, 95% CL -668.3, -134.5). The other RHC parameters did not show treatment effects.

6MWD

The mean baseline walk distance was longer for the selexipag group (394.7 m) compared to placebo (350.3 m). A mean increase in 6-min walk distance from baseline to Week 17 was observed with selexipag compared with placebo (treatment effect 24.2 m, 95% CL -23.7, 72.2).

Reference ID: 3814728

Table 9 Walk distance: Change from baseline to Week 17 during the double-blind treatment period, all-treated DB set

ACT-293987, Protocol: NS-304/-02
Change from baseline to Week 17 in walked distance during the double-blind study
Set: All-treated DB

Walk distance (meters)

	Placebo N=10	ACT-293987 N=33
Baseline		
n	10	32
Mean	350.3	394.7
Standard deviation	123.5	72.0
Standard error	39.1	12.7
95% CL of mean	261.9 , 438.7	368.7 , 420.6
Median	390.5	409.5
95% CL of median	215.0 , 465.0	368.0 , 450.0
Q1 , Q3	250.0 , 459.0	356.5 , 453.5
Min , Max	150.0 , 492.0	243.0 , 498.0
WEEK 17		
n	10	32
Mean	350.7	419.3
Standard deviation	139.6	106.3
Standard error	44.2	18.8
95% CL of mean	250.8 , 450.6	381.0 , 457.7
Median	378.5	407.5
95% CL of median	238.0 , 487.0	380.0 , 480.0
Q1 , Q3	250.0 , 460.0	358.0 , 491.5
Min , Max	87.2 , 520.0	223.0 , 658.0
Change from Baseline to WEEK 17		
n	10	32
Mean	0.4	24.7
Standard deviation	28.1	72.8
Standard error	8.9	12.9
95% CL of mean	-19.7 , 20.5	-1.6 , 50.9
Median	6.0	25.0
95% CL of median	-33.0 , 23.0	-2.0 , 42.0
Q1 , Q3	0.0 , 22.0	-15.0 , 73.0
Min , Max	-62.8 , 28.0	-173.0 , 230.0
TREATMENT EFFECT		
Mean		24.2
Standard deviation		65.5
Standard error		23.7
95% CL of mean		-23.7 , 72.2
Median		18.0
95% CL of median		-12.4 , 61.4
p-value WIlcoxon rank sum test		0.2218
p-value t-test		0.3129

CL=confidence limits.

Borg scale
Minimal median changes from baseline to Week 17 in Borg dyspnea score with selexipag and placebo did not indicate a treatment effect on dyspnea after the 6-minute walk test.

One patient on selexipag had an event that qualified as aggravation of PAH (3%) vs 2 (20%) on placebo. In the placebo group two patients worsened from NYHA class III to IV, one patient improved from class III to II; in the active group one patient worsened from class III to IV and

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one from class II to III, five patients improved (one from class II to I and four from class III to II). No treatment effect was observed in plasma NT pro-BNP concentrations.

NYHA functional class
All patients in the study were NYHA functional class II or III at baseline, with the selexipag group having a higher proportion of patients in class II than the placebo group (44% vs 20%). During the study, two patients in the placebo group and one in the active group worsened from functional class III to IV, one patient in the placebo group improved from III to II, whereas one patient in the active group improved from functional class II to I and four patients from class III to II. The proportions of patients who improved were similar in the two treatment groups (16% and 10% in the selexipag and placebo groups, respectively). The proportions of patients who worsened were not significantly different between the two groups (6% and 20% in the selexipag and placebo groups, respectively).

Table 10 NYHA functional class: Change from baseline to Week 17 during the double-blind treatment period, all-treated DB set

ACT-293987, Protocol: NS-304/-02
Change from baseline to Week 17 in NYHA functional class
Set: All-treated DB

				Week 17							
	n	Baseline	n	I		II		III		IV	
				N	%	N	%	N	%	N	%
Placebo	10	I	-	-		-		-		-	
		II	2	-		2	20.0%	-		-	
		III	8	-		1	10.0%	5	50.0%	2	20.0%
		IV	-	-		-		-		-	
		Improved patients:		1	10.0%						
		95% confidence limits:		0.3% - 44.5%							
		Worsened patients:		2	20.0%						
		95% confidence limits:		2.5% - 55.6%							
ACT-293987	32	I	-	-		-		-		-	
		II	14	1	3.1%	12	37.5%	1	3.1%	-	
		III	18	-		4	12.5%	13	40.6%	1	3.1%
		IV	-	-		-		-		-	
		Improved patients:		5	15.6%						
		95% confidence limits:		5.3% - 32.8%							
		Worsened patients:		2	6.3%						
		95% confidence limits:		0.8% - 20.8%							

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

This application is supported by only one clinical trial.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

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There are no obvious important efficacy issues that may impact the drug in the post marketing setting.

7.2.2. Other Relevant Benefits

None

7.3. Integrated Assessment of Effectiveness

The submitted evidence of benefit has met the statutory evidentiary standard. The benefits shown have been determined to be clinically meaningful. The effectiveness evidence will be provided in the labeling.

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8 Review of Safety

8.1. Safety Review Approach

The evaluation of clinical safety focused primarily on data from one pivotal Phase 3 study (GRIPHON, AC-065A302). Supportive data included safety information from subjects treated in the open-label extension to GRIPHON (AC-065A303), two Phase 2 PAH studies, and one Phase 2 study in Japanese subjects with PAH.

A number of safety topics of special interest were identified on the basis of nonclinical findings, previous clinical findings with other IP receptor agonists, or when a numerical imbalance was identified. AEs of special interest include eye disorders; hemorrhage; cerebrovascular hemorrhage; cerebrovascular ischemia; anemia; thrombocytopenia; hypotension; bone disorders; liver disorders; hyperthyroidism; rash; renal dysfunction; malignancies; MACE and prostacyclin-like AEs. The typical prostacyclin-associated AEs include diarrhea, nausea/vomiting, dizziness, headache, flushing, jaw pain/temporomandibular joint syndrome, myalgia, musculoskeletal pain, arthralgia and pain in extremity.

Reviewer's Quantitative Safety Assessment: An independent analyses of the safety databases using the applicant's datasets (STDM, Adam) was conducted as part of the review. The software used were R (version 3.0.2), JReview version 9.2.6 and MAED version 1.2. The data sources are indicated in footnotes to the tables and figures contained within this review.

8.1.1. Studies/Clinical Trials Used to Evaluate Safety

Studies included in the safety evaluation are summarized in ***Table 1***. The safety analysis datasets include all patients who received at least one dose of study treatment. Analysis sets comprise all available data up to the following cut-off dates: 27 April 2014 for GRIPHON (AC-065A302), and 10 March 2014 for all other studies.

Table 1. Clinical Studies Included in Safety Analysis

Study / Phase	Population	Design	Number Subjects by Treatment	Dosing Regimen
Completed clinical trials in patients with PAH				
GRIPHON (AC-065A302) / Phase 3 Includes Ophthalmology sub-study	PAH	Randomized, placebo-controlled, double-blind, parallel groups with dose titration and maintenance phases.	1152 (total) Selexapag*: 575 Placebo: 577	Selexipag 200 µg b.i.d. up to 1600 µg b.i.d. p.o. Placebo b.i.d. p.o.

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Study / Phase	Population	Design	Number Subjects by Treatment	Dosing Regimen
NS-304/02 / Phase 2	PAH	Open-labeled, uncontrolled	43 (total) 200 µg: 12 400 µg: 31	Single selexipag p.o. dose of 200 µg or 400 µg
		Randomized, placebo-controlled, double-blind, parallel groups	43 (total) Selexapag: 33 Placebo: 10	Selexipag 200 µg b.i.d. up to 800 µg b.i.d. p.o. Placebo b.i.d. p.o.
Ongoing clinical trials in patients with PAH (cut-off date of 10 March 2014)				
GRIPHON OL (AC-065A303) / Phase 3	PAH	Uncontrolled, open-label extension study	218	Selexipag 200 µg b.i.d. up to 1600 µg b.i.d. p.o.
NS-304/03 / Phase 3	PAH	Uncontrolled extension of NS-304/02	39	Selexipag 200 µg b.i.d. up to 1600 µg b.i.d. p.o.
AC-065A201 / Phase 2	PAH in Japanese patients	Uncontrolled, open-label	37 (interim data up to Week 16)	Selexipag 200 µg b.i.d. up to 1600 µg b.i.d. p.o.
*Note: 1 patient randomized to placebo received a single dose of selexapag due to dispensing error.				

GRIPHON was conducted worldwide at 181 sites in 39 countries in the following six regions: North America, Latin America, Western Europe, Eastern Europe, Australia and Asia.

In the 11 completed Phase 1 clinical pharmacology studies, a total of 411 subjects, including 385 healthy subjects, 18 subjects with hepatic impairment, and 8 subjects with severe renal impairment were exposed to selexipag. Of the 411 subjects, 139 were exposed to single doses of selexipag and 272 received multiple doses of selexipag up to 1800 µg b.i.d.

8.1.2. Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The primary source of safety data is the GRIPHON study (Pool 1) in terms of both number of patients and duration of observations. Data obtained in the treatment extension period is reported separately.

Pool 2 contains the maximum safety data available for PAH patients and includes data from double-blind and open label Phase 3 and Phase 2 studies as shown in ***Table 2***. Clinical trials conducted in Japanese PAH patients were not pooled because of differences in the way the data were collected.

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Table 2. Patients included in Pool 2 safety analysis set

Study number (acronym)	Phase	Indication	Control/ blinding/ design/dose	Number of patients, Safety set	
				Selexipag	Placebo
Total				773 (781) [a]	587
AC-065A302 (GRIPHON)	3	PAH	Randomized, placebo-controlled, DB, parallel group up to 1600 µg b.i.d.	575	577
AC-065A303 (GRIPHON OL)	3	PAH	Uncontrolled extension to AC-065A302 up to 1600 µg b.i.d. (ongoing)	218 (63 ex-selexipag, 155 ex-placebo)	-
NS-304/-02 AHP [b]	2	PAH	Uncontrolled single selexipag dose up to 400 µg	43	-
NS-304/-02 RTP [b]	2	PAH	Randomized, placebo-controlled, DB, parallel group up to 800 µg b.i.d.	33 (all ex-selexipag in AHP)	10 (all ex-selexipag in AHP)
NS-304/-03	2	PAH	Uncontrolled extension to NS-304/-02 up to 1600 µg b.i.d (ongoing)	39 (31 ex-selexipag, 8 ex-placebo)	-

[a] In total, 773 individual patients were exposed to selexipag in Pool 2. However, in the analysis, the 8 patients in study NS-304/-03 who had previously received placebo in the DB period of NS-304/-02 were counted twice (i.e., received selexipag in the acute hemodynamic period and the OL extension), bringing the total number in the statistical outputs to 781.
[b] Study NS-304/-02 comprised an AHP, in which all patients received a single selexipag dose (200 µg for the first 12 patients and 400 µg for the remaining 31 patients) followed by a RTP, which commenced the following day.
AHP = acute hemodynamic period, b.i.d. = twice daily, DB = double-blind, OL = open-label, PAH = pulmonary arterial hypertension, RTP = randomized treatment period.

Source: Sponsor's Table 7 in section 2.7.4 Summary of Clinical Safety

Reviewer's comment: The primary focus of the safety analysis is the GRIPHON study because the study contributes most data from double-blind treatments. Supportive safety data for Deaths, serious AEs and AEs of special interest are presented for studies in Pool 2.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Of the 575 selexipag-treated patients, the median duration of selexipag exposure was 71 weeks, with 367 (64%) patients receiving treatment for at least 1 year and 180 (31%) patients receiving treatment for at least 2 years (***Figure 1***).

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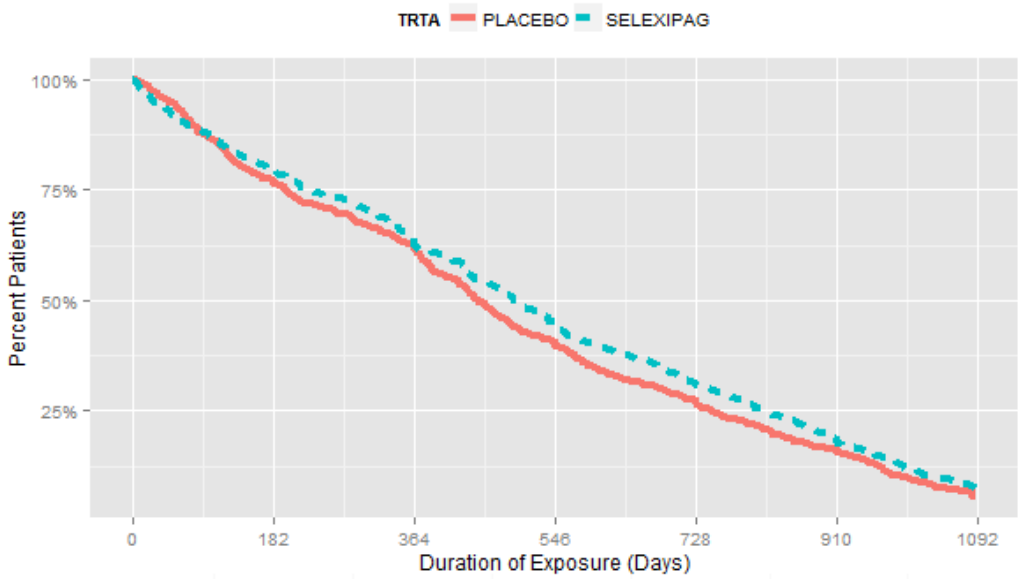
Figure 1. Duration of Exposure by Study Treatment (Safety Population, GRIPHON)



Source: Reviewer's analysis, p.ExpTRT.Out.png, using adexd.xpt
Abbreviations: TRTA=study treatment; SELEX=selexipag; PLC=placebo

There were no major differences in the duration of exposure for age, sex, race and region.

The distribution of patients within each dose level by study week in the titration and maintenance (up to week 26) phases are shown in ***Figure 2*** and ***Figure 3***, respectively. Of the 575 selexipag-treated patients, the median individual maintenance dose was 1200 µg bid and approximately 30% patient received an individual maintenance dose of 1600 µg bid by the end of the titration phase (Week 12, ***Figure 2***). During the maintenance phase, the distribution of patients within each dose level was fairly stable.

A summary of patient-year exposures by dose category is presented in ***Table 3***. There were 24% patients in selexipag-treated group down-titrated at least once from their individual maximum tolerated dose (IMD) compared to 11% in placebo group. In both groups, the main reason for down-titration was AEs, with prostacyclin-associated AEs more frequently reported in the selexipag group.

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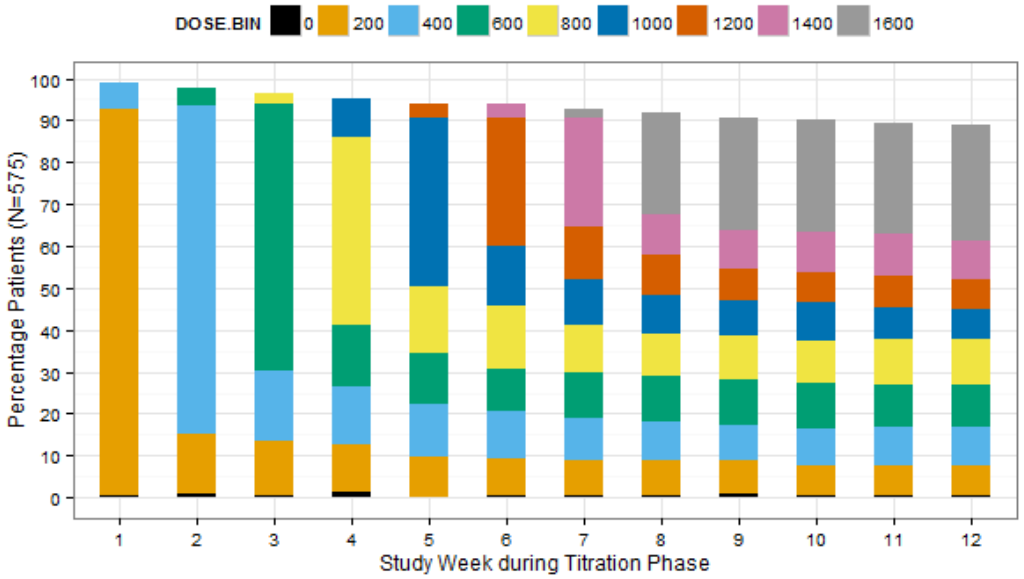
Figure 2. Exposure by Dose in Titration Phase (Safety Population, GRIPHON)

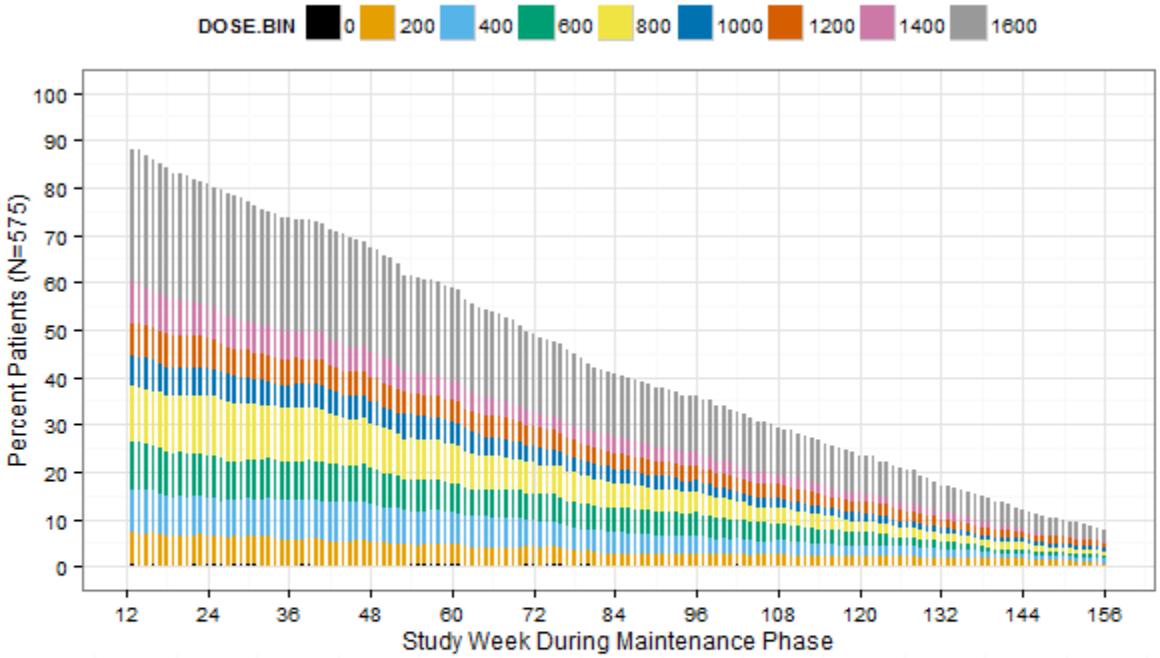


Number Patients

	1	2	3	4	5	6	7	8	9	10	11	12
1600							13	138	154	154	151	159
1400						17	148	56	52	54	58	52
1200					19	176	73	56	43	43	43	40
1000				53	233	84	63	52	48	51	43	41
800			15	257	91	85	64	59	62	59	64	64
600		24	366	84	69	59	64	62	61	63	57	56
400	36	450	96	80	74	64	58	54	50	50	52	55
200	530	83	73	65	54	51	46	47	44	42	41	40
0	4	5	4	8	1	3	4	3	6	2	4	3

Source: Reviewer's analysis, p.ExpDOSEW12.Out.png, using adexd.xpt
Abbreviations: DOSE.BIN = doses were binned by 200 mg increments for graphical representation and label represents the highest dose in the bin; N=number of subjects in selexipag-treatment group in safety population.

Figure 3. Exposure by Dose in Maintenance Phase (Safety Population, GRIPHON)



Number Patients	12	24	36	48	60	72	84	96	108	120	132	144	156
1600	162	146	137	127	113	94	76	68	56	45	33	22	14
1400	50	40	35	31	24	18	20	17	13	11	8	4	1
1200	40	38	31	30	25	24	19	18	18	14	11	8	6
1000	36	33	28	27	28	21	17	13	11	10	6	5	4
800	67	72	65	54	47	37	29	26	19	13	10	8	5
600	58	52	47	44	35	32	31	27	21	17	9	6	4
400	53	46	47	45	40	33	25	22	17	13	11	6	5
200	39	34	32	29	24	22	16	15	13	12	10	9	4
0	2	3	1	1	2	2		1	1				

Source: reviewer's analysis, p.ExpDOSEW156.Out.png, using adexd.xpt
Abbreviations: DOSE.BIN = doses were binned by 200 mg increments for graphical representation and label represents the highest dose in the bin; N=number of subjects in selexipag-treatment group in safety population.

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Table 3. Summary of Patient-Year Exposure by Individual Dose Category (Safety Population, GRIPHON)

	Selexipag N=575	Placebo N=577
Patient-years (Entire treatment period)	841.7	786.2
Patient-years - individual dose categories b.i.d. (µg)		
Missing	0.086	0.000
0	2.853	1.473
> 0-200	77.013	24.871
> 200-400	98.171	23.763
> 400-600	99.862	32.790
> 600-800	113.132	24.096
> 800-1000	63.310	40.454
> 1000-1200	69.977	36.775
> 1200-1400	64.895	47.496
> 1400-1600	252.389	554.374
> 1600	0.000	0.071

Source: Sponsor's Table 13 in 2.7.4 Summary of Clinical Safety

8.2.2. Relevant characteristics of the safety population:

The safety population in GRIPHON (pool 1) was predominantly female (80%) with a median age of 49 years (range: 18–80 years). The majority of patients (82%) were <65 years old, with 1% ≥ 75 years old. Mean BMI was 27 kg/m^2. The majority of patients were Caucasian (White/Hispanic; 75%) or Asian (21%), with most enrolled at centers in Western Europe/Australia (28%), Eastern Europe (26%), Asia (20%) and North America (17%). The study population is consistent with the demographics of the targeted patient population with PAH in the US.

The demographic characteristics of the patients included in Pool 2 were consistent with those in Pool 1.

8.2.3. Adequacy of the safety database

There is an acceptable extent of exposure to selexipag in GRIPON double-blind clinical trial for clinical safety evaluation. Overall, this study represented approximately 842 patient-years of selexipag exposure and approximately 786 patient-years of placebo.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

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There are no concerns by the reviewers that focus on data quality and integrity. All data were able to be reviewed and none was removed from the database. Audits of Individual sites by

office of scientific inspections found no significant deficiencies.

8.3.2. Categorization of Adverse Events

Analysis and reporting of AEs are based on Medical Dictionary for Regulatory Activities (MedDRA) version 16 (re-coded for studies that originally used an older or different coding system). Systems Organ Class (SOC), Preferred Term (PT) and Standard MedDRA Query (SMQ) definitions are taken from MedDRA. The definitions for treatment-emergent AEs are as follows:

- Treatment-emergent AEs: Onset date at Study Treatment Day 1 to end of treatment plus 7 days (EOT +7) or 30 days (EOT +30) or until the cut-off date for on-going clinical trials.
- Deaths were evaluated until study closure.
- AEs leading to discontinuation: AEs leading to discontinuation of study treatment are those for which the AE CRF tick box 'Permanently discontinued' of 'Action taken with study drug' has been marked.
- AEs leading to dose reduction: AEs leading to dose reduction of study treatment are those for which the AE CRF tick box 'Dose reduced' of 'Action taken with study drug' has been marked.

Independent sensitivity analyses of AEs and SAEs were conducted by grouping PTs according to a customized categorization of AEs for drugs used to treat cardiovascular and renal disorders. The sensitivity analysis was used to detect potential under-reported of AEs by splitting PTs across several higher level groupings.

<u>Adjudication of AEs</u>

The primary efficacy endpoint, time to first Morbidity/Mortality event, was adjudicated by an independent Critical Event Committee (CEC) blinded to study treatment and to the occurrence of any prostacyclin-associated AEs. The cause of death (related vs not related to PAH) was adjudicated by the CEC.

AEs associated with bleeding events were independently adjudicated by two external expert medical reviewers who were blinded to the study treatment assignment. The expert medical reviewers confirmed whether each of the cases qualified as a bleeding event and adjudicated the events according to the International Society of Thrombosis and Haemostasis criteria as either major, non-major or, when adjudication was not possible based on the available information, as unable to adjudicate. A major bleeding event was defined as the occurrence of at least one of the following events:

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- Fatal bleeding
- Symptomatic bleeding in a critical area or organ, such as intracranial, intra-spinal, intraocular, retroperitoneal, intra-articular, or intramuscular with compartment syndrome
- Bleeding causing a fall in hemoglobin level of at least 20 g/L (1.24 mmol/L) leading to transfusion of two or more units of whole blood or red cells

An Ophthalmology Safety Board (OSB) was established to assess the nature and relevance of treatment-emergent retinal abnormalities. The OSB was blinded to treatment received during double-blinded studies. In GRIPHON, an ophthalmology sub-study was implemented to collect additional ophthalmology safety data in 54 of the selexipag-treated patients and 48 of the placebo-treated patients and included fundoscopy/fundus assessment.

8.3.3. Routine Clinical Tests

Clinical testing in GRIPHON was adequate to detect laboratory tests, vital signs and ECGs. These assessments were conducted at baseline; at Weeks 4, 8, 16, and 26; at 1 year and every 6 months thereafter; and at end of study. The frequency of collection was adequate to detect changes laboratory parameters of special interest including hematology, thyroid markers, liver enzymes, blood pressure and ECGs.

8.4. Safety Results

8.4.1. Deaths

8.4.1.1. All-Cause Mortality

There were 205 patients who died up to study closure: 100 (17 %) in the selexipag group and 105 (18%) in the placebo group. A listing of standardized terms for death is presented by treatment arm in ***Table 4***. The most common causes of death are related to PAH and included disease progression, right heart failure and pulmonary arterial hypertension.

Table 4. All-Cause Death Shown by Standardized Death Terms with >1 Patient (Safety Population, GRIPHON)

Standardized Death Term	SELEXIPAG (N=575)		PLACEBO (N=577)	
	n	%	n	%
Pulmonary Arterial Hypertension	31	5.4	35	6.1
Disease Progression	24	4.2	30	5.2
Right Heart Failure	23	4.0	21	3.6
Sudden Death	5	0.9	6	1.0
Cardiac Arrest	4	0.7	3	0.5
Septic Shock	3	0.5	1	0.2
Cardiopulmonary Failure	2	0.4	1	0.2

Standardized Death Term	SELEXIPAG (N=575)		PLACEBO (N=577)	
	n	%	n	%
Unknown Cause Of Death	2	0.4	5	0.9
Acute Right Ventricular Failure	2	0.4	7	1.2
Acute Renal Failure	1	0.2	2	0.4
Cardiogenic Shock	1	0.2	2	0.4
Pulmonary Embolism	1	0.2	2	0.4
Cardiopulmonary Insufficiency	1	0.2	3	0.5
Sepsis	1	0.2	3	0.5
Pulmonary Hypertension	0	0	2	0.4
Respiratory Failure	0	0	2	0.4
Multiorgan Failure	0	0	3	0.5

Source: Reviewer's analysis, cdf.AdjDeath.csv, using Applicant dataset adsl.xpt.

In the OL extension study of GRIPHON (AC-065A303), a total of 61 deaths were reported: 18 (29%) in selexipag/selexipag group and 43 (28%) in placebo/selexipag group. The proportion of patients who died due to PAH was 21% and 25% in the selexipag/selexipag and placebo/selexipag groups, respectively.

Additionally, up to the cut-off date of 10 March 2014, 10 patients died in Phase 2 OL PAH studies (8 in NS-304/-03 and 2 in AC-065A201); the majority of cases were associated with PAH progression. One patient died in a Phase 2 CTEPH study while on selexipag; the death was reported as related to CTEPH. No patient died during study NS-304/-02.

No deaths were reported in any of the clinical pharmacology studies.

8.4.1.2. Serious AEs with Fatal Outcomes

Fatal SAEs were defined as SAEs with an outcome of death reported on the case report form (up to study closure) that had an AE onset date occurring from study Day 1 up to the date of last study drug intake +30 days. Fatal SAEs were reported in 55 (10%) and 43 patients (8%) in the selexipag and placebo groups. The total number of events was 92 in selexipag group and 81 in placebo group.

SAEs with a fatal outcome sorted by SOC and related PT are shown in ***Table 5***. There were more fatal SAEs in the selexipag group (>1 per 100) for General disorders and Cardiac disorders. The most commonly reported fatal SAEs (>1% incidence) were disease progression (SOC: General Disorders), PAH (SOC: Respiratory Disorders), Right Ventricular Failure (SOC: Cardiac Disorders) and sudden death (SOC: General Disorders). Overall, the reported SAEs with fatal outcome were consistent with underlying disease condition and there were no unexpected events detected.

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Table 5. SAE with Fatal Outcome (>1 Patient per PT in Selexipag) by MedDRA SOC and Related PT (Safety Population, GRIPHON)

SAE with Fatal Outcome (EOT + 30)	Selexipag (N=575)		Placebo (N=577)		Relative Difference (per hundred)
	N	%	n	%	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	27	4.7	20	3.47	1.23
Disease Progression	***18***	***3.13***	***12***	***2.08***	***1.05***
Sudden Death	***6***	***1.04***	***4***	***0.69***	***0.35***
Multi-Organ Failure	2	0.35	2	0.35	0
CARDIAC DISORDERS	23	4	17	2.95	1.05
Right Ventricular Failure	***7***	***1.22***	***7***	***1.21***	***0.01***
Cardiac Arrest	3	0.52	1	0.17	0.35
Cardiopulmonary Failure	3	0.52	1	0.17	0.35
Acute Right Ventricular Failure	2	0.35	3	0.52	-0.17
Cardio-Respiratory Arrest	2	0.35	2	0.35	0
Ventricular Fibrillation	2	0.35	0	0	0.35
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	22	3.83	19	3.29	0.54
Pulmonary Arterial Hypertension	***20***	***3.48***	***16***	***2.77***	***0.71***
INFECTIONS AND INFESTATIONS	6	1.04	3	0.52	0.52
Pneumonia	2	0.35	2	0.35	0
Septic Shock	2	0.35	0	0	0.35
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	3	0.52	0	0	0.52
RENAL AND URINARY DISORDERS	2	0.35	3	0.52	-0.17
Renal Failure Acute	2	0.35	3	0.52	-0.17

Source: Reviewer's analysis, tabFatalSAE.csv using Applicant dataset adae.xpt (302 study)
Abbreviations: SAE=serious adverse events; EOT=end of treatment

In study AC-065A303, a total of 55 patients had at least one SAE up to EOT + 3 days with a fatal outcome: 19 (30%) in selexipag/selexipag group and 36 (23%) placebo/selexipag group. The most frequently reported SAEs with fatal outcome were PAH worsening (11%) and right ventricular failure (9%).

8.4.2. Serious Adverse Events

8.4.2.1. SAEs in GRIPHON Double-Blind Study (Pool 1)

Table 6 presents an overall summary of SAEs. There was no concerning imbalance or pattern of SAEs in selexipag group compared to placebo.

Table 6. Summary of Serious Adverse Events (Safety Population, GRIPHON)

	Selexipag (N=575)	Placebo (N=577)

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Patients with at least 1 SAE	251	44%	272	47%
Annualized rate (per 100 patients treated in 1 year)	30		30	
Patients with at least 1 SAE with Fatal Outcome	49	9%	41	7%
Patients with at least 1 SAE leading to Discontinuation	102	18%	125	22%

Source: Reviewer's analysis, SAEtab.csv using Applicant dataset adae.xpt
Abbreviations: SAE=serious adverse event, n=number of patients in subset, %=percent patients in subset compared number of patients in safety population (N)
Cross reference: Table 42 in 2.7.4 Summary of Clinical Safety

SAEs categorized by MedDRA higher level terms (HLT) were investigated for any patterns or imbalances in the selexipag group (***Table 7***). Although the overall frequencies of SAEs by HLTs were low, there were numerical imbalances in cerebrovascular hemorrhage and ischemia. These AEs were further evaluated as AEs of special interest in *Analysis of Submission-Specific Safety Issues (Section 8.5)*.

Table 7. Incidence of SAEs by MedDRA High Level Term (≥0.5% more frequently in Selexipag group) and Related PT (Safety Population, GRIPHON)

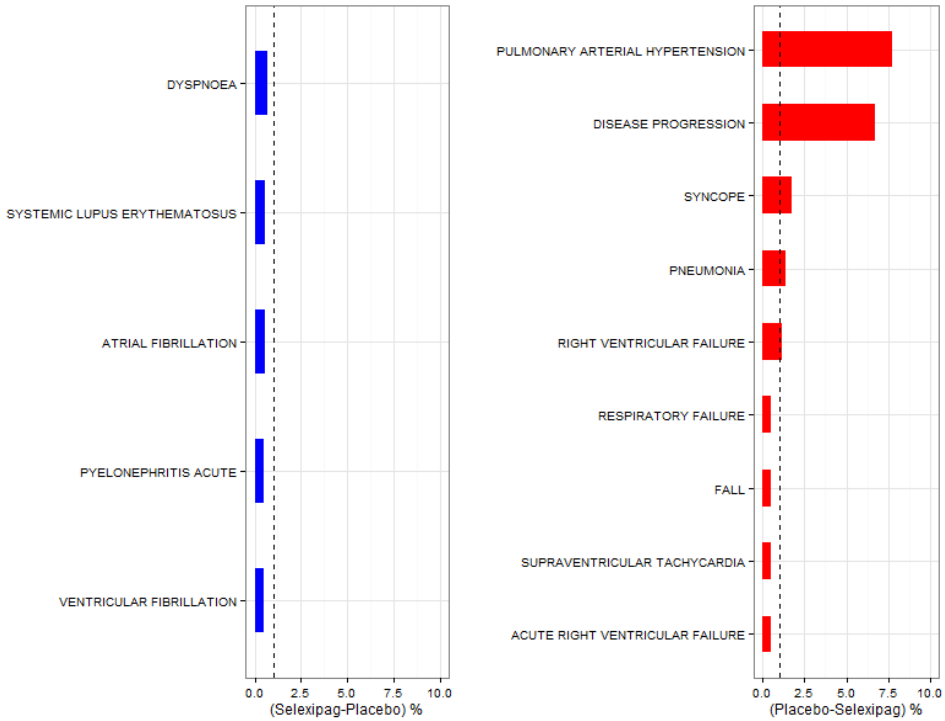
SAE HLT	SELEXIPAG (N=575)		PLACEBO (N=577)		Relative Difference (per hundred)
	n	%	n	%	
SEPSIS, BACTERAEMIA, VIRAEMIA AND FUNGAEMIA NEC	7	1.22	2	0.35	0.87
URINARY TRACT INFECTIONS	7	1.22	2	0.35	0.87
CENTRAL NERVOUS SYSTEM HAEMORRHAGES AND CEREBROVASCULAR ACCIDENTS	5	0.87	1	0.17	0.7
Cerebral Infarction	1	0.17	0	0	0.17
Cerebrovascular Accident	1	0.17	0	0	0.17
Haemorrhage Intracranial	1	0.17	0	0	0.17
Ischaemic Stroke	1	0.17	0	0	0.17
Subarachnoid Haemorrhage	1	0.17	0	0	0.17
Thalamic Infarction	0	0	1	0.17	-0.17
BREATHING ABNORMALITIES	19	3.3	16	2.77	0.53
LUPUS ERYTHEMATOSUS (INCL SUBTYPES)	4	0.7	1	0.17	0.53
ANAEMIAS NEC	6	1.04	3	0.52	0.52
CEREBRAL INJURIES NEC	3	0.52	0	0	0.52
Brain Herniation	1	0.17	0	0	0.17
Craniocerebral Injury	1	0.17	0	0	0.17
Subdural Haematoma	2	0.35	0	0	0.35
MUSCULOSKELETAL AND CONNECTIVE TISSUE PAIN AND DISCOMFORT	3	0.52	0	0	0.52

Source: Reviewer's analysis, df.serTabHLT.csv using Applicant dataset adae.xpt
Abbreviations: AE=adverse events; HLT=higher level term; SAE=serious adverse event; N=number of patients; %=percentage

Reference ID: 3814728

SAEs by PT that occurred in selexipag (left panel) and placebo (right panel) groups with a relative difference ≥0.5% are shown in ***Figure 4***. There was no over-reporting of a particular SAE in the selexipag group that raised a safety concern. In the placebo group, the frequent SAEs were related to underlying disease.

Figure 4. Commonly Reported SAEs by Treatment Group (Safety Population, GRIPHON)



Source: Reviewer's analysis using Applicant's dataset, adae.xpt from GRIPHON study.
Dashed line represents 1% relative difference.

FDA Sensitivity Analysis of SAEs (Safety Population, GRIPHON)

Table 8 lists the SAEs in custom AE categories sorted by Risk Ratio >2. This analysis did not identify any additional safety concerns that were not identified by the Applicant. Cerebral ischemia, prostacyclin-like AEs, and anemia were identified as AEs of special interest due to numerical imbalances in the selexipag group for further evaluation in *Analysis of Submission-Specific Safety Issues (**Section 8.5**)*.

Table 8. FDA Sensitivity Analysis of SAEs (Safety Population, GRIPHON)

FDA AE CATEGORIES	SELEXIPAG (N=575)		PLACEBO (N=577)		RISK RATIO	95% LL	95% UL
Cerebral Ischemia (Includes Stroke, ICH and TIA)	5	0.87%	1	0.17%	5.0	0.59	42.8
UTI	8	1.39%	2	0.35%	4.0	0.86	18.8
Prostacyclin-Like Effects	11	1.91%	3	0.52%	3.7	1.03	13.1
Infection, Viral	5	0.87%	2	0.35%	2.5	0.49	12.9

FDA AE CATEGORIES	SELEXIPAG (N=575)		PLACEBO (N=577)		RISK RATIO	95% LL	95% UL
Sepsis	7	1.22%	3	0.52%	2.3	0.61	9.0
Anemia	6	1.04%	3	0.52%	2.0	0.50	8.0
Dyspepsia, N, V, Indigestion, Epigastric Pain, Gastritis, Duoden	6	1.04%	3	0.52%	2.0	0.50	8.0

Cross reference: the sponsor's analyses of AE.

Table 33 *in Additional Safety Analysis, Section 13.3*
Abbreviations: LL=lower limit; UL=upper limit; ICH=intracranial hemorrhage; TIA=transient ischemic attack; UTI=urinary tract infections, N=nausea, vomiting

8.4.2.2. SAEs in Other Clinical Studies

In AC-065A303, 52% of the selexipag-treated patients had at least 1 SAE. In patients previously treated with selexipag in AC-065A302, the incidence was 57% compared to 50% in the group of patients previously treated with placebo. The most frequently reported SAEs were PAH worsening (23%) and right ventricular failure (15%). Other reported SAEs included pneumonia (3%), acute right ventricular failure (2%), and syncope (2%).

In study NS-304/-02, no SAEs were reported during the acute hemodynamic period of the study. During the double-blind period, 6 patients on selexipag (18%) and 4 patients on placebo (40%) had SAEs. Headache was reported as serious in 2 selexipag-treated patients.

In study NS-304/-03, a total of 25 patients (64.1%) had at least 1 SAE up to the cut-off date of 10 March 2014. The most frequently reported SAEs were PAH worsening (10 patients, 26%) and right ventricular failure (4 patients, 10%).

In the open-label PAH study AC-065A201, SAEs were reported for 4 patients up to Week 16. SAEs were hypoxia, dyspnea, right ventricular failure, vomiting, hypotension and PAH worsening.

Two SAEs were reported in the clinical pharmacology studies. An SAE of hepatic encephalopathy was reported in a subject with severe liver impairment in the study in subjects with hepatic impairment (AC-065-104). An SAE of hypotension (symptomatic) was reported in the TQT study (AC-065-106), which led to premature discontinuation of the subject from the study.

Reviewer's Comments: Independent analyses of the SAEs in GRIPHON DB Study through study closure are consistent with the Applicant's reporting of SAEs by Preferred Term. In the selexipag group, the frequencies of SAEs were low when evaluating by MedDRA High Level Term and Preferred Term. Numerical imbalances of cerebrovascular ischemia and hemorrhage were detected and clinical data were reviewed (see Sections 0 and 8.5.2). Overall, there was no concerning pattern or imbalance of SAEs in selexipag group.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

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As shown in ***Table 9***, the proportion of patients who prematurely discontinued study drug prior to study closure was higher in the placebo group (55%) compared to the selexipag group (49%). The reason for the high percentage of patients who discontinued was the occurrence of an MM event. When CEC-confirmed MM events were excluded, the proportion of patients who prematurely discontinued study drug was higher in the selexipag group (26%) compared to the placebo group (17%), with 8% and 6% in the respective groups discontinuing treatment during the titration phase. There was no clear pattern suggestive of any impact of sex, race, geographical location or BMI at baseline on discontinuation of selexipag treatment.

Table 9. Discontinuations of Study Drug in GRIPHON DB Study prior to Study Closure (Safety Population, GRIPHON)

	Selexipag (N=575)	Placebo(N=577)
Patients discontinued (includes MM events[1])	280 (49%)	319 (55%)
Patients discontinued (excludes MM events[1])	148 (26%)	97 (17%)
Due to AEs	117 (20%)	83 (14%)

Source: Reviewer's analysis, tab.dc1.csv, using adsl.xpt
Notes: [1]AE / death /clinical worsening event may be the reported reason for discontinuation of study drug, but the event may subsequently have been adjudicated by the CEC as a morbidity/mortality event.
Cross-reference: Table 33 in 2.7.4 Summary of Clinical Safety

Figure 5 shows AEs leading to discontinuation by PT with a relative difference in incidence >0.5% between treatment groups. For selexipag, AEs leading to discontinuation were mostly due to prostacyclin-related AEs. For placebo, AEs leading to discontinuation were related to PAH or disease progression.

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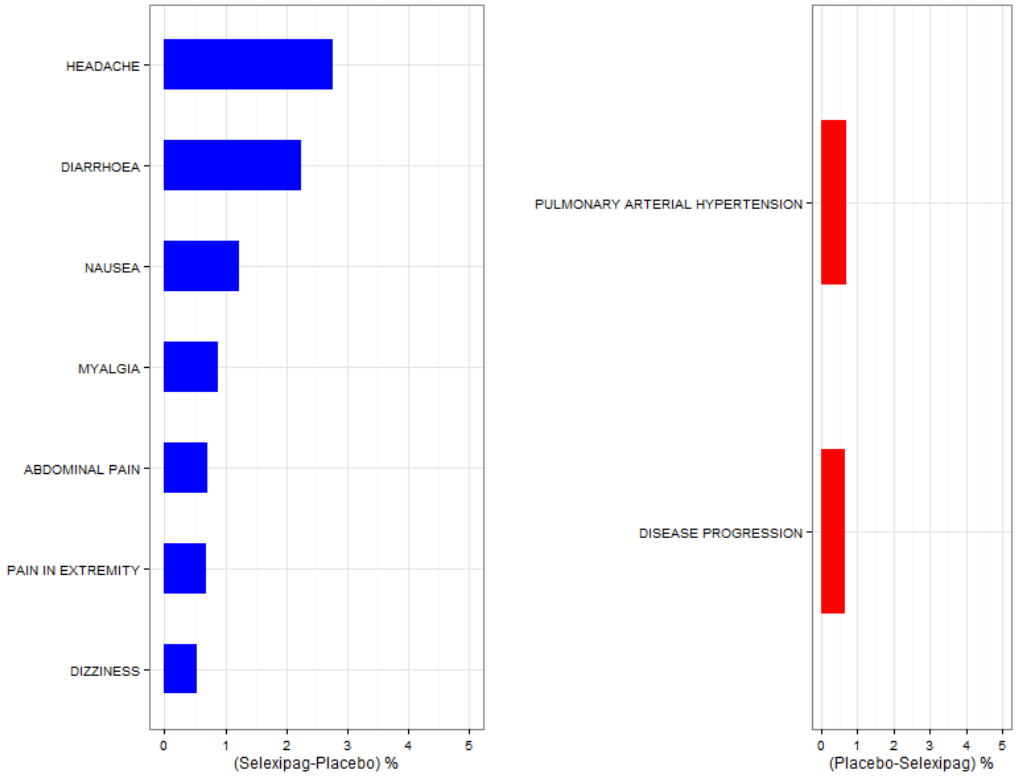
Figure 5. Relative Difference in Adverse Events by PT for Patients Who Discontinued Study Treatment Due to Adverse Events (Safety Population, GRIPHON)



Source: reviewer's analysis, p.AEDC.Out.png
Note: PTs are listed for AEs with relative difference in incidence >0.5%.

A total of 24% (52/218) of the selexipag-treated patients had at least 1 AE leading to discontinuation of study drug in study AC-065A303. The most frequently reported AEs were PAH (5 selexipag/selexipag, 14 placebo/selexipag) and right ventricular failure (2 selexipag/selexipag, 8 placebo/selexipag). Three patients were discontinued from study treatment due to AEs in study NS-304/-02. Two of these patients discontinued due to worsening PAH and the third patient due to AEs of headache, asthenia and myalgia. In OL study AC-065A201, one patient discontinued study treatment due to an AE of decreased blood pressure.

Reviewer's Comments: Review of AEs leading to discontinuation using both PT and MedDRA SOC showed that prostacyclin-associated AEs (i.e., diarrhea, nausea/vomiting, headache and myalgia) were more frequently reported for patients who discontinued selexipag treatment in GRIPHON DB study. The majority of patients with an AE discontinued at 200 µg bid (33%) and 400 µg bid (29%) selexipag dose levels.

8.4.4. Significant Adverse Events

Prostacyclin-like events were the most frequently reported AEs and were associated with treatment discontinuation and dose reduction. A summary of these events is presented in

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Table 10. The proportion of patients with at least one prostacyclin-related AE was 91% in Selexipag *vs*. 62% in the placebo group. The most frequently report AEs in selexipag were headache, diarrhea, nausea and jaw pain (***Figure 7***). Thirteen (2%) patients in selexipag reported at least one serous AE, but none resulted in a fatal outcome. Serious AEs that occurred in at least two patients were diarrhea, myalgia, pain in extremity, headache and vomiting.

There were 43 (8%) patients who discontinued selexipag treatment due to headache, diarrhea, nausea, pain in extremity, myalgia, dizziness, and vomiting. Prostacylin-related AEs led to selexipag dose reduction in 46% patients, which occurred more frequently during the titration phase (44% patients) compared to maintenance phase (9% patients). Evaluation of prostacyclin-associated AEs according to age subgroup showed that in selexipag-treated patients aged 65–74 years, a higher proportion (13%) discontinued treatment due to prostacyclin-related AEs, compared to their younger patients (6%).

Table 10. Summary of Prostacyclin-Related Adverse Events (Safety Population, GRIPHON)

Grouped PTs[1]	Selexipag (N=575)		Placebo (N=577)	
Patients with at least 1 AE	523	91%	359	62%
Annualized rate (per 100 patients in 1 year)	67		43	
Patients with at least 1 serious AE	13	3%	3	<1%
Patients with at least 1 AE with Fatal Outcome	0	0	1	<1%
Patients with at least 1 AE leading to Discontinuation	43	7%	10	2%
Patients with at least 1 AE leading to Dose Reduction	267	46%	65	11%

Source: Reviewer's analysis, TabDis.PR.csv using Applicant dataset adae.xpt
Abbreviations: AE=adverse event; N=number of patients in safety population: PT= MedDRA preferred term. Cross reference: Table 85 in 2.7.4 Summary of Clinical Safety
[1]pain in jaw, temporomandibular joint syndrome, arthralgia, musculoskeletal pain, myalgia, pain in extremity, flushing, nausea, vomiting, diarrhea, headache and dizziness

As shown in **Figure 6**, the time to first prostacyclin-related AE was shorter in the selexipag group and occurred during the titration phase (first 12 weeks). The Kaplan-Meier estimation of the median time to the first prostacyclin like-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.

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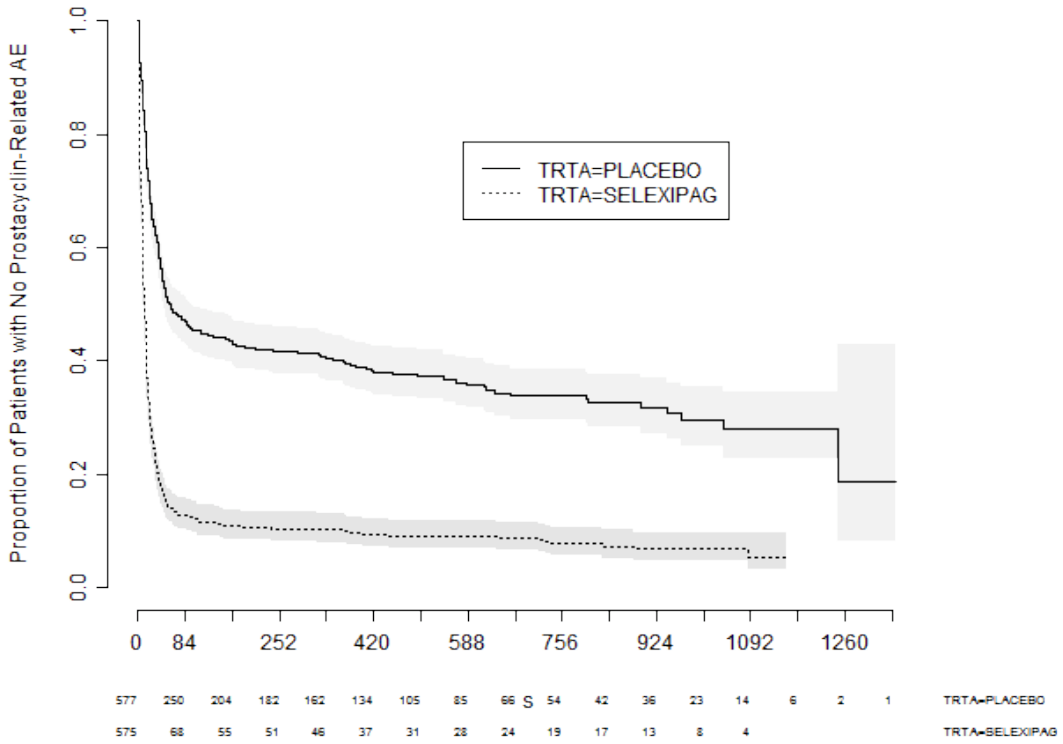
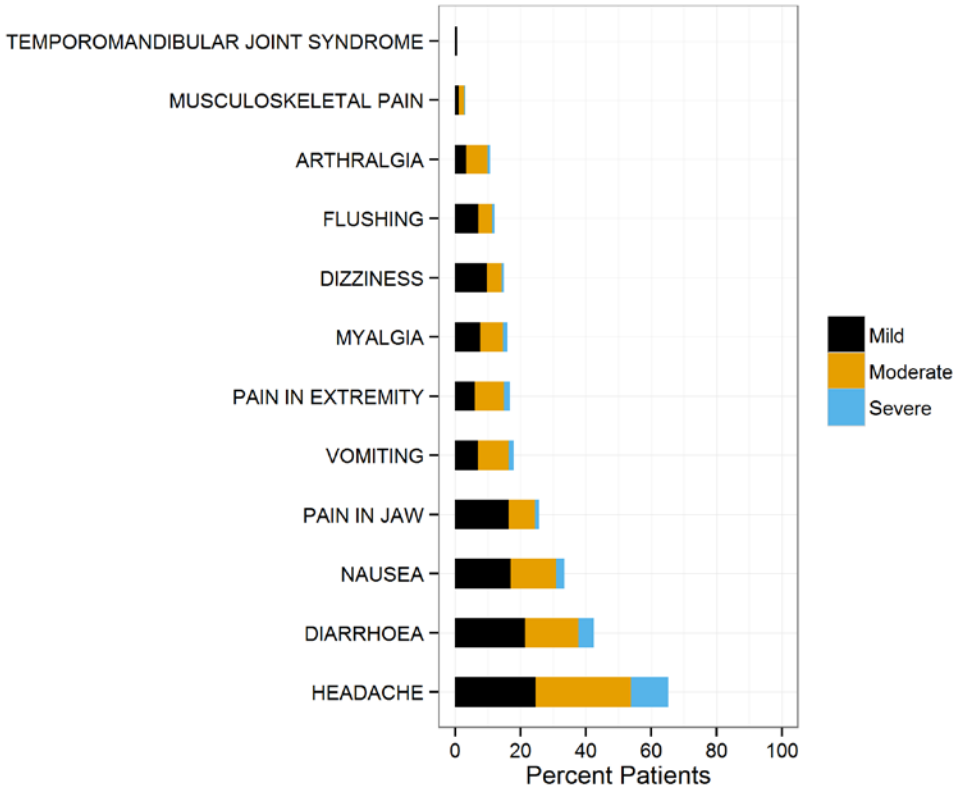
Figure 6. Kaplan-Meier Plot for First Occurrence of Prostacyclin-Related AEs (Safety Population, GRIPHON)



Reviewer's analysis, p.KMPR.png, using dataset adtae.xpt

The majority of the patients experienced mild (22%) or moderate (50%) intensity prostacyclin-related AEs (***Figure 7***). Severe-intensity AEs were reported in >2% patients for headache, diarrhea and nausea.

Figure 7. Bar Plot of Frequency and Severity of Prostacyclin-Related AEs (Safety Population, GRIPHON)

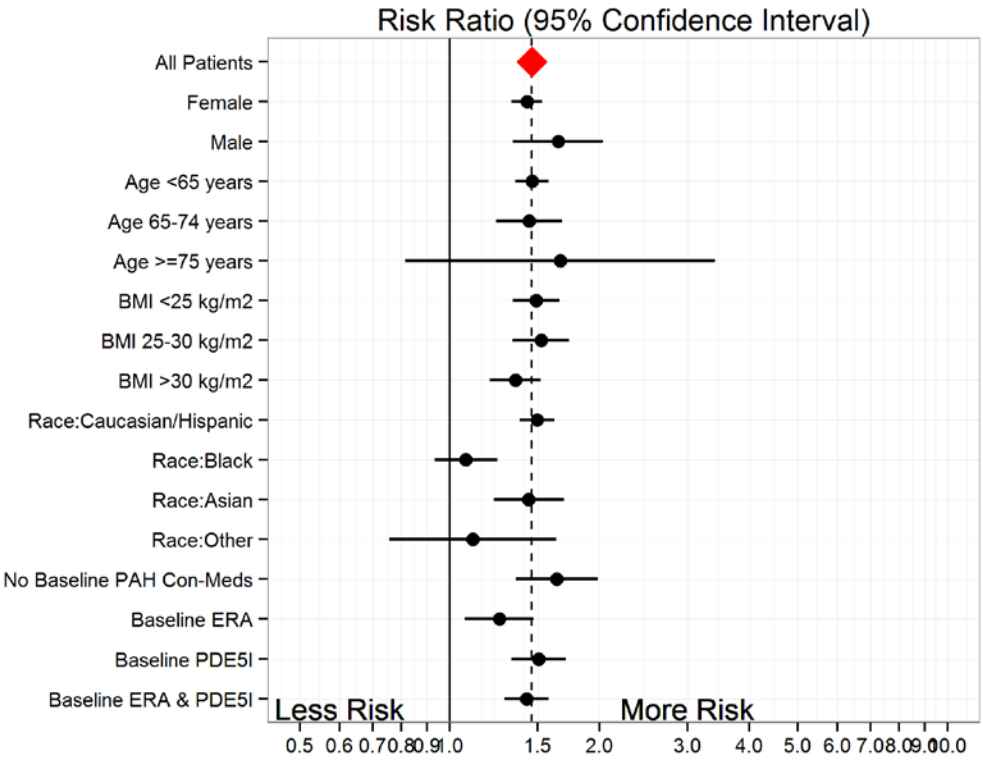


Source: Reviewer's analysis, TabSEVPT.PR.csv using Applicant dataset adae.xpt
Cross reference: Table 124 in 2.7.4 Summary of Clinical Safety

Subgroup evaluation of prostacyclin-related AEs showed that the frequencies of AEs were generally similar across sex, age, BMI, race and baseline PAH concomitant medications (***Figure 8***). Meaningful conclusions cannot be made for subgroups with small size such as:

- Age >75 y (8 in Selexipag and 5 in Placebo)
- Black race (13 in Selexipag and 12 in Placebo)
- Other race (9 in Selexipag and 10 in Placebo)

Figure 8. Subgroup Analysis for Prostacyclin-Related AEs (Safety Population, GRIPHON)



Source: Reviewer's analysis, p.forest.AEPD.png, using datasets adae.xpt, adbl.xpt and adcm.xpt
Abbreviations: BMI=body mass index, ERA= Endothelin receptor antagonist, PDE5I= Phosphodiesterase type-5 inhibitor. Risk ratio is computed as the proportion of patients with the event in selexipag group divided by the proportion of patients with the event in placebo group.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Table 11 presents adverse reactions more frequent in selexipag than placebo by >2%. These common AEs are related to the pharmacological activity of selexipag. AEs of special interest are presented in Analysis of Submission-Specific Safety Issues, Section 8.5.

Table 11. Common Adverse Reactions

	Selexipag (N = 575)			*Placebo (N = 577)*		
MedDRA PT	*Events*	*Number of subjects*	*Proportion (%)*	*Events*	*Number of subjects*	*Proportion (%)*
Headache	645	375	65	245	182	32
Diarrhoea	364	244	42	132	106	18
Pain in jaw	186	148	26	35	33	6
Nausea	262	192	33	127	105	18
Myalgia	120	92	16	36	34	6

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	Selexipag (N = 575)			*Placebo (N = 577)*		
MedDRA PT	*Events*	*Number of subjects*	*Proportion (%)*	*Events*	*Number of subjects*	*Proportion (%)*
Vomiting	144	104	18	53	49	8
Pain in extremity	139	97	17	58	44	8
Flushing	79	70	12	29	28	5
Arthralgia	81	62	11	56	44	8
Anaemia	55	48	8	38	31	5
Abdominal pain	60	48	8	39	33	6
Decreased appetite	35	34	6	20	19	3
Pain	23	18	3	3	3	1
Nasopharyngitis	104	75	13	95	63	11

Source: Reviewer's analysis, MAED output.

Reviewer's Comment: Table of common adverse reactions supports Applicant's Table 1 in the label.

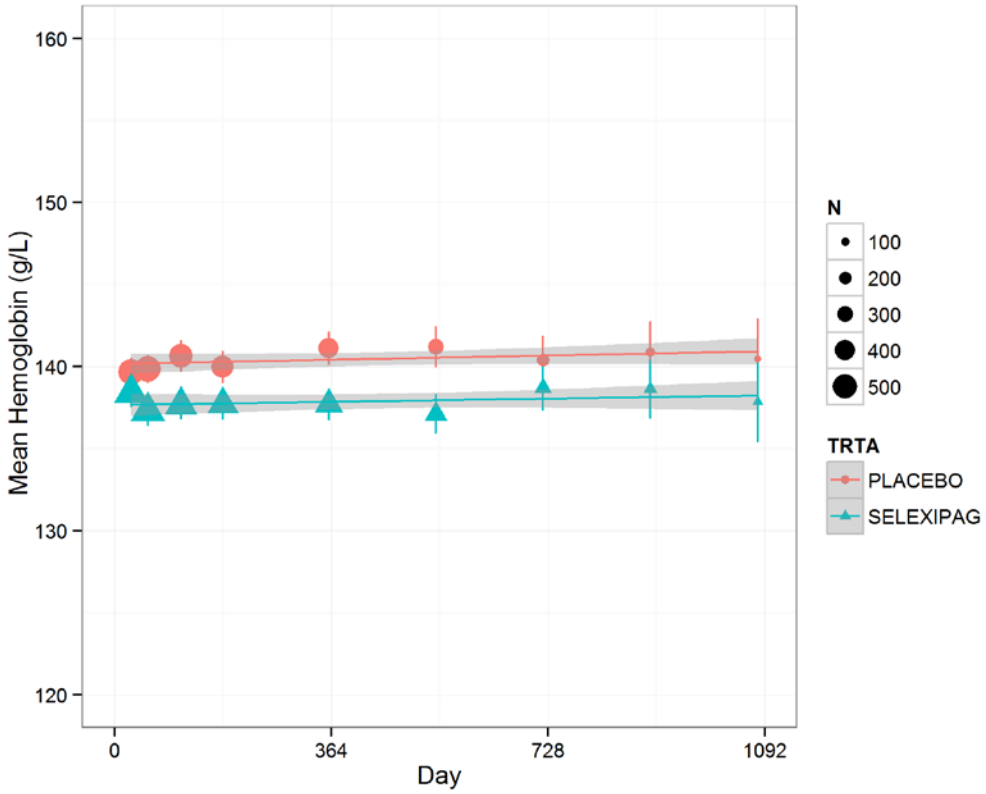
8.4.6. Laboratory Findings

Hematology

Figure 9 shows the time course of hemoglobin data for all subjects with non-missing lab values (n=555 for selexipag and n=562 for placebo). Based on linear regression, the mean decrease in hemoglobin was -2.35 g/L in the selexipag group; however, there was no trend for decreases with time (slope = -7.61e-04, p-value = 0.7) suggesting no further loss of hemoglobin. There were 7 subjects in selexipag and 5 subjects in placebo who had hemoglobin <80 mg/L.

Reference ID: 3814728

Figure 9. Mean±SE Hemoglobin *vs*. Study Day by Treatment (Safety Population, GRIPHON)

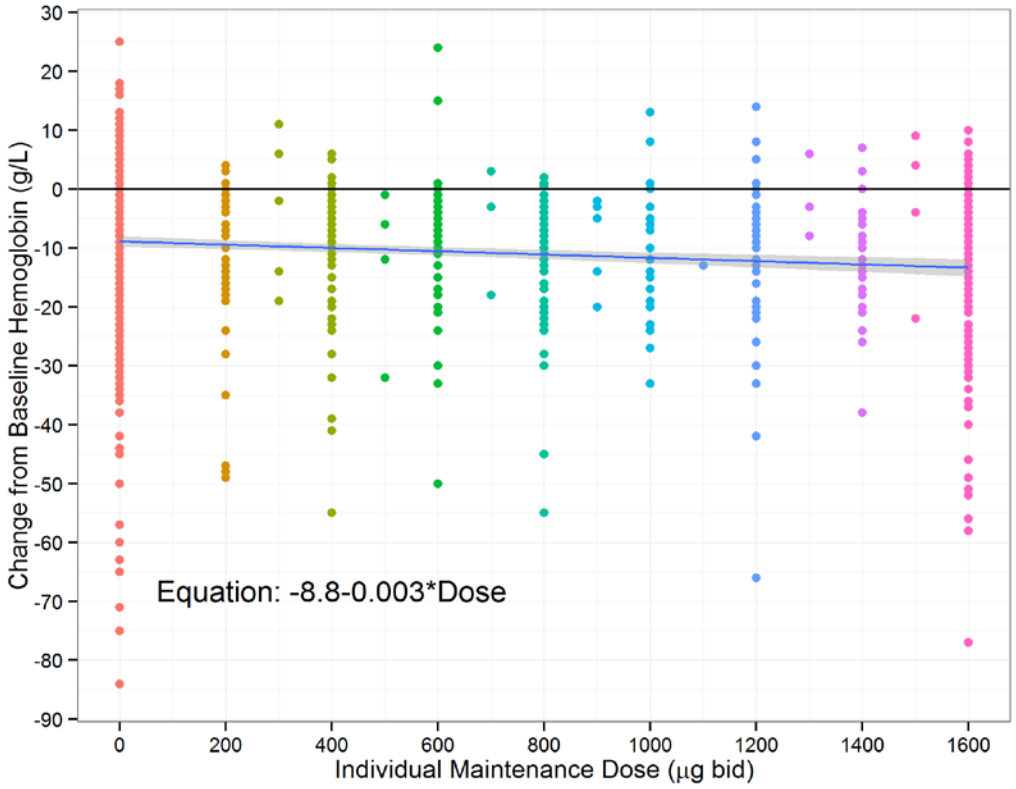


Reviewer's analysis, p.hgbvtim2.png, using dataset adhem.xpt
Scatterplot of observed data represented by filled circles for placebo and filled triangles for selexipag. The solid line is the slope of linear regression with 95% confidence interval shown by shading.

There was a trend for dose-related decreases in hemoglobin, with a slope of -0.003 g/L per µg selexipag (Figure 10). For this analysis, patients in the placebo arm were assigned a dose level of 0 µg. The covariates sex, age or race were not found to be significant (alpha = 0.05) in the regression model.

Reference ID: 3814728

Figure 10. Dose-Related Decreases in Hemoglobin



Source: Reviewer's analysis, p.hgbvDose.png, using dataset adhem.xpt
Abbreviations: bid=twice daily. Scatterplot of maximum decrease in hemoglobin, the solid line is the slope of linear regression with 95% confidence interval shown by shading.

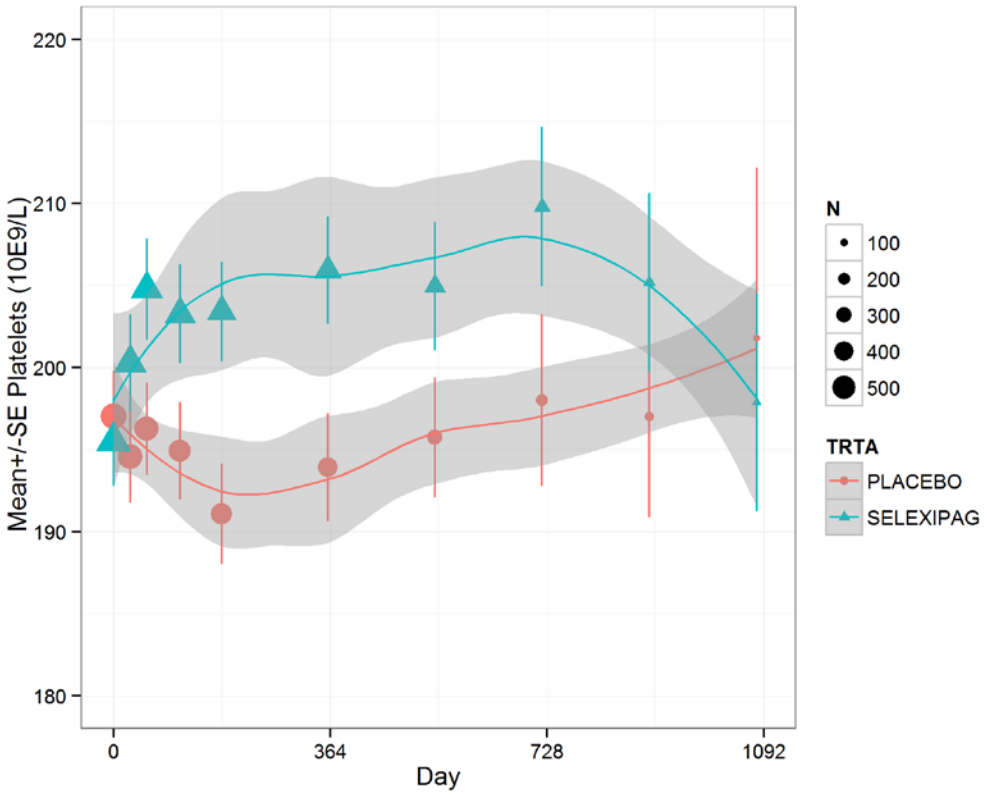
Platelets

The time course of mean platelets for selexipag and placebo groups is shown in **Figure 11**. There is no trend for platelets to decrease with time in the selexipag group. The proportion of patients who had marked decreases in platelets was similar for both treatment groups:

- Platelet count<75 GI/L: selexipag 2.2% and placebo 2.5%
- Platelet count <50 GI/L: selexipag 0.5% and placebo 0.4%

Reference ID: 3814728

Figure 11. Mean±SE Platelets vs. Study Day by Treatment (Safety Population, GRIPHON)



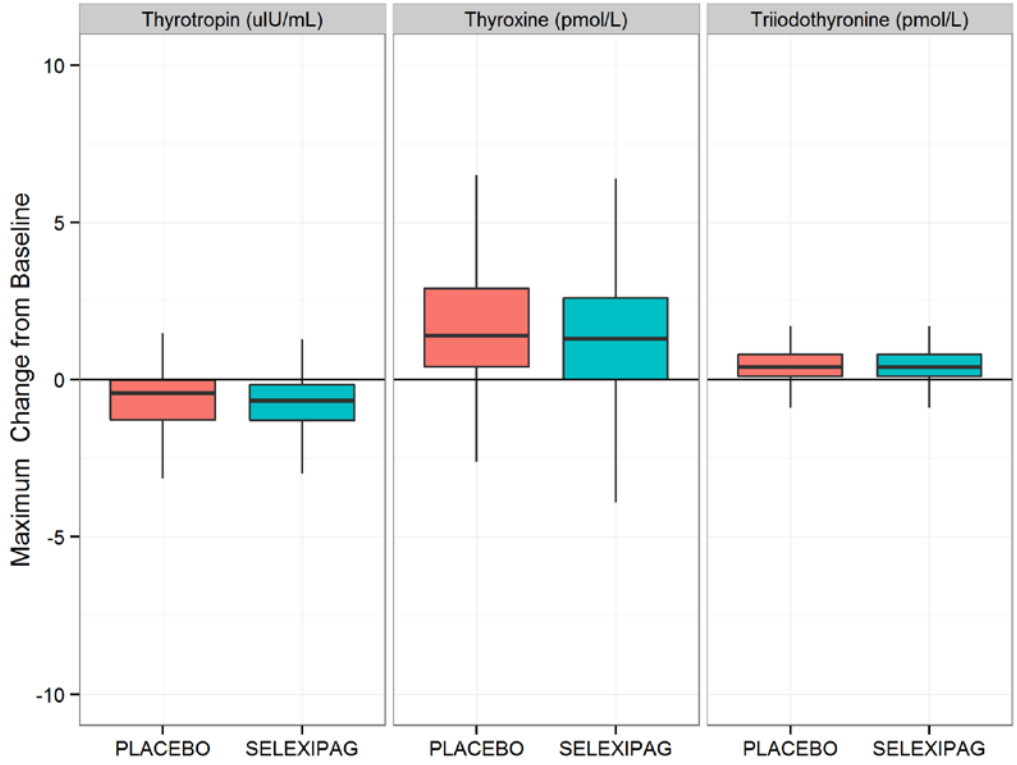
Source: Reviewer's analysis, p.Plvtim2.png, using dataset adhem.xpt
Scatterplot of observed data represented by filled circles for placebo and filled triangles for selexipag. The solid line is the loess smooth regression with 95% confidence interval shown by shading.

Thyroid Function Tests

Figure 12 shows maximum change from baseline in thyroid markers (TSH, T3 and T4) by treatment for all subjects with non-missing lab values. On a population level, there were no apparent differences in maximum change from baseline in these thyroid markers. The Applicant noted a small reduction in median TSH level (up to -0.3 MU/L from baseline) in the selexipag group at some visits (Sponsor's Figure 4 in 2.7.4 Summary of Clinical Safety).

Reference ID: 3814728

Figure 12. Boxplots of Maximum Change in Thyroid Biomarkers by Treatment in Subset of Patients with Non-Missing Data (Safety Population, GRIPHON)



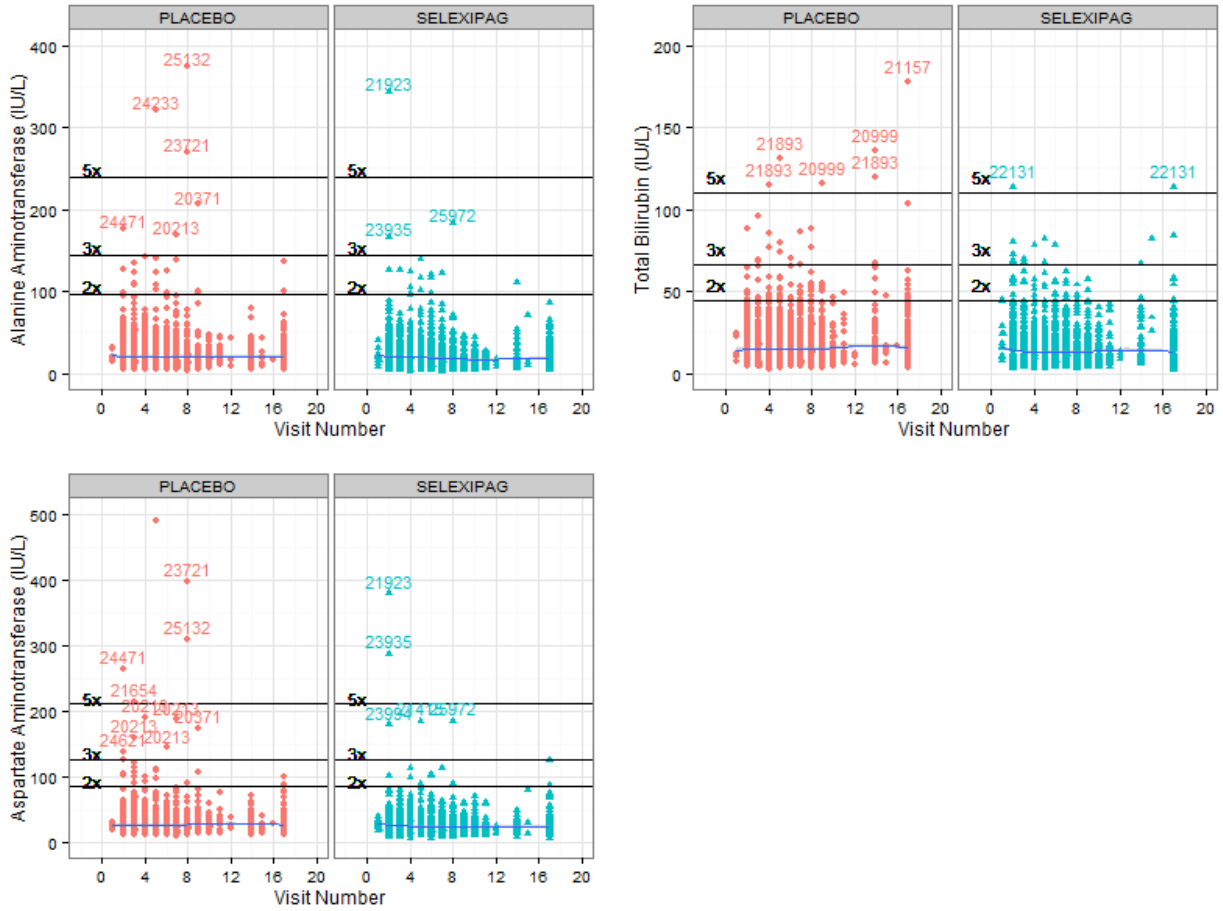
Source: Reviewer's analysis, p.THYvTRT.png based on dataset adthyr.xpt
Box represents the 25th, 50th and 75th percentile of observed data; whiskers represent 1.5*interquartile range. Data beyond end of whiskers are outliers and not plotted.
Number of subjects for thyrotropin (TSH), thyroxine (T4) and triiodohyronine (T3) are 257, 262 and 260 for placebo and 263, 264 and 264 for Selexipag, respectively.

Liver Enzymes

The frequency with marked increases in ALT, AST and Bilirubin was higher in the placebo group than in selexipag group (**Figure 13**). In the placebo group, there was one Hy's Law range case (Patient 3103-24233). The eDish plot shows that greater numbers of patients had increased ALT or increased bilirubin in the placebo group than in the selexipag group (**Figure 14**).

Reference ID: 3814728

Figure 13. Liver Function Tests by Visit Number



Reviewer's analysis, p.LFT.png based on Applicant's dataset adchem.xpt
Abbreviations: 2x=2 times upper limit normal; 3x= 3 times upper limit normal; 5x=5 times upper limit normal; IU= international units; L=liter
Scatterplot of observed data represented by filled circles for placebo and filled triangles for selexipag. The solid line is the loess smooth regression with 95% confidence interval shown by shading.
Cross reference: Table 75 in 2.7.4 Summary of Clinical Safety

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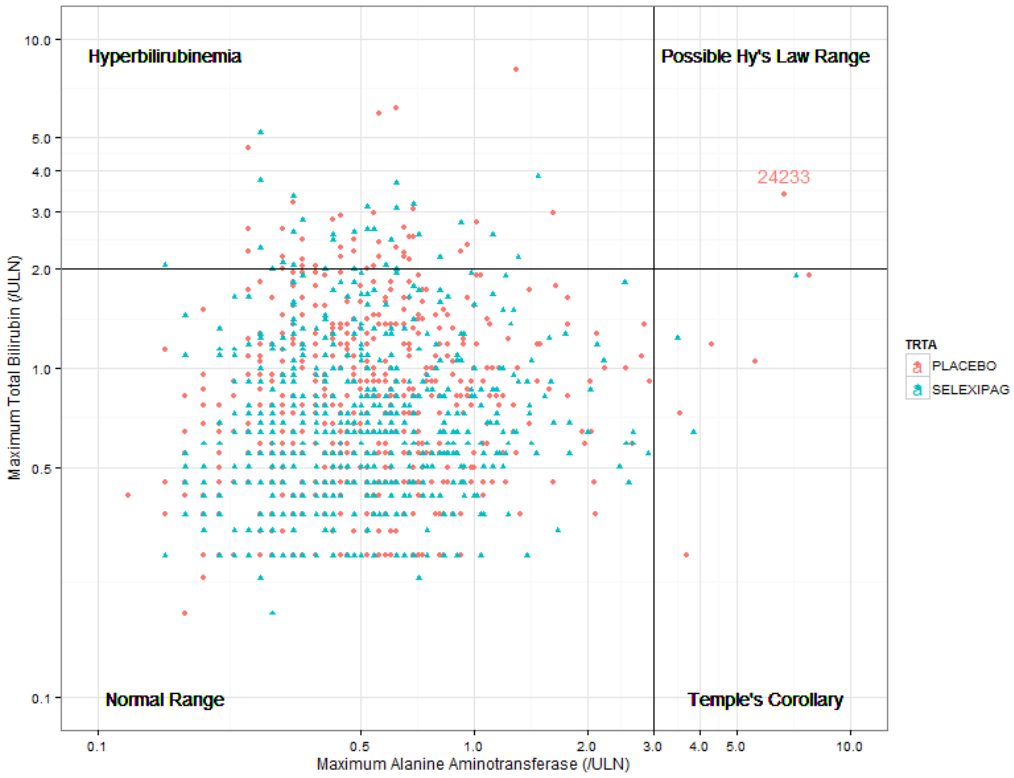
Figure 14. eDish Plot



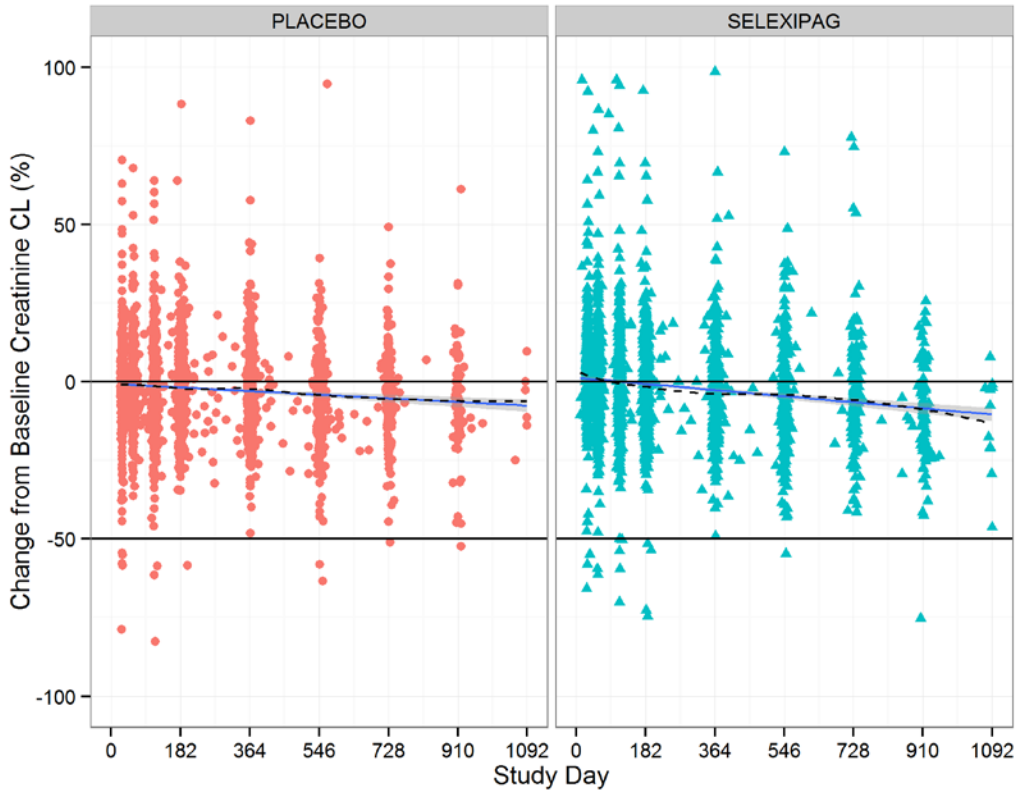
Reviewer's analysis, eDish.png based on Applicant's dataset adchem.xpt
Abbreviations: ULN=upper limit normal; TRTA=Actual Treatment Group for Safety Population.
Cross reference:

Creatinine Clearance

Creatinine clearance (CrCL) decreased over time in both treatment groups (**Figure 15**). The number of patients who had decrease in CrCL by more than 50% was the same (15 per group). Patients who had greater than 50% decreases had normal or mild renal impairment at baseline. Based on a linear regression model, there were no treatment, age or sex differences in the rate of CrCL decrease. This analysis is consistent with the Applicant's categorical analysis of abnormal creatinine levels, where 5.4% patients had creatinine >1.5 ULN compared to 6.0% patients in the placebo group (Table 12-20, CSR). Overall, there is no clinically meaningful imbalance of lab values indicating Selexipag causes renal damage.

Reference ID: 3814728

Figure 15. Scatterplot of % Change from Baseline Creatinine Clearance by Study Day (Safety Population, GRIPHON)



Reviewer's analysis, p.CRCLvTim.png based on dataset adchem.xpt.
Scatterplot of change in creatinine clearance, the solid blue line is the slope of linear regression with 95% confidence interval shown by shading and dashed black line is the loess smooth.

8.4.7. Vital Signs

Vital signs were similar between the selexipag and placebo groups. There was no safety signal detected from the vital sign data including blood pressure (***Figure 16*** and ***Figure 17***). Notable decreases from baseline in SBP (> 40 mmHg and to < 90 mmHg) were not reported more frequently in the selexipag group than in the placebo group.

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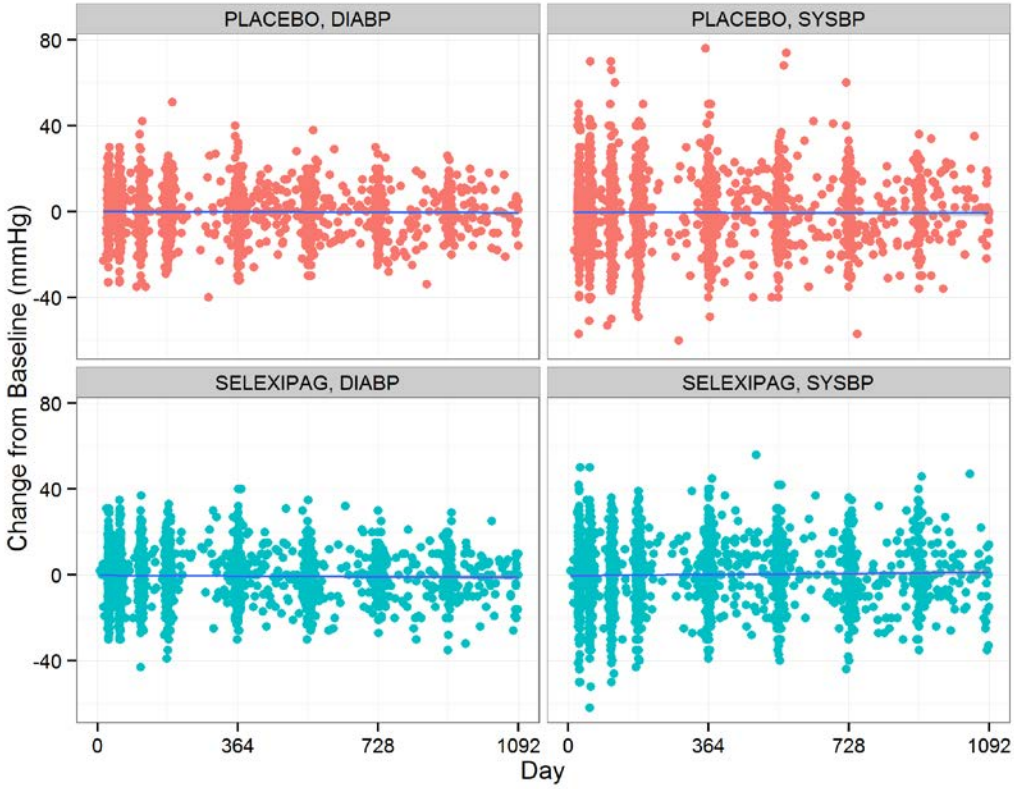
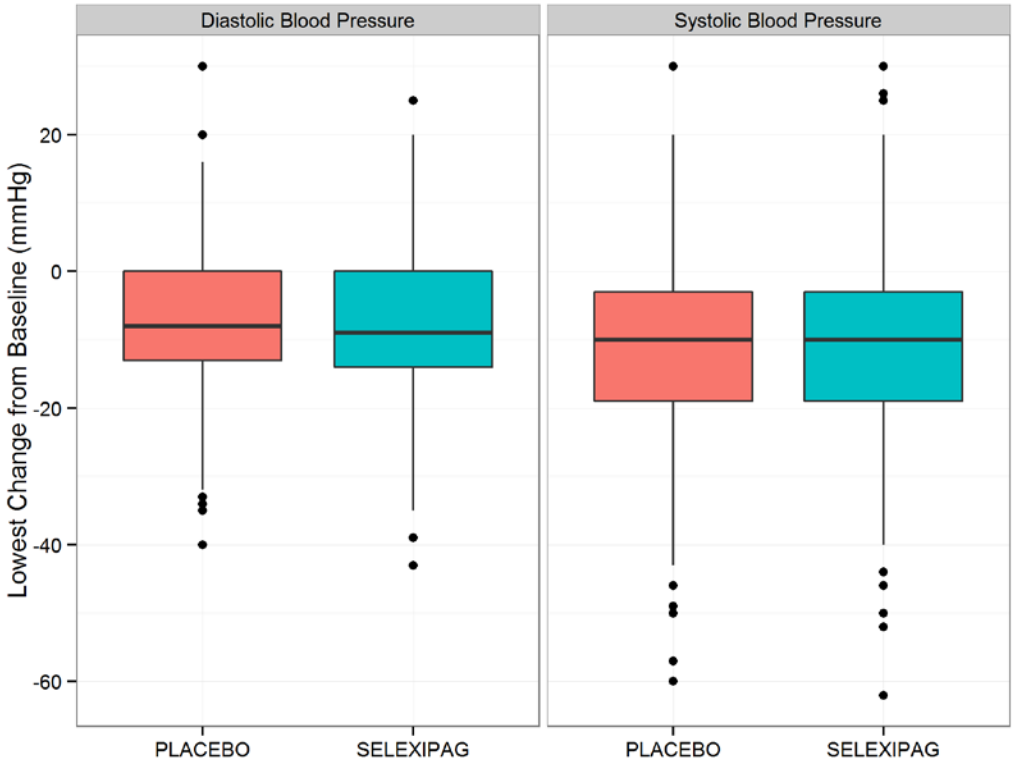
Figure 16. Time course of Change from Baseline Blood Pressure by Treatment (Safety Population, GRIPHON)



Reviewer's analysis, p.BPvTim.png based on dataset advs.xpt.
Scatterplot of change in blood pressure, the solid blue line is the loess smooth.
Abbreviations: DIABP=diastolic blood pressure; SYSBP=systolic blood pressure

Figure 17. Lowest Blood Pressure by Treatment Group (Safety Population, GRIPHON)



Reviewer's analysis, p.BPvTRT.png based on dataset advs.xpt
*Box represents the 25th, 50th and 75th percentile of observed data; whiskers represent 1.5*interquartile range. Data beyond end of whiskers are outliers.*
Number of subjects for diastolic BP and systolic BP are 526 and 536 for placebo and 529 and 532 for Selexipag, respectively.

8.4.8. Electrocardiograms (ECGs)

There were no clinically relevant differences between treatment groups in AEs/SAEs using Torsade de pointes/QT prolongations (SMQ). Negative results were found in the Thorough QT study (See Section 8.4.9).

8.4.9. QT

The FDA Interdisciplinary Review Team (IRT) reviewed the thorough QT study (AC-065-106) and found no significant QTc prolongation effect of selexipag (800 µg and 1600 µg b.i.d. The IRT noted that the highest tested dose of 1600 µg b.i.d. was unlikely to cover high exposures in patients with mild or moderate hepatic impairment or in patients receiving a strong CYP3A4 inhibitor. The possibility of QT prolongation in these scenarios cannot be ruled out based on the

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results of this study. Over the concentration range observed in this study, however, there was not a relationship between selexipag concentrations and QTc.

See IRT for QT studies consultation for more information (DARRTS date 03/25/2015).

8.4.10. Immunogenicity

Not applicable.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Eye and Retinal Disorders

Eye disorders were identified as a safety topic of special interest on the basis of nonclinical findings of tortuosity and dilatation of retinal blood vessels in rats at the end of a 2-year carcinogenicity study. There are numerical imbalances in the frequencies of eye and retinal disorders in the selexipag group compared to placebo (***Table 12).*** Sixty three (11%) patients in the selexipag group reported an eye/retinal adverse event compared to 45 (8%) patients in the placebo group. As presented in ***Table 13***, the AEs more frequently reported in selexipag group were eye pain (2%), increased lacrimation (<1%) and photophobia (<1%).

Three (<1%) patients had an SAE in the selexipag group; there were none is the placebo group. The SAEs were:

- Patient 20367 had SAEs of choroiditis (bilateral posterior uveitis) and cataract;
- Patient 22853 had an SAE of cataract; and
- Patient 21024 had SAEs of maculopathy and blurred vision.

Two patients (<1%) in the selexipag group discontinued study drug due to eye disorder AEs: Patient 22709 had diplopia and reduced visual acuity and Patient 21064 had eye pain. Four patients (%) in the selexipag group had the dose reduced due to eye disorder AE.

- Patients 21121 and 21684 had visual acuity reduced;
- Patient 24688 had photophobia; and
- Patient 25882 had increased lacrimation

Table 12. Summary of Eye and Retinal Adverse Events (Safety Population, GRIPHON)

SMQ "Retinal Disorders"	Selexipag (N=575)		Placebo (N=577)	
Patients with at least 1 AE	63	11%	45	8%
Annualized Rate (per 100 patients in 1 year)	8		5	
Patients with at least 1 serious AE	3	<1%	0	0
Patients with at least 1 AE with Fatal Outcome	0	0	0	0
Patients with at least 1 AE leading to Discontinuation	2	<1%	0	0
Patients with at least 1 AE leading to Dose Reduction	4	<1%	1	<1%

Source: Reviewer's analysis, TabDis.Eye.csv using Applicant dataset adae.xpt

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Abbreviations: AE=adverse events of special interest; N=number of patients in safety population; n=number of patients in subset; %=percentage of patients in subset
Cross reference: Table 46 in 2.7.4 Summary of Clinical Safety

Table 13. Eye Disorders with Relative Difference >0.2 by MedDRA SOC and Related PT (Safety Population, GRIPHON)

AE by MedDRA SOC and Related PT	Selexipag (N=575)		Placebo (N=577)		Relative Difference (per hundred)
EYE DISORDERS	63	11	45	8	3
Eye Pain	9	2	2	<1%	1
Lacrimation Increased	4	<1%	1	<1%	<1
Photophobia	4	<1%	1	<1%	<1
Conjunctival Hyperaemia	2	<1%	0	0	<1
Dacryostenosis Acquired	2	<1%	0	0	<1
Cataract	8	1	6	1	<1

Source: Reviewer's analysis, EyeTab.csv using Applicant dataset adae.xpt
Cross reference: Table 47 in 2.7.4 Summary of Clinical Safety

Ophthalmology Sub-study in GRIPHON

The ophthalmology sub-study was conducted in study AC-065A302 and included a total of 102 patients (54 selexipag, 48 placebo) at 33 sites in 22 countries. The assessments introduced in the sub-study included fundoscopy with digital pictures at the Baseline/Randomization Visit, Month 12 and EOS Visit (or discontinuation of study drug treatment). Fundus pictures were taken by the ophthalmologist / qualified ophthalmologist technician according to common guidelines and were transferred to an external central reading center. In case of treatment-emergent abnormal findings, the central reader could advise on additional ophthalmological check-up. The central reader had no access to clinical information or study treatment assignment at the time of evaluating the images.

No new post-baseline or worsening of baseline fundoscopy/fundus imaging findings was reported in the selexipag group. The OSB found no evidence of an increase in relevant adverse ocular effects in the selexipag group compared to the placebo group. In regards to retinal arterial tortuosity, the sub-study did not identify patients with treatment-emergent findings of this nature.

Reviewer's Comments: In response to an ophthalmology consult requested by the review team, Dr. Chambers reviewed the findings from the Ophthalmology Sub-Study and AEs related to Rentinal/Eye Disorders (Review dated 27 July 2015 in DARRTS). Specifically, Dr. Chambers noted that clinical relevance of the imbalance in reported ocular adverse events cannot be determined due to small number of events and the imbalance is driven primarily by eye pain, photophobia and retinal disorders which are of potential concern, but without a full description of the clinical circumstances, it is not possible. He recommended describing eye pain in the label. He also noted that the Ophthalmology Sub-Study included only taking and reviewing digital fundus

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pictures. There were no measures of visual function and no ascertainment of other potential ocular abnormalities. Furthermore, the Sub-study was too small to provide an adequate ocular assessment.

He recommends that any future ocular evaluation include a measurement of visual function.
Hemorrhage and Cerebrovascular Hemorrhage

Because prostacyclin receptor agonists inhibit platelet aggregation, bleeding events were identified as an AE of special interest. In vitro data showed that selexipag and its active metabolite (ACT-333679) had inhibitory effects on human platelet aggregation. AEs associated with bleeding events were independently adjudicated by two external expert medical reviewers who were blinded to the study treatment assignment and prostacyclin-like AEs. Individual AE were selected by PT belonging to MedDRA SMQ Hemorrhage (ex. Laboratory terms) and Gastrointestinal Hemorrhage. Each bleeding event was adjudicated as major or non-major according to ISTH criteria as described in Safety Review Approach, Section *8.1*.

The frequency of bleeding disorders in the selexipag and placebo groups was similar (***Table 14***). Ninety (16%) patients in the selexipag group reported a bleeding adverse event compared to 91 (16%) patients in the placebo group. As presented in ***Table 15***, the AEs more frequently reported in selexipag group compared to placebo were hematoma (<1%) and haematuria (<1%).

There was no difference in the frequency of adjudicated major bleeding; there were 14 (2%) patients with major bleed in selexipag and 12 (2%) patients in placebo. There was, however, a numerical imbalance in the selexipag group for cerebrovascular hemorrhage. Four patients had cerebrovascular hemorrhages that were adjudicated as major bleeding.

- Patient 6802-22582 died due to intracranial hemorrhage. The event was reported in the context of craniocerebral injury due to road traffic accident (the patient was a passenger).
- Patient 1002-20361 on concomitant warfarin therapy experienced a spontaneous subdural hematoma leading to a road traffic accident.
- Patient 1601-21242 had chronic subdural hematoma requiring surgical evacuation. Concomitant treatment with warfarin (initiated in 2007) was discontinued on the reported onset date of subdural hematoma. The event resolved while study drug was ongoing at an unchanged selexipag dose.
- Patient 4106-22372 had a subarachnoid hemorrhage that occurred following syncope attacks, reportedly due to multiple doses of opioid analgesics. He was receiving concomitant phenprocoumon and had an international normalized ratio (INR) of 4.9.

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Table 14. Summary of Combined Hemorrhage and Cerebrovascular Hemorrhage Adverse Events (Safety Population, GRIPHON)

SMQ Heamorrhage (ex. Laboratory terms) and Gastrointestinal Haemorrhage	Selexipag (N=575)		Placebo (N=577)	
Patients with at least 1 AE	90	16%	91	16%
Annualized Rate (per 100 patients treated in 1 year)	11		11	
Patients with at least 1 serious AE	23	4%	20	4%
Patients with at least 1 AE with Fatal Outcome	2	<1%	1	<1%
Patients with at least 1 AE leading to Discontinuation	3	<1%	4	<1%

Source: Reviewer's analysis, TabDis.Heme.csv using Applicant dataset adae.xpt
Abbreviations: AE=adverse events; N=number of patients in safety population; n=number of patients in subset; %=percentage of patients in subset
Cross reference: Tables 50 and 56 in 2.7.4 Summary of Clinical Safety

Table 15. Combined Hemorrhage and Cerebrovascular Hemorrhage Adverse Events with Relative Difference >0.2 by MedDRA SOC and Related PT (Safety Population, GRIPHON)

AE by MedDRA SOC and Related PT	Selexipag (N=575)		Placebo (N=577)		Relative Difference (per hundred)
	n	%	n	%	
VASCULAR DISORDERS	6	1.04	1	0.17	0.87
Haematoma	5	0.87	1	0.17	
Haemorrhage	1	0.17	0	0	
RENAL AND URINARY DISORDERS	4	0.7	1	0.17	0.53
Haematuria	3	0.52	1	0.17	
Haemorrhage Urinary Tract	1	0.17	0	0	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	7	1.22	4	0.69	0.53
Blood Blister	1	0.17	0	0	
Ecchymosis	3	0.52	2	0.35	
Petechiae	3	0.52	1	0.17	
Skin Haemorrhage	0	0	1	0.17	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	14	2.43	11	1.91	0.52
Contusion	7	1.22	7	1.21	
Periorbital Haematoma	3	0.52	1	0.17	
Post Procedural Haematoma	1	0.17	0	0	
Post Procedural Haemorrhage	1	0.17	0	0	
Procedural Haemorrhage	0	0	1	0.17	
Subcutaneous Haematoma	2	0.35	1	0.17	
Subdural Haematoma[1]	***2***	***0.35***	***0***	***0***	
Traumatic Haematoma	0	0	1	0.17	
NERVOUS SYSTEM DISORDERS	3	0.52	0	0	0.52
Cerebrovascular Accident	1	0.17	0	0	

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AE by MedDRA SOC and Related PT	Selexipag (N=575)		Placebo (N=577)		Relative Difference (per hundred)
	n	%	n	%	
Haemorrhage Intracranial[1]	***1***	***0.17***	***0***	***0***	
Subarachnoid Haemorrhage[1]	***1***	***0.17***	***0***	***0***	

Source: Reviewer's analysis, hemTab.csv using Applicant dataset adae.xpt
[1]Classified as Cerebrovascular Hemorrhage by the Applicant
Abbreviations: AE=adverse events; N=number of patients in safety population; n=number of patients in subset; %=percentage of patients in subset
Cross reference: Tables 51 and 56 in 2.7.4 Summary of Clinical Safety

In Pool 2, there were 13 additional patients treated with selexipag who had hemorrhage SAEs, of which 4 had a fatal outcome. Four of the SAEs were also reported as AEs leading to discontinuation of study treatment. Three of the hemorrhage SAEs with a fatal outcome were reported in study AC-065A303, and the fourth was reported in study NS-304/-03.
Patient 3802-22434 (selexipag/selexipag) had SAEs of esophageal hemorrhage and GI hemorrhage. The SAE of esophageal hemorrhage reported on Day 76 was resolved on Day 190. On Day 273, the patient had the SAE of GI hemorrhage, which led to study treatment discontinuation on Day 297 (fatal outcome).

- Patient 6601-22133 (selexipag/selexipag) died due to SAEs of disseminated intravascular coagulation and upper GI hemorrhage. The SAEs were reported on Day 21. The patient was receiving warfarin at baseline in the core study (AC-065A302). The patient received warfarin and vitamin K during the study.
- Patient 7002-22739 (selexipag/selexipag) died due to an SAE of post-procedural hemorrhage. The SAE was reported on Day 142 and was associated with kidney biopsy. The patient received heparin during the study.
- Patient 005-004 (selexipag/selexipag) had an SAE of subdural hematoma that required surgical evacuation. The patient received acenocoumarol during the study. Subsequently, the patient died due to cardiac arrest.

There were 2 cerebrovascular hemorrhage AEs reported in study NS-304/-03, one of which was fatal.

- Patient 005-004 (fatal SAE, described above)
- Patient 002-005 (selexipag/selexipag) had an SAE of subdural hematoma due to head trauma. It was reported by the investigator that head injury was due to fall probably related to acute alcohol abuse. The patient had a medical history of GI hemorrhage due to polyp in colon and received warfarin during the study.

Reviewer's Comments: Based on review of the clinical data for the patients who experienced cerebrovascular hemorrhage, these events do not appear to be related to selexipag treatment.

- *Blinded adjudication of bleeding events did not show an increased risk of major bleeding events in patients who received selexipag. The proportion of patients with major bleeding events was similar in both groups.*

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- *Of the four patients with cerebrovascular hemorrhage in DB study, one patient was in a car accident and the other three patients were taking concomitant anticoagulants (warfarin or phenprocoumon).*
- *There was no indication of increased bleeding risk with concomitant use of warfarin. A drug-interaction study with selexipag and warfarin (study QGUY/2006/NS304/-01 Part D) showed neither a pharmacokinetic nor pharmacodynamic interaction between selexipag and warfarin.*
- *Patient 1601-21242 discontinued warfarin but maintained selexipag at unchanged dose after the hematoma. The event resolved.*
- *Patient 4106-22372 was taking phenprocoumon and had an INR of 4.9 at time of the hemorrhage.*
- *In study AC-065-101, multiple-dose administrations of selexipag in healthy subjects had no relevant effect on platelet aggregation test parameters across doses from 400 µg up to 1800 µg b.i.d.*

8.5.2. Cerebrovascular Ischemia

The analysis of cerebrovascular ischemia using the SMQ "Ischaemic cerebrovascular conditions" is presented in ***Table 16***. There was an imbalance in the incidence of cerebrovascular events in selexipag-treated patients, which was driven by cerebrovascular ischemic events. There were 6 patients with such events, 5 in the selexipag group and 1 in the placebo group. Patients in the selexipag group were:

- Patient 7102-23096 was 67 y/o Asian female who had a cerebral infarction SAE. Medical history included thrombosis and arrhythmia.
- Patient 4902-23842 was a 30 y/o Caucasian female who had a transient ischemic attack SAE. The INR at the time of the event indicated that her warfarin treatment was suboptimal.
- Patient 7003-22761 was a 27 y/o Caucasian male who had an ischemic stroke SAE and was receiving no concomitant anticoagulant despite having an atrial septal defect and tricuspid valve incompetence.
- Patient 7301-23906 was a 58 y/o Caucasian female who had transient ischemic attack and cerebrovascular accident SAEs. Medical history included mitral valve incompetence, rheumatoid arthritis with vasculitis and essential hypertension. The events also resulted in discontinuation of study treatment.
- Patient 1601-21236 was a 40 y/o Caucasian female who had a non-serious transient ischemic attack AE. Medical history that included atrial tachycardia (treated by radiofrequency ablation) and ventricular septal defect.

In the placebo group, Patient 2003-21531 was a 30 y Caucasian female who had a thalamic infarction SAE. Medical history included factor V Leiden mutation and atrial septal defect.

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Table 16. Summary of Cerebrovascular Ischemia Adverse Events (Safety Population, GRIPHON)

SMQ "Ischaemic cerebrovascular conditions"	Selexipag (N=575)		Placebo (N=577)	
Patients with at least 1 AE	5	<1%	1	<1%
Annualized Rate (per 100 patients in 1 year)	0.6		0.1	
Patients with at least 1 serious AE	4	<1%	1	<1%
Patients with at least 1 AE with Fatal Outcome	0	0	0	0
Patients with at least 1 AE leading to Discontinuation	1	<1%	0	0

Source: Reviewer's analysis, TabDis.tia.csv, using Applicant dataset adae.xpt
Abbreviations: AE=adverse events; N=number of patients in safety population; n=number of patients in subset; %=percentage of patients in subset
Cross reference: Table 59 in 2.7.4 Summary of Clinical Safety

One additional cerebrovascular ischemia AE (cerebrovascular infarction) was reported in the Pool 2 studies. Patient 4501-23694 (selexipag/selexipag) in study AC-065A303 had an AE of cerebral infarction on Day 456. The patient discontinued study treatment on Day 649 due to an SAE of PAH worsening.

Reviewer's Comments: The cerebrovascular ischemic events in the selexipag group occurred in patients who, based on their medical history, had an elevated risk of such events.

Reviewer's Sensitivity Analysis for Cerebrovascular Hemorrhage and Ischemia

Sensitivity analysis did not identify any other patients with the relevant cerebrovascular AEs in GRIPHON DB study (***Table 17***).

Table 17. Sensitivity Analysis of Cerebrovascular Ischemia Adverse Events

FDA AE Categories	Selexipag (N=575)		Placebo (N=577)	
Intracranial hemorrhage (includes hemorrhagic stroke, SAH, SDH	4	0.70%	0	0
Stroke, TIA	5	0.87%	1	0.17%

Analysis was based on grouping the following PTs: brain stem haemorrhage, brain stem infarction, cerebellar haemorrhage, cerebellar infarction, cerebral infarction cerebrovascular accident, embolic cerebral infarction, embolic stroke, haemorrhagic cerebral infarction, haemorrhagic stroke, haemorrhagic transformation stroke, ischaemic cerebral infarction, ischaemic stroke, lacunar infarction, thalamic infarction, thrombotic cerebral infarction, thrombotic stroke, transient ischaemic attack.
Abbreviations: SAH=subarachnoid hemorrhage; SDH=subdural hematoma; TIA=transient ischemic attack.

8.5.3. Anemia

There was an imbalance in the incidence of anemia-related adverse events in selexipag group with 10% patients with at least one adverse event *vs*. 8% in the placebo group (***Table 18***). None of the AEs were fatal or led to discontinuation of treatment. All patients with serious anemia AE received blood transfusions.

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Table 18. Summary of Anemia-Related Adverse Events (Safety Population, GRIPHON)

SMQs "Haematopoietic erythropenia" (including both narrow and broad PTs) and "Haematopoietic cytopenias affecting more than one type of blood cell", or a PT containing the text "Anaemia"	Selexipag (N=575)		Placebo (N=577)	
Patients with at least 1 AE	60	10%	46	8%
Annualized Rate (per 100 patients in 1 year)	8		5	
Patients with at least 1 serious AE	6	1%	3	<1%
Patients with at least 1 AE with Fatal Outcome	0	0	0	0
Patients with at least 1 AE leading to Discontinuation	0	0	0	0

Source: Reviewer's analysis, TabDis.Anemia.csv using Applicant dataset adae.xpt
Abbreviations: AE=adverse events; N=number of patients in safety population
Cross reference: Table 61 in 2.7.4 Summary of Clinical Safety

The incidence of events by MedDRA SOC and related PT is presented in **Table 19**. The most common AE was anemia, with 8% patient having the AE in selexipag vs. 5% in placebo.

Table 19. Anemia-Related Adverse Events with Relative Difference >0.2 by MedDRA SOC and Related PT (Safety Population, GRIPHON)

AE by MedDRA SOC and Related PT	Selexipag (N=575)		Placebo (N=577)		Relative Difference (per hundred)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	56	10%	44	8%	2
Anaemia	48	8%	31	5%	3
Iron Deficiency Anaemia	5	<1%	15	3%	-2
INVESTIGATIONS	5	<1%	2	<1%	<1
Haematocrit Decreased	3	<1%	1	<1%	<1
Haemoglobin Decreased	3	<1%	2	<1%	<1

Source: Reviewer's analysis, TabDis.Anemia.csv using Applicant dataset adae.xpt
Abbreviations: AE=adverse events of special interest; N=number of patients in safety population; n=number of patients in subset; %=percentage of patients in subset
Cross reference: Table 62 in 2.7.4 Summary of Clinical Safety

Analysis of hemoglobin data is presented in Laboratory Findings, Section 8.4.6. There were small decreases in hemoglobin in the selexipag group, with a mean decrease of -0.3 g/dL. There was no apparent decrease with time. Furthermore, there was a shallow dose-response for change from baseline in hemoglobin providing evidence that these changes are related to selexipag treatment.

In study AC-065A303, anemia AEs (PTs: anemia, iron deficiency anemia, pancytopenia, and decreased hemoglobin) were reported for 16/218 (7%) patients. Of these patients, 2 had received DB selexipag treatment and 14 had received DB placebo treatment. In study NS-304/-

02, no anemia AEs were reported. In Pool 2, additional SAEs were reported in 2 patients, both in study NS-304/-03.

Reviewer's Comments: Although the mechanism is not fully understood, drugs used to treat PAH have been associated with anemia. The ERAs have anemia and dose-related decreases in hemoglobin resulting in hemoglobin monitoring in the label. The mean change from baseline hemoglobin was around -1 g/dL for macitentan, abrisentan and bosentan. Epoprostenol and riociguat are also associated with anemia, but not labeled with hemoglobin monitoring.

The applicant has not proposed language regarding anemia or hemoglobin monitoring in section 5 of selexipag label. Instead, anemia and hemoglobin decreases are reported as adverse reactions in section 6.1. This is acceptable because the mean change in hemoglobin is small (-0.3g/dL) and the incidence of anemia was low (8% for selexipag vs. 5% for placebo). Furthermore, there was not an imbalance in the number of patients reporting blood transfusions.

8.5.4. Thrombocytopenia

Thrombocytopenia is an AE of special interest due to the antiplatelet effect of selexipag. Slight decreases in platelet counts were observed in rats and dogs during nonclinical studies.

The overall proportions of patients with thrombocytopenia adverse events were similar in the selexipag and placebo groups. There were 2% patient in both selexipag and placebo with at least 1 adverse event (***Table 20***). Analysis of platelet lab data showed no trend for mean decreases in platelet counts in the selexipag group (***Figure 11*** in Section 7.4.2.1). The proportion of patients with marked decreases in platelets (<75 GI/L or <50 GI/L) was similar in both treatment groups.

Table 20. Summary of Thrombocytopenia Adverse Events (Safety Population, GRIPHON)

SMQs "Haematopoietic thrombocytopenia" (including both narrow and broad PTs) and "Haematopoietic cytopenias affecting more than one type of blood cell"	**Selexipag (N=575)**		**Placebo (N=577)**	
Patients with at least 1 AE	10	2%	11	2%
Annualized Rate (per 100 patients in 1 year)	5		4	
Patients with at least 1 serious AE	2	<1%	0	0
Patients with at least 1 AE with Fatal Outcome	0	0	0	0
Patients with at least 1 AE leading to Discontinuation	0	0	0	0

Source: Reviewer's analysis, TabDis.Throm.csv using Applicant dataset adae.xpt
Abbreviations: AE=adverse events; N=number of patients in safety population; n=number of patients in subset; %=percentage of patients in subset
Cross reference: Table 66 in 2.7.4 Summary of Clinical Safety

In study AC-065A303, AEs of decreased platelet count, thrombocytopenia, and pancytopenia were reported for 3 patients (1.4%), 2 patients (0.9%), and 1 patient (0.5%), respectively. No

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thrombocytopenia AEs were reported in the DB study NS-304/-02 and its OL extension NS-304/-03.

Reviewer's Comment: The thrombocytopenia AE data and the platelet count data do not suggest that selexipag has any effect on platelets at clinically relevant doses.

8.5.5. Hypotension

Hypotension was evaluated as an AE of special interest because of the vasodilatory effects of selexipag. Hypotension is a class effect of IP receptor agonists.

There are numerical imbalances in the frequencies of hypotension AEs in the selexipag group compared to placebo (***Table 21***). Thirty-six (6%) patients in the selexipag group reported an adverse event compared to 23 (4%) patients in the placebo group. As presented in ***Table 22***, the AEs more frequently reported in selexipag group were hypotension (5%) and orthostatic hypotension (1%). Clinically relevant cases (i.e., those with a fatal outcome, or those that were serious, or led to discontinuation of treatment or dose reduction) were reported for a similar proportion of patients in both treatment groups.

One patient had a serious AE with fatal outcome in the selexipag group. Patient 4902-23845 had MCTD and was receiving selexipag 200 µg b.i.d. and concomitant treatment with colchicine. She was hospitalized on Day 14 in a 'deteriorated' condition and died the same day. The reported causes of death were hypotension, hypoglycemia (blood glucose 35 mg/dL on admission), and bradycardia. The adjudicated cause of death was bradycardia.

The three other patients with SAEs in the selexipag group were:

- Patient 4001-20032 had hypotension and syncope (Day 329) due to dehydration following virtual colonoscopy investigation;
- Patient 1302-20785 had exertional syncope followed by an episode of hypotension (Day 40) and circulatory collapse; and
- Patient 2005-21596 had orthostatic hypotension and syncope.

Table 21. Summary of Hypotension Adverse Events (Safety Population, GRIPHON)

Grouped Preferred Terms for AEs	Selexipag (N=575)		Placebo (N=577)	
Patients with at least 1 AE	34	6%	22	4%
Annualized Rate (per 100 patients treated in 1 year)	4		3	
Patients with at least 1 serious AE	4	<1%	4	<1%
Patients with at least 1 AE with Fatal Outcome	1	<1%	0	0
Patients with at least 1 AE leading to Discontinuation	0	0	2	<1%
Patients with at least 1 AE leading to Dose Reduction	5	<1%	4	<1%

Source: Reviewer's analysis, TabDis.Hypo.csv using Applicant dataset adae.xpt
Abbreviations: AE=adverse events; N=number of patients in safety population; n=number of patients in subset; %=percentage of patients in subset

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Grouped PTs: Blood pressure ambulatory decreased, Blood pressure decreased, Blood pressure diastolic decreased, Blood pressure orthostatic decreased, Blood pressure systolic decreased, Diastolic hypotension, Hypotension, Mean arterial pressure decreased, Orthostatic hypotension, Procedural hypotension
Cross reference: Table 67 in 2.7.4 Summary of Clinical Safety

Table 22. Hypotension AEs with Relative Difference >0.2 by MedDRA SOC and Related PT (Safety Population, GRIPHON)

AE by MedDRA SOC and Related PT	Selexipag (N=575)		Placebo (N=577)		Relative Difference (per hundred)
	n	%	n	%	
VASCULAR DISORDERS	34	6%	21	4%	2
Hypotension	29	5%	18	3%	1
Orthostatic Hypotension	5	<1%	3	<1%	<1

Source: Reviewer's analysis, HypoTab.csv using Applicant dataset adae.xpt
Cross reference: Table 68 in 2.7.4 Summary of Clinical Safety

A slightly higher proportion of hypotension AEs in selexipag group vs. placebo group for patients who were receiving ERA and PDE5i therapy at baseline: 8.4% for selexipag vs. 3.0% for placebo (Applicant's Table 69 in 2.7.4 Summary of Clinical Safety, page 143).

The proportion of patients who had at least 1 hypotension AE in the selexipag group in Pool 2 was 6.5% compared to 5.9% in Pool 1. The slightly higher incidence of such AEs in Pool 2 was mainly driven by the AE PT hypotension. In addition to the events reported in Pool 1, one patient (Patient 3802-22434) in study AC-065A303 had a hypotension AE reported as serious. No patient discontinued study treatment due to hypotension AEs.

One serious event of symptomatic hypotension was reported in a healthy female subject in the Phase 1 TQT study (AC-065-106). The event occurred while study medication was progressively up-titrated to 1200 µg b.i.d. and resolved on the same day. Study drug was discontinued. In addition, 3 female subjects in the same study also discontinued study treatment due to non-serious hypotension events.

Reviewer's Comment: Although hypotension is considered to be a class effect of all PAH drugs, the clinical data shows selexipag has little effects on blood pressure (SBP and DBP) and the frequency of AEs were similar in selexipag and placebo groups. There was no pattern of hypotension AEs based on background treatment with ERAs and/or PDE5i. (b) (4) (b) (4) *there was no sub-group analysis of hypotension AEs and patient taking hypertensive con-meds.*

8.5.6. Thyroid Disorders

Thyroid disorders were evaluated as an AE of special interest on the basis of findings in 24-month carcinogenicity studies conducted in mice and rats, in which there was an increased

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incidence of thyroid adenomas. An analysis of the SMQ "Hyperthyroidism" is presented in ***Table 23***. The overall proportions of patients with such events in the selexipag and placebo groups were 15 patients (3%) and 8 patients (1%), respectively. AEs of hyperthyroidism and Basedow's disease were only reported in the selexipag group (***Table 24***).

The two patients in the selexipag group with SAEs were:

- Patient 4903-23873 reported hyperthyroidism 11 months after the start of treatment, with concurrent diagnoses of autoimmune thyroiditis and thyroid adenoma. Decreased TSH (from 0.92 MU/L at Baseline to 0.015 MU/L on Day 330) and increased free T3 (from 5.2 pmol/L at Baseline to 9.55 pmol/L on Day 330) were recorded for the patient. Selexipag was discontinued and the events were reported as resolved 3 weeks later.
- Patient 7001-22727 reported Basedow's disease 12 months after start of Selexipag treatment. The patient had decreased TSH (from 1.53 MU/L at Baseline to < 0.04 MU/L on Day 370 and 0.01 MU/L on Day 420) and increased free T3 (from 5.2 pmol/L at Baseline to > 16.9 pmol/L on Day 370 and Day 420). Treatment with metoprolol and thiamazole was initiated on Day 412. The event remained unresolved, and the patient continued treatment with selexipag.

Table 23. Summary of Thyroid Adverse Events (Safety Population, GRIPHON)

SMQ "Hyperthyroidism"	Selexipag (N=575)		Placebo (N=577)	
Patients with at least 1 AE	15	3%	8	1%
Annualized rate (per 100 patients treated in 1 year)	2		1	
Patients with at least 1 serious AE	2	<1%	0	0
Patients with at least 1 AE with Fatal Outcome	0	0	0	0
Patients with at least 1 AE leading to Discontinuation	1	<1%	1	<1%
Patients with at least 1 AE leading to Dose Reduction	0	0	1	<1%

Source: Reviewer's analysis, TabDis.Thyroid.csv using Applicant dataset adae.xpt
Abbreviations: AE=adverse events; N=number of patients in safety population
Cross reference: Table 71 in 2.7.4 Summary of Clinical Safety

Table 24. Hyperthyroidism AEs with Relative Difference >0.2 by MedDRA SOC and Related PT (Safety Population, GRIPHON)

AE by MedDRA SOC and Related PT	Selexipag (N=575)		Placebo (N=577)		Relative Difference (per hundred)
	n	%	n	%	
Endocrine Disorders	10	1.74	1	0.17	1.57
Hyperthyroidism	8	1.39	0	0	1.39
Autoimmune Thyroiditis	2	0.35	0	0	0.35

Source: Reviewer's analysis, X.csv using Applicant dataset adae.xpt
Cross-reference: Table 72 in in 2.7.4 Summary of Clinical Safety

Analysis of the thyroid markers (TSH, T3 and T4) by treatment for all subjects with non-missing lab values is shown in ***Figure 12*** in Laboratory Findings, Section 8.4.6. Additionally, there was no trend for decreases in TSH or increases in T3 or T4 by treatment, dose, age and sex.

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There were 3 additional non-serious AEs were reported in study AC-065A303 in patients who had received DB placebo treatment (hyperthyroidism, goiter, and chronic thyroiditis). The patient with the hyperthyroidism AE had a medical history of thyrotoxicosis (hyperthyroidism) and initiated treatment with thiamzol in response to the event. No hyperthyroidism AEs were reported in other studies.

Reviewer's Comments: The proposed mechanism for hyperthyroidism is susceptibility to autoimmune disease in PAH patients. According to a literature review by the Applicant as part of an information request issued by FDA on 04 May 2015, a substantial proportion of PAH patients have co-existing thyroid disease: 19–51% of PAH patients vs. 13% in general population. Cases of hyperthyroidism have been reported for epoprostenol during post-marketing use. In GRIPHON study, patients who developed hyperthyroidism either discontinued selexipag treatment (1 patient with SAE) or remained on selexipag without dose adjustments (9 patients). The Applicant is not recommending selexipag dose adjustments as part of the treatment of hyperthyroidism. (b) (4)

8.5.7. Liver Disorders

Liver disorders are common comorbidities in patients with PAH as a result of congestive hepatopathy due to increased central venous pressure resulting from right heart failure. Common symptomology is hepatic congestion and ascites.

The overall proportions of patients with liver adverse events in the selexipag and placebo groups were 7% and 6%, respectively (***Table 25***). There were more serious AEs in the selexipag group compared to placebo, although none of the serious AEs had a fatal outcome.

Table 25. Summary of Liver Disorder Adverse Events (Safety Population, GRIPHON)

	Selexipag (N=575)		Placebo (N=577)	
	n	%	n	%
Patients with at least 1 AE	42	7%	37	6%
Annualized rate (per 100 patients treated in 1 year)	5		4	
Patients with at least 1 serious AE	6	1%	3	<1%
Patients with at least 1 AE with Fatal Outcome	0	0	0	0
Patients with at least 1 AE leading to Discontinuation	0	0	2	<1%

Source: Reviewer's analysis, TabDis.Heme.csv using Applicant dataset adae.xpt
Abbreviations: AE=adverse events of special interest; N=number of patients in safety population; n=number of patients in subset; %=percentage of patients in subset
Cross reference: Table 73 in 2.7.4 Summary of Clinical Safety

The incidence of events by MedDRA SOC and related PT is presented in **Table 26**. The most common AEs were within the SOC of hepatobiliary disorders with 4% patients having an AE in

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selexipag vs. 2% in placebo. The AEs reported more frequently in the Selexipag group are ascites, hyperbilirubinaemia and hepatic cirrhosis.

Table 26. Incidence of Liver Disorder Adverse Events by SOC and Related PT

AE by MedDRA SOC and Related PT	Selexipag (N=575)		Placebo (N=577)		Relative Difference (per hundred)
	n	%	n	%	
HEPATOBILIARY DISORDERS	21	3.65	13	2.25	1.4
Drug-Induced Liver Injury	1	0.17	2	0.35	-0.18
Hepatic Cirrhosis	3	0.52	0	0	0.52
Hepatic Function Abnormal	2	0.35	1	0.17	0.18
Hepatic Steatosis	2	0.35	0	0	0.35
Hepatomegaly	3	0.52	3	0.52	0
Hyperbilirubinaemia	4	0.7	1	0.17	0.53
GASTROINTESTINAL DISORDERS	7	1.22	2	0.35	0.87
Ascites	7	1.22	1	0.17	1.05
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1	0.17	0	0	0.17
INVESTIGATIONS (Elevated LFTs)	20	3.48	24	4.16	-0.68

Source: Reviewer's analysis, TabDis.Heme.csv using Applicant dataset adae.xpt
Abbreviations: N=number of patients in safety population; n=number of patients in subset; %=percentage of patients in subset
Cross reference: Table 74 in 2.7.4 Summary of Clinical Safety

Elevated liver function tests were more frequent in the placebo group. Plots of ALT, AST and Total Bilirubin are presented in Section 7.4.2, ***Figure 13***. There was one patient in the placebo group with a possible Hy's Law case (***Figure 14***).

Reviewer's Comments: The reported AEs related to liver disorders including elevations of liver enzymes are consistent with known co-morbidities of PAH. The clinical data do not suggest that selexipag causes liver injury. There was an imbalance in the number of patients reporting ascites (selexipag 7, placebo 1). In response to a FDA Information Request (issued 13 May 2015), the Applicant noted that the majority of ascites cases were reported in the context of a concurrent event of right heart failure or liver disorder. Study drug was not stopped due to ascites in any patient. It was interrupted for one patient. Patient 1401-21080 was hospitalized for abdominal pain and assessment of ascites related to liver cirrhosis (secondary to portal hypertension), and a drainage for ascites was inserted. Selexipag was interrupted for 12 days and upon restarting, ascites did not recur. The Applicant is of the opinion that ascites is not causally related to selexipag treatment and is not including information in the label.

8.5.8. Renal Disorders

An analysis of the SMQs "Acute renal failure" or "Chronic kidney disease" is presented in ***Table 27***. Renal AEs were reported for 7% of patients in the selexipag group compared to 5% in the

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placebo group. The most frequently reported AEs in the selexipag group were acute renal failure and renal impairment (***Table 28***).

The proportion of patients who had renal disorder SAE was 2% and 1% in the selexipag and placebo groups, respectively. Two patients (Patient 2903-23038 and Patient 4005-20122) in the selexipag group and 3 (Patient 3101-24175, Patient 3126-25881, and Patient 6502-21862) in the placebo group had acute renal failure SAEs with fatal outcome.

Table 27. Summary of Renal Adverse Events (Safety Population, GRIPHON)

	Selexipag (N=575)		Placebo (N=577)	
Patients with at least 1 AE	42	7%	26	5%
Annualized rate (per 100 patients treated in 1 year)	5		3	
Patients with at least 1 serious AE	10	2%	7	1%
Patients with at least 1 AE with Fatal Outcome	2	<1%	3	<1%
Patients with at least 1 AE leading to Discontinuation	3	<1%	2	<1%
Patients with at least 1 AE leading to Dose Reduction	0	0	0	0

Source: Reviewer's analysis, TabDis.Renal.csv using Applicant dataset adae.xpt
Abbreviations: AE=adverse events of special interest; N=number of patients in safety population; n=number of patients in subset; %=percentage of patients in subset
Cross reference: Table 76 in 2.7.4 Summary of Clinical Safety

Table 28. Frequency of AEs of SMQs Acute renal failure and Chronic kidney disease with Relative Difference >0.2 by MedDRA SOC and Related PT (Safety Population, GRIPHON)

AE by MedDRA SOC and Related PT	Selexipag (N=575)		Placebo (N=577)		Relative Difference (per hundred)
	n	%	n	%	
RENAL AND URINARY DISORDERS	28	4.87	16	2.77	2.1
Renal Failure Acute	14	2.43	7	1.21	1.22
Renal Impairment	4	0.7	0	0	0.7
Renal Failure	3	0.52	4	0.69	-0.17
Lupus Nephritis	2	0.35	0	0	0.35
Renal Failure Chronic	2	0.35	1	0.17	0.18
INVESTIGATIONS	11	1.91	7	1.21	0.7
Blood Creatinine Increased	7	1.22	5	0.87	0.35
Blood Urea Increased	3	0.52	1	0.17	0.35
METABOLISM AND NUTRITION DISORDERS	8	1.39	8	1.39	0
Hyponatraemia	4	0.7	3	0.52	0.18
Hyperkalaemia	2	0.35	5	0.87	-0.52

Source: Reviewer's analysis, RenalAETab.csv using Applicant dataset adae.xpt
Cross-reference: Table 77 in 2.7.4 Summary of Clinical Safety

Reviewer's Sensitivity Analysis
Sensitivity analysis showed increased risk for renal failure in the selexipag group (***Table 29***).

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Table 29. Sensitivity Analysis of Renal Dysfunction Adverse Events (Safety Population, GRIPHON)

FDA AE Categories	Selexipag (N=575)		Placebo (N=577)		Risk Ratio (95% CI)
	n	%	n	%	
Elevated BUN or Creatinine, Anuria, Acute Renal Failure, Chronic Renal Failure, Oliguria	32	5.57	17	2.96	1.9 (1.0, 3.4)
Anuria, Acute Renal Failure	14	2.43	8	1.39	1.8 (0.7, 4.1)
Nephritis, Glomerulonephritis	2	0.35	2	0.35	1.0 (0.1, 7.1)

Cross reference: Reviewer's analysis, ***Table 34*** in Section 13.3.
Analysis was based on grouping the following PTs: acute prerenal failure, anuria, azotaemia, blood creatine increased, blood creatinine abnormal, blood creatinine increased, blood urea increased, blood urea nitrogen/creatinine ratio increased, cardiorenal syndrome, creatinine renal clearance abnormal, creatinine renal clearance decreased, glomerular filtration rate decreased, glomerulonephritis chronic, glomerulonephritis membranoproliferative, glomerulonephritis proliferative, glomerulonephropathy, hepatorenal failure, hepatorenal syndrome, hypercreatinaemia, hypercreatininaemia, lupus nephritis, nephritic syndrome, nephritis, nephritis autoimmune, nephritis interstitial, nephrogenic anaemia, nephropathy toxic, nephrotic syndrome, oliguria, postoperative renal failure, postrenal failure, prerenal failure, renal disorder, renal failure, renal failure acute, renal failure chronic, renal function test abnormal, renal impairment, renal insufficiency, renal ischaemia, tubulointerstitial nephritis, uraemic encephalopathy, urate nephropathy, urine output decreased.

Reviewer's Comments: Acute renal failure AEs were reported in both treatment groups; although there was a small numerical imbalance in the number of renal AEs in selexipag group. The number of clinically meaningful AEs (SAEs, SAEs with fatal outcome and AEs leading to discontinuation) were similar between groups. Furthermore, renal laboratory values (BUN, creatinine, creatinine clearance) did not suggest differences in rate of change in CrCL or extreme renal laboratory values between groups.

8.5.9. Rash and Skin Disorders

The analysis of rash using MedDRA HLGT "Angioedema and urticarial", HLT "Rashes, eruptions and exanthems NEC", HLT "Erythemas", HLT "Pruritus NEC", HLT "Photosensitivity and photodermatosis conditions" is presented in ***Table 30***. There were higher proportion of patients in the selexipag group with rash and skin AEs. However, the most frequent events of rash, erythema, pruritus and urticarial occurred in both groups. One patient in the selexipag group discontinued treatment due to a rash AE (Patient 2007-21658) and one patient in the placebo group had a rash SAE (severe skin rash; Patient 1301-20752).

Table 30. Summary of Rash and Skin Disorders (Safety Population, GRIPHON)

	Selexipag (N=575)		Placebo (N=577)	
Patients with at least 1 AE	64	11%	48	8%
Annualized rate (per 100 patients treated in 1 year)	8		6	
Patients with at least 1 serious AE	0	0	1	<1%

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Patients with at least 1 AE with Fatal Outcome	0	0	0	0
Patients with at least 1 AE leading to Discontinuation	1	<1%	0	0
Patients with at least 1 AE leading to Dose Reduction	0	0	4	<1%

Source: Reviewer's analysis, TabDis.Rash.csv using Applicant dataset adae.xpt
Abbreviations: AE=adverse events of special interest; N=number of patients in safety population; n=number of patients in subset; %=percentage of patients in subset
Cross reference: Table 79 in 2.7.4 Summary of Clinical Safety

Reviewer's Comments: Overall, there is no imbalance of clinically important rash and skin disorders in the selexipag group. Skin reactions have been reported with epoprostenol, treprostinil, iloprost, ambrisentan and bosentan therapy. The Applicant has listed rash as an adverse reaction in Section 6.1 Clinical Trial Experience of the proposed label.

8.5.10. Malignancies

The overall proportions of patients with malignancies were 1.9% in the selexipag and 0.7% in the placebo group (***Table 31***). Serious AEs were reported for seven patients in selexipag (*vs*. four patients in placebo) and two patients died.

- Patient 1008-25402 who had a medical history of SSc and smoking. On Day 550, she was diagnosed with a diffuse large B-cell lymphoma, which was reported as an SAE and resulted in discontinuation of study drug. She died due to sepsis following stem-cell transplantation.
- Patient 5001-22101 had SLE, cirrhosis and hepatitis C and was receiving concomitant azathioprine and prednisone. On Day 312 of selexipag treatment, it was reported that she had a metastatic colorectal carcinoma SAE. She died one month later.

The observed numerical imbalance regarding overall malignancies between selexipag and placebo derived from basal cell tumors (***Table 32***).

Table 31. Summary of Malignancies AEs (Safety Population, GRIPHON)

SMQs "Malignant tumours" or "Malignant lymphomas".	Selexipag (N=575)		Placebo (N=577)	
Patients with at least 1 AE	11	2%	4	<1%
Annualized rate (per 100 patients treated in 1 year)	1		0.5	
Patients with at least 1 serious AE	7	1%	4	<1%
Patients with at least 1 AE with Fatal Outcome	2	<1%	0	0
Patients with at least 1 AE leading to Discontinuation	1	<1%	0	0

Source: Reviewer's analysis, TabDis.Malignancies.csv using Applicant dataset adae.xpt
Abbreviations: AE=adverse events; N=number of patients in safety population
Cross reference: Table 83 in 2.7.4 Summary of Clinical Safety

Table 32. Frequency of All AEs of SMQs Malignant tumours" or "Malignant lymphomas" by MedDRA SOC and Related PT (Safety Population, GRIPHON)

Adverse Event by MedDRA SOC and Related PT	Selexipag (N=575)		Placebo (N=577)		Relative Difference (per
	N	%	n	%	

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					hundred)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	11	1.91	4	0.69	1.22
Basal Cell Carcinoma	4	0.7	0	0	0.7
Breast Cancer	1	0.17	3	0.52	-0.35
Breast Cancer Metastatic	1	0.17	0	0	0.17
Breast Cancer Recurrent	1	0.17	0	0	0.17
Colorectal Cancer Metastatic	1	0.17	0	0	0.17
Diffuse Large B-Cell Lymphoma	1	0.17	0	0	0.17
Keratoacanthoma	1	0.17	0	0	0.17
Lung Adenocarcinoma	1	0.17	0	0	0.17
Lymphangiosis Carcinomatosa	1	0.17	0	0	0.17
Malignant Melanoma	0	0	1	0.17	-0.17
Nodal Marginal Zone B-Cell Lymphoma	1	0.17	0	0	0.17

Source: Reviewer's analysis, MalignancieAETab.csv.csv using Applicant dataset adae.xpt
Cross-reference: Table 84 in 2.7.4 Summary of Clinical Safety

Pool 2 had an additional 3 patients with malignancy AEs, which were all serious and in one case had a fatal outcome. No additional cutaneous malignancies were reported in Pool 2. In study AC-065A303, an individual SAE of extranodal marginal zone B-cell lymphoma (mucosa-associated lymphoid tissue type) was reported in Patient 1201-20696 (ex-placebo) 68 days after the start of selexipag treatment.

In study NS-304/-03, malignancy SAEs were reported in 2 patients. Patient 006-002 had malignant lung neoplasm diagnosed on Day 453. The patient died due to an SAE of cardiac arrest. No autopsy was performed. The patient's medical history included bladder cancer. Patient 003-010 had a neuroendocrine tumor (gastric neoplasm) which was diagnosed on Day 1100.

Reviewer's Comments: There were no findings indicating genotoxicity or immunotoxicity of selexipag. In the 2-year carcinogenicity studies, selexipag caused an increased incidence of thyroid adenomas in mice and Leydig cell adenomas in rats at exposures that were more than 25-fold above human exposure. It is unlikely that numerical imbalance of basal cell malignancies have clinical relevance.

8.6. Specific Safety Studies/Clinical Trials

There were 2 specific safety studies, Thorough QT study and Ophthalmology Sub-Study in GRIPHON, which were described in previous sections.

8.7. Additional Safety Explorations

8.7.1. Human Carcinogenicity or Tumor Development

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Malignancy was an adverse event of special event interest because of small numerical imbalances for basal cell malignancies (4 in selexipag, 0 in placebo). The applicant should continue to monitor this safety signal during post-marketing use.

See Section 7.3.5.11 for more details.

8.7.2. Human Reproduction and Pregnancy

Selexipag has not been studied in pregnant or lactating women. Animal reproduction studies performed with selexipag showed no effects on embryofetal development and survival.

In GRIPHON, pregnancy was reported in 3 patients (1 selexipag, 2 placebo). An additional case was reported in the selexipag group 8 days after last study drug intake (Patient 7102-23091). Two patients (1 selexipag and 1 placebo) underwent therapeutic abortion and Patient 1308-26125 (placebo) had a ruptured ectopic pregnancy and underwent bilateral salpingectomy. Patient 7102-23091 gave birth to a healthy baby boy by caesarian section after 31 weeks of gestation.

In NS-304/-03, an SAE of pregnancy was reported (Patient 007-005). The OL study medication was discontinued. At 33 weeks of gestation, the patient gave birth to a female baby via Caesarean section. The baby had no neonatal abnormalities.

One female subject (Patient 116-1111 [placebo/moxifloxacin group]) was withdrawn from the study AC-065-106 by the investigator due to pregnancy (detected on Day 3 in the study). The subject underwent elective abortion

8.7.3. Pediatrics and Assessment of Effects on Growth

Pediatric patients: no efficacy, safety, growth and development data with selexipag are currently available for pediatric patients with PAH.

8.7.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

A total of 2 cases of selexipag overdose were reported, both in study NS-304/-03. In one case (Patient 003-002) the overdose was accidental. For the other patient (Patient 001-003), the physician instructed the patient to increase the dose beyond 1600 µg b.i.d. in violation of the protocol.

- Patient 003-002 accidently took a single dose of 3200 µg instead of 1600 µg. He reported nausea that resolved the next day and was considered as possibly related to study drug by the investigator.

- Patient 001-003 (on bosentan background therapy) was exposed for 104 days (study Days 1214–1318) to 2400 µg b.i.d. for 104 days, after which the dose was decreased to

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1800 µg b.i.d. for 30 days (study Days 1319–1349) and then to 1600 µg b.i.d. No new AEs were reported during the period of exposure to doses above 1600 g b.i.d.

There is no indication of any potential for abuse from clinical studies or from current knowledge of prostanoids in general.

Rebound effects have been described for i.v.-administered, short-acting prostacyclins. For both oral- and i.v.-administered drugs, a general warning of the risk for worsening of PAH upon sudden discontinuation or significant dose reduction is described in the label for epoprostenol, treprostinil, and oral treprostinil.

8.8. Safety in the Postmarket Setting

8.8.1. Safety Concerns Identified Through Postmarket Experience

Selexipag is not marketed in the US or another country.

8.8.2. Expectations on Safety in the Postmarket Setting

There are no previous postmarketing experiences with selexipag. Currently there is no need to institute additional risk management activities (REMS).

In addition, no obvious safety concerns for any important subpopulations have been identified.

Finally, there is no reason to believe that the way the drug was administered during clinical trials will be different from how it will be used after approval. No off-label uses are expected.

8.9. Additional Safety Issues From Other Disciplines

No additional safety issues have been identified by other disciplines.

8.10. Integrated Assessment of Safety

Clinical safety of selexipag in PAH patients was primarily evaluated based on the safety data from GRIPHON double-blind trial. This pivotal trial was the largest randomized, placebo-controlled trial to evaluate the Mortality/Morbidity rates in PAH patients. It included 575 patients treated with selexipag for a median of 71 weeks, representing 842 patient-years of exposure. The placebo group included 577 patients for a median of 64 weeks, representing 786 patient-years of exposure. The size of the database provided sufficient information to evaluate the safety of selexipag in PAH patients. Patients in GRIPHON were primarily female (80%), less than 65 years (83%) and Caucasian (White/Hispanic, 75%).

There was no significant imbalance of death, serious adverse events or AEs leading discontinuations that raised a major safety concern for selexipag.

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There was an unexpected imbalance of hyperthyroidism AEs reported in the selexipag group: 8 patients reported hyperthyroidism (1 was a SAE), 2 patients reported autoimmune thyroiditis and one patient reported an SAE of Basedow's Disease. No patients in the placebo group had these AEs. In clinical trials, hyperthyroidism was detected from scheduled thyroid function tests, which were included in the GRIPHON trial after increases in thyroid adenomas were observed in 24-month carcinogenicity studies. Nine of the 10 patients who developed hyperthyroidism continued taking selexipag without dose adjustments or discontinuations. (b) (4)

The Applicant is not recommending selexipag dose adjustments or dose discontinuations as part of the treatment of hyperthyroidism.

Common adverse events were those related to the pharmacology of the drug and included headache, diarrhea, nausea/vomiting, jaw pain, myalgia, arthralgia and flushing. These prostacyclin-like AEs are commonly reported for other prostanoids, such as epoprostenol, iloprost, treprostinil. Approximately 90% of patients taking selexipag experienced at least 1 AE. These AEs were dose-limiting (46% patients had dose reductions) and caused patients to discontinue treatment (7% patients). Subgroup analysis by sex, age, BMI, race/ethnicity and background PAH medications did not detect any specific population that was more sensitive to these AEs. However, no definitive conclusions could be made for subgroups that were represented in low numbers, such as patients >75 years (1%) and of various race/ethnicity groups (Black, 2%; Hispanic, 10%). The prostacyclin-like AEs will be managed through dose titration—increasing the selexipag dose in 200 µg bid increments at weekly intervals to achieve individualized maintenance doses. Patient who cannot tolerate the maintenance dose will have their dose reduced to the previous dose level. The sponsor has proposed administration of selexipag with food to increase the tolerability, even though selexipag was administered without regard to meals in GRIPHON.

A number of AEs of special interest were identified on the basis of nonclinical or previous clinical findings, or where a numerical imbalance was identified. Key AEs and pertinent negative findings are summarized. Additional negative findings included lack of an effect of selexipag on platelets, liver, renal function, and bone density.

(1) Bleeding events were investigated because IP receptor agonists inhibit platelet aggregation. In GRIPHON, each bleeding event was adjudicated by medical experts blinded to study treatment as major or non-major according to ISTH criteria (see Section 8.1). The frequency of bleeding disorders in the selexipag and placebo groups was similar: 90 (16%) patients in the selexipag group reported a bleeding adverse event compared to 91 (16%) patients in the placebo group. Furthermore, there was no difference in the frequency of adjudicated major bleeding; there were 14 (2%) patients with major bleed in selexipag and 12 (2%) patients in placebo.
(2) There were 6 cases of cerebrovascular hemorrhage in selexipag group (4 in GRIPHON and 2 in study NS-304/-03). These cases do not appear to be related to selexipag treatment: 2 cases were a result of trauma (car accident or fall secondary to alcohol

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abuse) and 4 cases were confounded with concomitant use of anticoagulant therapy (details are provided in Section 0).

(3) There was a slight imbalance in the incidence of ischemic events in selexipag-treated patients; there were 6 patients on selexipag and 1 patient on placebo in safety pool 2. The numbers are too small to draw any conclusions about any causal relationship between selexipag and ischemic events.

(4) Anemia was reported in 48 (8%) selexipag-treated patients compared to 5% placebo patients. The underlying mechanism is not known but other PAH medications are associated with anemia. In the selexipag group, there were small decreases in hemoglobin, mean decrease of -0.3 g/dL, that did not appear to further decrease with time. There was no imbalance across treatment groups in the rate of blood transfusions and no patients discontinued treatment because of anemia-related AEs.

(5) Although hypotension is considered a class effect of IP agonists, only modest effects of selexipag on blood pressure were detected. Thirty-six (6%) patients in the selexipag group reported an adverse event compared to 23 (4%) patients in the placebo group. A slightly higher proportion of hypotension AEs in the selexipag group vs. placebo group for patients who were receiving ERA and PDE5i therapy at baseline: 8.4% for selexipag vs. 3.0% for placebo. Clinically relevant cases were reported for a similar proportion of patients in both treatment groups.

(6) The proportion of patients who had at least 1 treatment-emergent AE of Retinal/Eye Disorder was 11% in the selexipag group compared to 8% in the placebo group. The difference was mainly driven by AEs of eye pain (1.6% selexipag, 0.3% placebo). An Ophthalmology Sub-Study conducted in GRIPHON was too small to provide an adequate ocular assessment. Therefore, uncertainty remains on the clinical relevance of the imbalance in retinal/eye disorders.

(7) There was a slight imbalance in the incidence of malignancy events in selexipag-treated patients. There were no findings indicating genotoxicity or immunotoxicity of selexipag, and in the 2-year carcinogenicity studies, selexipag caused an increased incidence of thyroid adenomas in mice and Leydig cell adenomas in rats at exposures that were more than 25-fold above human exposure. There was no thyroid adenoma reported in clinical trials. It's unlikely that the slight imbalance in malignancy events is of clinical relevance.

(8) There is no imbalance of clinically important rash and skin disorders in the selexipag group. Skin reactions have been reported with epoprostenol, treprostinil, iloprost, ambrisentan and bosentan therapy.

9 Advisory Committee Meeting and Other External Consultations

Not applicable.

10 Labeling Recommendations

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10.1. Prescribing Information

The Division will propose labeling that will be similar but not identical to what was submitted by the sponsor.

10.2. Patient Labeling

A medication guide and patient package insert will be made available.

10.3. Non-Prescription Labeling

Not applicable.

11 Risk Evaluation and Mitigation Strategies (REMS)

11.1. Safety Issue(s) that Warrant Consideration of a REMS

There are no important safety issues that warrant REMS.

11.2. Conditions of Use to Address Safety Issue(s)

Safety issues can be adequately managed through appropriate labeling.

11.3. Recommendations on REMS

REMS is not necessary because the safety issues can be adequately managed through appropriate labeling, and that additional requirements are not necessary to maintain a favorable benefit-risk balance.

12 Postmarketing Requirements and Commitments

None

13 Appendices

13.1. References

13.2. Financial Disclosure

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Covered Clinical Study (Name and/or Number): GRIPHON (AC-065A302)

Was a list of clinical investigators provided:	Yes x	No ☐ (Request list from Applicant)
Total number of centers identified: 181		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None known		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 45 (and there were 7 were due diligence was applied to tracking down sub-investigators).		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Please see module 1.3.4 of the NDA for complete description of each investigator with dislosable financial interests/arrangements. A total of 1156 patients participated in GRIPHON in multiple countries and sites. It is unlikely that any site would have sufficient influence or independent ability or impact of influence the overall conduct of the study or its outcomes.		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes x	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes x	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 7		
Is an attachment provided with the reason:	Yes x	No ☐ (Request explanation from Applicant)

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13.3. Additional Safety Analysis

A sensitivity analysis was conducted by grouping PTs according to a customized categorization of AEs for drugs used to treat cardiovascular and renal disorders. For this analysis, a new category named "Prostacyclin-like Effects" was added to capture this drug-specific set of events. AE Categories that occurred in Selexipag group with a Risk Ratio >1.2 are presented in ***Table 33*** for SAEs ***and Table 34*** for AEs***.*** Overall, the sensitivity analysis is in good agreement with the sponsor's analyses of AE.

Table 33. Sensitivity Analysis of SAEs: PTs Grouped by FDA Higher Level Term Sorted by Risk Ratio (Safety Population, GRIPHON)

AE CATEGORIES	SELEXIPAG (N=575)		PLACEBO (N=577)		RISK RATIO	95% LL	95% UL
	n	%	n	%			
Cerebral Ischemia (Includes Stroke, ICH, And TIA	5	0.87%	1	0.17%	5	1	43
UTI	8	1.39%	2	0.35%	4	1	19
Prostacycline-Like Effects	11	1.91%	3	0.52%	4	1	13
Infection, Viral	5	0.87%	2	0.35%	3	0	13
Sepsis	7	1.22%	3	0.52%	2	1	9
Anemia	6	1.04%	3	0.52%	2	1	8
Dyspepsia, N, V, Indigestion, Epigastric Pain, Gastritis, Duoden	6	1.04%	3	0.52%	2	1	8
AF	7	1.22%	4	0.69%	2	1	6
Cellulitis, Erysipelas	5	0.87%	3	0.52%	2	0	7
Solid Neoplasia, ALL (Benign, Malignant, Unknown	6	1.04%	4	0.69%	2	0	5
Autoimmune Disease	7	1.22%	5	0.87%	1	0	4
Arrhythmia	17	2.96%	13	2.25%	1	1	3
Elevated BUN Or Cr, Anuria, ARF, CRF, Oliguria	9	1.57%	7	1.21%	1	0	3
Dyspnea, SOB, Respiratory Distress	18	3.13%	15	2.60%	1	1	2
Bronchitis, Bronchiolitis, Tracheitis, Alveolitis, Bronchiectasis	13	2.26%	11	1.91%	1	1	3
Chest Pain (Not Angina Or Unknown	7	1.22%	6	1.04%	1	0	3

Reviewer's analysis based on dataset, adae.xpt
Continuity correction of 0.5 was used in computing the Risk Ration and 95% confidence intervals when the placebo arm had no events. These events are italicized.

Reference ID: 3814728

Table 34. Sensitivity Analysis of AEs: PTs Grouped by FDA Higher Level Term Sorted by Risk Ratio (Safety Population, GRIPHON)

AE CATEGORIES	SELEXIPAG (N=575)		PLACEBO (N=577)		RISK RATIO	95% LL	95% UL
	n	%	n	%			
Squamous Cell Ca Skin	*4*	*0.70*	*0*	*0.00*	*8*	*0*	*151*
Intracranial Hemorrhage (Includes Hemorrhagic Stroke, SAH, SDH	*4*	*0.70*	*0*	*0.00*	*8*	*0*	*151*
Irritability, Agitation, Stress, Tension, Restless, Anger, Homicidal Ideation	*4*	*0.70*	*0*	*0.00*	*8*	*0*	*151*
Macular Degeneration, Maculopathy	*4*	*0.70*	*0*	*0.00*	*8*	*0*	*151*
Ascites	7	1.22	1	0.17	7	1	57
Gangrene	*3*	*0.52*	*0*	*0.00*	*6*	*0*	*120*
VFib	*3*	*0.52*	*0*	*0.00*	*6*	*0*	*120*
TIA	*3*	*0.52*	*0*	*0.00*	*6*	*0*	*120*
Seizure	*3*	*0.52*	*0*	*0.00*	*6*	*0*	*120*
Hearing Loss, Deafness	*3*	*0.52*	*0*	*0.00*	*6*	*0*	*120*
Cerebral Ischemia (Includes Stroke, ICH, And TIA	6	1.04	1	0.17	6	1	50
Stroke, TIA	5	0.87	1	0.17	5	1	43
Lymphoma	*2*	*0.35*	*0*	*0.00*	*4*	*0*	*89*
Low Ca+	*2*	*0.35*	*0*	*0.00*	*4*	*0*	*89*
Axonal Demyelinating Neuropathy, Demyelination, Transverse Myeli	*2*	*0.35*	*0*	*0.00*	*4*	*0*	*89*
Restlessness, Agitation, Hyperkinesia	*2*	*0.35*	*0*	*0.00*	*4*	*0*	*89*
Polyuria, Increased Frequency	*2*	*0.35*	*0*	*0.00*	*4*	*0*	*89*
Hepatic Steatosis	*2*	*0.35*	*0*	*0.00*	*4*	*0*	*89*
Pancreatitis, Hyperamylasemia	*2*	*0.35*	*0*	*0.00*	*4*	*0*	*89*
Difficulty Walking, Gait Disturbance	*2*	*0.35*	*0*	*0.00*	*4*	*0*	*89*
Urticaria	6	1.04	2	0.35	3	1	15
Pulmonary Edema	3	0.52	1	0.17	3	0	29
Stroke (Includes Ischemic And Hemorrhagic	3	0.52	1	0.17	3	0	29
Dysuria	3	0.52	1	0.17	3	0	29
Hematuria	3	0.52	1	0.17	3	0	29
Myalgia, Myositis, Rhabdomyolysis	93	16.17	34	5.91	3	2	4
Thrombophlebitis, Thrombosis, Thrombus, Clot	8	1.39	3	0.52	3	1	10
AV Block	5	0.87	2	0.35	3	0	13
Diarrhea, Colitis, Enteritis, Proctitis, Gastroenteritis, C-Diff	251	43.65	121	21.04	2	2	2
Headache	376	65.39	187	32.52	2	2	2
Weight Loss, Catabolic State, Cachexia, Failure To Thrive	18	3.13	9	1.57	2	1	4

Reference ID: 3814728

AE CATEGORIES	SELEXIPAG (N=575)		PLACEBO (N=577)		RISK RATIO	95% LL	95% UL
	n	%	n	%			
Ischemic Stroke	2	0.35	1	0.17	2	0	22
Lung Transplant	2	0.35	1	0.17	2	0	22
Elevated BUN Or Cr, Anuria, ARF, CRF, Oliguria	32	5.57	17	2.96	2	1	3
Ecchymosis, Hematoma, Bruise	15	2.61	8	1.39	2	1	4
Anorexia, Decreased Appetite	34	5.91	19	3.30	2	1	3
Anuria, ARF	14	2.43	8	1.39	2	1	4
Sepsis	7	1.22	4	0.70	2	1	6
Dyspepsia, N, V, Indigestion, Epigastric Pain, Gastritis, Duoden	243	42.26	144	25.04	2	1	2
Arteriosclerosis, Vascular Disease, PVD, Bowel Ischemia	5	0.87	3	0.52	2	0	7
Dehydration, Volume Depletion	5	0.87	3	0.52	2	0	7
Diverticular Disease	5	0.87	3	0.52	2	0	7
Glaucoma, High Intraocular Pressure	5	0.87	3	0.52	2	0	7
Confusion, Delirium, Altered Mental Status, Disorientation, Coma	18	3.13	11	1.91	2	1	3
Ventricular Arrhythmia	8	1.39	5	0.87	2	1	5
Hypotension	29	5.04	19	3.30	2	1	3
Eye Other	32	5.57	21	3.65	2	1	3
Rash, Eruption, Dermatitis	33	5.74	22	3.83	2	1	3
Aflutter	9	1.57	6	1.04	2	1	4
Shock, Non-Cardiogenic	3	0.52	2	0.35	2	0	9
Bacteremia	3	0.52	2	0.35	2	0	9
Hepatic Failure, Cirhosis Progression	3	0.52	2	0.35	2	0	9
Esophagitis, Hiatal Hernia	3	0.52	2	0.35	2	0	9
Retinopathy, Retinal Disorders	3	0.52	2	0.35	2	0	9
Prostacyclin-Like Effects	518	90.09	352	61.22	1	1	2
Influenza	20	3.48	14	2.43	1	1	3
Bradycardia	7	1.22	5	0.87	1	0	4
Cataract	8	1.39	6	1.04	1	0	4
Fever, Rigors	25	4.35	19	3.30	1	1	2
Anemia	59	10.26	45	7.83	1	1	2
Vertigo; Vestibular Dysfunction	23	4.00	18	3.13	1	1	2
Cancer (Non-Squamous Cell	5	0.87	4	0.70	1	0	5
Low Na+	5	0.87	4	0.70	1	0	5
Angioedema, Angioneurotic Edema, Laryngeal Edema	11	1.91	9	1.57	1	1	3
Hyper/Hypo Thyroid, Thyroiditis, Goiter	23	4.00	19	3.30	1	1	2
GI Bleed	18	3.13	15	2.61	1	1	2
Conduction Disturbance	6	1.04	5	0.87	1	0	4

Reference ID: 3814728

AE CATEGORIES	SELEXIPAG (N=575)		PLACEBO (N=577)		RISK RATIO	95% LL	95% UL
	n	%	n	%			
Paresthesia, Hypoaesthesia	6	1.04	5	0.87	1	0	4
Arthralgia, Arthritis, Arthrosis	70	12.17	60	10.43	1	1	2

Reviewer's analysis based on dataset, adae.xpt
Continuity correction of 0.5 was used in computing the Risk Ration and 95% confidence intervals when the placebo arm had no events. These events are italicized.

Reference ID: 3814728

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARYANN GORDON
09/02/2015

CHRISTINE E GARNETT
09/02/2015

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 207947 **Applicant: Actelion** **Stamp Date:**

Drug Name: selexipag **NDA/BLA Type: NDA** **12/22/2014**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				electronic
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
6.	Is the clinical section legible so that substantive review can begin?	x			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	x			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	x			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	x			
11.	Has the applicant submitted a benefit-risk analysis for the product?	x			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			x	
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number AC-065A302/GRIPHON A multicenter, double-blind, placebo-controlled Phase 3 study assessing the safety and efficacy of selexipag on morbidity and mortality in patients with pulmonary arterial hypertension. Sample size: 1156 subjects were randomized Arms: selexipag (individualized dose in range of 200-1600 ug bid) and placebo	x			

Reference ID: 3696306

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication:PAH Study Number AC-065A302/GRIPHON A multicenter, double-blind, placebo-controlled Phase 3 study assessing the safety and efficacy of selexipag on morbidity and mortality in patients with pulmonary arterial hypertension.	x			One SPA study
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			x	PAH studies for most applicants use large percentages of foreign subjects. It is assumed that the disease and its treatments are similar around the world.
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	x			AC-065-106
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	x			Pool 1: 575 patients received at least one dose of selexipag. Pool 2: 773 patients received at least one dose of selexipag up to 1600 µg b.i.d., with 472 and 243 of patients treated for a duration of at least 1 and 2 years,

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					respectively.
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	x			Investigator verbatim terms were coded to MedDRA PTs using the most recent MedDRA dictionary available at the time. The pooled AE data were coded according to MedDRA v. 16.0 and, therefore, the results of the pooled safety analyses do not necessarily match the results provided in the individual CSRs, where previous versions may have been used.
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			x	Orphan status
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	x			
DATASETS					

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	x			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	x			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __x__Yes____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None known at this time.

Maryann Gordon, MD 2-3-15

Reviewing Medical Officer Date

Clinical Team Leader Date

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

Reference ID: 3696306

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Reference ID: 3696306

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/s/

MARYANN GORDON
02/03/2015

SHARI L TARGUM
02/06/2015