Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Selexipag

Proprietary Product Name: Uptravi

Sponsor: Actelion Pharmaceuticals Pty Ltd

November 2016

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
≥	At or greater than
≤	At or lesser than
ΔΔQTcI	baseline-adjusted, placebo-corrected effect on QTcI
<	Less than
>	Greater than
6-MWD	6-minute walk distance
6-MWT	6-minute walk test
ACT-293987	selexipag/NS-304
ACT-333679	MRE-269, the active metabolite of selexipag
ADP	adenosine-5'-diphosphate
ADR	Adverse drug reaction
AE	Adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APTT	activated partial thromboplastin time
APTT $AUC_{(0\text{-}144h)}$	area under the APTT versus time curve to 144 h post-dose
$APTT_{max}$	the maximum APTT value
AST	Aspartate transaminase
AUCSS	area under the curve at steady state (over one dosing interval)
AUCτ	area under plasma concentration-time curve during a dose interval
AUC_{0-24h}	area under the plasma concentration-time curve from time of administration until 24 hours post-dose
bd	Twice daily
BCRP	breast cancer resistant protein

Abbreviation	Meaning
BMI	body mass index
BMP	bone morphogenetic protein
BMPR	bone morphogenetic protein receptor
BP	Blood pressure
bpm	Beats per minute
BSEP	bile salt export pump
cAMP	cyclic adenosine monophosphate
CAMPHOR	Cambridge Pulmonary Hypertension Outcome Review
CEC	Critical Event Committee
CES1	carboxylesterase 1
CHD	Congenital heart disease
CHO	Chinese hamster ovary
CK	creatine kinase
CNS	central nervous system
CYP	cytochrome P450
CI	Confidence interval
Cl	clearance
CL	Confidence limit
CLcr	creatinine clearance
CLpop	population-typical clearance
CLr	renal clearance
C_{max}	Maximum plasma concentration
C_{max},ss	maximum plasma concentration at steady-state
CrCL	creatinine clearance
CSR	Clinical Study Report
CTD	connective tissue disease

Abbreviation	Meaning
Ctrough	plasma concentration at the end of one dose interval
$C_{trough,ss}$	plasma concentration at the end of one dose interval at steady-state
CTx	carboxy-terminal telopeptide
CTx	serum C-telopeptides
CV	coefficient of variation
CVb	inter-subject coefficient of variation
CVw	Intra-subject coefficient of variation
DB	Double-blind
DBP	diastolic blood pressure
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EC	endothelial cell
EC_{50}	half-maximal effective concentration
EMA	European Medicines Agency
eNOS	endothelial nitric oxide synthase
GD	gestation day
GI	gastrointestinal
GLP	Good Laboratory Practice
HD	high dose
hERG	human ether-à-go-go-related gene
hPASMC	human pulmonary artery smooth muscle cells
EOS	End-of-study
EOT	End-of-treatment
ERA	Endothelin receptor antagonist
EU	European Union

Abbreviation	Meaning
FAS	Full analysis set
FC	Functional class
FDA	Food and Drug Administration
Fe%	amount of total radioactivity eliminated in the urine over the collection period, expressed as a percentage of the administered dose
GCP	Good Clinical Practice
Hb	Hb
HR	**heart rate**
IC_{50}	half maximal inhibitory concentration
ICH	International Conference on Harmonisation
IL	interleukin
IMD	individual maintenance dose
IMP	investigational medicinal product
IMTD	individual maximum tolerated dose
INR $AUC_{0\text{-}144h}$	area under the INR versus time curve to 144 h post-dose
INR	International normalised ratio
INRmax	maximum INR value
INRtmax	time taken to achieve the maximum INR value
IP	Prostacyclin
iPAH	idiopathic PAH
IV	intravenous
IVRS	interactive voice response system
k12, k21, k34, k43	transfer rate constants (compartment 1 to compartment 2, etc) ka - absorption rate constant
ke	elimination rate constant (selexipag)
Kel	terminal elimination rate constant (fractional turnover rate)

Abbreviation	Meaning
Ki	inhibition constant
Km	elimination rate constant (metabolite ACT-333679)
Km	Michaelis-Menten constant
kmet	metabolism rate constant (from parent to metabolite)
kt	transfer rate constant
L	Litre
LB	lower bound
LC-MS/MS	liquid chromatography with tandem mass spectrometry
LLOQ	Lower limit of quantification
LOQ	limit of quantification
LD	low dose
LVEDP	left ventricular end diastolic pressure
m	metre
MACE	major adverse cardiovascular events
MAP	mean arterial pressure
MDCKII	Madin-Darby canine kidney tubular epithelium type II
MD	mid dose
MRP2	multidrug resistance-associated protein 2
MDRD	Modification of Diet in Renal Disease
MED	minimal erythema dose
mg	Milligram
mL	Millilitre
MM	morbidity/mortality
mPAP	mean pulmonary artery pressure
ms	millisecond
MTD	maximum tolerated dose

Abbreviation	Meaning
NADPH	nicotinamide adenine dinucleotide phosphate (reduced)
NCx	serum N-telopeptides
NO	nitric oxide
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NONMEM	nonlinear mixed effects modelling (software)
NS-304	selexipag
NT pro-BNP	NT pro-brain natriuretic peptide
NYHA	New York Heart Association
NZW	New Zealand White
OAS	ophthalmological sub-study analysis set
OATP	organic anion-transporting polypeptide
OCT	organic cation transporter
OL	Open-label
OSB	ophthalmology safety board
P1NP	procollagen type 1 N-terminal propeptide
PAH	Pulmonary arterial hypertension
PAP	pulmonary arterial pressure
PAT	platelet aggregation test
PCWP	pulmonary capillary wedge pressure
PD	Pharmacodynamics
PDE-5	phosphodiesterase-5
PDE-5i	PDE-5 inhibitor
PDGF	platelet-derived growth factor
PGE_1	prostaglandin E_1
PGI_2	Prostacyclin

Abbreviation	Meaning
P-gp	P-glycoprotein
PI	phototoxic index
PK	Pharmacokinetics
PND	post-natal day
PO	per os (oral (gavage))
PopPK/PD	population pharmacokinetic(s)/pharmacodynamic(s)
PPS	Per-protocol set
PR	Pulse rate
P-selectin	platelet-selectin
PT	prothrombin time
PT $AUC_{0\text{-}144h}$	area under the PT versus time curve to 144 h post dose
PT	Preferred term
PVR	pulmonary vascular resistance
QAS	Quality of Life analysis set
QoL	Quality of Life
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected with Bazett's formula
QTcF	QT interval corrected with Fridericia's formula
QTcI	QT interval corrected using the individualised formula
RBC	Red blood cell
RR	R-to-R interval
SC	Subcutaneous
SAE	serious adverse event
SAEM	stochastic approximation expectation maximisation
SAF	Safety analysis set
SAS	statistical analysis system (software)

Abbreviation	Meaning
SBP	Systolic blood pressure
SC	Subcutaneous
SD	Standard Deviation
SMC	smooth muscle cell
SE	standard error
SMQ	Standardised MedDRA queries
sOC	serum osteocalcin
SOC	System Organ Class
SRFI	severe renal function impairment
sTM	soluble thrombomodulin
$t_{1/2}$	terminal elimination half-life
TEAE	Treatment emergent adverse event
TGA	Therapeutic Goods Administration
TGF-β	transforming growth factor beta
Tlag	lag time (absorption)
T_{max}	time to reach maximum plasma concentration
T_{max},ss	time to reach maximum plasma concentration at steady-state
UB	upper bound
UGT	uridinediphosphate-glucuronosyltransferase
ULN	Upper limit normal
US	United States
UV	ultraviolet light
V/F	apparent volume of distribution (of selexipag)
Vd	volume of distribution
Vm/F	apparent volume of distribution of the central compartment for the metabolite

Abbreviation	Meaning
Vp/F	apparent volume of distribution of the central compartment for the parent
versus	versus
Vss	volume of distribution at steady-state
vWF	von Willebrand Factor
WHO	World Health Organisation
µg	µg
τ	dosing interval

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	18 March 2016
Date of entry onto ARTG	24 March 2016
Active ingredient(s):	Selexipag
Product name(s):	Uptravi
Sponsor's name and address:	Actelion Pharmaceuticals Ltd 13/B Narabang Way, Belrose NSW 2085
Dose form(s):	Film-coated tablet
Strength(s):	200, 400, 600, 800, 1000, 1200, 1400 and 1600 µg
Container(s):	Aluminium (Al)/Al blister pack
Pack size(s):	200 µg: 10, 60 or 140 tablets. All other strengths: 60 tablets
Approved therapeutic use:	*Uptravi, is indicated for the treatment of:* • *idiopathic pulmonary arterial hypertension* • *heritable pulmonary arterial hypertension* • *pulmonary arterial hypertension associated with connective tissue disease* • *pulmonary arterial hypertension associated with congenital heart disease with repaired shunts* • *pulmonary arterial hypertension associated with drugs and toxins* *in patients with WHO functional class II, III or IV symptoms.*
Route(s) of administration:	Oral (PO)
Dosage:	The goal is to reach the individually appropriate dose for each patient (the individualised maintenance dose). The recommended starting dose of Uptravi is 200 µg given twice daily, approximately 12 hours apart. The dose is increased in increments of 200 µg given twice daily, usually at weekly intervals, until adverse pharmacological effects that cannot be tolerated or medically managed are experienced, or until a maximum dose of 1600 µg twice daily is reached. During dose titration, it is recommended not to discontinue treatment in the event of expected pharmacological side effects since they are usually transient or manageable with symptomatic treatment

	(see Adverse Effects). If a patient reaches a dose that cannot be tolerated the dose should be reduced to the previous dose level. See PI for further details.
ARTG number (s):	234161, 234160, 234159, 234166, 234162, 234163, 234165, 234164

Product background

This AusPAR describes the application by the sponsor Actelion Pharmaceuticals Ltd to register selexipag, a new chemical entity, for the treatment of subtypes of pulmonary arterial hypertension (PAH) as monotherapy or in combination with an endothelin receptor antagonist (ERA) or a phosphodiesterase type 5 (PDE5) inhibitor or in combination with both; as follows:

For the treatment of:

- *idiopathic pulmonary arterial hypertension*
- *heritable pulmonary arterial hypertension*
- *pulmonary arterial hypertension associated with connective tissue disease*
- *pulmonary arterial hypertension associated with congenital heart disease with repaired shunts*
- *pulmonary arterial hypertension associated with drugs and toxins in patients with WHO functional class II, III or IV symptoms.*

Uptravi is effective in combination with an endothelin receptor antagonist (ERA) or a phosphodiesterase-5 (PDE-5) inhibitor, or in triple combination with an ERA and a PDE-5 inhibitor, or as monotherapy.[1]

Selexipag is an oral, selective, prostacyclin receptor (IP receptor) agonist, and is structurally and pharmacologically distinct from prostacyclin and its analogues. Eight strengths of Uptravi are proposed (see *Submission details* above).

The vasculo-protective effects of prostacyclin (PGI_2) are mediated by the IP receptors. Decreased expression of IP receptors and decreased synthesis of prostacyclin are believed to contribute to the pathophysiology of pulmonary arterial hypertension (PAH). Stimulation of the IP receptor by selexipag and its active metabolite (which is approximately 37 times more potent than selexipag) leads to vasodilatory as well as anti-proliferative and anti-fibrotic effects.

The following is the proposed dosage and administration:

> *The goal is to reach the individually appropriate dose for each patient (the individualised maintenance dose).*
>
> *The recommended starting dose of Uptravi is 200 µg given twice daily, approximately 12 hours apart. The dose is increased in increments of 200 µg given twice daily, usually at weekly intervals, until adverse pharmacological effects that cannot be tolerated or medically managed are experienced, or until a maximum dose of 1600 µg twice daily is reached. During dose titration, it is recommended not to discontinue treatment in the event of expected pharmacological side effects since they are usually transient or manageable with symptomatic treatment (see ADVERSE EFFECTS). If a patient reaches a dose that cannot be tolerated the dose should be reduced to the previous dose level.*

[1] Proposed Australian Product Information, Uptravi

PAH is characterised by vasculopathy and remodelling of the pulmonary circulation resulting in narrowing of the arterial lumen and impaired vasodilation. This leads to an increase in pulmonary arterial pressure (PAP) and pulmonary vascular resistance (PVR), which limits the ability of the right ventricle to pump blood through the lungs and thereby causing shortness of breath, and eventually resulting in right heart failure and death. PAH is thought to be mediated through an up-regulated endothelin-1 system, defective prostacyclin synthase activity and abnormalities of the nitric oxide pathway. Current treatments for PAH are aimed at these main pathways: ERAs (inhibit the effects of elevated endothelin-1 and thus reduce vasoconstriction, smooth muscle cell proliferation and pulmonary vessel fibrosis), prostacyclin analogues (relax and reduce proliferation of vascular smooth muscle cells) and PDE5 inhibitors and the soluble guanylate cyclase agonist, riociguat (potentiate the anti-platelet, anti-proliferative and vasodilatory effects of nitric oxide).

Specific pharmaceutical treatments registered for the treatment of PAH include oral bosentan, ambrisentan, macitentan, riociguat, tadalafil and sildenafil, inhaled nitric oxide and iloprost, intravenous epoprostenol and subcutaneous treprostinil. Imatinib has also been orphan designated for PAH. The currently approved IP receptor agonists for the treatment of PAH in Australia are parenterally administered and include epoprostenol, iloprost and treprostinil. Approved indications for IP receptor agonists are:

Epoprostenol

> *Flolan is indicated for the long-term treatment, via continuous intravenous infusion, in WHO functional class III or class IV patients with:*
>
> *Idiopathic pulmonary arterial hypertension*
>
> *Familial pulmonary arterial hypertension*
>
> *Pulmonary arterial hypertension associated with the scleroderma spectrum of diseases*

Iloprost

> *Treatment of patients with primary pulmonary hypertension or secondary pulmonary hypertension due to connective tissue disease or drug-induced, in moderate or severe stages of the disease. In addition, treatment of moderate or severe secondary pulmonary hypertension due to chronic pulmonary thromboembolism, where surgery is not possible.*

Treprostinil

> *Remodulin is indicated as a continuous subcutaneous infusion for the treatment of pulmonary arterial hypertension in patients with NYHA class III-IV to diminish symptoms associated with exercise.*

There are two specific EU guidelines adopted by the TGA relevant to this submission, besides the general guidelines:

- EMEA/CHMP/EWP/356954/2008: Guideline on the Clinical Investigations of Medicinal Products for the Treatment of Pulmonary Arterial Hypertension. Effective: 28 May 2010
- EMA/CHMP/213972/2010: Paediatric Addendum to the CHMP Guideline on the Clinical Investigations of Medicinal Products for the Treatment of Pulmonary Arterial Hypertension. Effective: 1 August 2014

Regulatory status

Selexipag was designated an orphan drug on 25 September 2014. Selexipag has not been previously considered by the TGA's Advisory Committee on Prescription Medicines (ACPM).

Uptravi has been approved in the USA, Europe, Canada, New Zealand, Switzerland, Korea and Japan and is under evaluation in Taiwan, Turkey, Hong Kong and Brazil. The approved indication in the US is as follows:

> *Uptravi is indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression and reduce the risk of hospitalization for PAH.*
>
> *Effectiveness was established in a long-term study in PAH patients with WHO Functional Class II-III symptoms.*
>
> *Patients had idiopathic and heritable PAH (58%), PAH associated with connective tissue disease (29%), PAH associated with congenital heart disease with repaired shunts (10%) [see Clinical Studies (14.1)]*

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

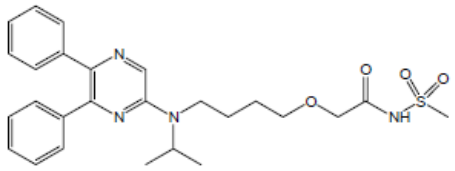
II. Quality findings

Drug substance (active ingredient)

Selexipag is a pale yellow crystalline powder that is practically insoluble in water. In the solid state selexipag is very stable, is not hygroscopic, and is not light sensitive.

Selexipag is made by chemical synthesis. It is an achiral molecule. Various polymorphic forms (Form I, II and III) were shown to exist but the polymorphic form made for use in clinical and commercial batches is Form I. Form II was the most thermodynamically stable, however, Form I was selected as it has the highest melting point. It was only in the polymorphic form were only observed on storage. Figure 1 shows the chemical structure of selexipag.

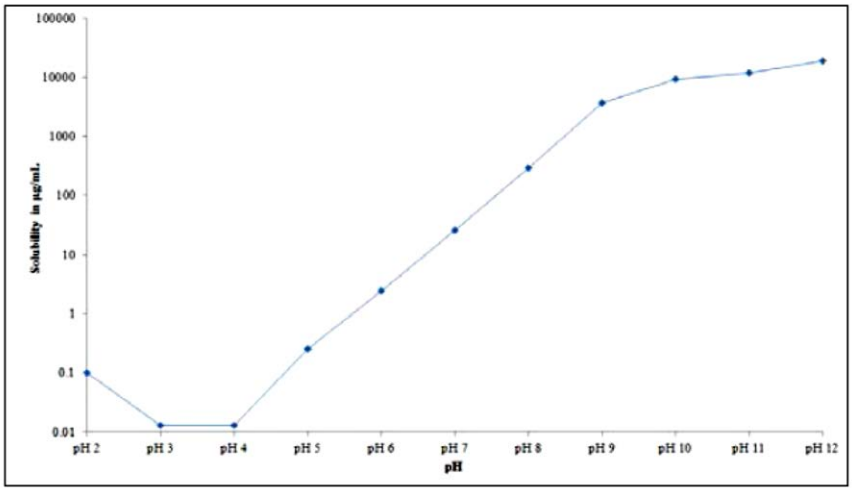
Figure 1: Chemical structure of selexipag



Selexipag exhibits pH dependant solubility (pH solubility profile below). Selexipag is considered to be a BCS Class[2] II drug (Figure 2).

[2] The Biopharmaceutics Classification System (BCS) is a guidance for predicting the intestinal drug absorption provided by the U.S. Food and Drug Administration. According to the BCS, drug substances are classified as follows: Class I: high permeability, high solubility; Class II: high permeability, low solubility; Class III: low permeability, high solubility; Class IV: low permeability, low solubility.

Figure 2: Solubility versus pH for selexipag



The drug substance is micronised. Due to the poor solubility of the drug substance, particle size control is considered to be a critical quality attribute as this may affect tablet disposition. Appropriate particle size controls have been applied by the finished product manufacturer. The limits have been proposed on the basis of a bioequivalence study conducted in dogs in which the dogs were administered three formulations, each manufactured using a different median particle size of the drug substance (mean particle size: 3.1, 6.7, 9.4 µm). The use of a bioequivalence study in dogs was acceptable as it was considered predictive of the impact of particle size distribution on bioavailability in humans, particularly for poorly soluble drugs. Impurities have been controlled according to the ICH[3] guidelines. Furthermore, polymorphic form III is controlled at a limit of no more than (NMT) 6% in the active pharmaceutical ingredient (API) on the basis that levels of up to 6% were observed in development batches. All other tests imposed on the drug substance by the finished product manufacturer are standard for an API and include appearance, colour, clarity of solution, identification, assay, heavy metals, residue on ignition, loss on drying, particle size distribution, microbial tests and residual solvents.

Drug product

The proposed Uptravi tablets are film-coated, immediate release tablets. They are not scored. Each tablet has a different colour and the 200, 400, 600, 800, 1000, 1200, 1400 and 1600 µg strengths are debossed with '2', '4', '6', '8', '10', '12', '14' and '16', respectively. The formulation for each tablet is conventional and the tablets are composed of mannitol, maize starch, hydroxypropylcellulose, low substituted hydroxypropylcellulose and magnesium stearate in the core and hypromellose, propelyene glycol, carnauba wax and one or more of titanium dioxide, iron oxide red, iron oxide black and iron oxide yellow in the film-coat, depending on tablet strength.

The container/closure system proposed is Al/Al blister packs with desiccant. For the 200 µg strength tablets, pack sizes of 10, 60 and 140 tablets are proposed. For all other strengths, a pack size of 60 tablets is proposed. The primary pack label for the 140 tablet pack size of the 200 µg strength product includes the statement 'For Dispensing Use Only'.

In the pivotal placebo-controlled Phase III study (AC-065A302/GRIPHON) only the 200 µg film-coated tablet strength was administered up to 1600 µg twice daily, which was the highest dose allowed in this study. For patient convenience, other tablet strengths were

[3] International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

developed and a clinical Study AC-065-108 was conducted to demonstrate bioequivalence between 1600 µg selexipag administered as 8 film-coated tablets of 200 µg and 1600 µg selexipag administered as a single film-coated tablet of 1600 µg at steady-state.

The manufacturing process for selexipag film-coated tablets is divided into nine steps: dry blending, wet granulation, drying, milling, lubrication, compression, film-coating, polishing and packaging. The manufacturing process is considered to be a non-standard process due to the high potency of the drug and has therefore been appropriately validated using three commercial scale batches of each strength. Potential changes in polymorphic form were only able to be studied with a limit of detection of 50% in the finished product. The optimisation of the drug substance manufacturing process to minimise the formation of other polymorphs, the absence of an increase in Form II and Form III in Form I on storage in the API and the dissolution and pharmacokinetics of the drug product collectively provide assurance that the risk of polymorphic form conversion in the finished product is low and the impact is also low.

The finished product is appropriately controlled using the finished product specifications. The specifications include acceptable tests and limits for appearance, colour, diameter, average mass, identity, uniformity of dosage units, water content, assay, related substances (degradation products), dissolution and microbial quality. The sponsor has identified two impurities and has appropriately controlled these at release and shelf-life. The shelf-life limit for ACT-609440 is based on the ICH qualification threshold and that of ACT-333679 has been qualified on the basis that it is a human metabolite.

The dissolution medium was dictated by the pH-solubility of selexipag. Selexipag has low solubility especially at low pH values. A dissolution limit of no less than (NLT) 80% (Q) at 30 minutes was set and this is considered appropriate.

A shelf-life of 36 months 'Store below 30°C. Protect from Moisture' is recommended in Al/Al blister packs stored within a carton.

Chemistry and quality control aspects are considered acceptable.

Biopharmaceutics

Study AC-065-108

A single-centre, open-label, randomised, two-period, two-treatment, crossover study in healthy male subjects to demonstrate bioequivalence of 1600 µg selexipag administered as eight tablets of 200 µg. The results demonstrated bioequivalence between 1 film-coated tablet of 1600 µg and 8 film-coated tablets of 200 µg selexipag.

This study showed that the 1 x 1600 µg selexipag tablet and the 8 x 200 µg selexipag tablets administered following a multiple-dose up-titration regimen were bioequivalent.

Table 1: C_{max} and $AUC_{0\text{-}tau}$ 90% Confidence intervals for selexipag versus ACT-333679

90% CI	Selexipag	ACT-333679
$C_{max\ (ss)}$	95.20-114.16%	94.04 107.40%
$AUC_{0\text{-}tau}$	92.40 – 106.24%	95.01-106.16%

QGUY/2006/NS304/-01

A Phase I study to investigate the safety, tolerability and pharmacokinetics (including food effect) of single and multiple oral rising doses of NS-304 and its interaction with warfarin

in healthy male volunteers showed that the effect of food on the pharmacokinetics (PK) of selexipag and ACT-333679 was small.

In the presence of food, median time to reach maximum plasma concentration (T_{max}) of both selexipag and ACT-333679 was delayed (2.75 and 4.0 h, respectively) compared to in the absence of food (1.0 and 2.5 h, respectively). Peak plasma concentration (C_{max}) of selexipag decreased by 35% whereas the area under the plasma concentration-time curve from 0 to infinity ($AUC_{0-\infty}$) numerically increased by approximately 10% in the presence of food. The C_{max} and the $AUC_{0-\infty}$ of ACT-333679 decreased by 48% and 27% respectively, in the presence of food.

The geometric mean terminal elimination half-life ($t_{1/2}$) was slightly longer (1.76 h) when selexipag was administered in fed compared to fasting (1.28 h) state. For the metabolite, ACT-333679, the geometric mean $t_{1/2}$ was slightly shorter (10.6 h) in fed compared to fasting (12.0 h) state

The 90% CIs of the geometric mean ratios (fed versus fasted) for C_{max} and AUC of selexipag were not completely inside the pre-defined bioequivalence limits for absence of a food effect, that is, 0.80 to 1.25. For ACT-333679, the 90% CIs of the geometric mean ratios for C_{max} and AUC were outside the pre-defined limits for absence of a food effect

NS304/P1/01: Single- and Multiple-Dose Study of NS-304 in Healthy Adult and Elderly Male Japanese Volunteers (Phase I) showing that the effect of food on the pharmacokinetics (PK) of selexipag and ACT-333679 was small.

In the presence of food, T_{max} of selexipag and ACT-333679 was delayed (1.9 and 3.3 h, respectively) versus in the absence of food (1.0 and 2.8 h, respectively). The mean $t_{1/2}$ for selexipag was 1.32 h in the presence of food compared to 1.67 h in the absence of food. However, food had no effect on the mean $t_{1/2}$ of ACT-333679. Exposure (C_{max} and $AUC_{0-\infty}$) to selexipag in the presence of food was lower (approximately 33% and 16%, respectively) compared to in the absence of food. No effect of food was observed on the C_{max} of ACT-333679, while the $AUC_{0-\infty}$ in the presence of food was numerically 12% lower. The geometric mean ratio (fed versus fasted) and its 90% CI for C_{max} of selexipag was outside the bioequivalence range of 0.8 to 1.25, indicating the presence of a food effect on C_{max} of selexipag. The geometric mean ratio and its 90% CI for ACT-333679 C_{max} were within the bioequivalence range of 0.8 to 1.25, indicating no effect of food on C_{max} of ACT-333679. The ratio (fed versus fasted) for the geometric mean $AUC_{0-\infty}$ for selexipag and ACT-333679 was 0.853 and 0.879, respectively, and 90% CIs were outside the bioequivalence range of 0.8 to 1.25.

The PI states that the tablets may be taken with or without food. This is a clinical matter that will be considered by the clinical evaluator.

Quality summary and conclusions

Registration is recommended with respect to chemistry, quality control and bioavailability aspects.

III. Nonclinical findings

Introduction

The sponsor has applied to register a new chemical entity, selexipag, for the treatment of adult patients with pulmonary arterial hypertension (PAH). In support of the efficacy and safety of selexipag, a comprehensive dossier of high quality nonclinical studies has been submitted. The pivotal toxicological studies were performed to Good Laboratory Practice

(GLP) standards and were conducted in the sponsor's laboratories and in other well-recognised laboratories. All the sponsor's studies have been evaluated.

PAH patients typically show a progressive increase in pulmonary vascular resistance and consequent heart failure. The pathogenesis of the condition is ascribed to the combined effects of widespread narrowing or obliteration of the pulmonary arteriolar bed, sustained vasoconstriction, and in situ thrombosis. Histological features of affected vessels commonly include intimal thickening and medial hypertrophy, due to proliferation of endothelial and smooth muscle cells, together with fibrosis and invasion by inflammatory cells. PAH is thought to be initiated when toxin induced apoptosis of endothelial cells leads to an endothelium that is abnormal and no longer acts in proper co-ordination with neighbouring cell types, leading to the formation of aberrant structures. In addition to structural changes in vessel walls, the dysfunctionality of the endothelium in PAH patients is reflected in altered production of various critical molecules that mediate vascular tone and vessel wall structure, including: nitric oxide, prostacyclin, endothelin-1, and platelet-derived growth factor. Prostacyclin is a potent vasodilator of human pulmonary arteries, as well as being an inhibitor of platelet aggregation and of smooth muscle cell proliferation. Consistent with it playing a role in PAH pathogenesis, prostacyclin production is decreased in the PAH lung. Accordingly, treatment of PAH patients with drugs, such as prostacyclin receptor agonists, represents a means of attempting to restore the balance between vasoconstriction and vasodilation in the lung.

Pharmacology

Primary pharmacology

Selexipag belongs to the same pharmacological class (prostacyclin (prostaglandin I_2) receptor (IP) agonist) as prostanoid drugs, such as iloprost and trepostinil, which have been approved by the TGA for treatment of PAH. However, whereas iloprost and trepostinil are analogues of the natural IP receptor agonist, prostacyclin, selexipag is a non-prostanoid and is not a chemical analogue of prostacyclin. Selexipag is a prodrug that is converted to the active form, ACT-333679, by hydrolysis. Both selexipag and ACT-333679 were used (where appropriate) in pharmacology studies that also included various comparator drugs.

Studies using membrane preparations from cells expressing human IP receptor showed that the binding affinity of ACT-333679 was approximately 13 times stronger than its pro-drug (K_i = 19.8 compared to 263.0 nM) and was intermediate to the values for iloprost (K_i = 8.6 nM) and treprostinil (K_i = 35.5 nM). ACT-333679 was approximately15 times more potent than its pro-drug (50% effective dose (EC50) = 11.5 compared to 177 nM) but was less potent than iloprost in a functional assay for cyclic adenosine monophosphate (cAMP) levels in Chinese hamster ovary (CHO) cells expressing human IP receptors. In cell studies comparing the ability to recruit β-arrestin (promotes receptor internalisation and blocks further G-protein-mediated signalling) following human IP receptor binding, ACT-333679 and selexipag showed greatly reduced efficacy compared to iloprost suggesting that they are not full agonists. Similarly, ACT-333679 showed reduced efficacy compared to iloprost at increasing cAMP levels in human pulmonary artery smooth muscle cells (SMCs). Consistent with their lower potency for β-arrestin recruitment, ACT-333679 and selexipag did not induce major IP receptor internalisation, whereas drugs such as iloprost produced loss of membrane-associated IP receptor and accumulation in the peri-nuclear region. This suggests that selexipag exposure may not lead to a rapid loss of cellular responsiveness (tachyphylaxis). The potency and maximal efficacy of ACT-333679 for increasing cAMP levels was shown to vary depending on cellular IP receptor density. This supports the need to titrate selexipag doses when treating patients.

Unlike iloprost, which had very similar EC_{50} values (0.13–0.18 nM) at the human, rat, and dog IP receptor orthologues, selexipag and ACT-333679 showed marked species differences. EC_{50} values for ACT-333679 at the rat and dog IP receptors were 18 and 82 times higher, respectively, than at the human receptor.

In vitro studies with cultures of human pulmonary artery SMCs showed that ACT-333679 had both potent anti-proliferative activity (IC_{50} = 2.9 nM compared to iloprost = 0.10 nM) and the ability to induce cellular shape changes consistent with relaxation (EC_{50} values were 4.3, 157, and 0.12 nM for ACT-333679, selexipag, and iloprost, respectively). ACT-333679 was also shown to inhibit radioactively labelled [^{3}H] proline incorporation (expected to be predominantly associated with the synthesis of the extracellular matrix proteins collagen and fibronectin) by cultures of normal human lung fibroblasts, suggesting that it has anti-fibrotic activity.

ACT-333679 was shown to be effective at inhibiting platelet aggregation in monkey and human plasma (50% inhibitory concentration (IC_{50}) = 0.21 µM, which is approximately3 times clinical C_{max}), but not in rat or dog plasma.

Haemodynamic effects of selexipag were studied using both normal rats and rat models of PAH. Selexipag dosing of rats with monocrotaline induced PAH was shown to produce a significant increase in survival that was associated with reductions in pulmonary arterial wall hypertrophy and right ventricular systolic pressure. Selexipag was also shown to be effective at reducing mean arterial pressure (MAP) in spontaneously hypertensive rats and, unlike treprostinil, there was no evidence for induction of tachyphylaxis by selexipag. Consistent with that finding, twice daily dosing of normal rats with selexipag at 3 mg/kg for up to 4 weeks increased femoral skin blood flow without an apparent effect of the treatment period.

The sponsor's primary pharmacology studies support the proposed mechanism of action and indication for selexipag.

Secondary pharmacodynamics and safety pharmacology

Incubation of ACT-333679 (10 µM) or selexipag (10 µM) with a panel of receptors, ion channels, transporters, and enzymes suggested only the EP4 and TP prostanoid receptors as possible targets. Further studies examined the binding of both compounds to membrane preparations from cells expressing one of the human prostanoid receptors. EP1 (K_i for ACT-333679 = 138 µM), EP2 (K_i = 5.83 µM), EP3 (K_i = 13.8 µM), EP4 (K_i = 4.87 µM), DP (K_i = 2.57 µM), FP (K_i = >173 µM), and TP (K_i = 20.9 µM) prostanoid receptors all showed low affinity binding of ACT-333679, and similarly low affinity binding of selexipag. Hence, the binding affinity of ACT-333679 for other human prostanoid receptors is at least 130 times lower than that for the IP receptor (K_i = 19.8 nM for IP compared to 2.57 µM for DP). The predicted C_{max} for ACT-333679 at steady state for PAH patients given the recommended maximum is 29.1 ng/mL (69 nM), and the unbound drug fraction in human plasma is <2.0%, giving a free drug concentration of <1.4 nM. As the above membrane-binding assays are performed in the absence of added protein, this suggests that off-target effects at prostanoid receptors are unlikely to occur in patients.

ACT-333679 at concentrations up to 30 µM had no effect on peak tail current in hERG[4] transfected CHO-K1 cells. Selexipag at 3 or 10 µM had no effect on peak tail current, but produced slight inhibition (approximately85% of control) at 30 µM. The free fraction C_{max}

[4] **hERG** (the **h**uman ***E**ther-à-go-go*-**R**elated **G**ene) is a gene (*KCNH2*) that codes for a protein known as K_v11.1, the alpha subunit of a potassium ion channel. This ion channel (sometimes simply denoted as 'hERG') is best known for its contribution to the electrical activity of the heart that coordinates the heart's beating (i.e., the hERG channel mediates the repolarizing I_{Kr} current in the cardiac action potential).

for selexipag in PAH patients is about 30,000 times lower than the highest tested concentration, suggesting that selexipag has little potential for QT interval prolongation[5].

Safety pharmacology studies examined effects of ACT-333679/selexipag on blood coagulation, cardiac function, central nervous system (CNS) function, gastric function and intestinal transport, renal function, respiration, and uterine contraction.

Bleeding time, CNS function, intestinal transport, renal function, and respiration were examined using rats given a single oral dose of selexipag at 0, 10 (low dose (LD), 30 (mid dose (MD)), or 100 (high dose (HD)) mg/kg. The HD prolonged bleeding time although the increase was not statistically significant. The MD and HD caused hypothermia and prolonged hexobarbital-induced sleep, and the HD had an analgesic effect. All doses produced significant decreases in the volume of gastric juice and total acid output and in charcoal transport along the intestine. All doses significantly decreased urinary chloride (Cl^-) excretion and the sodium (Na^+)/potassium (K^+) ratio, whilst urine volume and urinary Na^+ excretion were significantly decreased at the MD and HD. At 1 h after dosing, MD and HD animals showed significant increases in respiratory frequency and tidal volume. Effects on cardiac function were studied using dogs given a single oral dose of selexipag at 0, 1, 3, or 10 mg/kg. Selexipag produced a dose dependent increase in heart rate (HR) but had no significant effect on electrocardiogram (ECG) parameters. As the LD in the rat and dog studies produces a C_{max} for ACT-333679 of approximately1 and approximately2 µg/mL (at least 30-times the predicted patient C_{max}), respectively, it is unlikely that any of the animal findings have relevance to human treatment.

Organ bath incubation of electrically-stimulated guinea pig papillary muscle and of guinea pig right atrium showed shortened action potential duration at 30 and 100 µM selexipag and increased contractile force and heart rate of the right atrium at 100 µM selexipag or ACT-333679. Organ bath incubation of rat uterus showed a significant decrease in the frequency of uterine contraction in the presence of ACT-333679 at 30 or 100 µM, but the amplitude of spontaneous uterine contraction was not significantly altered. As these organ bath incubations are performed in the absence of added protein, the effects seen are occurring at ACT-333679/selexipag concentrations that are tens of thousands-times higher than those in PAH patients. Hence, they are unlikely to have relevance to human treatment.

Pharmacokinetics

Passive permeability values for selexipag and ACT-333679 across Madin-Darby Canine Kidney Epithelial (MDCKII) cell monolayers were in the ranges 5.4 to 9.1 x 10-6 cm/s and 9.2 to 23.2 x 10-6 cm/s, respectively, indicating that both compounds have good permeability across cell membranes. T_{max} for ACT-333679 and selexipag was typically around 1 to 3 h after oral dosing with selexipag of both rodents and dogs suggesting rapid absorption and conversion to the active drug. $t_{1/2,\beta}$ values for ACT-333679 were approximately5 h in rats and approximately7 h in cynomolgus monkeys. Except at very high doses, exposure to ACT-333679/selexipag increased approximately dose-proportionally. Bioavailability of ACT-333679 in rats was approximately55% and in monkeys was approximately34%. PK parameters generally showed no significant differences between the sexes in the species examined.

Both ACT-333679 and selexipag showed a high level of binding (>95%) to serum protein from all species tested. Binding was independent of drug concentration over the range 0.1 to 1 µg/mL. Both compounds also showed similar, high-level binding to human albumin and α_1-acid glycoprotein and those proteins were presumed to be the in vivo carriers.

[5]The QT interval represents electrical depolarization and repolarization of the ventricles. A lengthened QT interval is a marker for the potential of ventricular tachyarrhythmias like torsades de pointes and a risk factor for sudden death.

Distribution studies in rats orally dosed with radioactively labelled [^{14}C] selexipag showed that at 1 h after dosing (approximately T_{max}), radioactivity was widely distributed with the highest concentrations in liver (14 times plasma concentration) followed, in order, by small intestine, stomach, and lung (about twice plasma concentration). The lowest radioactivity concentrations were in cerebrum, cerebellum, eyeball, and testis and, at 1 h after dosing, were around one tenth of the plasma value. These results suggest that [^{14}C] selexipag-derived radioactivity crosses the blood-brain-barrier poorly. The radioactivity concentration in most tissues declined in parallel with that in plasma, such that radioactivity was undetectable in tissues (other than kidney and liver) by 72 h post-dosing. Comparison of radioactivity elimination in pigmented and albino rats suggested that selexipag and/or its metabolites might have weak affinity for melanin.

The conversion of selexipag to ACT-333679 was shown to occur following incubation with rat plasma. However, plasma from other species (dogs, monkeys, and humans) did not perform this conversion, although hepatic microsomal preparations from all species performed the conversion. Inhibitor studies suggested that the hepatic enzyme carboxylesterase 1 (CES1) may be mainly responsible for converting selexipag to ACT-333679. These results suggested that, following intestinal absorption by dogs, monkeys, or humans, selexipag is converted to ACT-333679 in the liver. In rats, however, conversion occurs both in the blood stream and in the liver.

ACT-333679 was the major metabolite found in plasma and faeces following selexipag dosing of rats or dogs. Selexipag also showed limited metabolism by cytochrome P450 (CYP) enzymes, undergoing CYP2C8-catalysed hydroxylation reactions and CYP3A4-catalysed hydroxylation and dealkylation reactions. ACT-333679 was shown to undergo glucuronidation, predominantly by UGT1A3, and the 1-*O*-β-glucuronide of ACT-333679 was identified as the major metabolite of selexipag in rat bile. In vitro and in vivo studies identified various metabolites derived from selexipag, however, aside from ACT-333679 and conjugation products, individual metabolites were generally present at low levels and there were no prominent qualitative or quantitative differences between human metabolites and those produced in animal systems.

Because ACT-333679 contains a carboxylate group, it can undergo conversion by UDP-glucuronosyltransferase to a 1-*O*-β-glucuronide (see above). Acyl glucuronides can undergo intramolecular acyl migration, resulting in the formation of isomeric glucuronides. Such acyl glucuronides can be reactive with proteins leading to the formation of covalent drug-protein adducts, which may initiate toxicity/immune responses. Incubation of the 1-*O*-β-glucuronide of ACT-333679 with human serum albumin for up to 24 h was shown to result in approximately22% of the compound covalently bound to the protein. The significance of this finding was explored by quantifying covalent protein binding in liver and serum following oral dosing of male rats with [^{14}C] selexipag. However, only relatively low levels of adducts were found and it was concluded that the chemical reactivity of selexipag glucuronides is unlikely to be of toxicological concern.

Mass balance studies using [^{14}C] selexipag were conducted in rats, dogs, and cynomolgus monkeys. Excretion of radioactivity after oral dosing was predominantly (approximately 80 to 90%) via faeces in rats and dogs. Human studies also demonstrated predominant excretion via faeces. In monkeys, however, excretion after oral dosing was predominantly (approximately 64%) via urine. Biliary excretion was demonstrated in both rats and dogs.

Conclusion

The PK data suggest that the animal models used provide a reasonable basis for extrapolation of toxicity findings to humans.

Pharmacokinetic drug interactions

Studies incubating ACT-333679 or selexipag with human liver microsomes suggested that both compounds are weak, competitive inhibitors (K_i values ≥2 μM) of a few CYPs, primarily CYP2C8 and CYP2C9. Such inhibition is unlikely to be of practical significance. The evidence also suggested that neither compound acted as a time dependent inhibitor of CYP2C8, CYP2C9, CYP2D6, or CYP3A4 activity.

Several studies examined induction of drug metabolism following exposure to ACT-333679/selexipag. Rats given a daily oral dose of selexipag at up to 10 mg/kg (produces a C_{max} for ACT-333679 of approximately1 μg/mL, at least 30 times the predicted patient C_{max}) for 7 days showed no significant changes in the overall activities of various hepatic drug-metabolising systems. Similarly, in vitro cell culture experiments suggested that both selexipag and ACT-333679 are weak activators (EC_{50} values of 2.6 μM and 3.1 μM, respectively) of the human pregnane X receptor (induces various metabolic enzymes, including CYP3A4). At a more specific level, in vitro exposure of human hepatocytes to selexipag or ACT-333679 at up to 10 μM for 72 h produced no increase in CYP1A2 activity and an approximately2 to 3 fold increase in CYP3A4 activity. CYP mRNA[6] levels were measured following exposure of in vitro cultures of human hepatocytes for 68 h to selexipag or ACT-333679 at concentrations from 0.1 to 100 μM. There was no induction of CYP1A2, concentration dependent induction of CYP2B6 (up to approximately3 to 6 fold at 30 μM selexipag), up to approximately2 to 5 fold induction of CYP2C9 at 100 μM drug, and up to approximately20 fold induction of CYP3A4 at 30 μM drug. As the drug concentrations producing induction of CYP mRNA synthesis are well outside the patient range, this effect is not expected to influence patient treatment.

Identification of uptake/efflux transporters of ACT-333679/selexipag was performed using cell lines expressing relevant human proteins. Selexipag and ACT-333679 were shown to be substrates of the hepatic drug-uptake transporters OATP1B1 and OATP1B3. Both drugs were also shown to act as inhibitors of OATP1B1 and OATP1B3, with IC_{50} values of approximately2 to 4 μM. Selexipag appears to be a weak substrate of P-gp, whereas ACT-333679 is not a substrate of P-gp. Neither ACT-333679 nor selexipag showed significant inhibition of the transport of other drugs by P-gp. ACT-333679 was shown to be a substrate of BCRP (mediates efflux from intestinal epithelium) whereas selexipag was not a substrate. Both ACT-333679 (IC_{50} = 5.6 μM) and selexipag (IC_{50} = 1.9 μM) showed inhibition of BCRP. ACT-333679 was not a substrate of the efflux transporters multidrug resistance-associated protein 2, bile salt export pump, and multidrug and toxin extrusion 1, and neither ACT-333679 nor selexipag showed significant inhibition of these proteins. Selexipag also showed inhibition of OAT1 (IC_{50} = 1.4 μM) and both selexipag and ACT-333679 showed inhibition of OAT3 (IC_{50} approximately 1 to 2 μM).

The inhibitory effects seen on transport proteins all occurred at concentrations far exceeding those reported in patients. In addition, both selexipag and ACT-333679 were shown to be weak inducers of metabolic enzymes. Accordingly, it can be concluded that selexipag treatment is unlikely to produce significant pharmacokinetic interactions with other drugs.

[6] mRNA the template for protein synthesis; the form of RNA that carries information from DNA in the nucleus to the ribosome sites of protein synthesis in the cell.

Toxicology

Acute toxicity

Single-dose toxicity studies, using oral dosing, were performed with rats and dogs.

The maximum non-lethal oral doses of selexipag in rats (250 mg/kg) and dogs (200 mg/kg) produced C_{max} values for ACT-333679 of approximately36 and 53 µg/mL, respectively (more than one thousand times the estimated C_{max} (29.1 ng/mL) for PAH patients given 1600 µg twice a day (bd)). The clinical signs in rats were consistent with an exaggerated pharmacological effect of the test article (vasodilation) and included flaccidity, hyperpnoea, hypothermia, and flush. Premature decedents commonly showed pulmonary congestion and oedema, and inflammatory cell infiltration in the lamina propria of the glandular stomach. Dogs also showed stool abnormalities and death due to intussusception.

These results suggest that selexipag, when delivered via the clinical route, is of moderate toxicity.

Repeat-dose toxicity

Pivotal studies were performed with mice, rats, and dogs and had durations of up to 2 years. All studies used once daily, oral dosing, which is consistent with the route and frequency of clinical dosing. The design of the studies was consistent with the relevant guideline (CPMP/SWP/1042/99 Rev 1 Guideline on repeated dose toxicity).

Relative exposure

Relative exposures to ACT-333679/selexipag were calculated relative to estimated $AUC_{0\text{-}24\,h}$ values from population PK analysis of data from PAH patients given steady-state selexipag doses of 1600 µg bd. Relative exposures to ACT-333679, at the No observable adverse effect level (NOAEL) dose, were moderately high for rodents (approximately40 for daily dosing of mice for 2 years and approximately15 for daily dosing of rats for 6 months) and very high for dogs (approximately140 for daily dosing for 9 months) (see Table 2).

Table 2: Relative exposure in repeat-dose toxicity and carcinogenicity studies[a]

Species	Study number	Study duration day of TK sampling	Dose mg/kg/day [b]	Sex	$AUC_{0\text{-}24\,h}$ µg·h/mL[c]	Exposure ratio[c, d]
Mouse (B6C3F1/Crlj)	**T-08.292** (B-5938)	13 weeks (91)	**100**[e], 300, 500	♂	**12.40**, 51.50, 71.50 (12.20, 52.10, 90.00)	**34**, 141, 195 (110, 469, 811)
				♀	**9.990**, 39.80, 58.00 (10.10, 44.40, 74.00)	**27**, 109, 158 (91, 400, 667)

Species	Study number	Study duration day of TK sampling	Dose mg/kg/day [b]	Sex	AUC_{0-24h} µg·h/mL[c]	Exposure ratio[c, d]
	T-10.648 (B-5939)	2 years (181) [carcinogenicity]	**125**, 250, 500[f]	♂	**13.90**, 31.70, 67.50 (11.60, 36.80, 84.40)	**38**, 87, 184 (105, 332, 760)
				♀	**16.00**, 30.80, 65.50 (18.60, 36.70, 91.70)	**44**, 84, 179 (168, 331, 826)
Rat (SD)	**T-08.275** (TX-1308)	4 weeks (28)	20, 60, 180	♂	12.20, 38.79, 137.3 (0.3176, 2.148, 8.770)	33, 106, 375 (3, 19, 79)
				♀	9.541, 36.28, 303.5 (0.5100, 2.918, 24.76)	26, 99, 829 (5, 26, 223)
	T-08.276 (TX-1339)	4 weeks (28)	2, **6**, 60	♂	0.2145, **1.400**, 50.94 (0, 0.00890, 2.103)	0.6, **3.8**, 139 (0, 0.08, 19)
				♀	0.1211, **0.9491**, 63.60 (0, 0.04139, 4.087)	0.3, **2.6**, 174 (0, 0.4, 37)
	T-08.285 (B-5895)	26 weeks (178)	**6**, 25, 100	♂	**4.77**, 22.7, 76.3 (0.229, 1.43, 5.33)	**13**, 62, 208 (2, 13, 48)
				♀	**6.79**, 45.7, 202	**19**, 125, 552

Species	Study number	Study duration day of TK sampling	Dose mg/kg/day [b]	Sex	AUC_{0-24h} µg·h/mL[c]	Exposure ratio[c, d]
					(0.286, 2.81, 18.8)	(2.6, 25, 169)
	T-10.649 (B-5940)	2 years [carcinogenicity]	10, 30, 100	♂	7.62, 25.4, 90.7 (0.342, 1.69, 7.78)	21, 69, 248 (3.1, 15, 70)
				♀	11.4, 26.9, 162 (0.630, 2.18, 13.3)	31, 73, 443 (5.7, 20, 120)
Dog (beagle)	**T-08.277** (TX-1309)	2 weeks (14)	**2**, 6, 20	♂	**50.76**, 154.1, 576.0 (7.504, 24.27, 77.18)	**139**, 421, 1574 (68, 219, 695)
				♀	**67.82**, 154.9, 531.9 (6.721, 25.08, 103.4)	**185**, 423, 1453 (61, 226, 932)
	T-08.290 (TX-1360)	4 weeks (24)	**1.5**, 3, 6	♂	**39.66**, 82.90, 159.1 (5.386, 13.07, 29.21)	**108**, 227, 435 (49, 118, 263)
				♀	**54.56**, 85.61, 201.4 (7.286, 14.37, 35.44)	**149**, 234, 550 (66, 129, 319)
	T-08.286 (B-5896)	9 months (39 weeks)	1, **2**, 4	♂	23.1, **40.5**, 109 (2.55, 8.15, 21.3)	63, **111**, 298 (23, 73, 192)

Species	Study number	Study duration day of TK sampling	Dose mg/kg/day [b]	Sex	AUC_{0-24h} µg·h/mL[c]	Exposure ratio[c, d]
				♀	35.7, **<u>58.9</u>**, 120 (2.88, 6.54, 18.0)	98, **161**, 328 (26, 59, 162)
Human (PAH patients)	Document no. **D-14470**	steady state	[1600 µg bd]	♂+♀	0.366 (0.111)	–

[a] All listed studies are GLP compliant; [b] doses given PO; [c] ACT-333679 values are unbracketed and selexipag values are bracketed; [d] animal:human plasma AUC_{0-24h}; [e] values at NOAEL dose are bolded and underlined (where no value is so indicated, NOAEL was < low dose); [f] NOEL (carcinogenicity) is boxed.

Major toxicities

Similar clinical signs were noted in repeat-dose toxicity studies as were found for single-dose studies and these often represented an exaggerated pharmacological effect of the test article (that is, associated with vasodilation).

Premature deaths of mice given high doses of test article were often associated with flaccidity (exaggerated pharmacology), whilst deaths in the MD and HD groups, during the late stages of the mouse carcinogenicity study, were often associated with gastrointestinal (GI) tract lesions such as erosion/ulcer in the stomach and/or duodenum. However, the cause of demise for many HD females was unclear. Notably, however, survival at the end of the 2 year dosing period was significantly higher for all male mouse groups receiving selexipag as compared to controls, although HD female mice showed a significant decrease in survival. The rat 2 year carcinogenicity study showed somewhat different mortality trends, with comparable survival at the end of the dosing period for controls and all male groups receiving test article, whilst HD females showed significantly increased survival compared to controls. Such results suggest that selexipag does not have prominent off-target effects in rodents.

Selexipag dosing was associated with increased ossification of spongy bones in both rat and dog studies. In the rat 2 year carcinogenicity study, females in all test article treated groups showed an increased incidence and/or severity of ossification. In the dog 2 and 4 week studies, MD and/or HD animals showed increased ossification of spongy bones and increases in haemopoietic tissue and fibrosis in bone marrow. Such effects may be explicable based on findings that agents that decrease systemic blood pressure and increase blood perfusion induce increased bone mass[7] or they may reflect off-target activity (PGE_2 has been shown to induce heterotopic ossification[8]).

[7] Marenzana M. and Arnett T.R. (2013) The key role of the blood supply to bone. *Bone Research*, **3**: 203–215.
[8] Jee W.S., Ueno K., Deng Y.P. and Woodbury D.M. (1985) The effects of prostaglandin E_2 in growing rats: increased metaphyseal hard tissue and cortico-endosteal bone formation. *Calcified Tissue International*, **37**: 148–157.

Hepatocyte hypertrophy was noted in the HD groups of the mouse 13 week and rat 26 week studies and in most groups of the mouse and rat 2 year carcinogenicity studies. This effect is likely an adaptive response to xenobiotic exposure involving increased synthesis of metabolic enzymes. Given the high exposure ratios at which this effect is induced, it is unlikely to be of relevance to clinical use of selexipag.

Intussusception was a significant cause of death in dogs given high doses of selexipag. The basis of this effect is unclear but might be related to test article induced vomiting and/or an off-target effect on intestinal motility, which is known to be regulated by prostaglandins. It might be relevant that in in vitro studies ACT-333679 showed some ability (EC_{50} = 660 nM) to activate the canine (although not the human or rat) EP4 prostanoid receptor. Intussusception was not found in the rodent studies and its occurrence at very high exposure ratios in dogs suggests that it is unlikely to be of relevance to clinical use of selexipag.

Effects of selexipag dosing on thyroid follicular and Leydig cells in mice and rats, respectively, are discussed below in the carcinogenicity section.

Genotoxicity

Selexipag and ACT-333679 were not mutagenic at up to 5 mg/plate, in both the presence and absence of metabolic activation, in standard *Salmonella typhimurium* and *Escherichia coli* strains. Tests of in vitro clastogenicity, using Chinese hamster lung fibroblasts, showed that ACT-333679 was negative (in both the presence and absence of metabolic activation), whereas selexipag was positive (at a concentration producing cytotoxicity) in the absence (but not the presence) of metabolic activation. Under in vivo conditions (mouse bone marrow micronucleus test), selexipag was negative for induction of micronuclei. It was also shown, using the alkaline Comet assay, that selexipag did not induce deoxyribonucleic acid (DNA) strand breaks or alkali-labile lesions in hepatocytes following oral administration to rats. The assays used and the conditions employed were consistent with the relevant European medicines Agency (EMA) guideline[9]. These results indicate that selexipag and ACT-333679 are not of genotoxic concern for patients.

Carcinogenicity

Two year, GLP compliant studies were performed using mice and rats of both sexes given daily oral doses of selexipag. The HD was shown to produce clinical signs and histopathological changes in both species. The species chosen, doses used, numbers of animals per dose group and so on are consistent with relevant guidelines.[10]

For both species, selexipag dosing, up to and including the HD (relative exposure = approximately180 (mouse) and approximately300 (rat)), did not increase the overall incidence of tumours or tumour bearing animals of either sex. Selexipag dosing was associated with non-statistically significant increases in the incidence of thyroid and Leydig cell tumours in mice and rats, respectively, which were correlated with hyperplasia/hypertrophy of thyroid follicular and Leydig cells. The induction of thyroid and Leydig cell tumours in rodents by various drugs is thought to reflect unique aspects of rodent biology that are not relevant to humans.[11] LD male rats showed a statistically significant increase in the incidence of anterior pituitary adenomas. However, this change was not considered to be test article related, since it was not dose dependent.

[9]CPMP/ICH/141/95 Genotoxicity: Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals
[10] ICH S1C(R2) Dose Selection for Carcinogenicity Studies of Pharmaceuticals; CPMP/ICH/299/95 Carcinogenicity: Testing for Carcinogenicity of Pharmaceuticals; CPMP/SWP/2877/00 Note for Guidance on Carcinogenic Potential.
[11] Alison R.H., Capen C.C. and Prentice D.E. (1994) Neoplastic lesions of questionable significance to humans. *Toxicologic Pathology*, **22**: 179–186.

Studies were performed examining mechanistic bases for the putative induction of thyroid and Leydig cell tumours by selexipag. No evidence was found for a direct effect of selexipag on the pituitary-testicular endocrine axis in rats, and so the basis for any testicular effects was unclear. Selexipag dosing of mice was, however, shown to induce hepatic drug metabolising enzymes resulting in imbalance of thyroid hormones, consistent with findings for other drugs inducing thyroid follicular cell hyperplasia/hypertrophy.[11]

The animal results suggest that selexipag is not of carcinogenic concern for patients. This conclusion is consistent with the lack of activity shown by selexipag in in vivo assays for genotoxicity.

Reproductive toxicity

The studies presented are GLP compliant and their scope and design is appropriate and consistent with the relevant guideline.[12]

Results from oral dosing of pregnant rats with [^{14}C] selexipag showed rapid distribution of radioactivity into fetuses (fetal concentration at 4 h after dosing was about a third of the maternal value) and subsequent clearance of radioactivity from fetuses with similar kinetics to that of dams. This suggests that selexipag and/or metabolites undergo placental transfer. Similarly, dosing of lactating rats showed excretion of radioactivity into milk and subsequent elimination of radioactivity from milk and plasma with similar kinetics.

Daily oral dosing with selexipag was used to examine possible effects on fertility (male and female rats), embryofetal development (rats and rabbits), pre and postnatal development (rats), and juvenile development (dogs). Rat fertility (both sexes) showed no adverse effects from relatively high doses of selexipag (exposure ratios of approximately130; see Table 3). General toxicity for pregnant rats and rabbits was seen at much lower doses (exposure ratios of approximately10 times those expected in humans at NOAEL). The effects seen (flaccidity, weight loss and so on) were similar to those found in repeat-dose toxicity studies. Embryofetal development studies suggested moderate sensitivity to selexipag dosing (exposure ratios at NOAEL of 9 for rats and 37 for rabbits), with higher doses producing a significant decrement in fetal rat weight. There was, however, no evidence for the induction of developmental variations or abnormalities in either species. A pre/postnatal dosing study in rats showed no effects on birthing or on the viability or physical development of liveborns after birth (exposure ratios up to 26). Possible effects on juvenile development were studied using pups given a daily oral dose of selexipag for up to 39 weeks. Potentially adverse effects were seen in both sexes after 39 weeks of dosing at exposure ratios of ≥ 40. These adverse effects included delayed closure of epiphyseal growth plates, increased thickness of compact bone, and delayed sexual maturation. These effects were at least partly related to decreased body weight gain. Dosing of pups at an exposure ratio of approximately40 did not, however, produce adverse effects when the dosing period was 26 weeks.

[12] CPMP/ICH/386/95 Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility

Relative exposure

Table 3: Relative exposure in reproductive and developmental toxicity studies[a]

Species	Study type (number)	Treatment period day of sampling	Dose mg/kg/day[b]	Sex	AUC_{0-24h} µg·h/mL[c]	Exposure ratio[c, d]
Rat SD	Fertility and early embryo development (**T-08.287** (R-950))	♂ = 2 weeks pre-mating + 2-weeks mating; ♀ = 2 weeks pre-mating, during mating, and till GD7 (15)	6[e], 20, **60**[e]	♂	3.65, 12.3, **48.9** (0.160, 0.709, 4.30)	10, 34, **134** (1.4, 6.4, 39)
				♀	3.00, 8.62, **47.8** (0.107, 0.502, 2.88)	8.2, 24, **131** (1.0, 4.5, 26)
	Embryofetal development (**T-08.288** (R-951))	GD7–17 (GD17)	2, 6[f], 20	♀	0.920, 3.35, 12.9 (0.0406, 0.156, 1.16)	2.5, 9.2, 35 (0.4, 1.4, 10)
	Pre-/post-natal development (**T-12.054** (R-1048))	GD7–PND21 (dams) (PND21)	2, 6, **20**	♀	0.236, 2.46, **9.56** (–, 0.193, 1.17)	0.6, 6.7, **26** (–, 1.7, 11)
Rabbit NZW	Embryofetal development (**T-08.289** (R-952))	GD6–GD18 (GD18)	3, 10, 30	♀	1.15, 4.09, 13.7 (0.0228, 0.144, 1.56)	3.1, 11, 37 (0.2, 1.3, 14)
Dog beagle	Juvenile development (**T-12.357** (AB09680))	26 weeks (starting PND 27–32) (181)	1, 3	♂	20.90, 55.20 (2.360, 8.270)	57, 150 (21, 75)
				♀	14.30, 52.80 (2.330, 7.190)	39, 144 (21, 65)
		39 weeks (starting PND 27–32) (272)	1, 3, 6/4	♂	16.40, 44.70, 48.80 (2.920, 7.270,	45, 122, 133 (26, 65, 113)

Species	Study type (number)	Treatment period day of sampling	Dose mg/kg/day[b]	Sex	AUC_{0-24h} µg·h/mL[c]	Exposure ratio[c, d]
					12.50)	
				♀	13.00, 45.40, 50.30 (2.660, 6.030, 8.100)	36, 124, 137 (24, 54, 73)

[a] All listed studies are GLP compliant; [b] doses given PO; [c] ACT-333679 values are unbracketed and selexipag values are bracketed; [d] animal:human plasma AUC_{0-24h} based on human values of 0.366 and 0.111 µg·h/mL for ACT-333679 and selexipag, respectively; [e] values at NOAEL dose are bolded (paternal or maternal fertility/reproductive performance), underlined (paternal or maternal general toxicity), or boxed (embryofetal or juvenile toxicity) (where no value is so indicated (*i.e.* 39-week juvenile dog study), NOAEL was <LD); [f] same value for both general maternal toxicity and embryofetal toxicity; GD=Gestational day; PND=Postnatal day.

Pregnancy classification

The sponsor has proposed Pregnancy Category B. This should be modified to Pregnancy Category B1[13] ('*Studies in animals have not shown evidence of an increased occurrence of fetal damage*'). This category is appropriate based on the results of the sponsor's reproductive toxicity studies.

Local tolerance

Selexipag was well tolerated and did not produce local irritation in a rabbit dermal irritation test.

Phototoxicity

Exposure of mouse 3T3 cells to ACT-333679 or selexipag plus UV-A showed that both compounds can induce a high level of phototoxicity. The enhancement of toxicity by ultraviolet (UV)-A was seen at drug concentrations approximately0.3 to 3 µg/mL, which is much higher than the concentrations found in patients. As there is no evidence for the drug accumulating in skin, the risk of phototoxic skin damage is probably negligible.

Paediatric use

Selexipag is not proposed for paediatric use. Studies in rat pups showed induction of intestinal intussusception at high exposure ratios, which might be a concern for human juvenile use.

[13] Full details of Pregnancy Category B1: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.

Nonclinical summary

- The nonclinical studies were comprehensive and of high quality and the pivotal toxicological studies were performed to GLP standards.
- Selexipag is a pro-drug that is converted to the active form, ACT-333679, by carboxylesterase activity in the liver. Although ACT-333679 is a prostacyclin receptor (IP) agonist, it is a non-prostanoid and (unlike other drugs of the same pharmacological class) is not a chemical analogue of prostacyclin.
- Primary pharmacology studies demonstrated that ACT-333679 has nanomolar range affinity for the IP receptor. The binding affinity of ACT-333679 was approximately13 times stronger than that of selexipag and was intermediate to that of the prostacyclin analogues, iloprost and treprostinil.
- Cellular studies showed that ACT-333679 (unlike the prostacyclin analogue iloprost) did not induce major IP receptor internalisation. This suggests that ACT-333679 is not a full agonist and may not induce tachyphylaxis.
- In vitro studies with human pulmonary artery SMCs showed that ACT-333679 has both potent anti-proliferative activity (IC_{50} = 2.9 nM compared to iloprost = 0.10 nM) and the ability to induce cellular shape changes consistent with relaxation. ACT-333679 also showed potential anti-fibrotic activity towards normal human lung fibroblasts, and was effective at inhibiting platelet aggregation in human plasma.
- Selexipag dosing of rats with monocrotaline induced PAH produced a significant increase in survival that was associated with reductions in pulmonary arterial wall hypertrophy and right ventricular systolic pressure. Selexipag was also effective at reducing MAP in spontaneously hypertensive rats and, unlike treprostinil, did not induce tachyphylaxis.
- Secondary pharmacodynamic testing of selexipag and ACT-333679 against a panel of receptors, ion channels, enzymes, and transporters suggested that off-target effects are unlikely at clinically relevant concentrations. Similarly, it was shown that the binding affinity of ACT-333679 for other human prostanoid receptors is at least 130 times lower than that for the IP receptor. This suggests that off-target effects at prostanoid receptors are unlikely to occur in patients.
- Studies with hERG-transfected cells suggested that selexipag treatment of patients has little potential for QT interval prolongation.
- Safety pharmacology studies examined the effects of ACT-333679/selexipag on blood coagulation, cardiac function, CNS function, gastric function and intestinal transport, renal function, respiration and uterine contraction. Effects were seen at ACT-333679/selexipag concentrations that are tens of thousands-times higher than those in PAH patients. Hence, they are unlikely to have relevance to human treatment.
- Both ACT-333679 and selexipag showed a high level of binding (>95%) to serum protein from all species tested. Binding was independent of drug concentration over the range 0.1 to 1 μg/mL. Both compounds showed a high level of binding to albumin and α1-acid glycoprotein and did not appear to distribute into red blood cells. Studies in rats orally dosed with [^{14}C] selexipag showed rapid and wide distribution of radioactivity, including into lung. Lowest radioactivity concentrations were in brain and testis, suggesting that selexipag and/or metabolites cross the blood-brain barrier poorly.
- ACT-333679 was the major metabolite of selexipag. Selexipag also showed limited metabolism by CYP enzymes, undergoing CYP2C8-catalysed hydroxylation reactions and CYP3A4-catalysed hydroxylation and dealkylation reactions. ACT-333679 undergoes glucuronidation, predominantly by UGT1A3.

- Selexipag and ACT-333679 showed inhibitory effects on some transport proteins but only at concentrations far exceeding those reported in patients. In addition, both compounds were shown to be weak inducers of metabolic enzymes. This suggests that selexipag treatment is unlikely to produce significant pharmacokinetic interactions with other drugs.
- Maximum non-lethal, single, oral doses of selexipag in rats and dogs produced C_{max} values for ACT-333679 that were more than one thousand times the estimated C_{max} for PAH patients given the highest recommended dose of selexipag. Clinical signs in animals were largely consistent with an exaggerated pharmacological effect of the test article (vasodilation).
- Repeat-dose toxicity studies were performed with mice, rats and dogs and had durations of up to 2 years. Selexipag did not have prominent off-target effects in rodents, with survival at the end of the 2 year dosing period often showing no adverse effect even at high exposure ratios. Selexipag dosing was associated with increased ossification of spongy bones in both rat and dog studies. This effect may be explicable based on literature findings that agents that decrease systemic blood pressure and increase blood perfusion induce increased bone mass. Intussusception was a significant cause of death in dogs given high doses of selexipag. The occurrence of this effect at very high exposure ratios suggests that it is unlikely to be of relevance to clinical use of selexipag.
- Selexipag and ACT-333679 were negative for induction of mutations in standard bacterial reverse mutation assays and ACT-333679 was negative for clastogenicity in vitro. Although selexipag showed clastogenicity in the absence (but not the presence) of metabolic activation, it was negative in the in vivo mouse micronucleus test and also in the Alkaline Comet assay following oral administration to rats.
- Two year carcinogenicity studies were performed using mice and rats of both sexes given daily oral doses of selexipag. No increase in the overall incidence of tumours or tumour-bearing animals of either sex was found for either species. Selexipag dosing was associated with non-statistically significant increases in the incidence of thyroid and Leydig cell tumours in mice and rats, respectively, which were correlated with hyperplasia/hypertrophy of thyroid follicular and Leydig cells. The induction of thyroid and Leydig cell tumours in rodents by various drugs is thought to reflect unique aspects of rodent biology that are not relevant to humans.
- Following oral dosing of pregnant rats with [^{14}C] selexipag, there was rapid distribution of radioactivity into fetuses; suggesting that selexipag and/or metabolites undergo placental transfer. Similarly, dosing of lactating rats showed excretion of radioactivity into milk. Rat fertility studies (both sexes) showed no adverse effects from selexipag dosing at exposure ratios (animal: human) up to approximately130. Embryofetal development studies using rats and rabbits showed no evidence for teratogenicity at exposure ratios up to approximately35. Repeat dosing of pups for up to 9 months produced bone changes; however, this was seen at relatively high exposure ratios.
- Selexipag showed no evidence for local irritation in a rabbit dermal irritation test.
- Both selexipag and ACT-333679, when combined with UV-A exposure, produced marked phototoxicity in the mouse 3T3 cell assay. However, this effect is probably irrelevant at the drug concentrations occurring in patients.

Nonclinical conclusions and recommendation

- The sponsor has presented a very high quality and comprehensive dossier of nonclinical studies that contains no significant deficiencies.
- The sponsor's primary pharmacology studies support the proposed mechanism of action and indication for selexipag.
- The secondary pharmacodynamics and safety pharmacology studies suggested that off-target effects (even at other prostanoid receptors) are unlikely at clinically relevant concentrations.
- Selexipag appears to pose neither genotoxic nor carcinogenic risks for patients.
- Selexipag showed no evidence for teratogenicity or effects on fertility in animal testing. The sponsor has proposed Pregnancy Category B. This should be modified to Pregnancy Category B1 ('*Studies in animals have not shown evidence of an increased occurrence of fetal damage*'). This category is appropriate based on the results of the sponsor's reproductive toxicity studies.
- There are no nonclinical objections to registration.
- Amendments to the draft Product Information were recommended but these are beyond the scope of this AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

PAH is characterised by vasculopathy and remodelling of the pulmonary circulation resulting in narrowing of the arterial lumen and impaired vasodilation. This leads to an increase in pulmonary arterial pressure (PAP) and pulmonary vascular resistance (PVR), which limits the ability of the right ventricle to pump blood through the lungs and thereby causing shortness of breath, and eventually resulting in right heart failure and death. According to the sponsor, 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. Mediators of these pathological changes include reduced prostacyclin synthase activity and variably reduced IP receptor expression, an up-regulated endothelin-1 (ET-1) system, and abnormalities of the nitric oxide pathway. Current pharmacological therapies for PAH are therefore targeted towards these three mediator pathways: endothelin receptor antagonists (ERA) which inhibit the effects of elevated ET-1 levels and thus reducing vasoconstriction, smooth muscle cell proliferation and pulmonary vessel fibrosis; prostacyclin (epoprostenol) and its analogues which relax and reduce proliferation of vascular smooth muscle cells; and phosphodiesterase type 5 inhibitors (PDE-5i) and the soluble guanylate cyclase agonist, riociguat, which potentiates the anti-platelet, anti-proliferative, and vasodilatory effects of nitric oxide.

According to the sponsor, the utility of IP receptor agonism in the treatment of patients with PAH had been shown with epoprostenol and supported by studies on symptomatic endpoints with the prostacyclin (PGI_2) analogues iloprost, treprostinil, and beraprost, but that these treatments of PAH had been approved based on their symptomatic effects and

no long-term controlled studies focusing on long-term clinical outcomes (morbidity/mortality) of PAH disease have been previously conducted with an agent targeting the IP receptor. In addition, the short elimination half-life of prostacyclin and most of its analogues approved for treatment of PAH requires administration of these drugs by continuous intravenous (IV) or subcutaneous (SC) infusion or multiple daily inhalations, and these modes of administration can potentially introduce risks of rapid-onset, overdosing or underdosing, thus affecting tolerability and efficacy. The sponsor was therefore of the opinion that there was an unmet medical need in the availability of a long-acting, oral pharmacological agent targeting the prostacyclin pathway for which efficacy has been demonstrated using clinically relevant endpoints associated with PAH disease progression and hospitalisation due to PAH, in a patient population representative of current treatment strategies.

Comments: The clinical rationale is sound. The currently approved IP receptor agonists for the treatment of PAH in Australia include epoprostenol, iloprost and treprostinil. Epoprostenol is to be administered by continuous intravenous infusion, and is approved for the indication of

'*long-term treatment, via continuous intravenous infusion, in WHO functional class III or class IV patients with:*

Idiopathic pulmonary arterial hypertension

Familial pulmonary arterial hypertension

Pulmonary arterial hypertension associated with the scleroderma spectrum of diseases'[14]

Iloprost is a prostacyclin analogue and is to be administered by inhalation. It is approved for the indication of '*treatment of patients with primary pulmonary hypertension or secondary pulmonary hypertension due to connective tissue disease or drug-induced, in moderate or severe stages of the disease. In addition, treatment of moderate or severe secondary pulmonary hypertension due to chronic pulmonary thromboembolism, where surgery is not possible*.'[15]

Treprostinil is a prostacyclin analogue and is to be administered by continuous subcutaneous infusion. It is approved for the indication of *'treatment of pulmonary arterial hypertension in patients with NYHA class III-IV to diminish symptoms associated with exercise.'*[16] Beraprost is an oral synthetic analogue of prostacyclin, but is not currently approved for use in Australia. A check through the FDA and EMA website shows that it is also not currently approved in these jurisdictions. According to the sponsor, Beraprost is approved in Japan and South Korea.

In December 2013, oral, extended-release treprostinil (Orenitram) was approved by the FDA '*for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise capacity. The study that established effectiveness included predominately patients with WHO functional class II-III symptoms and aetiologies of idiopathic or heritable PAH (75%) or PAH associated with connective tissue disease (19%). When used as the sole vasodilator, the effect of Orenitram on exercise is about 10% of the deficit, and the effect, if any, on a background of another vasodilator is probably less than this. Orenitram is probably most useful to replace subcutaneous, intravenous, or inhaled treprostinil, but this use has not been studied*'[17]. The approved dosing

[14] Australian PI for epoprostenol, November 2014
[15] Australian PI for iloprost, June 2013
[16] Australian PI for treprostinil, July 2007
[17] FDA Prescribing Information for Orenitram, December 2013

regimen is by individualised titration, with recommended starting dose of 0.25 mg bd, and increasing the dose as tolerated (recommended increment is 0.25 mg to 0.5 mg bd every 3 to 4 days) to achieve optimal clinical response.

Contents of the clinical dossier

Scope of the clinical dossier

The submission contained the following clinical information:

- Eleven clinical pharmacology studies, including 11 that provided pharmacokinetic data and 4 that provided pharmacodynamic data.
- Two population pharmacokinetic analyses.
- One pivotal efficacy/safety study (AC-065A302 [GRIPHON])
- Two other efficacy/safety studies (Studies NS-304/-02 [a Phase II, placebo-controlled study] and AC-065A201 [a Phase II, uncontrolled, open-label study in Japanese patients[18]])
- Integrated Summary of Efficacy, Integrated Summary of Safety, independent ophthalmology board safety report, two exploratory Phase II studies looking at indication unrelated to this submission (AC-065B201: efficacy and safety of selexipag in patients with chronic thromboembolic pulmonary hypertension [CTEPH]; AC-065B202: open-label extension study of selexipag in CTEPH patients who have completed Study AC-065B201)

Paediatric data

The submission did not include paediatric data. The sponsor is not using data in this submission to support the use of selexipag in a paediatric population. The sponsor has provided the completed TGA Paediatric Development Plan and a copy of the EU Paediatric Investigation Plan (PIP). These paediatric development plans are appropriate.

Good clinical practice

The clinical studies reviewed in this evaluation were in compliance with CPMP/ICH/135/95 Note for Guidance on Good Clinical Practice.

Pharmacokinetics

Studies providing pharmacokinetic data

Table 4 shows the studies relating to each pharmacokinetic topic and the location of each study summary.

Table 4: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	*
PK in healthy adults	General PKs	QGUY/2006/ NS-304-01	PKs of single and multiple oral rising doses; PKs of a single oral dose of selexipag under fasting and non-fasting conditions; and PK interaction between selexipag and warfarin

[18] This study is ongoing at the time of this submission and interim data are presented.

PK topic	Subtopic	Study ID	*
		PS003	PKs of a 100 µg oral dose of selexipag in a 10ml solution
	Bioequiva-lence	AC-065-108	Bioequivalence between 1600 µg selexipag bd administered as a single film-coated tablet and as 8 film-coated tablets of 200 µg
	Multi-dose	AC-065-101	PKs of selexipag and ACT-333679 after multiple-ascending doses of selexipag administered orally bd
		AC-065-102	Photosensitising potential and PKs of 800 µg and 1,200 µg selexipag bd
		AC-065-106	Cardiac repolarisation and PKs following 800 and 1600 µg selexipag bd
	Mass balance	186933	Absorption and excretion kinetics following administration of [^{14}C] selexipag
Special Populations	Hepatic Impairment	AC-065-104	Effect of mild, moderate, and severe hepatic impairment on the PKs of selexipag and ACT-333679
	Renal Impairment	AC-065-105	PKs of selexipag and ACT-333679 in subjects with SRFI and healthy subjects
	Japanese	NS304p101	PKs of selexipag in healthy adult and elderly male Japanese volunteers
PK interactions	Kaletra	AC-065-109	Effects of multiple-dose lopinavir/ritonavir on the PKs of single-dose selexipag
PopPK	Healthy subjects	AC-065-106-PPK	PopPK characteristics of selexipag and its metabolite ACT-333679
	Target population§	AC-065A302-PPK	PopPK/PD characteristics of selexipag and its metabolite ACT-333679

* Indicates the primary aim of the study.
§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacokinetics

The 200 µg commercial dose formulation is identical to that used in the pivotal Phase III trial and the differences between film-coated tablets used in the other clinical studies and the commercial formulation are the colour and debossing of the tablets.

No dedicated studies examined the PKs of selexipag/ACT-333679 in the target population.

For further details of absorption, distribution, metabolism and excretion as well as PopPK study summaries, please see *Pharmacokinetics, Evaluator's conclusions on pharmacokinetics* in Attachment 2 as well as *Overall conclusions and risk/benefit assessment*, *Clinical, Pharmacokinetics* below.

Questions arising from the PK studies

For details see *Clinical questions* below and in Attachment 2.

Pharmacodynamics

Studies providing pharmacodynamic (PD) data

As all of the trials that contain information regarding selexipag PDs also contain relevant PK data they are listed in Table 4 above.

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacodynamics

Mechanism of action

Selexipag is a selective non-prostanoid prostacyclin IP receptor agonist.

Primary PD

No dedicated PD studies examined the primary PD effects of selexipag or its active metabolite ACT-333679.

6-MWD PK/PD modelling

6-MWD at steady state showed a significant increase with increasing exposure, from 369 m with no exposure (placebo) to 392 m with high exposure.

Plasma NT pro-BNP showed a statistically significant decrease with higher exposure, from 667 with no exposure (placebo) to 475 ng/mL with high exposure.

Secondary PD

Steady-state levels of selexipag were associated with mild increases in the HR with the largest placebo-corrected change-from-baseline HR reaching 6 bpm to 7 bpm at 1.5 to 3 h after dosing with 800 µg selexipag and 9 bpm to 10 bpm at the same time-points following dosing with 1600 µg selexipag.

Neither selexipag nor the active selexipag metabolite affects cardiac repolarisation or cardiac conduction.

It is impossible to either confirm or reject the possibility that selexipag and ACT-333679 possess photosensitising potential.

There was a significant inverse correlation between total bilirubin and exposure. For instance, total bilirubin levels decreased from 12.03 µmol/L to 10.58 µmol/L at low (placebo) and high exposure levels, respectively.

Leukocyte, erythrocyte and haemoglobin (Hb) levels were all significantly and inversely correlated with selexipag/ACT-333679 exposure.

Selexipag had no relevant effects on platelet aggregation, blood coagulation markers, vWF, sTM, and P-selectin, or on bone turnover markers, sOC, P1NP, CTx, and NTx.

Time course of PDs

*T*he maximum increases in placebo-corrected changes-from-baseline HR occurred between 1.5 h and 3 h following administration of either 800 µg or 1600 µg selexipag.

Relationship between drug concentration and PDs

There was no relationship between drug exposure and changes in QTc, SBP, DBP, MAP or HR.

There was a statistically significant relationship between the probability of occurrence of a prostacyclin-like associated AE and drug exposure, PAH aetiology, and PAH co-medication.

There was no evidence that the number of treatment-emergent haemorrhages or gastrointestinal haemorrhages correlated with drug exposure

PD interactions

Steady state levels of selexipag and ACT-333679 did not affect the INR $AUC_{0\text{-}144h}$, INRmax or INRtmax of warfarin.

Limitations of PD studies

No dedicated PD studies examined the primary PDs of selexipag/ACT-333679 in the target population.

Dosage selection for the pivotal studies

The dosage regimen in the pivotal study was individual titration starting from 200 µg bd and increasing in weekly increments of 200 µg bd until the individual maximum tolerated dose was achieved, or up to a maximum of 1600 µg bd The sponsor has provided the rationale for the up-titration regimen, that up-titration to an individual patient's highest tolerated dose was the generally accepted treatment regimen for prostacyclin receptor agonists as starting treatment with high doses of these compounds was associated with poor tolerability due to typical prostacyclin-associated pharmacological effects (e.g. headache, diarrhoea, jaw pain, myalgia, flushing, and nausea). In addition, results from Phase 1 studies with selexipag showed that starting at lower doses and up-titrating improved tolerability.

Results from Phase 1 studies showed that the highest tolerated dose in healthy subjects was 1600 µg bd The starting dose of 200 µg bd in the pivotal study was based on safety and tolerability data from the Phase 1 study QGUY/2006/NS304/-01, which showed a comparable tolerability profile of multiple doses of both 200 µg and 400 µg bd on initiation with the lower dose. Titration steps of 200 µg bd were introduced based on the understanding that the first up-titration step to 400 µg bd would result in a dose that had shown acceptable tolerability as a starting dose in study QGUY/2006/NS304/-01.

Comment: The rationale for the dose selection and dosing regimen for the pivotal Phase III trial is sound. The sponsor has also confirmed that the 200 µg commercial dose formulation is identical to the 200 µg tablet used in the pivotal Study AC-065A302.

Efficacy

Studies providing efficacy data for the proposed indication of treatment of pulmonary arterial hypertension (PAH) in patients with WHO functional Class II, III or IV symptoms

Support for the efficacy of selexipag for the proposed indication is based on the results of a single, long-term, pivotal Phase III study (AC-065A302/GRIPHON) in 1156 patients with symptomatic PAH. Additional supportive efficacy data is drawn from a Phase II, placebo-controlled study (NS-304/-02) and from an open-label, uncontrolled Phase II study in Japanese patients (AC-065A201). The sponsor has also provided an integrated summary of efficacy (ISE), which was composed of appendices (statistical plans, tables and figures) referenced to in in the sponsor's Summary of Clinical Efficacy).

Evaluator's conclusions on efficacy for the proposed indication

Overall, the study design, study inclusion and exclusion criteria, and study endpoints of the pivotal Phase III study (AC-065A302) were appropriate and in line with the recommendations of the TGA-adopted EMA guidelines on the clinical investigation of medicinal products for the treatment of pulmonary arterial hypertension. The study primary endpoint (composite) allowed evaluation of the effect of selexipag (administered in dosing regimen of initial 12 week up-titration from 200 µg bd until the individual maximum tolerated dose [IMTD; up to maximum dose of 1600 µg bd] and then maintained at IMTD for the next 14 weeks up to Week 26) on all-cause mortality and PAH related morbidity, while the study secondary endpoints allowed evaluation of the effect of selexipag on exercise capacity (6MWD[19]) and clinical symptoms (NYHA/WHO functional class[20] and CAMPHOR questionnaire[21]). Baseline demographic and disease characteristics were comparable between treatment groups, and were generally consistent with the target patient population. The majority of patients (80.5% in selexipag group and 78.7% in placebo group) had concomitant PAH specific medication at baseline.

Analysis of the primary efficacy endpoint (that is, time to first morbidity/mortality[22] [MM] event up to EOT + 7 days) showed that the relative risk reduction for the occurrence of a MM event with selexipag compared to placebo was 40% (1-sided unstratified log-rank $p < 0.0001$). Additional analyses of the primary efficacy endpoint in the per protocol set and sensitivity analyses on the primary efficacy endpoint yielded results generally consistent with those of the main analysis, showing a reduced risk of MM event during treatment on selexipag compared to placebo. Exploratory endpoints involving analyses of time to first MM event up to study closure, and analyses of time to first MM event excluding certain

[19] The 6-min walk distance (6MWD) is a simple, standardised measure of functional status and exercise capacity.
[20] Details of NYHA classes
[21] The Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) is a disease-specific assessment tool used for the evaluation and follow-up of patients with pulmonary hypertension (PH).
[22] Components of composite primary efficacy endpoint: death (all causes); hospitalisation due to worsening of PAH; worsening of PAH requiring lung transplant or balloon atrial septostomy; worsening of PAH requiring initiation of parenteral infusion of PGI_2 or long-term oxygen therapy; disease progression confirmed by decrease by ≥ 15% in 6MWD from baseline (in 2 or more tests conducted on different days within 2 weeks) and worsening of WHO FC (for patients in NYHA/WHO FC II or III at baseline); disease progression confirmed by decrease by ≥ 15% in 6MWD from baseline (in 2 or more tests conducted on different days within 2 weeks) and necessity of additional PAH-specific therapy (for patients in NYHA/WHO FC III or IV at baseline).

components of the composite primary endpoint[23] also yielded results generally consistent with the primary efficacy analysis.

See *Evaluator's conclusions on efficacy* in Attachment 2 for full details as well as *First round assessment of benefits* and *First round assessment of benefit-risk balance* below for more discussion.

Safety

Studies providing safety data

A summary of trials that contributed to safety data in PAH patients is presented in Table 5. The sponsor has also provided, in the summary of clinical safety, pooled safety data of 4 studies: Study AC-065A302 and its ongoing open-label extension (AC-065A303), and study NS-304/-02 and its ongoing open-label extension (NS-304/-03). This pooled safety data analyses were evaluated for the purpose of this submission, and results were found to be consistent with the safety findings in the pivotal study, and did not raise any additional safety concerns.

[23] Time from randomisation to first MM event (excluding "disease progression") up to EOT +7 days; time from randomisation to first MM event (excluding "disease progression") up to study closure; time from randomisation to first MM event (excluding "disease progression" and "initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH") up to EOT +7 days; time from randomisation to first MM event (excluding "disease progression" and "initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH") up to study closure.

Table 5: Trials contributing to safety data of selexipag in PAH patients

(i) Completed clinical trials in patients with PAH

Study	Phase	Study objectives	Patients in safety analysis set	Median treatment duration (weeks)	Treatment/ dose/ route/ regimen	Type of control / blinding / design
AC-065A302 (GRIPHON)	3	Efficacy, safety and PK/PD of selexipag in patients with PAH	1152 Selexipag: 575 Placebo: 577	Selexipag: 70.6 Placebo: 63.9	Selexipag 200 µg b.i.d. up to 1600 µg b.i.d. p.o. Placebo b.i.d. p.o.	Placebo-controlled, parallel-group, randomized, DB treatment Event-driven study (morbidity/mortality events)
NS-304/-02	2	Safety, tolerability, PK, and preliminary efficacy (proof-of-concept) of selexipag in patients with PAH	Acute hemodynamic period			
			43 Selexipag 200 µg: 12 400 µg: 31	Single dose	Single selexipag p.o. dose of 200 µg or 400 µg	OL, uncontrolled
			DB, placebo-controlled period			
			43 Selexipag: 33 Placebo: 10	Selexipag: 21.3 placebo: 20.9	Selexipag 200 µg b.i.d. up to 800 µg b.i.d. p.o. Placebo b.i.d. p.o.	Placebo-controlled, parallel-group, randomized, DB treatment Change from baseline to Week 17 in outcome measures (primary = PVR)

b.i.d. = twice daily, DB = double-blind, OL = open-label, PAH = pulmonary arterial hypertension, p.o. = oral, PK = pharmacokinetic, PD = pharmacodynamic, PVR = pulmonary vascular resistance.

(ii) Ongoing clinical trials in patients with PAH

Study	Phase	Study objectives	Patients in safety analysis set	Median treatment duration (Weeks)	Treatment/ dose/ route/ regimen	Type of control/blinding
AC-065A303 (GRIPHON OL)	3	Long-term safety of selexipag in patients with PAH	218[a]	37.2[a]	Selexipag 200 µg b.i.d. up to 1600 µg b.i.d. p.o.	Single-arm, OL treatment, extension study
NS-304/-03	2	Long-term safety of selexipag in patients with PAH	39[a]		Selexipag 200 µg b.i.d. up to 1600 µg b.i.d. p.o.	Single-arm, OL treatment, extension study
AC-065A201	2 Japanese registration trial	Efficacy, safety and pharmacokinetics.	37[b]	16.3[b]	Selexipag 200 µg b.i.d. up to 1600 µg b.i.d. p.o.	Uncontrolled, OL

b.i.d. = twice daily, OL = open-label, PAH = pulmonary arterial hypertension, p.o. = oral.
[a] Preliminary data up to cut-off date of 10 March 2014
[b] Interim data up to Week 16

Patient exposure

In Study AC-065A302, the median duration of study treatment was 70.7 weeks (range: 0.3–216.7 weeks) in the selexipag group and 63.7 weeks (range: 0.7–192.0 weeks) in the placebo group (Table 6). The proportion of patients who received study treatment for a cumulative duration of at least 1 year was 63.8% in the selexipag group and 62.6% in the placebo group. The proportion of patients who received study treatment for a cumulative duration of at least 2 years was 31.3% in the selexipag group and 27.4% in the placebo group. Overall, 28.3% of patients in the selexipag group received selexipag at an individual maintenance dose (IMD) of 1600 µg bd (that is, the maximum selexipag dose allowed in the study) (Table 7).

Table 6: Duration of study treatment in study AC-065A302, safety analysis set (SAF)

	Selexipag N=575	Placebo N=577
Duration of study treatment (weeks)		
Non-missing	575	577
Mean	76.4	71.2
Standard deviation	50.45	48.32
Min, Q1	0.3 , 32.0	0.7 , 28.6
Median	70.7	63.7
Q3 , Max	117.1 , 216.7	107.1 , 192.0
Cumulative duration of study treatment [n %]		
Non-missing	575	577
At least 0 weeks	527 91.7%	545 94.5%
At least 16 weeks	494 85.9%	494 85.6%
At least 26 weeks	457 79.5%	444 76.9%
At least 52 weeks	367 63.8%	361 62.6%
At least 78 weeks	259 45.0%	235 40.7%
At least 104 weeks	180 31.3%	158 27.4%
At least 130 weeks	107 18.6%	94 16.3%
At least 156 weeks	43 7.5%	31 5.4%
At least 182 weeks	7 1.2%	4 0.7%
At least 208 weeks	1 0.2%	-

One patient randomised to placebo received a single dose of 8 tablets of selexipag due to an error in the dispensation of the medication bottle. This patient was assigned to the selexipag group in the safety analysis set (SAF).

Table 7: Individual maintenance dose (IMD) of selexipag in AC-065A302, SAF

	Selexipag N=575 n	%
b.i.d. dose	573	99.7%
0 mcg	15	2.6%
200 mcg	68	11.8%
400 mcg	65	11.3%
600 mcg	62	10.8%
800 mcg	82	14.3%
1000 mcg	35	6.1%
1200 mcg	42	7.3%
1400 mcg	41	7.1%
1600 mcg	163	28.3%
Other than per protocol dosing regimen	2	0.3%

IMD is defined as the selexipag b.i.d. dose to which patient was exposed for the longest duration in the maintenance period or for patients who did not enter maintenance as the highest tolerated selexipag b.i.d. dose to which patient was exposed during the titration period.
In 15 of the 575 patients (2.6%), selexipag IMD was set to 0 as these patients only received the initial selexipag 200 mcg dose during the titration period and discontinued at this dose

In Study NS-304/-02, all 43 patients in the study received a single dose of selexipag during the acute haemodynamic testing period (200 µg for the first 12 patients and 400 µg for the remaining 31 patients). All patients also received double-blind treatment, and the median total exposures to study drug were similar in the 2 treatment groups (149.0 and 146.0 days in selexipag and placebo groups, respectively) (Table 8). Among patients receiving selexipag, the final dosage was 800 µg bd (maximum selexipag dose allowed in the study) for 14 patients (42.4%), 600 µg bd for 7 patients (21.2%), 400 µg bd for 6 patients (18.2%), 200 µg bd for 4 patients (12.1%), and missing for the two patients who were discontinued prematurely. Among patients on placebo, the final optimised dosage was placebo 800 µg bd for all except one, who was discontinued on Day 61 and had a missing final optimised dosage.

Table 8: Summary of double-blind treatment exposure, all-treated DB set, Study NS-304-02

	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

In Study AC-065A201 the median exposure to study drug in the safety set was 114 days (Table 9). Seven patients (18.9%), 2 patients (5.4%), 3 patients (8.1%) and 6 patients (16.2%) were treated with the maximum final maintenance dose of 1600 µg (maximum

selexipag dose allowed in the study), 1400 mcg, 1200 µg and 1000 µg bd, respectively (Table 10).

Table 9: Summary of exposure to the study drug (SS), Study AC-065A201

	N=37
Total Exposure (days)	
n	37
Mean	106.4
Standard deviation	30.7
Standard error	5.0
Median	114.0
Q1 , Q3	111.0, 119.0
Min , Max	1, 140
1<= <=28	2 (5.4%)
29<= <= 56	2 (5.4%)
57<= <=84	0 (0.0%)
85<= <=112	9 (24.3%)
113<= <=140	24 (64.9%)
Maintenance dose exposure (days)	
n	34
Mean	60.6
Standard deviation	22.9
Standard error	3.9
Median	60.5
Q1 , Q3	40.0, 77.0
Min , Max	29, 114
29<= <= 56	14 (41.2%)
57<= <=84	14 (41.2%)
85<= <=112	5 (14.7%)
113<= <=140	1 (2.9%)
Cumulative Dose (10^3 ug)	
n	37
Mean	171.02
Standard deviation	85.32
Standard error	14.03
Median	173.00
Q1 , Q3	122.00, 241.80
Min , Max	0.2, 314.4
< 50	4 (10.8%)
50 <= < 100	3 (8.1%)
100 <= < 200	18 (48.6%)
200 <= < 300	8 (21.6%)
300 <=	4 (10.8%)

Table 10: Distribution of FMD, Safety set (SS), Study AC-065A201

	NS-304 N=37
Maintenance dose (ug/day)	
N	37
400	2 (5.4%)
800	2 (5.4%)
1200	5 (13.5%)
1600	7 (18.9%)
2000	6 (16.2%)
2400	3 (8.1%)
2800	2 (5.4%)
3200	7 (18.9%)
Missing	3 (8.1%)

In Study AC-065A303 (GRIPHON-OL), the median duration of study treatment (up to data cut-off date of 10 March 2014) was 37.2 weeks, with 34.4% of patients receiving study treatment for a cumulative duration of at least 1 year (Table 11). Of the 218 selexipag-

treated patients in Study AC-065A303, 26.6% received selexipag at an IMD of 1600 µg bd (the maximum selexipag dose allowed in the study) (Table 12).

Table 11: Duration of study treatment in AC-065A303, SAF (subset treated in study AC-065A303)

	Selexipag N=218
Duration of study treatment (weeks)	
Non-missing	218
Missing	0
Mean	47.0
Standard deviation	38.45
Min, Q1	0.9 , 14.6
Median	37.2
Q3 , Max	71.3 , 160.0
Cumulative duration of study treatment [n %]	
Non-missing	218
At least 8 weeks	192 88.1%
At least 16 weeks	158 72.5%
At least 26 weeks	135 61.9%
At least 52 weeks	75 34.4%
At least 78 weeks	48 22.0%
At least 104 weeks	24 11.0%
At least 130 weeks	9 4.1%
At least 156 weeks	2 0.9%
Duration of study treatment interval [n %]	
Non-missing	218
<= 8 weeks	28 12.8%
>8 - <= 16 weeks	33 15.1%
>16 - <= 26 weeks	22 10.1%
>26 - <= 52 weeks	60 27.5%
>52 - <= 78 weeks	27 12.4%
>78 - <= 104 weeks	24 11.0%
>104 - <= 130 weeks	15 6.9%
>130 - <= 156 weeks	7 3.2%
>156 - <= 182 weeks	2 0.9%

Table 12: Individual maintenance dose (IMD) of selexipag in AC-065A303, SAF (subset treated in study AC-065A303)

	Selexipag N=218
b.i.d. dose	216 99.1%
0 mcg	3 1.4%
200 mcg	20 9.2%
400 mcg	26 11.9%
600 mcg	23 10.6%
800 mcg	21 9.6%
1000 mcg	21 9.6%
1200 mcg	21 9.6%
1400 mcg	23 10.6%
1600 mcg	58 26.6%
Other than per protocol dosing regimen	2 0.9%

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

In Study NS-304/-03, 39 patients were exposed to selexipag up to 1600 µg bd for up to 5.4 years.

Comment: Overall, the study drug exposure is adequate to assess the safety profile of selexipag.

Safety issues with the potential for major regulatory impact

Haematological effect

The association between selexipag use and the occurrence of anaemia is described under *AEs of special interest* in Attachment 2.

Postmarketing data

Not applicable.

Evaluator's conclusions on safety

See *Evaluator's conclusions on safety* in Attachment 2 for full details as well as *First round assessment of risks* and *First round assessment of benefit-risk balance* below.

First round benefit-risk assessment

First round assessment of benefits

The benefits of selexipag in the proposed usage are:

- Treatment of PAH in terms of potential benefits in reducing morbidity/mortality and in symptom relief.

Efficacy results in the pivotal study (AC-065A302) showed that there was a statistically significant relative risk reduction of 40% (1-sided unstratified log-rank $p < 0.0001$) with selexipag compared to placebo for the occurrence of a morbidity or mortality event up to 7 days after the last study drug intake (primary endpoint). The number-needed-to-treat was 7.1 at 2 years, suggesting that 7 patients needed to be treated with selexipag in order to prevent one morbidity or mortality event in up to 2 years as compared to placebo. The relative risk reduction with selexipag compared to placebo for the occurrence of death due to PAH or hospitalisation due to PAH worsening up to 7 days after the last study drug intake was 30% (1-sided unstratified log-rank $p = 0.0031$).

Further analyses suggested that these observed effects were largely due to risk reduction of morbidity (especially hospitalisation due to PAH worsening and disease progression) rather than mortality, with results showing that overall survival (death from randomisation up to study closure) was comparable between selexipag and placebo (all-causality death: hazard ratio [selexipag over placebo] of 0.97, 1-sided unstratified log-rank $p = 0.4214$; death due to PAH: hazard ratio of 0.86, 1-sided unstratified log-rank $p = 0.1763$). Competing risks analysis to explore the treatment effect on the components of the primary endpoint also showed that patients on selexipag had statistically significantly lower risk of disease progression ($p < 0.0001$) and hospitalisation for PAH worsening ($p = 0.0402$) than patients on placebo, but no statistically significant difference was observed between selexipag and placebo for the risk of death ($p = 0.0827$) or for the risk of PAH worsening ($p = 0.5342$). However, it is noted that the study was not powered for mortality endpoints.

Analyses of the effect of selexipag on symptom relief in terms of improvements in exercise capacity (6MWD) were supportive of the beneficial effect of selexipag on symptom relief in patients with PAH. Results showed that after 6 months of treatment, the median treatment effect in 6MWD of selexipag versus placebo (that is, placebo-corrected median change from baseline in 6MWD) was 12.0 m (1-sided Wilcoxon-Mann-Whitney $p = 0.0027$). Analyses of changes in 6MWD over time showed that this treatment effect was generally sustained up to Month 30. The clinical significance of a treatment effect of 12.0m is unclear. It is noted that the sponsor has not pre-defined in the statistical analysis plan or protocol what would constitute a clinically relevant treatment effect. The EMA guidelines on the clinical investigation of medicinal products for the treatment of pulmonary arterial hypertension cited as an example that deterioration in 6-MWT could be defined as a decrease of 15 % from baseline but did not provide guidance as to a clinically relevant treatment effect. There are currently 3 IP receptor agonists approved for the treatment of PAH in Australia, and clinical results (in terms of 6-MWT) described in the respective TGA

approved PIs were, for epoprostenol: '*Results of the 12-week study showed that exercise capacity was improved in the 56 patients treated with FLOLAN (median distance walked in 6 minutes, 316m at 12 weeks vs 270m at Baseline), but it decreased in the 55 patients treated with conventional therapy alone (192m at 12 weeks vs 240 m at Baseline; p<0.001 for the comparison of the treatment groups).*'; for iloprost: '*at week 12, at least 10% increase in the six minute walking distance as compared to baseline was noted in 37.6% of the iloprost group and 25.5% of the control group (p = 0.059*).'; for treprostinil: '*the median change from baseline on Remodulin was 10 metres and the median change from baseline on placebo was 0 metres, the median between-treatment difference over placebo was 16 metres*.' The clinical significance of the treatment effect of 12.0m in 6MWD will be raised as a clinical question for the sponsor.

However, analyses of the effect of selexipag on symptom relief in terms of changes in NYHA/WHO FC, CAMPHOR questionnaire symptom scores and Borg dyspnoea index all showed comparable results between selexipag and placebo. The difference in the proportion of patients with absence of worsening from Baseline in NYHA/WHO FC at Week 26 between the selexipag and placebo groups was not statistically significant (77.8% with selexipag versus 74.9% with placebo, 2-sided Breslow-Day p = 0.1916), although the proportion of patients with absence of worsening from Baseline in NYHA/WHO FC, and that of patients with improvement from Baseline in NYHA/WHO FC was mostly numerically higher in the selexipag group compared to the placebo group from Week 4 up to Month 36, and the proportion of patients who had worsened NYHA/WHO FC compared to Baseline was mostly numerically lower in the selexipag group than in the placebo group from Week 8 up to Month 36.

Subgroup analyses in the pivotal Study AC-065A302 on the primary efficacy endpoint, on time from randomisation to first of death due to PAH or hospitalisation due to PAH worsening up to EOT + 7 days, and on the absolute change from Baseline to Week 26 in 6MWD, showed that the treatment effect of selexipag across the subgroups were generally consistent with those in the overall study population, and there was no statistically significant heterogeneity of treatment effects across subgroups based on the interaction tests, including subgroups of PAH aetiology at baseline, NYHA/WHO FC, and concomitant PAH specific therapy at baseline.

Prostacyclin receptor agonists currently approved in Australia for treatment of PAH were epoprostenol, iloprost and treprostinil, none of which could be administered orally (epoprostenol is to be administered by continuous IV infusion, iloprost by inhalation, and treprostinil by continuous SC infusion). The availability of a prostacyclin receptor agonist that can be taken orally is therefore a potential benefit in increasing the ease of administration which can in turn increase patient compliance and reduce potential complications associated with IV or SC infusions.

First round assessment of risks

The main risks of selexipag in the proposed usage are:

- Prostacyclin-associated symptoms
- Anaemia
- Hypotension

As would be expected for a prostacyclin receptor agonist, the incidence of prostacyclin-associated AEs in the pivotal Study AC-065A302 was higher in the selexipag group compared to in the placebo group (91.0% versus 62.2%), the most commonly-reported with selexipag being headache (65.2%), diarrhoea (42.4%) and nausea (33.4%). However, most of these AEs in the selexipag group were mild to moderate in severity (71.8%), and the incidence of prostacyclin-associated SAEs with selexipag was low (2.3%).

Consistent with the expected pattern with an IP receptor agonist, the incidence of these prostacyclin-associated AEs with selexipag was higher during the initial up-titration period compared to during the maintenance period. In patients who were on selexipag in Study AC-065A302 and then continued on selexipag in the open-label Study AC-065A303, prostacyclin-associated AEs were less frequently reported in AC-065A303 compared to in AC-065A302, suggesting a possibility of development of tolerability or amelioration of these AEs over time. Analyses of exposure-adjusted rates by prevailing dose at the time of AE onset showed that there was no clear dose dependent trend for the occurrence of these prostacyclin-associated AEs with selexipag. Subgroup analyses showed that the frequencies of these AEs with selexipag were mostly similar between patients < 65 years old and those 65 to 74 years old. However, the incidence of these AEs with selexipag relative to placebo was mostly greater in patients who were treated with selexipag in addition to other PAH medications, compared to those who received selexipag monotherapy.

Selexipag-treated patients in the pivotal Study AC-065A302 had a higher incidence of AEs denoting anaemia compared to the placebo group (10.4% versus 8.0%). However, none of these anaemia events were fatal or led to discontinuation of study treatment, and the incidence of anaemia events reported as SAEs was low in the selexipag group (1%), as was the proportion of selexipag patients who received at least one blood transfusion (2.1%; comparable with incidence with placebo of 2.3%), and the proportion of selexipag patients with Hb concentration decreases to < 80 g/L at any time post-baseline (1.3%). Mean absolute changes in Hb from baseline up to Month 36 with selexipag was modest, ranging from -3.4 to -0.16 g/L, and this decrease in Hb was apparent within 3 months of the start of treatment and was not progressive over time. This was supported by observations that in patients who were on selexipag in Study AC-065A302 and then continued on selexipag in the open-label Study AC-065A303 the incidence of Hb < 80 g/L remained comparable between Studies AC-065A303 and AC-065A302 (2.0% versus 3.2%) while that of Hb < 100 g/L was lower in Study AC-065A303 compared to Study AC-065A302 (9.8% versus 19.0%). This observed higher incidence of anaemia AEs with selexipag versus placebo appeared to be unrelated to any increased bleeding risk with selexipag. Analysis of anaemia AEs by individual maximum tolerated dose category during the titration period showed a dose dependent trend, with an increase in frequency of these AEs with increasing dose (from 6.7% with 0 µg bd to 13.6% with 1600 µg bd). The incidence of anaemia AEs in patients who received selexipag in addition to other PAH specific medications was higher compared to those with no PAH specific concomitant medication (4.5% with no concomitant PAH therapy versus 11.1% to 14.9% with concomitant PAH therapy). As this effect on Hb concentrations is an adverse effect that is able to be monitored by routine laboratory tests, these findings allowed clinicians to identify high-risk patients and treatment periods and be more vigilant in monitoring of Hb levels. The sponsor has not presented any data looking the reversibility of this effect. This will be brought up as a clinical question for the sponsor in Section 12.

Selexipag treated patients in the pivotal Study AC-065A302 had a higher incidence of hypotension AEs compared to the placebo group (5.9% versus 3.8%). However, the incidences of clinically relevant cases of hypotension (that is, those with a fatal outcome, or were serious, or led to discontinuation of treatment) were low and comparable with that in placebo group (0.7% in both groups). Analyses of BP measurements over time showed that changes from baseline in SBP and DBP with selexipag were small and comparable with that in the placebo group, and did not show any progression over time (mean changes from baseline with selexipag in SBP: ranged from −2.0 to 1.5 mmHg; DBP: -1.6 to −0.1 mmHg). Analyses of exposure-adjusted rates by prevailing dose at the time of AE onset showed that there was no clear dose dependent trend for the occurrence of these hypotension AE rates with selexipag. However, the incidence of hypotension AEs in patients who received selexipag in addition to other PAH-specific medications was higher

compared to those with no PAH-specific concomitant medication (3.6% with no concomitant PAH therapy versus 4.3% to 8.4% with concomitant PAH therapy). It is also noted by the evaluator that this is an adverse effect that is able to be monitored by routine blood pressure measurements.

First round assessment of benefit-risk balance

The benefit-risk balance of selexipag, given the proposed usage, is favourable.

Efficacy results showed relative risk reduction of selexipag over placebo for the occurrence of combined mortality or morbidity events as well as beneficial effect on exercise capacity in terms of improvements in 6MWD. Although analyses in the pivotal study suggested that the use of selexipag did not improve survival, the study had not been powered for survival analyses. Safety results raised concerns mainly with respect to prostacyclin-associated symptoms, decreases in Hb and hypotension. However, the prostacyclin associated symptoms that developed with selexipag were mostly mild to moderate in severity. These adverse effects also occurred more frequently during the initial up-titration period compared to during the maintenance period and results had suggested a possibility of development of tolerability or amelioration of these effects over time. The decrease in Hb appeared to occur within 3 months of the start of treatment and thereafter was not progressive over time. The decreases were also modest, and the incidence of anaemia SAE and the proportion of selexipag patients with decreases of Hb to < 80 g/L post-baseline or had needed to receive at least one blood transfusion were low. In addition, this is an adverse effect that is able to be monitored by routine laboratory assessments. Although there was a higher incidence of hypotension AEs with selexipag compared to placebo, the incidence of clinically relevant cases of hypotension was low and the decreases in BP from baseline with selexipag were modest and did not show any progression over time. In addition, this is an adverse effect that is able to be monitored by routine blood pressure measurements.

The posology of oral administration is a potential benefit in increasing the ease of drug administration, which can in turn increase patient compliance. None of the prostacyclin receptor agonists currently approved in Australia for treatment of PAH (epoprostenol, iloprost and treprostinil) could be administered orally. With regards to the proposed dosing regimen of up-titration to individual maximum well tolerated dose, results generally supported the proposed dosing regimen. Analysis on the primary efficacy endpoint of the pivotal study by individual maintenance dose (IMD) categories showed comparable effects across the IMD categories. In addition, safety analyses by prevailing dose at the time of AE onset showed that there was no clear dose dependent trend for the exposure-adjusted overall AE or SAE rates with selexipag.

The proposed indication for selexipag, as stated in the proposed PI, is

for the treatment of:

- *idiopathic pulmonary arterial hypertension*
- *heritable pulmonary arterial hypertension*
- *pulmonary arterial hypertension associated with connective tissue disease*
- *pulmonary arterial hypertension associated with congenital heart disease with repaired shunts*
- *pulmonary arterial hypertension associated with drugs and toxins*

in patients with WHO functional class II, III or IV symptoms.

Uptravi is effective in combination with an endothelin receptor antagonist (ERA) or a phosphodiesterase-5 (PDE-5) inhibitor or in triple combination with an ERA and a PDE-5 inhibitor, or as monotherapy'

Subgroup analyses in the pivotal study on the primary efficacy endpoint and the endpoint of change from Baseline to Week 26 in 6-MWD showed that the treatment effects of selexipag in the subgroups of PAH aetiology at baseline, concomitant PAH specific therapy at baseline, and NYHA/WHO FC were generally consistent with those in the overall study population. In addition, subgroup analyses in the pivotal study of adverse events by baseline PAH aetiology showed that the overall incidence of AEs was generally comparable among the selexipag groups across the different PAH aetiology categories. Safety results suggested that the incidence of prostacyclin-associated AEs, anaemia AEs and hypotension AEs with selexipag was higher in patients who were treated with selexipag in addition to other PAH medications, compared to those who received selexipag monotherapy. However, as noted above, the majority of these AEs in the overall study population (the majority of whom had concomitant PAH specific medication at baseline [80.5% in selexipag group]), were not severe or serious, and changes in Hb and blood pressures were modest and not progressive, and were monitorable with routine laboratory assessments or blood pressure measurements. It is noted that the sample size for the study population with aetiology of heritable PAH and PAH associated with drugs and toxins was small (2.2% [n=26] and 2.3% [n=27], respectively). However, this reflects the composition of the target patient population in clinical practice. The proposed indication wording with specification of the aetiologies covered by the indication is necessary as PAH is a disease condition with diverse aetiologies and as the study population in the pivotal study is limited to particular aetiologies these need to be stated clearly in the proposed PI. This proposed indication wording with specification of the aetiologies is also consistent with indication wording for the other currently approved IP receptor agonists in Australia.

With regards to the use of selexipag in patients across WHO FC of II to IV, it is noted that the majority of subjects in the pivotal study were of WHO FC II (45.8%) and III (52.5%), with only 1.0% (11/1156) in WHO FC IV. However, this reflects the composition of the target patient population in clinical practice. Subgroup analyses of the efficacy and safety endpoints in this small group of patients with baseline WHO FC IV would not have been viable in view of the very small sample size. The sponsor had performed efficacy subgroup analyses based on subgroups of baseline WHO FC I or II versus III or IV, and results were generally consistent with that of the overall study population. However, results of safety subgroup analyses based on subgroups of baseline WHO FC I or II versus III or IV were not presented in this submission. This would be raised as a clinical question to the sponsor.

First round recommendation regarding authorisation

It is recommended that the application for the registration of selexipag for the treatment of pulmonary arterial hypertension in adult patients of WHO Functional Class II to IV be approved. This is subject to a satisfactory response to the clinical questions raised (see below).

Clinical questions

Pharmacokinetics

Question 1

Can the sponsor please provide an explanation for the 1.3 fold increase in selexipag $C_{trough,ss}$ following administration of the single tablet form of 1600 µg selexipag bd compared to when it was administered as 8 x 200 µg selexipag bd in Study AC-065-108?

Question 2

The evaluator could not identify a request for a biowaiver for the intermediate dose strengths in the evaluation materials. Therefore, can the sponsor please direct the evaluator to the location of the request for a biowaiver or provide a statement for a request for a biowaiver if it has not been provided by the sponsor?

Question 3

The 1.9 fold increase in $C_{trough,ss}$ for ACT-333679 identified in patients with PAH compared to healthy subjects in the PopPK/PD Study AC-065A302-PPK is unexpected. Can the sponsor please explain why they believe this is occurring and whether it is of concern, especially regarding the incidence of AEs in healthy subjects compared to patients with PAH? For instance, would the dose-dependent increase in HR identified in Study AC-065-106 be potentiated in subjects with PAH compared to healthy subjects?

Question 4

The PopPK Study AC-065A302-PPK provides a comparison of selexipag PKs in healthy subjects and in patients with PAH following dosing with 1600 µg bd This comparison indicates that differences in selexipag PKs exist between the two populations, in particular that there is a 1.9 fold increase in C_{trough} in patients with PAH compared to healthy subjects (Table 13). The two studies used to source the data for this comparison (that is, Study AC-065-106 for healthy subjects and Study AC-065A302 for patients with PAH) also examined the PKs of selexipag following 800 µg bd dosing. Can the sponsor therefore identify whether the same differences in selexipag PKs exist between healthy subjects and patients with PAH following 800 µg bd dosing, and in particular is selexipag Ctrough affected to the same extent in subjects with PAH at the lower selexipag dose?

Table 13: Study AC-065A302. Comparison of model prediction of PK parameters for a reference healthy subject based on healthy and patient model for steady-state doses of 1600 µg bd

	$C_{trough,\ SS}$ Selexipag (ng/mL)	$C_{trough,\ SS}$ ACT-333679 (ng/mL)	$C_{max,SSs}$ Selexipag (ng/mL)	$C_{max,\ SS}$ ACT-333679 (ng/mL)	AUC_{SS} Selexipag (h*ng/mL)	AUC_{SS} ACT-333679 (h*ng/mL)
AC-065-106*	0.17	4.5	15.7	22.5	42.4	153
AC-065A302*	0.18	8.5	21.5	29.1	55.6	183
Fold-change	↑ 1.1 x	↑ 1.9 x	↑ 1.3 x	↑ 1.3 x	↑ 1.3 x	↑ 1.2 x

* Subject-specific parameters were set to typical for healthy subjects: body weight 80 kg, sex male, bilirubin 13 µmol/L, naïve to PAH co-medication.

Pharmacodynamics

No questions at this time.

Efficacy

Question 1

Please comment on the clinical significance of a treatment effect in 6MWD of 12.0m.

Rationale for question:

As described above, the clinical significance of a treatment effect of 12.0m is unclear. It is noted that the sponsor has not pre-defined in the statistical analysis plan or protocol what would constitute a clinically relevant treatment effect. There are currently 3 approved IP receptor agonists for the treatment of PAH in Australia, and clinical results (in terms of 6-MWT) described in the respective TGA-approved PI were, for epoprostenol: '*Results of the 12-week study showed that exercise capacity was improved in the 56 patients treated*

with FLOLAN (median distance walked in 6 minutes, 316m at 12 weeks vs 270m at Baseline), but it decreased in the 55 patients treated with conventional therapy alone (192m at 12 weeks vs 240 m at Baseline; p<0.001 for the comparison of the treatment groups).'; for iloprost: '*at week 12, at least 10% increase in the six minute walking distance as compared to baseline was noted in 37.6% of the iloprost group and 25.5% of the control group (p = 0.059).*'; for treprostinil: '*the median change from baseline on Remodulin was 10 metres and the median change from baseline on placebo was 0 metres, the median between-treatment difference over placebo was 16 metres*.'

Safety

Question 1

Please comment on whether there is any data that has looked at the reversibility of the effect of selexipag in Hb concentrations, and provide these data or analyses results.

Rationale for question:

As described above, it is noted that the decreases from baseline of Hb concentrations with selexipag were modest, appeared to occur within 3 months of the start of treatment and thereafter were not progressive over time. However, no data was presented with regards to reversibility of this effect. Knowing the reversibility of this effect would guide clinicians in the duration necessary in the monitoring of Hb concentrations in patients who have ceased selexipag.

Question 2

Please provide safety results on subgroups of patients with baseline WHO FC I or II versus III or IV.

Rationale for question:

As described above, the sponsor is proposing use of selexipag for the treatment of PAH patients with WHO FC II to IV. It is noted that the majority of subjects in the pivotal study were of WHO FC II and III with only 1.0% (11/1156) in WHO FC IV, but that this reflects the composition of the target patient population in clinical practice and that subgroup analyses of the efficacy and safety endpoints in this small group of patients with baseline WHO FC IV would not have been viable in view of the very small sample size. The sponsor had performed efficacy subgroup analyses based on subgroups of baseline WHO FC I or II versus III or IV, and efficacy results were generally consistent with that of the overall study population. However, corresponding safety results comparing these subgroups were not provided.

Second round evaluation of clinical data submitted in response to questions

For details of the sponsor's responses to the *Clinical questions* and the evaluation of these responses please see Attachment 2.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of selexipag in the proposed usage are unchanged from those identified in the First round.

Second round assessment of risks

After consideration of the responses to clinical questions, the risks of selexipag in the proposed usage are unchanged from those identified in the First round.

Second round assessment of benefit-risk balance

The benefit-risk balance of selexipag, given the proposed usage, is favourable. The benefit-risk balance in the subgroups in the proposed indication of

For treatment of

- *idiopathic pulmonary arterial hypertension*
- *heritable pulmonary arterial hypertension*
- *pulmonary arterial hypertension associated with connective tissue disease*
- *pulmonary arterial hypertension associated with congenital heart disease with repaired shunts*
- *pulmonary arterial hypertension associated with drugs and toxins*
  in adult patients with WHO functional class II, III or IV symptoms, to be used in combination with an endothelin receptor antagonist (ERA) or a phosphodiesterase-5 (PDE-5) inhibitor, or in triple combination with an ERA and a PDE-5 inhibitor, or as monotherapy

has been assessed and is found to be favourable.

Second round recommendation regarding authorisation

It is recommended that the application for the registration of selexipag be approved for the proposed indication (see above).

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (EU-RMP version 1 dated 27 November 2014 (data lock point 27 April 2014) with Australian Specific Annex version 1.0 dated 24 February 2015) which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 14.

Table 14: Summary of ongoing safety concerns

Important identified risks	Hypotension
Important potential risks	Pulmonary oedema associated with PVOD
	Hyperthyroidism
	Anaemia
	Medication error
	Off-label use (including paediatric patients
Missing information (or limited)	Use in paediatric patients
	Use in elderly over 75 years old
	Use in pregnancy and lactation
	Use in patients with severe hepatic impairment
	Use in patients using dialysis
	Concomitant use with strong inhibitors of CYP2C8, UGT1A3 and UGT2B7 or inducers of CYP2C8, UGT1A3 and UGT2B7

Pharmacovigilance plan

Routine pharmacovigilance have been proposed to monitor all the safety concerns. The sponsor proposes no additional pharmacovigilance activities.

Risk minimisation activities

The sponsor has proposed routine risk minimisation to mitigate all the 'important identified risks' and 'important potential risks'. No risk minimisation has been proposed for 'missing information'. Additional risk minimisation proposed in Australia is a patient titration guide that will be provided with the PI and CMI to prescribers.

Reconciliation of issues outlined in the RMP report

Table 15 summarises the first round evaluation of the RMP, the sponsor's responses to issues raised by the evaluator and the evaluation of the sponsor's responses.

Table 15: Reconciliation of issues outlined in the RMP Evaluation Report (Round 1)

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
1. Safety considerations may be raised by the nonclinical and clinical evaluators. It is	*The sponsor confirms that any safety concerns raised by the nonclinical, clinical and Risk Management Plan (RMP)*	The sponsor's response is satisfactory.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
important to ensure that the information provided in response to these includes a consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.	*evaluators will be addressed. Safety considerations, where relevant, will also be addressed in the RMP and/or the Australian Specific Annex.*	
2. As outlined in the draft PI, selexipag has not been found affecting platelet functions in the clinical trial. The sponsor also identifies a 'mild accelerating effect on heart rate' in the PI. These appear to be consistent with the pharmacodynamic and pharmacological effects of selexipag. Nonetheless, due to limited evidence provided by clinical trials, the sponsor should commit to monitoring and reporting these events through Periodic Safety Update Reports (PSURs).	*The sponsor agrees to monitor and report adverse experience regarding increased heart rate and abnormal platelet function via PSURs on a regular basis. In addition, the following changes to the PI are proposed:* *Heart rate* *The sponsor proposes the following addition of information on heart rate in the precautions section of the product information:* *Increase in heart rate:* *Uptravi may cause a moderate increase in heart rate after each dose.* *The sponsor also proposes to amend the adverse effects section of the PI as follows:* *Inclusion of sinus tachycardia in the tabulated list of adverse reactions as uncommon (selexipag n=5, incidence 0.9%, vs placebo n=2, incidence 0.3% [GRIPHON CSR, Module 5.3.5.1, table 15-182]) and addition of information on heart rate data [GRIPHON CSR, Module 5.3.5.1, table 15-277] and proportions of sinus tachycardia [GRIPHON CSR, Module 5.3.5.1, table 15-278] from ECG findings.* *Description of selected adverse*	The sponsor's response is satisfactory. The content of PI awaits the final determination by the Delegate.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	reactions included: *Increase in heart rate:* *In the Phase III placebo-controlled study in patients with PAH a transient increase in mean heart rate of 3–4 bpm at 2-4 hours post-dose was observed. ECG investigations showed sinus tachycardia in 11.3% of patients in the selexipag group compared to 8.8% in the placebo group.-* *The sponsor can also confirm that it will monitor and report these events through Periodic Benefit-Risk Evaluation Reports (PBRERs).* *The updated AU PI is provided.*	
3. It is noted that the sponsor has advised in the PI that selexipag is effective in combination with ERA and/or a PDE-5 inhibitor. It is also noted that products treating PAH often have common safety concerns such as undesired haemodynamic changes. The sponsor should clarify whether selexipag should be avoided in combination treatment with any other drug classes that are used for PAH.	*The sponsor provides below a benefit-risk assessment of the various combination therapy options studied in GRIPHON…* *…* ***Conclusion*** *A positive benefit-to-risk assessment has been established for all subgroups of concomitant PAH background therapies. Across all subgroups by PAH background therapy, nearly identical efficacy was demonstrated for the primary study endpoint. The respective safety experience is largely defined by the profiles of the individual drugs. Small differences in the incidence of individual AEs and laboratory abnormalities do not affect the positive benefit-risk profile for any tested combination. The sponsor is of the opinion that selexipag in combination with an ERA, a PDE-5i or the combination of both is equally safe and effective.* *Overall, the concomitant use of other PAH-specific medications does not appear to present any additional safety concerns. The overall impact of selexipag on Hb is modest and the observed effects on the basis of concomitant PAH-specific medication showed no clear pattern. For hypotension, the effect of selexipag on blood pressure was*	The sponsor's response is satisfactory.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	small and there was a general absence of hypotension SAEs, irrespective of concomitant PAH-specific medication use. In terms of tolerability, concomitant use of other PAH medications resulted in an increase in the incidence of some of the AEs associated with their use and also of those associated with selexipag, particularly headache, diarrhoea and nausea. *Despite multifactorial reasons for patients being treated with none, one or two PAH-specific medications prior to entry into GRIPHON, a trend for a more severe baseline disease state in patients with combination therapy compared to treatment-naïve patients is evident. The treatment effect of selexipag in the primary endpoint was consistent across categories of background treatment. In line with published data in PAH patients, the treatment effect on exercise capacity was larger in treatment-naïve patients compared to those pre-treated. The AE safety profile of each sub-group appears to be driven largely by the individual contributions of the respective PAH-specific medications.* *The use of selexipag on top of existing PAH background therapy targeting endothelin and nitric oxide pathways, as well as in monotherapy, is in line with current PAH treatment guidelines.*[24] *The mentioned references are provided in updated Module 5.4 Literature References.*	
4. Given the limited evidence could be provided by clinical trials for this first in class product, the sponsor should consider the need to	*The sponsor will provide further long-term safety information through routine pharmacovigilance (PV) monitoring and submission of PBRERs in accordance with the ICH guideline E2C (R2). In addition,*	The evaluator has noted that two planned Post-authorisation safety study (PASS) studies

[24]Galiè N. et al., 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. European Heart journal DOI: http://dx.doi.org/10.1093/eurheartj/ehv317 ehv317 First published online: 29 August 2015.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
further characterise the safety profile through additional pharmacovigilance activities.	*further long-term safety data will emerge from the GRIPHON open-label and NS-304/-03 studies. A CSR will be provided once the studies are completed.* *As an additional PV activity, Actelion is in discussion with the Committee for Medicinal Products for Human Use (CHMP) regarding setting up a long-term, multicenter, prospective, real-world, non-interventional (observational) Uptravi (selexipag) post-authorisation safety study. Participating sites will invite all consecutive adult PAH patients who have either initiated Uptravi in routine clinical practice < 3 months prior to or at enrolment or during observation (Uptravi exposed patients), or were never treated with Uptravi (Uptravi unexposed patients). It will also provide additional information on patients over the age of 75 years. This registry will be conducted in Europe.* *Data collection will include patients' medical history, disease characteristics, Uptravi treatment pattern, prior and/or concomitant PAH-specific and non-specific treatments, the clinical course, data on the 'important safety risks' (hypotension, anemia / decreased Hb concentration, pulmonary oedema associated with pulmonary veno-occlusive disease, hyperthyroidism, major adverse cardiac events, acute renal failure and renal function impairment, light-dependent non-melanoma skin malignancy, bleeding events, ophthalmological effects associated with retinal vascular system, gastrointestinal disturbances denoting intestinal intussusception [ileus or obstruction]), hospitalisation and all-cause death during observation.* *The planned observation period for each patient enrolled in the study will be at least 18 months from study enrolment or until death,*	have been included in the updated EU-RMP. One is the study referred by the sponsor and the other is to monitor the occurrence of the important potential risk - medication error, and to measure the effectiveness of the additional risk minimisation activities. It is noted that neither studies are referred in the ASA. The sponsor should update the ASA to include these studies as additional pharmacovigilance activities and analyse their applicability in the Australian context. The sponsor should also make plans to evaluate the coverage and effectiveness of the additional risk minimisation activities locally or provide compelling justification for not doing so. A summary table as shown in the sample ASA template on the TGA website (https://www.tga.gov.au/book/australian-specific-annex-template) should also be included to capture all the activities to be conducted and/or relevant to Australia. In addition, the study protocols should be provided to the TGA for review when they become available.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	withdrawal of consent, loss to follow-up, or Uptravi discontinuation. Based on sample-size estimations (approximately 1450 Uptravi users, and 1850 Uptravi unexposed patients, 3 years' recruitment), the registry will last at least 4 years, resulting in long-term follow-up (> 18 months) for a sizeable proportion of the patients. *In summary, this approach allows for a robust description of the disease characteristics and clinical course of PAH patients receiving Uptravi and will allow further characterisation of Uptravi's long-term safety profile to complement the data in the GRIPHON study and the routine PV data in the Actelion safety database (ARGUS™).*	
5. The sponsor should provide a table comparing the risk minimisation activities proposed in Australia and in the EU (https://www.tga.gov.au/book/australian-specific-annex-template). Wording pertaining to important safety concerns in the proposed Australian PI and CMI should be included in the table.	*The ASA has been amended to include the activities table detailing all planned risk minimisation measures in the Australian context and the EU RMP context. The table includes a comparison of the content and wording of the currently proposed EU Summary of Product Characteristics (SmPC) and the proposed Australian PI and CMI for all of the specified ongoing safety concerns and missing information, and also includes a rationale and justification for any observed differences.* *The EU RMP version 2 (dated 21 July 2015) and the amended ASA are provided in updated Pharmacovigilance Systems and Risk Management Plan for Australia, respectively.*	The sponsor's response is satisfactory. The evaluator has noted the inclusion of Table 1 in the ASA.
6. The sponsor should clarify whether the Australian patient titration guide would be the same as that provided in the EU-RMP. The patient titration guide is a 36 page pack that target patients. In comparison, the Dear Healthcare	*The EU RMP tools have been revised mid-way through the EMA evaluation procedure. The revised EU RMP (version 2) has been provided in the updated Pharmacovigilance Systems, and now includes three tools, as follows:* – *Dear Healthcare Professional Letter (DHPL)*	The evaluator has noted the inclusion of the DHPL, HCP titration card and the patient titration guide. It is noted that educational materials are also distributed to nurses and

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
Professional Letter (DHPL), proposed in the EU but not in Australia, is a more concise document targeting healthcare professionals. It is recommended that this DHPL is distributed in Australia be included as an additional risk minimisation activity in the ASA.	– *Laminated HCP Titration Card* – *Patient Titration Guide* *These same tools will be implemented in Australia and have been provided in the updated ASA.* *Please note that the CMI and packaging artwork provided has had to be amended to maintain alignment with the updated RMP tools. The amended CMI is provided and the carton labels and blister strips are provided.*	pharmacists in the EU. The sponsor should provide the educational materials to pharmacists and nurses who are involved in patient caring and counselling in Australia. A copy of the CMI should be included in the patient titration guide to ensure patients receive all the intended educational materials. The evaluator has noted that the sponsor has conducted market research and user test to optimise patient materials as outlined in the EU-RMP. The sponsor should continue to evaluate the effectiveness of the additional educational materials.
7. In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft product information document be revised as follows: a. Patients with moderate or severe lung disease: patients with moderate or severe obstructive and restrictive lung diseases have been excluded from clinical trials. The sponsor has stated in the EU-RMP that selexipag is not indicated for treatment of pulmonary hypertension due to lung disease and/or	*The study protocol for GRIPHON contained several standardised eligibility criteria, including those regarding moderate or severe lung disorder and left ventricular dysfunction, with the aim to enrol a PAH population devoid of diagnoses potentially confounding the diagnosis of PAH (Dana Point group I).* *Patients with the above indicated conditions will be excluded by default as the proposed indication for selexipag is for PH Group 1 (PAH) patients only, according to the 2009 Dana point classification.[25] Patients with underlying conditions as per Question 7a and 7b above fall under the PH Groups 3 and 2, respectively, and are thus not indicated for treatment with*	The sponsor's justification is noted. Although patients with obstructive lung disease and left ventricular dysfunction are often excluded from clinical trials, they are both related to pulmonary hypertension (the EU-RMP acknowledges that left heart disease represents the most frequent cause of PH). This means there is a potential for these patients be prescribed selexipag for off-label treatment of pulmonary hypertension. Adequate information

[25] Simonneau G. et al., (2009). Updated Clinical Classification of Pulmonary Hypertension Vol. 54, No. 1, Suppl S

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
hypoxia. This information should be reflected adequately in the PI. b. Patients with left ventricular dysfunction have been excluded from clinical trials. The sponsor has stated in the EU-RMP that selexipag is not indicated for treatment of pulmonary hypertension due to left heart disease. This information should be reflected adequately in PI.	*selexipag.* *Given that these underlying criteria were not based on a specific safety concern but rather intended to ensure a more homogeneous study population and the proposed indication is exclusively aimed at PAH patients, no specific wording regarding these criteria is deemed necessary by the sponsor.*	is required for prescribers to make informed decisions. The recommendations remain for the final determination by the Delegate.

Summary of recommendations

It is considered that the sponsor's response to the TGA has adequately addressed most of the issues identified in the RMP evaluation report. Outstanding issues are summarised below.

Outstanding issues

Issues in relation to the RMP

Details of the 3 outstanding issues are detailed in Table 15 (Recommendations 4, 6 and 7). The recommendations remain for the final determination by the Delegate.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice is not sought for this submission.

Key changes to the updated RMP

In their response to the TGA the sponsor provided an updated EU-RMP version 2 dated 21 July 2015 (data lock point 27 April 2014) with Australian Specific Annex version 2.0 dated 21 October 2015. Key changes from the version evaluated in the first round are summarised below (Table 16).

Table 16: Key changes to the updated RMP and ASA:

Section	Key change
Safety specification	• The following safety concerns are added: *Important potential risks:* fatal major adverse cardiovascular events (MACE) not due to PAH progression, acute renal failure, bleeding events, light-dependent non-melanoma skin malignancies, ophthalmological effects associated with retinal vascular system, gastrointestinal disturbances denoting intestinal intussusception (manifested as ileus or obstruction) • The risk of 'anaemia, decreased Hb' has been upgraded from an important potential risk to an important identified risk.
Pharmacovigilance activities	Two PASS studies are added: • Registry of product use in routine clinical practice to monitor the following safety concerns: hypotension, anaemia / decreased Hb concentration, pulmonary oedema associated with pulmonary venoocclusive disease (PVOD), hyperthyroidism, fatal MACE not due to PAH progression (defined as cases with fatal outcome with conditions such as haemorrhagic or ischaemic stroke, myocardial infarction (MI) and/or sudden death), acute renal failure, light-dependent non-melanoma skin malignancies, bleeding events, ophthalmological effects associated with retinal vascular system, gastrointestinal disturbances denoting intestinal intussusception (ileus or obstruction); • A PASS study to measure the use of the additional risk minimisation measure (RMM) tools, patients' and their HCPs' (prescribing physician and if applicable nurse) knowledge and behaviour (use) related to the RMM to prevent medication errors; and to describe the occurrence of medication errors during the Uptravi titration phase.

The evaluator has no objection to the above changes and recommends to the Delegate that the updated version is implemented.

Suggested wording for conditions of registration

RMP

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

The suggested wording is:

> *Implement EU-RMP version 2 dated 21 July 2015 (data lock point 27 April 2014) with Australian Specific Annex version 2.0 dated 21 October 2015, to be revised to the satisfaction of the TGA, should be implemented.*

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The quality evaluator has recommended approval with respect to chemistry, quality control and bioavailability aspects. The drug substance is micronised and has poor solubility and impurities have been controlled according to the ICH guidelines. There are 8 strengths of tablets proposed which are film coated, unscored and immediate release. In the pivotal Phase III study (GRIPHON) only the 200 µg film-coated tablet strength was administered up to 1600 µg twice daily, which was the highest dose allowed in this study. For patient convenience, other tablet strengths were developed and a clinical Study AC-065-108 was conducted to demonstrate bioequivalence between 1600 µg selexipag administered as 8 film-coated tablets of 200 µg and 1600 µg selexipag administered as a single film-coated tablet of 1600 µg at steady-state. Selexipag exhibits linear pharmacokinetics across all the proposed strengths despite the drug's BCS Class II nature, suggesting that dissolution is not critical to drug absorption. There are potential changes in polymorphic form of selexipag however the evaluator was satisfied that the risk of polymorphic form conversion was low. The sponsor has identified two impurities and has appropriately controlled these at release and shelf-life. A shelf-life of 36 months and stored below 30°C is proposed. Biopharmaceutic studies showed there was an effect of food on the pharmacokinetics of selexipag and ACT-333679 (one study showed 90% CIs of the geometric mean ratios (fed versus fasted) for C_{max} and AUC of selexipag were not completely inside the pre-defined bioequivalence limits of 0.80 to 1.25 and for ACT-333679, the 90% CIs of the geometric mean ratios for C_{max} and AUC were outside the pre-defined limits; T_{max} and $t_{1/2}$ were also longer). The PI states that the tablets may be taken with or without food. An acceptable biowaiver was provided for the intermediate strengths.

Nonclinical

The nonclinical evaluator had no objections to the registration of selexipag. The nonclinical studies were comprehensive and of high quality, and the pivotal toxicological studies were performed to GLP standards.

Selexipag is a pro-drug that is converted to the major active metabolite, ACT-333679, by carboxylesterase activity in the liver. Although ACT-333679 is a prostacyclin receptor (IP) agonist, it is a non-prostanoid and (unlike other drugs of the same pharmacological class) is not a chemical analogue of prostacyclin. The sponsor's primary pharmacology studies support the proposed mechanism of action. The secondary pharmacodynamic and safety pharmacology studies suggested that off-target effects (even at other prostanoid receptors) are unlikely at clinically relevant concentrations. Selexipag showed limited metabolism by CYP enzymes, undergoing CYP2C8 catalysed hydroxylation reactions and CYP3A4 catalysed hydroxylation and dealkylation reactions. Treatment of patients has little potential for QT interval prolongation and dosing was associated with increased ossification of spongy bones in both rat and dog studies. This effect may be explicable based on literature findings that agents that decrease systemic blood pressure and increase blood perfusion induce increased bone mass. Intussusception was a significant cause of death in dogs given high doses of selexipag but is unlikely to be of clinical relevance. Selexipag appears to pose neither genotoxic nor carcinogenic risks for patients however it was associated with non-statistically significant increases in the incidence of thyroid and Leydig cell tumours in mice and rats, respectively, which were correlated with hyperplasia/hypertrophy of thyroid follicular and Leydig cells. The induction of thyroid and Leydig cell tumours in rodents by various drugs is thought to reflect unique aspects of rodent biology that are not relevant to humans. Selexipag showed no evidence for teratogenicity or effects on fertility in animal testing and is Category B1 in pregnancy. It undergoes placental transfer and is excreted into milk of lactating rats.

Clinical

The clinical evaluator has recommended approval for the proposed indication.

Pharmacokinetics

Some of the findings from the pharmacokinetic studies included:

- The absolute bioavailability of selexipag is unknown.
- Selexipag C_{max} was 35% lower in the fed state than in the fasted state, whereas AUC_{0-t} and AUC_{0-inf} were approximately 10% higher in the fed state. C_{max} and $AUC_{0-\infty}$ of ACT-333679 decreased by 48 and 27%, respectively, in the presence of food. Food intake delayed the absorption of selexipag with median T_{max} increasing from 1 h in the fasting state to 2.8 h in the fed state.
- Following multiple doses of selexipag bd ranging from 400 µg to 1800 µg, the C_{max} and AUC_{0-12} values for ACT-333679 were found to increase less than dose proportionally.
- No accumulation of selexipag was identified at steady state.
- Vd was estimated as 41.7 L, 99.7% bound to human plasma proteins.
- Median T_{max} of ACT-333679 occurred between 2.25 h and 2.75 h of dosing and the mean $t_{1/2}$ ranged from 9.40 h to 12.65 h (Study QGUY/2006/NS-304).
- A mass balance study identified elimination was primarily in the faeces and almost 12% of the selexipag dose was eliminated via the urine.
- The AUC_{ss} values for selexipag and ACT-333679 were 30% and 20% higher, respectively, in patients with PAH than in healthy subjects; $C_{trough,ss}$ for ACT-333679 in patients with PAH was 1.9 fold higher than in healthy subjects.
- Hepatic impairment: Selexipag C_{max} and AUC_{0-inf} were increased by approximately 2 fold in subjects with mild liver impairment and 2.8 fold and 4.5 fold higher in moderate hepatic impairment. For the active metabolite, C_{max} and AUC_{0-inf} were similar (1.18 fold and 0.97 fold higher, respectively) in both groups in mild hepatic impairment and AUC_{0-inf} was increased >2 fold in moderate hepatic impairment. In the 2 subjects with severe hepatic impairment compared to healthy subjects, the dose normalised selexipag C_{max} and AUC_{0-inf} were 2.3- and 3.0 fold higher, respectively, and the dose normalised C_{max} and AUC_{0-inf} of ACT-333679 were 1.2- and 2.9 fold higher, respectively.
- Renal impairment: There was an approximately1.7 fold increase in selexipag C_{max}, AUC_{0-12}, and AUC_{0-inf} in patients with severe renal impairment. For ACT-333679, there was a 1.43 fold and 1.61 fold increases in C_{max} and AUC_{0-inf}, respectively.
- Age: C_{max} and AUC_{0-inf} of ACT-333679 were decreased by 34% and 36%, respectively, in elderly compared to younger subjects. With multiple dosing and after a meal, ACT-333679 C_{max} and AUC_{0-12} decreased by 16% and 19%, respectively, in elderly compared to younger subjects.
- Gender: A male subject was predicted to have a 13% lower AUC_{ss} for ACT-333679 than a female reference subject.
- Body weight: For a patient with a body weight of 51 kg, selexipag exposure was 30% higher and ACT-333679 exposure was 20% higher than a reference patient with a body weight of 70 kg.
- Interactions: Selexipag had no effect on the C_{max} or AUC of either R- and S-warfarin, C_{max} and AUC_{0-inf} of selexipag were 2.07 and 2.24 fold higher when administered with

lopinavir/ritonavir. C_{max} and $AUC_{0\text{-}inf}$ of ACT-333679 increased 1.3 and 1.1 fold, respectively, when administered with lopinavir/ritonavir.

- PAH co-medication did not influence the PKs of selexipag but were a significant covariate of the elimination rate constant of ACT-333679 and combination use was predicted to result in a 30% lower ACT-333679 $AUC_{\tau,ss}$.
- Selexipag is a weak substrate of P-gp, organic anion-transporting polypeptide (OATP) 1B1 and OATP1B3; not a substrate of breast cancer resistance protein (BCRP); does not affect P-gp-mediated efflux; inhibited uptake transporters organic cation transporter (OCT) 1 and OCT2 and the efflux transporters bile salt export pump(BSEP), Multidrug and toxin extrusion protein (MATE) 1, MATE2K, and Multidrug resistance-associated protein (MRP) 2; and induces the expression of CYP3A4, CYP2C9, and CYP2B6.

Pharmacodynamics

Some of the findings from the pharmacodynamic studies included:

- Both the primary and secondary pharmacodynamic effects of selexipag can be mainly attributed to the activity of metabolite ACT-333679.
- Plasma NT pro-BNP showed a decrease with higher exposure.
- Selexipag was associated with mild increases in heart rate (HR) with the largest placebo-corrected change-from-baseline HR reaching 6-7 beats per minute (bpm) at 1.5 to 3 h after dosing with 800 µg selexipag and 9-10 bpm at the same time-points following dosing with 1600 µg selexipag.
- Selexipag did not affect cardiac repolarisation or conduction.
- The 6-MWD at steady state showed a significant increase with increasing exposure, there was a significant inverse correlation between total bilirubin and selexipag exposure; leukocyte, erythrocyte and Hb levels were all inversely correlated with selexipag/ACT-333679 exposure; and blood pressure and heart rate did not demonstrate statistically significant relationships with drug exposure in PAH patients.

Efficacy

Dose selection

Dose selection was based on the up-titration regimen of 200mg bd to 1600mg bd as tolerated in the pivotal study, given that high doses of prostacyclin receptor agonists produce known adverse effects and poor tolerability. A Phase I study confirmed 1600 mg bd was the highest tolerated dose.

Study AC-065A302 (GRIPHON)

This was a Phase III, multi-centre, multi-national, randomised, double-blind, parallel-group, placebo-controlled morbidity and mortality study to compare the efficacy and safety of selexipag 200 to 1600 µg bd with placebo in 1156 patients with PAH (groups 1.1 to 1.4 of the Updated Dana Point 2008 Clinical Classification (Table 17), that is, idiopathic PAH, heritable PAH, drug or toxin induced PAH, or PAH associated with connective tissue disease, congenital heart disease with simple systemic-to-pulmonary shunt [at least 1 year after surgical repair], or human immunodeficiency virus (HIV) infection), modified NYHA/WHO Functional Class I to IV and with a 6MWD of between 50 and 450 m.

Table 17: Clinical Classification of Pulmonary Hypertension

DANA POINT, 2008; J Am Coll Cardiol**, 2009; 54:43-54**

1 Pulmonary arterial hypertension (PAH)

1.1 Idiopathic PAH

1.2 Heritable

1.2.1 Bone morphogenetic protein receptor type 2

1.2.2 activin receptor-like kinase type 1, endoglin (with or without hereditary hemorrhagic telangiectasia)

1.2.3 Unknown

1.3 Drug- and toxin-induced

1.4 Associated with

1.4.1 Connective tissue diseases

1.4.2 HIV infection

1.4.3 Portal hypertension

1.4.4 Congenital heart diseases

1.4.5 Schistosomiasis

1.4.6 Chronic hemolytic anemia

1.5 Persistent pulmonary hypertension of the newborn

1' Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)

2 Pulmonary hypertension owing to left heart disease

2.1 Systolic dysfunction

2.2 Diastolic dysfunction

2.3 Valvular disease

3 Pulmonary hypertension owing to lung diseases and/or hypoxia

3.1 Chronic obstructive pulmonary disease

3.2 Interstitial lung disease

3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern

3.4 Sleep-disordered breathing

3.5 Alveolar hypoventilation disorders

3.6 Chronic exposure to high altitude

3.7 Developmental abnormalities

4 Chronic thromboembolic pulmonary hypertension (CTEPH)

5 Pulmonary hypertension with unclear multifactorial mechanisms

5.1 Hematologic disorders: myeloproliferative disorders, splenectomy

5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis: lymphangioleiomyomatosis, neurofibromatosis, vasculitis

5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders

5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

Study treatments were to be taken bd in an up-titration regimen (200 µg bd initially then up-titrated during the initial 12 weeks in weekly increments of 200 µg bd until the individual maximum tolerated dose of a maximum of 1600 µg bd) and then maintained at that dose for the next 14 weeks (to Week 26). After Week 26, doses could be increased again up to 1600 µg bd if needed. Doses could be reduced if not tolerated. Background PAH specific therapy with approved ERAs and/or PDE-5 inhibitors was allowed if subjects had been on a stable dose for at least 3 months prior to the baseline visit, and the dose was to remain unchanged during study treatment up to Week 26. Following a morbidity event, patients could join the open-label extension Study AC-065A303 (GRIPHON OL), an ongoing open-label, uncontrolled study to assess the long-term safety of selexipag. The study had 90% power and one-sided $\alpha = 0.005$ to detect a 35% reduction in the primary endpoint. Secondary endpoints were assessed in a hierarchical manner. Protocol deviations were similar in both groups but study discontinuation was high at 50% selexipag versus 57% placebo (mostly due to confirmed primary endpoint). Baseline disease and demographic characteristics were comparable between the groups (80% female, mean age 48 years, mean body mass index (BMI) 26.8, mean 2.4 years since PAH diagnosis; 56% idiopathic PAH, 2.2% heritable PAH, 2.3% drug/toxin PAH, 29% connective tissue disease PAH, 9.5% congenital heart disease PAH and 0.9% HIV PAH; 46% NYHA/WHO class II, 53% Class III and 1% Class IV). Baseline 6MWD was 358.5m on selexipag and 348m on placebo. Baseline concomitant PAH medication use was high (80.5% on selexipag and 78.7% on placebo) with ERA use at 16.4% versus 13.1%, PDE5 inhibitors at 32.9% versus 31.8% and both at 31.2% versus 33.8% (mostly bosentan and sildenafil) respectively.

A protocol amendment during the study to detect a smaller treatment effect was undertaken, therefore the primary endpoint was analysed with and without patients who had an event prior to this date. When analysed with patients who had an event prior to the protocol amendment, the primary endpoint occurred in 27% on selexipag versus 41.6% on placebo (HR 0.60, 99% CI: 0.46, 0.78, $p<0.0001$ one sided; Table 18) corresponding to a 16.5% absolute risk reduction at 3 years or a 40% relative risk reduction. The benefit of selexipag was mainly attributed to a reduction in hospitalisation for PAH worsening (13.6% of patients in the selexipag group versus 18.7% in the placebo group) and disease progression (6.6% with selexipag versus 17.2% with placebo). Deaths were slightly higher in the selexipag group than placebo at 4.9% versus 3.1%. Sensitivity analyses and per protocol analyses yielded similar results to the primary analysis, including the analysis without patients prior to the protocol amendment.

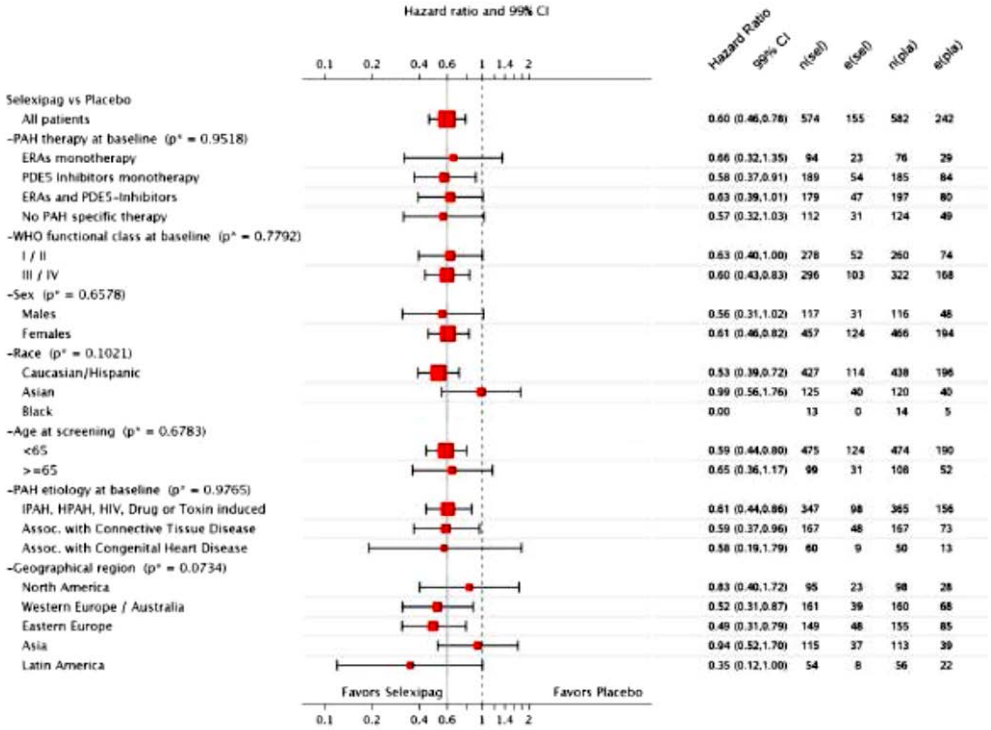
Table 18: Summary of type of first CEC-confirmed MM event up to 7 days after last study drug intake in AC-065A302 treatment period, analysis *including* CEC-confirmed MM events up to 16 August 2011, FAS, Study AC-065A302.

	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.

Analyses of the occurrence of a first morbidity/mortality event in the treatment groups across the subgroups of gender, race/ethnicity, PAH therapy at baseline, PAH aetiology at baseline, NYHA/WHO FC at baseline, age at screening, and geographical region yielded results that were generally consistent with those in the overall study population. Patients who had selexipag monotherapy had similar benefit to those who were given selexipag as add-on to ongoing ERA monotherapy, PDE-5 inhibitor monotherapy or both an ERA and a PDE-5 inhibitor. The benefit was similar across the low (200 and 400 µg bd), medium (600, 800 and 1000 µg bd) and high (1200, 1400 and 1600 µg bd) dosing groups after patients were titrated to the highest tolerated dose. Outcomes were similar based on PAH subgroups of connective tissue disease, congenital heart disease or a combined group of idiopathic, heritable, HIV, drug or toxin (Figure 3). There appeared to be no benefit for Asian patients with no single factor to explain the finding.

Figure 3: Time from randomisation to first CEC-confirmed MM event up to EOT + 7 days– forest plot for subgroup analyses, FAS, study AC-065A302



* = 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.

Secondary efficacy endpoints, including events prior to the protocol amendment, demonstrated the following:

- 6 Minute Walk Distance: Median change was 4.0 m in the selexipag group and −9.0 m in the placebo group, difference of 12.0 m (99% CI: 1, 24; 1-sided Wilcoxon-Mann-Whitney p = 0.0027).
- NYHA/WHO FC: There was no significant difference in worsening from baseline in NYHA/WHO functional class.
- Death or hospitalisation: 17.8% in the selexipag group and 23.5% in the placebo group died due to PAH or were hospitalised due to PAH worsening up to 7 days after last study drug intake. The difference was driven by hospitalisation due to PAH.
- All-cause-mortality: 17.4% and 18.0% in the selexipag and placebo groups, respectively, died.
- Quality of Life: The difference in median absolute change in CAMPHOR 'Symptoms' score was 0.0 and for 'Breathlessness' was also 0.0.

Study NS-304/-02

This Phase IIa study in 43 patients examined haemodynamic effects and efficacy of selexipag. Primary efficacy analysis in the double-blind period showed that at Week 17, pulmonary vascular resistance (geometric mean and 95% CI) was 80.7% (72.8, 89.6) and 115.9% (106.5, 126.1) of the baseline values in the selexipag and placebo groups, respectively. The median treatment effect on selexipag (versus placebo) was 0.41 L/min/m^2 (95% CI: 0.10, 0.71) for cardiac index and -427 dyn·s/cm^5 (95% CI: −668.3, −134.5) for systemic vascular resistance. Other haemodynamic variables did not show clear treatment effects with selexipag. Another study, AC-065A201, also examined pulmonary vascular resistance in 37 Japanese patients.

Safety

Patient exposure in GRIPHON was a median 71 weeks on selexipag with 64% of patients exposed for 1 year and 31% for 2 years. Overall, 28% of patients on selexipag received a dose of 1600 µg bd. The incidence of all-causality TEAEs and death was comparable between selexipag and placebo groups. The most commonly reported TEAEs in the selexipag group were headache (65.2% with selexipag versus 32.8% with placebo); diarrhoea (42.4% versus 19.1%), nausea (33.6% versus 18.5%) and jaw pain (25.7% versus 6.2%). Other notable TEAEs were vomiting (18.1% versus 8.5%), pain in extremity (16.9% versus 8%), myalgia (16% versus 5.9%), flushing (12.2% versus 5%), arthralgia (10.8% versus 7.6%), anaemia (8.3% versus 5.4%) and hypotension (5% versus 3.1%). Treatment related TEAEs showed a similar pattern. The incidence of deaths was comparable between selexipag and placebo groups (17.4% and 18.0%) with the most common cause being PAH. Serious AEs with a fatal outcome were slightly higher on selexipag (9.6% versus 7.4%). Overall SAEs were lower in the selexipag group (43.8%) compared to placebo (47.1%) with the most common being PAH (14.4% versus 22.0% with placebo) and right ventricular failure (5.9% versus 7.1%). Discontinuations due to TEAEs were lower on selexipag (32% versus 37%) and mostly due to PAH. Liver function and renal function changes were comparable between selexipag and placebo and there were no Hy's Law cases on selexipag. Liver disorder events in the selexipag and placebo groups were 7.3% and 6.4%, respectively (SAEs 1% versus 0.5%). Renal dysfunction events were reported in 7.3% of patients on selexipag compared to 4.5% on placebo, mainly due to acute renal failure (2.4% versus 1.2%). None of the acute renal failure events in the selexipag group were reported in the context of hypotension. Bone turnover markers and ECG variables did not trigger safety concerns.

Eyes were examined due to tortuosity and dilatation of retinal blood vessels seen in a long term study in rats. Eye disorders in the selexipag and placebo groups occurred in 11.0% and 7.8%, respectively (mostly eye pain at 1.6% versus 0.3%) and retinal disorders in 3.5% versus 1.9%. Eye disorders were reported as SAEs for 0.5% (3 patients) in the selexipag group and 0% in the placebo group. Fundoscopy examination in a subset of patients showed no new post-baseline or worsening of baseline fundoscopy/fundus imaging findings in the selexipag group, while 4 patients in the placebo group had treatment emergent worsening. An ophthalmology safety board set up to examine findings did not recommend any additional ocular safety studies or post-approval ocular monitoring measures and concluded the findings in rats were not clinically relevant.

Prostacyclin AEs occurred in 91.0% in the selexipag group compared with 62.2% in the placebo group**.** *Bleeding* events were investigated due to the effect of prostacyclin receptor agonists of inhibiting platelet aggregation. Overall, the proportion of patients with haemorrhage AEs was similar in the selexipag (15.5%) and placebo group (15.8%) with most due to epistaxis. Cerebrovascular/intracranial bleeds were reported for 4 (0.7%) patients on selexipag versus none on placebo. There did not appear to be a dose response relationship. Thrombocytopenia frequency was similar in both groups.

Major adverse cardiovascular events occurred in 2.4% in the selexipag group and 1.4% in the placebo group. *Anaemia* was reported in 10.4% on selexipag versus 8% on placebo but the proportion requiring a blood transfusion was similar. Anaemia increased with increasing dose. Anaemia was more frequent in selexipag patients who were taking concomitant treatment for PAH: concomitant ERA monotherapy: 14.9% with selexipag versus 9.2% with placebo; PDE5i monotherapy: 11.1% versus 5.4%; ERA and PDE5i: 11.2% versus 10.7%. Decreases in Hb were observed on selexipag and were mostly apparent within the first 3 months. Decreases in Hb concentrations to < 100 g/L at any time post-baseline were reported for 8.8% of selexipag-treated patients and 5.0% placebo-treated patients. *Hypotension* was higher in the selexipag group (5.9%) compared to the placebo group (3.8%), primarily non-serious cases, with clinically relevant cases

similar to placebo. Concomitant treatment with PDE5 inhibitors and ERAs increased the risk. Overall changes in blood pressure were small and similar between groups but there was a higher proportion of patients (9.7%) in the selexipag group who had SBP < 90 mmHg compared to 6.7% in the placebo group and patients with decrease from baseline in DBP of > 20 mmHg was higher in the selexipag group (16.6%) than in the placebo group (13.1%).

Thyroid disorders were higher in the selexipag group (2.1%; 12 patients of which 2 were SAEs) than in the placebo group (0.5%; 3 patients, none were SAEs). AEs denoting hyperthyroidism (hyperthyroidism and Basedow's disease) were reported for 9 (1.6%) patients in the selexipag group compared to no cases on placebo. T3 and T4 did not show significant changes but TSH showed a small reduction in the selexipag group. *Rash* and skin disorder events occurred in 11.1% in the selexipag group and 8.3% in the placebo group. *Bone disorders* were investigated due to increased bone ossification seen in dogs. Bone disorder AEs in the selexipag and placebo groups were 30.4% and 11.4%, respectively, mainly driven by jaw pain (25.7% with selexipag versus 5.7% with placebo). Bone pain occurred in 1.6% versus 0.3%. Fractures occurred at a similar rate. *Malignancies* occurred in 1.9% (n=11) in the selexipag group and 0.7% (n=4) in the placebo group, mainly due to cutaneous malignancies and blood and lymphatic system malignancies.

The open label extension study, *AC-065A303 (GRIPHON-OL)*, had a median duration of exposure (to 10 March 2014) of 37 weeks with the most commonly reported AEs being headache (54.6%), diarrhoea (35.8%), PAH (25.7%), pain in jaw (21.1%) and nausea (20.2%). Deaths occurred in 61 patients with 20.6% and 24.5% in the selexipag/selexipag and placebo/selexipag groups dying due to PAH (high possibly because all patients in the extension study had experienced a morbidity event in the pivotal study). SAEs occurred in 52% with the most common being PAH (23%) and right ventricular failure (15%). Discontinuations due to AEs occurred in 24% of patients and mostly due to PAH and right ventricular failure. Changes from baseline in Hb concentrations over time were variable and did not show a decreasing trend. Changes in vital signs over time were variable and did not show any particular trend over time. Patients with SBP<90mmHg were 14.3%. Decreases in DBP of >20 mmHg occurred in 16.8%.

Subgroups: The overall incidence of AEs was generally comparable among the selexipag groups in the different PAH aetiology categories and age groups. AEs were greater in patients who were treated with selexipag in addition to other PAH medications, compared to those who received selexipag monotherapy (concomitant PDE5i monotherapy and ERA + PDE5i combination therapy were 38.2% and 39.4%, respectively, compared to 24.6% in those who received ERA monotherapy, or no concomitant PAH therapy). Safety in WHO Functional class II versus III indicated more AEs, SAEs and laboratory abnormalities in class III patients. The CER discusses the findings from the other studies.

Risk management plan

The RMP evaluator has accepted the EU Risk Management Plan for Uptravi (selexipag), version 2, dated 21 July 2015 (data lock point 27 April 2014), with the Australian Specific Annex, version 2.0, dated 21 October 2015, included with submission PM-2014-04586-1-3, and any subsequent revisions, as agreed with the TGA.

Three outstanding matters which should be followed up by the sponsor with the RMP evaluator and in the Pre-ACPM Response where required (see above Risk Management Plan, Outstanding issues).

Risk-benefit analysis

Delegate's considerations

Efficacy

Selexipag given orally twice daily in an up-titration regimen has demonstrated a statistically and clinically significant reduction in the primary endpoint of time to first morbidity/mortality event in patients with PAH of 40% relative risk reduction or 16.5% absolute risk reduction. This benefit was similar across the three pre-specified dosing groups of low, medium and high and was driven by a reduction in hospitalisation due to PAH and disease progression with a slightly higher proportion of patients with death as the first event in the selexipag group (4.9% versus 3.1% in the placebo group), although the study was not powered for mortality endpoints. The sponsor did additional survival analyses and suggested that the analysis of death up to end of treatment in Study GRIPHON was biased by informative censoring, which could happen when death occurred predominantly after the occurrence of the primary endpoint morbidity event, and when the primary endpoint event led directly to the discontinuation of study treatment. Due to this, the sponsor looked at analyses of survival up to study closure, which would not have this informative censoring bias. Results showed that overall, all cause death from randomisation up to study closure was reported in 17.4% and 18.0% of patients in the selexipag and placebo groups, respectively (hazard ratio of 0.97, 1-sided unstratified log-rank p = 0.4214). Death due to PAH up to study closure was reported in 12.2% and 14.3% of patients in the selexipag and placebo groups, respectively.

The secondary efficacy endpoint of 6 minute walk distance showed only marginal benefit with a placebo subtracted improvement in distance of 12 m. However this result is in the context of about 80% of patients also on other background PAH treatments. The sponsor provided further data to compare this result with other treatments for PAH and noted that the placebo corrected median treatment effect on 6MWD in the subset of patients treated with selexipag as monotherapy in GRIPHON was 34 m and comparable to other monotherapy studies. There was no significant difference in worsening of NYHA/WHO functional class or quality of life scores.

Safety and RMP

The overall safety profile of selexipag appeared consistent with a prostacyclin receptor agonist with headache, diarrhoea, nausea and jaw pain being the most common. Prostacyclin related AEs were more common during the up-titration phase and with concomitant PAH treatments than the maintenance phase. Other notable events included vomiting, extremity pain, myalgia, flushing, arthralgia, anaemia and hypotension. AEs were generally comparable across different PAH aetiologies and age groups and did not appear to be dose dependent except for anaemia. Serious AEs and discontinuations due to AEs were less frequent on selexipag than placebo. Safety data from the extension study was supportive.

Adverse events of special interest that were slightly more frequent on selexipag included: anaemia, hypotension, eye/retinal disorders, thyroid disorders/hyperthyroidism and rash. Reductions in Hb mostly occurred within the first 3 months and hypotension cases that were clinically relevant were low. Anaemia (higher incidence in PAH treated patients) and hypotension (prostacyclin receptor agonist class effect) were more frequent in patients receiving concomitant PAH treatments but both can be monitored. Thyroid adenomas were seen in mice and thyroid disorders in patients were slightly higher on selexipag. Hyperthyroidism was slightly higher on selexipag and thyroid function testing is recommended in the PI. Rash (associated with prostacyclin receptor agonists) was slightly higher on selexipag. Malignancies (cutaneous and blood and lymphatic) appeared to be slightly more frequent but the explanation is unclear given also that selexipag was not

genotoxic or carcinogenic in animals. The small increases in eye disorders and retinal changes are unclear but changes were also seen in rats with tortuosity and dilatation of retinal blood vessels. The sponsor is not proposing to include any specific monitoring but the Delegate recommends the PI include information on this finding.

An acceptable RMP has been provided but there were some outstanding recommendations which the Delegate endorses and the sponsor should address in the Pre-ACPM Response.

WHO subgroups

Efficacy and safety in the PAH subgroups requested appeared acceptable but there is very limited data in patients with PAH associated with drugs and toxins (2.3% of patients) and heritable PAH (2.2% of patients). Traditionally, heritable patients have been included in the indications of other PAH treatments but drugs/toxins has not been included. Patients with HIV associated PAH represented 0.9% of patients in the pivotal study but the sponsor has not requested this subgroup for the indication. Internationally, the US and European indications do not include the drugs/toxins subgroup. A recently approved treatment for PAH from Actelion, macitentan, had initially requested the inclusion of drugs/toxins subgroup. This subgroup was also a small population in the pivotal study (3%). ACPM's advice at the time was that the indication should only include those subgroups of WHO Group 1 for which sufficient data have been provided. The product was subsequently approved without this subgroup.

ACPM's advice is requested on whether selexipag's indication should include the drugs/toxins subgroup.

WHO Functional Class IV

WHO Functional class IV patients represented 1% of the study population in the pivotal study and therefore the data is too limited to conclusively establish efficacy and safety in this subgroup. The sponsor has requested this group be included in the indications however internationally, the US and European indications do not include this group. Recent approvals for PAH treatments here have included this group, even though they also had a similarly small population in their dataset, for example macitentan had 2% with Class IV in its pivotal study. On a pragmatic basis this group could be included given that patients are worsening and this may be best left to clinical judgement on whether continued treatment is appropriate.

ACPM's advice is requested on the inclusion of WHO Functional Class IV patients in the Indication.

Combination treatments

The sponsor is requesting a claim in the Indications of '*Uptravi is effective in combination with an endothelin receptor antagonist (ERA) or a phosphodiesterase-5 (PDE-5) inhibitor, or in triple combination with an ERA and a PDE-5 inhibitor, or as monotherapy*'. Although patients were allowed to continue treatment with these medicines during the study with an unchanged dose, the study was not designed or powered to test whether a specific combination was superior to monotherapy. The subgroup analysis of the primary endpoint indicated that there was no additional benefit from combination therapy compared with selexipag monotherapy with similar hazard ratios based on baseline PAH treatment (ERA monotherapy HR 0.66, PDE5 inhibitor monotherapy 0.58, ERA and PDE5 inhibitors 0.63 and no specific PAH treatment 0.57). Adverse events were greater in patients who were treated with selexipag in addition to other PAH medications, compared to those who received selexipag monotherapy. Given this, then the inclusion of such a statement may be more appropriate in the Dosage and Administration section of the PI as a statement that selexipag can be used with these other products. Internationally, the US PI does not include a statement about combination use in the Indications but a statement has been requested by the sponsor for the EU and Canadian indications that selexipag can

be used as monotherapy and in combination with ERAs and/or PDE5 inhibitors. Recent PAH treatments approved here such as macitentan and riociguat include combination therapy use statements in the indications.

Asian patients

The primary efficacy endpoint did not appear to demonstrate a benefit for Asian patients or patients from Asia on selexipag compared to placebo. Although the explanation for this finding is unclear, it was noted that these patients were younger and had slightly less disease. Further analysis indicated that for the primary efficacy endpoint, the Kaplan-Meier (KM) estimate for event-free survival in the selexipag arm up to Month 30 was similar between patients in the Asian (61.1%) and non-Asian (62.1%) regions, while in the placebo arm, the KM estimates were 60.4% and 46.8%, respectively, suggesting that the observed primary efficacy endpoint results were largely due to differences in the placebo groups between the Asian and non-Asian subpopulations. In view of these findings, the sponsor concluded that the results were likely to represent random variation, to which the clinical evaluator agreed

Data deficiencies

No dedicated studies examined the pharmacokinetics of selexipag in the target population and no dedicated pharmacodynamic studies examined the primary pharmacodynamic effects of selexipag or its active metabolite. It is unclear if selexipag has photosensitising potential. There is limited long term safety data. There is a lack of data in other PAH subgroups and in paediatric age groups. Data is limited in heritable, drug/toxin and HIV associated PAH and in patients with WHO Functional class I and IV.

Conditions of registration

The following are proposed as conditions of registration and the sponsor is invited to comment in the Pre-ACPM response:

1. The implementation in Australia of the EU Risk Management Plan for Uptravi (selexipag), version 2, dated 21 July 2015 (data lock point 27 April 2014), with the Australian Specific Annex, version 2.0, dated 21 October 2015, included with submission PM-2014-04586-1-3, and any subsequent revisions, as agreed with the TGA.
2. The following study reports must be submitted to the TGA, in addition to those identified and/or agreed in the RMP/ASA, as soon as possible after completion, for evaluation as Category 1 submission(s):
    a. Study GRIPHON-OL (AC-065A303)

Questions for the sponsor

The sponsor is requested to address the following issues in the Pre-ACPM Response:

1. Please clarify if the timing of food intake in the pivotal clinical study, GRIPHON, was controlled or were patients allowed to take the tablets without regard to food.
2. A report on polymorphic form detection will be provided to the US-FDA by 1/2016 along with a second by 12/2016 in case the sensitivity reached is not deemed sufficient and an alternative analytical method is needed. The sponsor should provide an assurance that these reports will also be provided to the TGA.
3. The sponsor is requested to update the GMP status for one of their sites that is due to expire.
4. Please provide an update on the GRIPHON OL study including any potential safety findings, after the last cut-off date of 10 March 2014.

5. Please provide a justification based on the efficacy and safety data and pathophysiology to support inclusion of the PAH subgroup associated with drugs/toxins. Include the results for the primary endpoint in patients only with drugs/toxins related PAH.
6. Are any further studies planned in specific subgroups of PAH that have not been fully covered at present or in any other subtypes of pulmonary hypertension?
7. Is the sponsor conducting any specific studies or further investigations into the ocular findings seen with selexipag?

Summary of issues

The primary issues with this submission are as follows with further information detailed above:

1. WHO Functional Class IV patients represented 1% of the study population in the pivotal study. The sponsor has requested this group be included in the Indications. Internationally, the US and European indications do not include this group. Recent approvals here for PAH have included this group even though they also had a similarly small population in their dataset. On a pragmatic basis the inclusion of this group could be supported given that patients are worsening and therefore it would be best left to clinical judgement on whether continued treatment is appropriate.
2. The sponsor is requesting a claim in the Indications of '*Uptravi is effective in combination with an endothelin receptor antagonist (ERA) or a phosphodiesterase-5 (PDE-5) inhibitor, or in triple combination with an ERA and a PDE-5 inhibitor, or as monotherapy*'. Although patients were allowed to continue treatment with these medicines during the study with an unchanged dose, the study was not designed to test whether a specific combination was superior to monotherapy. Adverse events were also more frequent on combination treatment. Given this, then the inclusion of such a statement may be more appropriate in the Dosage and Administration section of the PI. Internationally, the US does not include a statement about combination use in the Indications but a statement has been requested by the sponsor for the EU indication. Recent PAH treatments approved here such as macitentan and riociguat include combination therapy use statements in the Indications.
3. The sponsor is requesting the subgroup of '*pulmonary arterial hypertension associated with drugs and toxins*' however there is limited data to support this group's inclusion in the Indications (2.3% of the population). Internationally, the US and European indications do not include the drugs/toxins subgroup. The population size is similar to the heritable group (2.2%) however this is usually combined with the idiopathic group. It is unclear if the pathophysiology is similar enough and the data sufficient to extrapolate to this group.
4. Anaemia, hypotension, eye/retinal disorders, thyroid disorders/hyperthyroidism, rash and some malignancies were slightly more frequent on selexipag than placebo, in addition to prostacyclin receptor agonist effects.

Proposed action

The Delegate had no reason to say, at this time, that the application for Uptravi should not be approved for registration, pending further advice from ACPM.

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. Should the indication include WHO Functional class IV patients?

2. Is the data sufficient to support combination therapy with endothelin receptor antagonists, phosphodiesterase type 5 inhibitor or both and should this claim be included in the Indications or in the Dosage and Administration section of the PI?
3. Should the indication include patients with pulmonary arterial hypertension associated with drugs and toxins?
4. Is the safety profile of selexipag adequately covered in the PI?

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

ACPM advice ought by Delegate

The Delegate is seeking advice from the ACPM to four specific issues, on which the applicant would like to comment as follows:

1. Should the indication include WHO Functional class IV patients?

The sponsor is of the opinion that the therapeutic indication for Uptravi® (selexipag) should include WHO functional class IV.

Although there were few patients with WHO functional class (FC) IV in GRIPHON at baseline, important information regarding the treatment effect of selexipag in these patients can be gained from the subsequent survival in the 75 patients randomised to placebo in GRIPHON and who were classified as WHO FC IV at double-blind treatment discontinuation. Of these 75 patients, 43 started selexipag within GRIPHON open-label (OL), while 32 were treated with any other modification and/or addition to their pulmonary arterial hypertension (PAH) therapy outside GRIPHON OL. Selexipag doses achieved in the 43 patients treated within GRIPHON OL were similar to those in the overall study population in GRIPHON. Of note, these data are based on a post hoc analysis and patients were not re-randomised in the OL extension study.

A clinically relevant trend to improved survival up to study closure was observed in patients in WHO FC IV newly treated with selexipag: hazard ratio (HR) selexipag versus non-selexipag 0.74 (95% confidence interval [CI]: 0.40, 1.38; log rank p = 0.3631), corresponding to nearly 9 months' increase in time to reach 50% (median) survival, in favour of selexipag. Although not statistically significant, due to the limited number of events overall, this still constitutes substantial experience with selexipag and strongly suggests a clinically important benefit of selexipag compared to alternative therapies also in WHO FC IV patients.

The safety findings reflected the severity of the condition but were otherwise consistent with those in the overall GRIPHON study population. No safety signals that would affect the benefit-risk assessment of selexipag in patients in WHO FC IV were detected.

Overall, the sponsor agrees with the Delegate's comment that on a pragmatic basis it is best left to clinical judgement as to whether continuing treatment in patients with WHO FC IV PAH is appropriate. The above GRIPHON data support this approach. Thus, the sponsor is of the opinion that the therapeutic indication for Uptravi (selexipag) should not exclude WHO FC IV. This approach maintains consistency with the Australian approvals for Flolan (epoprostenol), Adempas (riociguat), Ventavis (iloprost), Remodulin (treprostinil) and the endothelin receptor antagonists Tracleer (bosentan), Opsumit (macitentan) and Volibris (ambrisentan), most if not all of which were approved for patients with WHO FC IV based on limited data in this group. Of note, the Australian PI now contains the following precaution:

Selexipag has only been studied in a limited number of patients with WHO functional Class IV

2. *Is the data sufficient to support combination therapy with endothelin receptor antagonists, phosphodiesterase type 5 inhibitor or both and should this claim be included in the Indications or in the Dosage and Administration section of the PI?*

GRIPHON enrolled a broad population of PAH patients representative of current standards of medical care, with only approximately 20% of patients not on treatment with any PAH-specific medicine at baseline, while 80% were already on treatment with at least one PAH-specific medicine, and > 30% on treatment with both an endothelin receptor antagonist (ERA) and a phosphodiesterase type 5 inhibitor (PDE-5i). This latter group has not been studied in previous trials, and GRIPHON is the first study in PAH showing an effect on disease progression events on top of two other PAH medicines. Prospectively defined subgroup analyses included the above four subgroups and were presented in the submission.

The distribution of patients by IMD cohort (low, medium, high) was comparable across the background PAH specific medication subgroups (Table 19).

Table 19: Distribution of patients in GRIPHON with/without PAH-specific medications by IMD-selexipag group. Full Analysis Set.

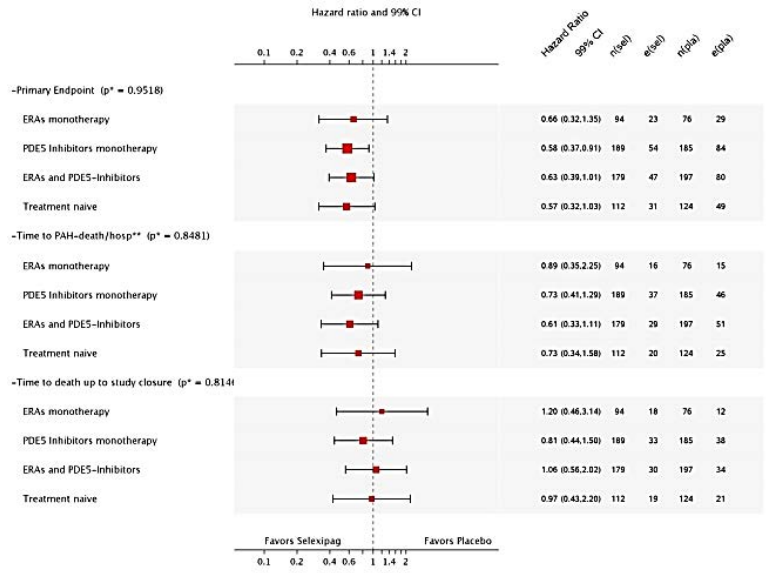
IMD category	No PAH-specific therapy N = 111	ERA monotherapy N = 89)	PDE-5i monotherapy N = 184	ERA + PDE-5i therapy N = 175
200–500 µg b.i.d.	28 (25.2)	26 (29.2)	43 (23.4)	36 (20.6)
600–1100 µg b.i.d.	34 (30.6)	27 (30.3)	54 (29.4)	65 (37.1)
1200–1600 µg b.i.d.	49 (44.1)	36 (40.5)	87 (47.3)	74 (42.3)

Note: excluding patients randomized to selexipag with IMD = 0 or other

b.i.d. = twice daily; ERA = endothelin receptor antagonist; IMD = individual maintenance dose; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type-5 inhibitor.

For morbidity and mortality related study endpoints, and particularly for the primary endpoint, there was full consistency in the treatment effect across subgroups by baseline PAH-specific therapy. All treatment interaction tests were negative (Figure 4).

Figure 4: Key efficacy data in GRIPHON by PAH background therapy at baseline-Forest plot. 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.
** Time to PAH-death or PAH-hospitalization up to EOT + 7 days
Events with CEC-confirmed onset date up to 16 Aug 2011 are included as events.
Figure FMMTGRE_F - Produced by zeeja1 on 08JUL15 - Data dump of 12JUN2014

CI = confidence interval; ERA = endothelin receptor antagonist; IMD = individual maintenance dose; PAH = pulmonary arterial hypertension; PDE5 = phosphodiesterase type 5.

Overview of safety data by PAH background therapy

Adverse events by concomitant PAH background medication were previously discussed in the sponsor's response to the TGA's request for further information. The safety profile of combination therapy groups was compatible with the known safety profile of the individual compounds without evidence for incremental toxicity upon combination therapy with selexipag.

Conclusion

The effect of selexipag on the primary endpoint as well as other key efficacy endpoints on top of a PDE-5i and/or an ERA was fully consistent with that seen in monotherapy. The safety profile of each background therapy subgroup appeared to be driven largely by the individual contributions of the respective PAH-specific medications. These results, especially the consistency of findings in patients on 2 concomitant PAH-specific therapies, demonstrate the utility of selexipag in these populations.

Consistent with the PI of recently approved PAH products, Opsumit (macitentan) and Adempas (riociguat), the sponsor is of the opinion that the therapeutic indication for Uptravi (selexipag) should include the combination therapeutic use statement. The demonstration of benefit of selexipag over 2 approved PAH medicines of different pharmacological classes, is unique.

3. Should the indication include patients with pulmonary arterial hypertension associated with drugs and toxins?

The sponsor is of the opinion that the therapeutic indication for Uptravi (selexipag) should include *pulmonary arterial hypertension associated with drugs and toxins* for the following reasons:

In the GRIPHON study, subgroup analysis per PAH disease aetiology was performed by combining the groups of idiopathic PAH (IPAH), heritable/familial PAH (HPAH), drug-induced PAH, and PAH secondary to HIV, as these aetiologies have very similar disease characteristics and response to PAH-specific treatments. In the GRIPHON study, 27

subjects (17 selexipag and 10 placebo) with PAH associated with drugs/toxins were randomised, representing 2.3% of the total study population.

Pathophysiology

In the current classification of pulmonary hypertension (PH), PAH is defined as Group 1 and includes IPAH, HPAH, PAH associated with different conditions such as connective tissue disease or congenital heart disease, HIV infection and exposure to drugs or toxins.[26] All these subgroups of PAH share common alterations in the signalling pathways and similar histological findings, that is, intense remodelling of non-muscularised arteries.[25] A retrospective analysis of a 109 case cohort of PAH associated with fenfluramine exposure showed similar clinical, functional, haemodynamic, and genetic features as a control cohort of IPAH patients.[27]

Efficacy data

Below, the sponsor provides descriptive efficacy data focusing on morbidity/mortality and change in 6MWD for IPAH and drug/toxin-induced PAH separately. Efficacy was comparable across these subgroups, showing that the clustering is appropriate, due to the similar pathophysiology and response to treatment.[28]

Morbidity/mortality

The proportion of patients with a Critical Event Committee (CEC) confirmed first morbidity/mortality event was lower in the selexipag group than in the placebo group for IPAH and drug-induced PAH groups (Table 20). Due to the limited number of patients and events in the drug-induced PAH group, no formal statistical testing on the primary endpoint was conducted.

Table 20: Summary of type of first CEC-confirmed morbidity/mortality even p to 7 days after last study drug intake by PAH aetiology-IPAH and drug induced PAH Full Analysis Set

	IPAH		Drug/toxin PAH	
	Selexipag N=312 n (%)	Placebo N=337 n (%)	Selexipag N=17 n (%)	Placebo N=10 n (%)
Patients with morbidity / mortality event	93 (29.8)	151 (44.8)	3 (17.6)	2 (20.0)
Death	16 (5.1)	13 (3.9)	-	-
Hospitalisation for PAH worsening	47 (15.1)	63 (18.7)	1 (5.9)	1 (10.0)
PAH worsening resulting in need for lung transplant/balloon atrial septostomy	-	1 (0.3)	-	-
Parentral prostanoid therapy or chronic oxygen therapy	6 (1.9)	8 (2.4)	1 (5.9)	-
Disease progression	24 (7.7)	66 (19.6)	1 (5.9)	1 (10.0)

CEC = Critical Event Committee; IPAH = idiopathic pulmonary arterial hypertension; PAH = pulmonary arterial hypertension.

[26] Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2009;54(1 Suppl):S43–54.

[27] Souza R, Humbert M, Sztrymf B, Jaïs X, Yaïci A, Le Pavec J, et al. Pulmonary arterial hypertension associated with fenfluramine exposure: report of 109 cases. Eur Respir J 2008;31(2):343-8.

[28] Galiè N, Corris PA, Frost A, Girgis RE, Granton J, Jing ZC, et al. Updated treatment algorithm of pulmonary arterial hypertension. J Am Coll Cardiol 2013;62(25 Suppl):D60-72.

In the subgroup of patients with drug/toxin-induced PAH, the treatment effect (location shift using Hodges-Lehmann method) on 6MWD for selexipag versus placebo was 33.5 m (99% CI: −134, 362) (Table 21).

Table 21: Change from baseline to Week 26 in median 6MWD at trough by PAH aetiology using main imputation algorithm-IPAH, and drug induced PAH Full Analysis Set

	IPAH Selexipag N=312 Placebo N=337	Drug/toxin PAH Selexipag N=17 Placebo N=10
Treatment effect (99% CI)* meters	10.0 (-6, 26)	33.5 (-134, 362)

* treatment effect (selexipag vs placebo) location shift using Hodges-Lehmann method

** One-sided Wilcoxon-Mann-Whitney (Non-parametric ANCOVA with covariate 6MWD at Baseline)
6MWD = 6-minute walk distance; CI = confidence interval; IPAH = idiopathic pulmonary arterial hypertension; PAH = pulmonary arterial hypertension.

Safety data

A review of individual profiles of subjects with drug/toxin-induced PAH did not reveal differences between selexipag and placebo subjects and the safety profile of selexipag in this PAH subgroup was consistent with the safety profile in the IPAH subgroup.

Conclusion

Although the number of patients with PAH associated with drug/toxins enrolled in the GRIPHON study was limited, the efficacy and safety data were consistent with data in IPAH patients. Available data indicate a common pathophysiological pathway in IPAH and drug/toxin-associated PAH. It has been shown that patients with PAH associated with drug/toxins and IPAH share common clinical, haemodynamic and functional features. Importantly, the current PH treatment guidelines do not differentiate between individual Group 1 (PAH) aetiologies concerning the indication and type of treatment and rather focus on the patients' WHO functional class.[29,30]

It is noteworthy that iloprost (Ventavis), a synthetic prostacyclin analogue, is approved in Australia for use in patients with '*primary pulmonary hypertension or secondary pulmonary hypertension due to connective tissue disease or drug-induced, in moderate or severe stages of the disease*', thereby providing reassurance that agents acting as prostacyclin receptor agonists are known to be effective in patients with drug-induced PAH.

Consistent with this, the sponsor is of the opinion that the therapeutic indication for Uptravi (selexipag) should include *pulmonary arterial hypertension associated with drugs and toxins* given the very close similarity between these conditions and the available study data. Of note, the Australian PI now contains the following precaution:

Selexipag has only been studied in a limited number of patients with PAH due to drugs or toxins.

4. Is the safety profile of selexipag adequately covered in the PI?

The selexipag Australian PI has been reviewed against the PIs of other prostacyclin receptor agonists.

[29] Barst RJ, Gibbs JS, Ghofrani HA, Hoeper MM, McLaughlin VV, Rubin LJ, et al. Updated evidence-based treatment algorithm in pulmonary arterial hypertension. J Am Coll Cardiol 2009;54(1 Suppl):S78-84.

[30] Galiè N, Corris PA, Frost A, Girgis RE, Granton J, Jing ZC, et al. Updated treatment algorithm of pulmonary arterial hypertension. J Am Coll Cardiol 2013;62(25 Suppl):D60-72.

The sponsor agrees to add to the Australian PI the contraindications agreed with the EU CHMP in order to provide consistency with the product information for other IP receptor agonists ('iloprost contraindications'), as listed below:

- Severe coronary heart disease or unstable angina.
- Myocardial infarction within the last 6 months.
- Decompensated cardiac failure if not under close medical supervision.
- Severe arrhythmias.
- Cerebrovascular events (for example, transient ischaemic attack, stroke) within the last 3 months
- Congenital or acquired valvular defects with clinically relevant myocardial function disorders not related to pulmonary hypertension.

With these additions the sponsor is of the opinion that the safety profile of selexipag is adequately covered in the AU PI.

Responses to 'Questions for the sponsor'

1. *Please clarify if the timing of food intake in the pivotal clinical study, GRIPHON, was controlled or were patients allowed to take the tablets without regard to food.*

The GRIPHON protocol stipulated that '*the study drug should be taken with food' and subjects were informed accordingly through the Subject Information Leaflet: 'You will be asked to take the tablets orally (by mouth) twice a day, once in the morning and once in the evening, preferably with food*'. In contrast to the short Phase I studies in which subjects took study drug in the clinic in a controlled environment, subjects enrolled in GRIPHON were expected to take study drug at home for the duration of the study. No information on timing of study drug versus food intake was collected in the GRIPHON study.

2. *A report on polymorphic form detection will be provided to the US FDA by 1/2016 along with a second by 12/2016 in case the sensitivity reached is not deemed sufficient and an alternative analytical method is needed. The sponsor should provide an assurance that these reports will also be provided to the TGA.*

The sponsor provides assurance that the reports on polymorphic form detection will be provided to the TGA.

3. *The sponsor is requested to update the GMP status for one of their sites that is due to expire.*

The sponsor provides assurance that all manufacturing sites have current GMP pre-clearance.

4. *Please provide an update on the GRIPHON OL study including any potential safety findings, after the last cut off date of 10 March 2014.*

After the cut-off date of 10 March 2014, the following safety reports including updates of GRIPHON OL have been previously submitted to TGA:

The 4th Development Safety Update Report (DSUR) for selexipag submitted to the TGA on 6 May 2015 summarised the safety data for selexipag received by Actelion Pharmaceuticals Ltd from all ongoing clinical trials during the reporting period from 17 March 2014 to 16 March 2015. In summary, it was concluded that the nature and severity of the reported events reflect the safety profile of selexipag as described in the Investigator's Brochure and as anticipated to occur in the studied populations of PAH, chronic thromboembolic pulmonary hypertension, Raynaud's phenomenon and arteriosclerosis obliterans associated with intermittent claudication. The events described in this report did not change the safety profile of selexipag as proposed in the Uptravi product information.

In line with FDA requirements to submit a safety update after submission of a New Drug Application (NDA), a 120 Day safety update report was prepared with cut-off date 10 September 2014 and for completeness, data on deaths after the cut-off date up to 16 March 2015. This report concluded that there were no new or unexpected safety findings and the additional safety data did not alter the original interpretation of the benefit-risk profile as presented in the sponsor's Summary of Clinical Safety and Clinical Overview.

The Data Monitoring Committee of the GRIPHON OL study has met three times since March 2014. At all meetings (21 November 2014, 3 June 2015, and 14 December 2015), the committee did not indicate the presence of any new potential safety issue.

Please note, that as the first regulatory approval (US) was received on 21 December 2015, the first PSUR will be generated 6 months after this date, with the cut-off date 20 June 2016.

5. *Please provide a justification based on the efficacy and safety data and pathophysiology to support inclusion of the PAH subgroup associated with drugs/toxins. Include the results for the primary endpoint in patients only with drugs/toxins related PAH.*

Please refer to the sponsor's response to *ACPM Advice Sought by Delegate*: Question 3 above.

6. *Are any further studies planned in specific subgroups of PAH that have not been fully covered at present or in any other subtypes of pulmonary hypertension?*

In the frame of the EU paediatric investigational plan (PIP), the sponsor is planning to study the safety and efficacy of selexipag in the paediatric population aged 1 to 17 years. Study design and endpoints are currently under discussion with the EU Paediatric Committee (PDCO). No studies are planned in other specific subgroups of PAH.

7. *Is the sponsor conducting any specific studies or further investigations into the ocular findings seen with selexipag?*

A comprehensive review of ocular safety data from Phase I-III studies with selexipag by the Ophthalmology Safety Board (OSB) and documented in an independent OSB report included in the marketing authorisation application (MAA) concluded that there were no ocular safety findings associated with the systemic administration of selexipag at the doses tested in healthy subjects or patients with the target diseases investigated. The OSB did not recommend any additional ocular safety studies or post approval ocular monitoring measures. No dedicated studies investigating ocular safety of selexipag have been initiated or are planned. Ophthalmological effects associated with the retinal vascular system will be assessed as part of safety assessments in the European post-authorisation observational cohort safety study (PASS) in PAH. Note: At their latest scheduled meeting on 19 November 2015, the OSB met to review the latest available ophthalmology safety data from selexipag studies since the initial selexipag OSB report. No new safety signal, or any change from the conclusions in the selexipag OSB report with regard to ocular safety were identified.

Responses to RMP recommendations

Recommendation 4

The PASS studies had not been conceived when the ASA was submitted. Both studies are now included in the latest EU RMP (version 4 dated 22 December 2015) and protocol synopses have been provided.

The EU PASS observational cohort study of PAH patients exposed and unexposed to Uptravi® (selexipag) in routine clinical practice will collect data on patient demographics, disease characteristics and clinical course of PAH, and estimate the incidence rates during the observation period of all-cause death and major adverse cardiovascular events (MACE), as well as provide further characterisation of the safety profile of Uptravi for

important identified or potential risks. This will follow patients with and without selexipag treatment.

Uptravi will be a Section 100 medication in Australia, prescribed only from Medicare-approved 'Designated Centres'. Uptravi will therefore be prescribed only by PAH specialists who will normally be familiar with the risks of administering other IP receptor agonists, and having the necessary facilities to oversee close monitoring of patients. Nevertheless, the sponsor will ensure that a Prescriber Pack containing the risk minimisation tools will be provided to prescribers/nurses in all Designated Centres to ensure they are fully familiar with the specific titration schedule and safety concerns when prescribing Uptravi.

Given the similarity of patient characteristics between Australian[31] and Europe[32,33], the sponsor is confident that data from the EU PASS observational cohort study will be representative of the Australian context. The sponsor is therefore of the opinion that undertaking the observational cohort study in Australia would provide very limited additional benefit to risk minimisation in Australian patients.

The second EU PASS study will evaluate medication error risk minimisation measures (RMM) for the Uptravi titration phase via a series of surveys with prescribers and patients. The sponsor recognises the importance of this study in monitoring the effectiveness of the educational materials, particularly the titration guides, in minimising potential medication errors.

Consequently it is proposed that this PASS is conducted in Australia along similar timelines to its conduct in the EU, and results provided to the TGA upon its completion.

The sponsor will amend the ASA accordingly after approval to also take account of the final approved PI text and commits to providing both PASS study protocols once these are finalised.

Recommendation 6

As Uptravi is a Section 100 medication that will only be prescribed from Medicare-approved Designated Centres, there will only be a relatively small number of potential prescribers in Australia (approximately 100). All Designated Centres will receive educational material as detailed in the RMP and as described in response to Recommendation 4 above. The prescribers and nurses will have the primary responsibility for ensuring that patients understand and adhere to the titration schedule at treatment initiation.

As described above, the sponsor commits to undertake the PASS study that will evaluate medication error risk minimisation measures for the Uptravi titration phase also in Australia. Via a series of surveys the study will review awareness (existence of material), knowledge (content understanding), and use of the risk minimisation measures. In addition, the occurrence of 'wrong dose' medication errors self-reported by the patient will be recorded. Every titration pack will contain a copy of both the titration guide booklet and the CMI. The sponsor will continue to evaluate the effectiveness of the educational materials via the PASS.

[31] Keogh A for the Registry Steering Committee. Pulmonary Hypertension Society of Australia and New Zealand (PHSANZ). Australian and New Zealand PHT Registry 3rd annual report, 2015.

[32] UK Audit 2014 Health and Social Care Information Centre, National Audit of Pulmonary Hypertension. Fifth Annual Report: Key findings from the National Audit of Pulmonary Hypertension for the United Kingdom, Channel Islands, Gibraltar and Isle of Man. Report for the audit period April 2013 to March 2014.

[33] Hoeper MM, Huscher D, Ghofrani HA, Delcroix M, Distler O, et al. Elderly patients diagnosed with idiopathic pulmonary arterial hypertension: Results from the COMPERA registry. Int J Cardiol 2013;168(2):871-80.

Recommendation 7

The sponsor has added mentioning of these exclusion criteria to the AU PI text. The fifth paragraph in section *Efficacy in Patients with Pulmonary Arterial Hypertension* has been modified as follows (new added text in italics):

Idiopathic or heritable PAH was the most common aetiology in the study population (58%) followed by PAH due to connective tissue disorders (29%), PAH associated with congenital heart disease with repaired shunts (10%), and PAH associated with other aetiologies (drugs and toxins [2%] and HIV [1%]). *Patients with left ventricular dysfunction, moderate or severe obstructive or restrictive lung disease, moderate or severe hepatic impairment, or severe renal insufficiency were excluded from the study*.

Advisory Committee Considerations

The ACPM resolved to recommend to the TGA delegate of the Minister and Secretary that:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the delegate and considered Uptravi film-coated tablet containing 200 µg, 400 µg, 600 µg, 800 µg, 1000 µg, 1200 µg, 1400 µg and 1600 µg of selexipag to have an overall positive benefit–risk profile for the indication**;**

Uptravi, is indicated for the treatment of:

- idiopathic pulmonary arterial hypertension
- heritable pulmonary arterial hypertension
- pulmonary arterial hypertension associated with connective tissue disease
- pulmonary arterial hypertension associated with congenital heart disease with repaired shunts.
- pulmonary arterial hypertension associated with drugs and toxins
- in patients with WHO functional class II, III or IV symptoms.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration and advised on the inclusion of the following;

- Negotiation of Product Information and Consumer Medicines Information to the satisfaction of the TGA.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following:

- a statement in the Dosage and Administration section *on combination therapy such as;*

  the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients with WHO functional class (FC) II–III, either as combination therapy in patients insufficiently controlled with an endothelin receptor antagonist (ERA) and/or a phosphodiesterase type 5 (PDE-5) inhibitor, or as monotherapy in patients who are not candidates for these therapies

- a statement in the Precautions section of the PI, to be reflected in relevant section of the CMI, to accurately reflect the extent of the data in patients classified WHO FC class IV similar to;

Studies with selexipag have been mainly performed in PAH patients classified as WHO functional Class II and III. Selexipag has only been studied in a limited number of patients with WHO functional Class IV. (Pivotal trial enrolled only 11 patients in FC IV, of whom only 3 received active drug). Selexipag has only been studied in a limited number of patients with PAH due to drugs or toxins.

The PI needs considerable amendment including;

- The statement '*Each round film-coated tablet contains 200 µg (respectively 400, 600, 800, 1000, 1200, 1400, or 1600 µg) selexipag'* needs clarification…'200 µg or multiples thereof (respectively….)' etc.
- The statement on use in pregnant women suggests there are some data; however; in rats and rabbits, selexipag crossed the placental barrier into the foetus. There are no data regarding paediatric exposure of selexipag. A replacement statement could be 'Use in pregnancy should be avoided. Pregnant women were excluded from the trial and there is no data in human pregnancy.'
- The statement on use in dialysis is different in the Australian PI compared to the US. The discrepancy should be reconciled.
- There is a lack of sufficient data to support the statement on the potential interaction of this product with hormonal contraceptives

The CMI also needs amendment, including;

- The statement '*It relieves the symptoms of PAH and improves the course of the disease*' is considered inaccurate. This product may have shown '*relieves (lessens) symptoms'* but the data has not clearly shown (for example, a change in mortality) that the course is altered
- The descriptions of cardiac contra-indications in the CMI do not correlate well with those in the PI.
- Pregnancy is contraindicated in PAH. There is no evidence regarding use of this medicine in human pregnancy. The current statement is inadequate, as is the statement on breast feeding.
- The recommended dose should not reference children

Specific Advice

The ACPM advised the following in response to the delegate's specific questions on this submission:

1. *Should the indication include WHO Functional class IV patients?*

The ACPM advised that, despite the WHO Class IV representing only 1% of the study cohort, this very small patient group should be included. Cessation of medical therapy at deterioration/ end of life should be clinically guided and undertaken in consultation with the patient.

A precautionary statement could be included in the PI detailing the nature of the data available in this special population.

2. *Is the data sufficient to support combination therapy with endothelin receptor antagonists, phosphodiesterase type 5 inhibitor or both and should this claim be included in the Indications or in the Dosage and Administration section of the PI?*

The ACPM advised that as selexipag was seen to be equally effective across these groups and there is no evidence of superiority or data from add-on studies, the statement is reasonable to include in the Dosage and Administration section of the PI.

Under *Interactions with other medicines* the ACPM suggested adding: '*patients on combination PAH therapy experienced a greater number of adverse events*'.

3. Should the indication include patients with pulmonary arterial hypertension associated with drugs and toxins?

The ACPM was of the view that given the similar pathophysiology within the PAH subgroups and the similar, although very limited data, in the drugs and toxins subgroup and the IPAH subgroup, that the data and sponsor's justification are sufficient to support including this subgroup in the Indications. The committee noted that a precaution will be included to note the limited evidence available.

4. Is the safety profile of selexipag adequately covered in the PI?

The list of adverse events is suitable but should include information on malignancies, eye disorders and anaemia in the *Adverse Effects* section.

- As malignancies (non-melanoma skin malignancies and lymphoproliferative disorders) are data endpoints in RMP these should be specified in the PI and CMI.
- With regard to eyes, a statement such as; Initial concerns about eye effects (tortuosity and dilatation of retinal arterioles in rats) did not appear to translate into a human concern in a small study. However, it was a small study so the collection of data on eye effects should be included in the RMP
- Anaemia is seen more frequently, but appeared non progressive.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Uptravi selexipag 200 µg, 400 µg, 600 µg, 800 µg, 1000 µg, 1200 µg, 1400 µg, 1600 µg film coated tablets blister pack for and oral administration, indicated for:

Uptravi, is indicated for the treatment of

- idiopathic pulmonary arterial hypertension
- heritable pulmonary arterial hypertension
- pulmonary arterial hypertension associated with connective tissue disease
- pulmonary arterial hypertension associated with congenital heart disease with repaired shunts
- pulmonary arterial hypertension associated with drugs and toxins
- in patients with WHO functional class II, III or IV symptoms.

Specific conditions of registration applying to these goods

- The selexipag EU-Risk Management Plan (EU-RMP), version 2, dated 21 July 2015 (data lock point 27 April 2014), with the Australian Specific Annex, version 2.0, dated 21 October 2015, included with submission PM-2014-04586-1-3, and the RMP agreements from the Pre-ACPM Response of 20 January 2016, included with submission PM-2014-04586-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

- The following study reports must be submitted to the TGA, in addition to those identified and/or agreed in the RMP/ASA, as soon as possible after completion, for evaluation as Category 1 submission(s):
  - Study GRIPHON-OL (AC-065A303).

Attachment 1. Product Information

The PI for Uptravi approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

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https://www.tga.gov.au