01 April 2016
EMA/272184/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Uptravi

International non-proprietary name: selexipag

Procedure No. EMEA/H/C/003774/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Table of contents

1. Background information on the procedure 6
1.1 Submission of the dossier 6
1.2 Steps taken for the assessment of the product 7

2. Scientific discussion 8
2.1 Introduction 8
2.2 Quality aspects 8
2.2.1 Introduction 8
2.2.2 Active Substance 8
2.2.3 Finished Medicinal Product 11
2.2.4 Discussion on chemical, pharmaceutical and biological aspects 13
2.2.5 Conclusions on the chemical, pharmaceutical and biological aspects 13
2.2.6 Recommendation(s) for future quality development 13
2.3 Non-clinical aspects 14
2.3.1 Introduction 14
2.3.2 Pharmacology 14
2.3.3 Pharmacokinetics 18
2.3.4 Toxicology 21
2.3.5 Ecotoxicity/environmental risk assessment 29
2.3.6 Discussion on non-clinical aspects 29
2.3.7 Conclusion on non-clinical aspects 31
2.4 Clinical aspects 31
2.4.1 Introduction 31
2.4.2 Pharmacokinetics 32
2.4.3 Pharmacodynamics 38
2.4.4 Discussion on clinical pharmacology 40
2.4.5 Conclusions on clinical pharmacology 43
2.5 Clinical efficacy 44
2.5.1 Dose response studies 44
2.5.2 Main study 46
2.5.3 Discussion on clinical efficacy 70
2.5.4 Conclusions on clinical efficacy 74
2.6 Clinical safety 75
2.6.1 Discussion on clinical safety 88
2.6.2 Conclusions on clinical safety 90
2.7 Risk Management Plan 90
2.8 Pharmacovigilance 102
2.9 Product information 102
2.9.1 User consultation 102
2.9.2 Additional monitoring 102

3. Benefit-Risk Balance 103

4. Recommendations 112

List of abbreviations

6MWD	6-minute walk distance
6MWT	6-minute walk test
ADME	Absorption, distribution, metabolism, excretion
AS	Active substance
AUC	Area under plasma concentration-time curve
AUC_{τ}	Area under plasma concentration-time curve during a dose interval
$AUC_{0-\infty}$	Area under plasma concentration-time curve from 0 to infinity
AUC_{0-t}	Area under plasma concentration-time curve from 0 to 't' h
b.i.d.	Twice a day
CAMPHOR	Cambridge Pulmonary Hypertension Outcome Review
CEC	Critical Event Committee
CES	carboxylesterase
CFU	Colony Forming Units
CHD	congenital heart disease
CI	Confidence interval
C_{max}	Maximum plasma concentration
$C_{max,ss}$	Maximum plasma concentration at steady-state
CTD	Connective tissue disease
CTEPH	Chronic thromboembolic pulmonary hypertension
C_{trough}	Plasma concentration at the end of one dose interval
$C_{trough,ss}$	Plasma concentration at the end of one dose interval at steady-state
Cu/C	concentration of free (unbound) to total plasma concentration
CV	Coefficient of variation
CVb	Inter-subject coefficient of variation
CVw	Intra-subject coefficient of variation
DMC	Data Monitoring Committee (also referred to as DSMB, Data Safety Monitoring Board)
DSMB	Data Safety Monitoring Board
eGFR	estimated glomerular filtration rate
EOS	End of study
ERA	Endothelin receptor antagonist
GC	Gas Chromatography
GCP	Good Clinical Practice
GLP	good laboratory practice
GMP	Good Manufacturing Practice
HCl	Hydrochloric acid
HIV	Human immunodeficiency virus
HPAH	Heritable pulmonary arterial hypertension (formerly familial PAH)
HPLC(/DAD)	High performance liquid chromatography (/Diode Array Detector)
ICH	International Conference on Harmonisation
IMP	Investigational medicinal product
IPAH	Idiopathic pulmonary arterial hypertension
IPC	In-process control
IP receptor	Prostacyclin receptor, PGI2 receptor
IR	Infrared
LC-MS/MS	Liquid chromatography coupled to tandem mass spectrometry
LVEDP	Left ventricular end diastolic pressure

MACE	Major adverse cardiovascular events
MAP	Mean arterial pressure
mPAP	Mean pulmonary arterial pressure
mRAP	Mean right atrial pressure
NMR	Nuclear Magnetic Resonance
NS304	selexipag
NT pro-BNP	N-terminal pro-brain natriuretic peptide
NYAH	New York Heart Association
PDE5	Phosphodiesterase type-5
Ph. Eur.	European Pharmacopoeia
OL	Open-label
PK	Pharmacokinetic(s)
PD	Pharmacodynamic(s)
RH	Relative humidity
QC	Quality control
SAD	Single-ascending dose
SD	Standard deviation
SE	standard error
SRFI	severe renal function impairment
t	Time
$t_{½}$	Terminal elimination half-life
t_{max}	Time to reach maximum plasma concentration
$t_{max,ss}$	Time to reach maximum plasma concentration at steady-state
UGT	uridine-glucuronosyltransferase
USP	United States Pharmacopoeia
UV	Ultraviolet
WHO	World Health Organization

1. Background information on the procedure

1.1 Submission of the dossier

The applicant Actelion Registration Ltd. submitted on 1 December 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Uptravi, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 April 2013.

Uptravi, was designated as an orphan medicinal product EU/3/05/316 on 26 August 2005. Uptravi was designated as an orphan medicinal product in the following indication: Treatment of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension.

Following the CHMP positive opinion at the time of the review of the orphan designation by the Committee on Orphan Medicinal Products (COMP), this product was withdrawn from the Community Register of designated orphan medicinal products on 17 February 2016 upon request of the sponsor.

The applicant applied for the following indication:

Uptravi is indicated for the long-term treatment of pulmonary arterial hypertension (PAH; WHO Group I) in adult patients with WHO functional class (FC) II – IV. 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.

Efficacy has been shown in a PAH population including idiopathic and heritable PAH, PAH associated with connective tissue disorders, and PAH associated with congenital heart disease with repaired shunts (see section 5.1).

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that selexipag was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) PIP P/0154/2013 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0154/2013 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

Applicant's request(s) for consideration

New active Substance status

The applicant requested the active substance selexipag contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Protocol Assistance

The applicant received Protocol Assistance from the CHMP on 24 February 2006 and 26 April 2007. The Protocol Assistance pertained to non-clinical and clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2 Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Martina Weise Co-Rapporteur: Concepcion Prieto Yerro

- The application was received by the EMA on 1 December 2014.
- The procedure started on 24 December 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 16 March 2015. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 25 March 2015.
- During the meeting on 23 April 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 23 July 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 3 September 2015.
- During the CHMP meeting on 24 September 2015, the CHMP agreed on a list of outstanding issues to be addressed in writing and oral explanation by the applicant.
- On the 29th of September, the Applicant requested an extension of the clock-stop of one month to address the List of Outstanding Issues, which the CHMP agreed to.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 16 November 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 4 and 14 December 2015.
- During the CHMP meeting on 17 December 2015 outstanding issues were addressed by the applicant during an oral explanation before the CHMP. The CHMP agreed on a 2nd list of outstanding issues to be addressed in writing.
- The applicant submitted the responses to the 2nd CHMP List of Outstanding Issues on 22

December 2015.

- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the 2nd List of Questions to all CHMP members on 8 and 13 January 2016.
- During the meeting on 25-28 January 2016, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Uptravi.
- The CHMP adopted a report on similarity of Uptravi with Volibris, Opsumit and Adempas on 28 January 2016.
- Following a request from the European Commission dated 24 February 2016 to further motivate its opinion dated 28 January 2016, in light of the overall data submitted by the applicant and the scientific discussion within the Committee, the CHMP adopted on 1 April 2016 a revised positive opinion for granting a Marketing Authorisation to Uptravi.

2. Scientific discussion

2.1 Introduction

2.2 Quality aspects

2.2.1 Introduction

Uptravi is presented as immediate release film-coated tablets containing 200 µg, 400 µg, 600 µg, 800 µg, 1000 mg, 1200 µg, 1400 µg and 1600 µg of selexipag as active substance.

Other ingredients in the tablet cores are mannitol (E421), maize starch, low substituted hydroxypropyl cellulose, hydroxypropyl cellulose, and magnesium stearate. Ingredients in the film coating include: hypromellose, propylene glycol, titanium dioxide, iron oxide yellow (E172), iron oxide red (E172), iron oxide black (E172) and carnauba wax, as described in section 6.1 of the SmPC.

The finished product is available in polyamide / aluminium / high-density polyethylene / polyethylene with an embedded desiccant agent / high-density polyethylene blister sealed with an aluminium foil (Alu/Alu blister with desiccant), as described in section 6.5 of the SmPC.

2.2.2 Active Substance

General information

The chemical name of the active substance selexipag is 2-{4-[(5,6-diphenylpyrazin-2-yl) (isopropyl) amino] butoxy}-N-(methylsulfonyl) acetamide, corresponding to the molecular formula $C_{26}H_{32}N_4O_4S$ and has a relative molecular mass 496.62 g/mol. It has the following structure:

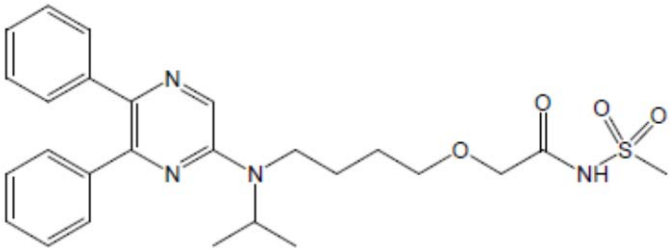


Figure 1*: Selexipag structure*.

The structure of the active substance has been confirmed by elemental analysis IR, ^{1}H- and ^{13}C-NMR spectroscopy, mass spectroscopy, UV spectroscopy and X-ray powder diffraction, all of which support the chemical structure.
It appears as a pale yellow crystalline powder, non-hygroscopic powder. Selexipag shows different solubility characteristics in aqueous solutions and is insoluble at pH 2 to 4, freely soluble at pH 8 and very soluble from pH 9 to pH 12. Its dissociation constant pKa was found 2.6 when determined by UV method. Its logP in 1-octanol/water was found to be 2.2, in 1-octanol/aqueous HCl pH 1.2 was found 3.0, and in 1-octanol/aqueous phosphate buffer, pH 6.9 was found 2.1.
Selexipag is achiral. Three crystal forms named Form I, II and III are identified and discussed. All selexipag batches manufactured so far correspond to the polymorphic form I which is sufficiently stable at room temperature. The amounts of Form II and III have been also monitored during stability studies of the clinical batches and registration batches. For all batches, no change in the amount of Form II and Form III can be observed for all conditions tested.

Selexipag is considered a new active substance from a quality perspective. The applicant compared its structure with active substances within authorised products in the EU and demonstrated that it is not a salt, ester, ether, isomer, mixtures of isomers, complex or derivative (e.g. pro-drug or metabolite) of any of them.

Manufacture, characterisation and process controls

Selexipag is synthesized by a single manufacturer in four main steps using four well-defined starting materials with acceptable specifications as shown in figure 1. Three intermediate products are described. Critical steps have been defined and the in-process controls (IPCs) used to ensure the process performs as expected are described. Satisfactory information on the molecular formulae, weights, yield ranges, chemical structures of the starting materials, intermediates, reagents and solvents, operating conditions such as temperatures, mixing times and the in-process controls was provided. Any reprocessing, following ICH Q7 (crystallisation step or other appropriate chemical or physical manipulation steps that are part of the established manufacturing process), will be preceded by careful evaluation to ensure that the quality of the intermediate or active substance is not adversely impacted. The manufacturing process was optimised to address an increase of an impurity and levels of the undesired polymorphic form III.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

The active substance is packaged into two low-density anti-static polyethylene bags and closed with resealable tie-wraps. The bags are placed into a high-density polyethylene drum closed with a lid. The polyethylene bags comply with the relevant EC regulations and Ph. Eur. requirements.

Specification

The active substance specification includes appropriate tests and limits for: appearance and colour

(visual inspection), clarity and colour of solution (Ph. Eur.), identity (IR, HPLC), residue on ignition/ sulfated ash (Ph. Eur.), heavy metals (Ph. Eur.), loss on drying (Ph. Eur.), assay (HPLC), related substances (HPLC), residual solvents (GC), particle size (laser light diffraction) and microbiological quality (Ph. Eur.).

Form II is exempted from routine control in the final active substance because it was never detected in any batch manufactured and during stability studies. Two solvents are routinely tested since these solvents are used in the final step of the manufacturing process. The proposed limit of ACT-333679 is considered acceptable form a toxicological point of view because this is the active metabolite of selexipag.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standard used for testing has been presented.

Batch analysis results from three registration batches and three validation batches all of commercial scale were provided. The submitted batch analysis data comply with the specifications and confirm that the manufacture is sufficiently robust and provide reassurance that the process yields active substance of consistent quality. However, following the manufacturing process optimisation, only one batch has been manufactured- the last validation batch. Therefore in order to demonstrate consistent quality the active substance following the process optimisation the CHMP recommended to investigate first three active substance batches (Continuous Process Verification Batches) intensively and the batch analysis certificates and a Continuous Process Verification Summary Report for these batches should be provided once the three batches have been manufactured i.e., presumably in 2019.

Stability

Stability data on three commercial scale and one supportive clinical batch of active substance in the intended commercial packaging for up to 36 months (48 months for the clinical batch) under long term conditions at 25 °C/60 % RH and for up to six months under accelerated conditions at 40 °C/75 % RH according to the ICH guidelines were provided. The parameters tested were appearance, content of polymorphic form III (not routinely performed), loss on drying, related substances, assay, microbial limit (not routinely performed) and particle size distribution (not routinely performed). The same analytical procedures as for the release analysis were used, which had been shown to be stability indicating.

No significant changes or trends were observed either at long-term conditions or accelerated conditions. The results comply with the current specifications. Similar results were obtained for the supportive clinical batch and the registration batches. However none of the stability batches have been manufactured using the optimised manufacturing process, therefore the CHMP recommended that further stability data from the first three continuous Process Verification Batches to demonstrate consistent quality of the active substance should be provided.

The stability of the active substance was also investigated one batch under stress conditions according to the Notes for Guidance Q1A (R2) and ICH Q1B. Samples were exposed to heat and moisture, light (solid state and solution), acidic, basic and oxidising conditions. Hydrolysis occurred under both acidic and basic conditions. Degradation was also noted under oxidising conditions (hydrogen peroxide). Light exposure of the substance in solution resulted in a significant increase of three impurities. In solid state though, selexipag was shown to be not sensitive to light.

Based on presented stability data, the proposed retest period of 48 months below 25 °C is acceptable.

2.2.3 Finished Medicinal Product

Description of the product and pharmaceutical development

Uptravi is an immediate release film-coated tablet. Tablets are debossed with a number indicating the strength and also have different colours to allow strength differentiation.

Potential changes of the polymorphic form were investigated and the impact on the dissolution and stability of selexipag film-coated tablets has been investigated too. Although process-induced phase transitions might potentially occur to a certain extent, they would be below the limit where they would have an impact on the properties of the finished product. In addition since no evidence for the polymorphic change was detected in tablets stored for 18 months at 30°C/75% RH and additionally stored for 1 week at 80°C and for 1 month at 60°C.

Once the compatibility of the active substance with different excipients was studied, further studies were conducted which led to the selection of binder and disintegrant and diluents, and to the optimisation of the composition. Some of them were subjected to photostability studies leading to the conclusion that the core tablets were light-sensitive.

Due to the photo-sensitivity of the core tablets it was decided to apply a coating. After testing several formulations with different combinations of these pigments the formulation to be used in clinical batches was established.

Tablets of 100, 200, 400 and 800 µg were used in clinical trials. The strength of 200 µg was used in all clinical trials, including the phase 3 pivotal study were only this strength was used to administer doses up to 1600 µg. Tablets of 1600 µg were used in the in-vivo bioequivalence study intended to demonstrate the equivalence of administering a single tablet of 1600 µg and 8 tablets of 200 µg. The bioequivalence of the intermediate strengths is supported by in-vitro dissolution tests conducted at all dose strengths in dissolution media with pH: 1.2, 4.5, 5.5 and 6.8. Since it is known that selexipag has a low solubility especially in low pH aqueous buffer values, sink conditions for all strengths are achieved at pH 6.8 only which is the pH of the dissolution medium used for routine QC testing. At pH values where sink conditions may not be achievable for all strengths, in vitro dissolution may differ between different strengths. For that reason, similarity of the dissolution profile has been demonstrated at the same dose as per the guideline on the investigation of bioequivalence. As far as the discriminatory power of the QC dissolution method this has been demonstrated with regard to manufacturing and formulation changes.
The composition of core tablets used during the clinical trials was always the same proposed for marketing authorisation and used to manufacture the 'registration batches' manufactured at commercial scale for the validation of the manufacturing process and for the formal stability studies.
The exact colour of each tablet strength has been modified during development as it became apparent that more strengths are needed in the clinic, however the coatings used contained the same qualitative and quantitative composition in non-colouring components (hypromellose and propyleneglycol) and differing only in the amounts of the same four pigments tested during development (titanium dioxide and iron oxides red,yellow and black). These changes in the quantitative composition of the coloring agents are not considered to affect either the performance characteristics of the tablets (e.g., dissolution rate) or the stability behavior.
Development batches during pharmaceutical and clinical development were manufactured in different sites but from the optimisation studies onwards all batches (e.g. registration and stability) have been manufactured at the proposed site.
The manufacturing process as such could be considered as standard considering the dosage form (immediate release tablets) and the kind of operations used for manufacture. Nevertheless the very

low load of active substance in the tablets (between 0.148 % and 1.185 % w/w of the core tablet) poses a challenge to the manufacturing process. Considering this and the type of the dosage form it was deemed reasonable that the critical quality attributes were the uniformity of the blends during the manufacture, the content uniformity of the tablets (both coated and uncoated) and the comparison of the dissolution behaviour of the tablets. In addition, degradation of the active substance (particularly when stored under stress conditions) was detected and related to some extent with some manufacturing parameters and has been addressed in the DoE optimization of the manufacturing process.

Uptravi tablets are packed in Alu/Alu blister with embedded desiccant. The selected primary packaging is common for this dosage form and the included desiccant has been shown to be protective against degradation of active substance, in particular hydrolysis, as it has been confirmed in the stability studies. The packaging material (including the desiccant) complies with the relevant EU regulations and Ph.Eur. requirements.

Manufacture of the product and process controls

The product manufacture comprises the following main steps: dry blending, wet granulation, drying, milling, lubrication, compression, coating, polishing and packaging. Due to the low drug load, the process is considered to be a non-standard process. Critical steps have been identified and a number of measures were implemented to mitigate the risk of content uniformity failure together with adequate in-process controls for this type of manufacturing process and pharmaceutical form.
The manufacturing process has been validated at commercial scale with three batches of each strength and one additional validation batch of each strength will be added before commercialisation. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The finished product release and shelf life specification include tests and limits for: appearance, colour and diameter (visual/calliper), average tablet mass (gravimetry), identification (HPLC/DAD), content uniformity of dosage units (Ph. Eur.), water content (Ph. Eur), assay and content per tablet (HPLC), impurities (HPLC), dissolution (Ph. Eur.- HPLC) and microbial quality (Ph. Eur).
The tests and acceptance criteria were set generally in accordance to ICH Q6A. For the actual limits set for degradation products the results of clinical batches and stability data of registration batches and to the thresholds established in the guideline ICH Q3(B) on impurities in new drug products were also considered. In addition, mention is made to the fact that ACT-333679 is a know metabolite of selexipag.
Considering that no evidence for the polymorphic change from Form I to Form II, or Form III was detected in tablets during stability and stress studies, it is considered justified that a test for Forms II and III not to be included in the finished product specification.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standard used for testing has been presented.

Batch analyses results of three commercial scale batches for each strength of Uptravi were provided and all batches meet the specification.

Stability of the product

Initially only five strengths (i.e. 200, 400, 800, 1200 and 1600 µg) were considered for development and stability studies were initiated with them. When it was decided to develop further intermediate strengths (600, 1000 and 1400 µg) additional stability studies were initiated and, in addition, a reduced testing approach applying bracketing /matrixing was applied. The design of stability studies is

deemed satisfactory as it is according to the guidelines ICH Q1A on stability testing and ICH Q1D on bracketing and matrixing designs. The justification for using a reduced testing scheme for intermediate strengths is supported.

Stability data on three commercial scale batches per strength (for 200, 400, 800, 1200 and 1600 µg) stored under long term conditions (25 ºC / 60% RH) and intermediate conditions 30 ºC / 75% RH for up to 24 months and for up six months under accelerated conditions (40 ºC / 75% RH) were provided. In addition stability data for three commercial scale batches per strength (for 600, 1000 and 1400 µg) stored under long term conditions (25 ºC / 60% RH) and intermediate conditions 30 ºC / 75% RH for up to 12 months and for up six months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were also provided. All the stability batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.
Samples were tested for appearance, colour, assay, degradation products, dissolution and microbial quality. The analytical procedures used were the same as for release and were shown to be stability indicating.

All results remain within shelf-life specifications for all the samples tested at all the sampling time points under all storage conditions. No significant change was observed except for degradation products. The levels of degradation products show a consistent increase under all storage conditions. The increase is more relevant for the lower dose strengths and for higher temperature and relative humidity. The applicant presented results of statistical analysis of stability data as per Appendix A of guideline ICH Q1E to support the extrapolation of these conclusion to the remaining three strengths (600, 1000 and 1400 µg). The statistical analysis is considered acceptable.

Photostability of selexipag 200, 400, 600, 800, 1000, 1200, 1400 and 1600 µg film-coated tablets has been investigated in accordance with the ICH guideline Q1B. No significant difference in appearance, color and assay could be observed between samples exposed to intense light and control samples. No increase of known impurities was observed and no new impurities above the limits were observed. Therefore Uptravi film-coated tablets can be considered as photo stable and it is not necessary to store the product protected from light.

Based on the presented data, the proposed 3 year shelf life without any special storage conditions as stated in the SmPC are acceptable.

2.2.4 Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance has been presented in a satisfactory manner. The development, manufacture and controls of the finished product have been sufficiently documented and justified. The results of tests of active substance and finished product carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5 Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6 Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress,

the CHMP recommends the following points for investigation:

1. The first three active substance batches should be investigated intensively and the batch analysis certificates and a Continuous Process Verification Summary Report for these batches should be provided once the three batches have been manufactured.

2. Further stability data from the first three continuous to demonstrate consistent quality of the active substance should be provided.

2.3 Non-clinical aspects

2.3.1 Introduction

PAH is characterized by pulmonary vasoconstriction, vascular cell proliferation and vascular hypertrophy leading to an increase in pulmonary artery pressure, right ventricular hypertrophy and right heart failure (Stearman et al. 2014). Endothelial dysfunction plays a key role in the pathogenesis of PAH and loss of expression of PGI_2-synthase represents one of the phenotypic alterations present in the pulmonary endothelial cells in severe PH (Tuder et al. 1999, Stearman et al. 2014). A decreased expression of the IP receptor has been found in the remodeled pulmonary arterial smooth muscle.

The applicant provided non clinical data from a full non clinical programme as detailed below. The non clinical studies performed with selexipag are summarized. In most original reports of the in-vitro functional assays, the Applicant has given IC_{50}/EC_{50} values for the total concentrations. In the following the values for free IC_{50}/EC_{50} values are also given, taking the extent of protein binding in the incubation media into account.

2.3.2 Pharmacology

Selexipag is an orally active non-prostanoid prostacyclin (PGI_2) receptor agonist with a long-half-life, selectivity for the IP receptor minimizing off-target effects especially in the gastrointestinum and a lack of IP receptor desensitization processes which avoids the development of tachyphylaxis. The active metabolite ACT-333679 is at least 16-fold more potent than selexipag in cellular systems and is present at 3- to 4-fold higher plasma concentrations than the parent drug at steady-state in humans.

The receptors sensitive to prostaglandins D_2, E_2, F_{2a}, I_2 and thromboxane A_2 are termed the DP, EP, FP, IP and TP receptors, respectively (Whittle et al. 2012, Yokohama et al. 2013).

Prostanoid receptors are classified into three groups according to molecular evolution, associated primary G proteins and second messengers: cluster 1 consists of the relaxant EP2, EP4, IP and DP1, which are coupled with G_{sa} proteins and therefore activate AC to increase cAMP; cluster 2 consists of the contractile EP_1, FP and TP, which couple with G_{qa} and increase intracellular calcium concentrations; cluster 3 consists of the inhibitory receptor EP_3, which is coupled with G_{ia} and which can couple to both elevation of intracellular calcium and a decrease in cAMP (review in Yokohama et al. 2013). Prostacyclin (prostaglandin I_2, PGI_2), synthesized from arachidonic acid by the sequential action of cyclooxygenase and PGI_2 synthase in endothelial cells, is a potent vasodilator, antithrombotic and antiplatelet agent. PGI_2 plays a role in the development of pulmonary hypertension: in human pulmonary hypertension, IP expression is decreased; overexpression of PGI_2 synthase reduces elevated pulmonary blood pressure, and IP knockout mice developed more severe pulmonary hypertension and vascular remodelling after chronic hypoxic exposure (review in Smyth and Fitzgerald 2002).

The human prostanoid IP receptor has been cloned and demonstrated to be a member of the G-protein-coupled receptor gene superfamily (Boie et al. 1994). IP receptors are distributed widely throughout the body with high expression in the lung, heart and kidney, and activation of IP receptors is coupled to the formation of the second messenger cAMP (review in Smyth 2002). Prostanoids are potent vasodilators and possess antithrombotic and antiproliferative properties; whereas the pharmacological properties of prostanoids acting via the IP receptor are similar, they differ markedly in pharmacokinetics (e.g. half-lives are 2 min for prostacyclin, but 30 - 80 min for treprostinil; review in Olschewski et al. 2004). Several PGI_2 analogues have been approved for the treatment of PAH, including epoprostenol (intravenous), iloprost (inhaled), treprostinil (intravenous, subcutaneous and inhaled (oral in US only)) and beraprost (oral in Japan and South Korea only). These PGI_2 analogues are non-selective IP receptor agonists, since they also activate other prostanoid receptors such as the EP_3 and EP_4 receptors. The EP_3 receptor is responsible for gastric contraction and vomiting induced by PGI_2 analogues (Morrison et al. 2010, Kan et al. 2002).

Primary pharmacodynamic studies

In-vitro:

Selexipag and its main metabolite ACT-333679 have high affinity to prostacyclin (PGI_2) receptors expressed in CHO cells with K_i values of 263 and 19.8 nM, respectively, and both substances show selectivity for this receptor, since binding to 7 other prostanoid receptors (EP_{1-4}, DP, FP and TP) occurred at much higher (micromolar) concentrations (Kuwano et al. 2007). In contrast, PGI_2 analogues (e.g. beraprost) have lower selectivity for PGI_2 versus other prostanoid receptors.

Selexipag and its main metabolite ACT-333679 increased intracellular cAMP concentrations in CHO cells expressing the human prostacyclin (PGI_2) receptor with EC_{50} values of 177 and 11.5 nM, respectively, and, therefore, metabolite ACT-333679 was about 16-fold more potent compared to selexipag in this assay.

In HEK 293 cells expressing prostanoid receptors and using stimulation of adenylate cyclase as the parameter, ACT-333679 and selexipag demonstrated pronounced species differences at the IP receptor, whereas iloprost did not. The EC_{50} values for free substances at the human, rat and dog IP receptors were 4, 170 and 1100 nM for selexipag, respectively, and 0.17, 3.1 and 14 nM for metabolite ACT-333679, respectively, demonstrating sensitivity in the order human > rat > dog. Whereas selexipag was inactive at EP_2 and EP_4 receptors, ACT-333679 was weakly active at the EP_2 receptor, but similar active at the dog EP_4 receptor (EC_{50} value of 18 nM) compared to the IP receptor.

In human pulmonary arterial smooth muscle cells, ACT-333679 increased the intracellular cAMP concentration with an EC_{50} value of 265 nM (re-calculated free EC_{50} value of 7.4 nM) and was a partial agonist (31% of the maximum response).

Agonist-activated G protein-coupled receptors (GPCR) couple to G proteins to induce a cellular response, and are subsequently phosphorylated by the G protein-coupled receptor kinases (GRKs); the GRK-phosphorylated receptor then acts as a substrate for the binding of arrestins, which uncouple the receptor and G protein, desensitizing the agonist-induced response and leading to the development of tachyphylaxis (review in Kelly et al. 2008). In CHO cells expressing the IP receptor, ACT-333679 and selexipag had lower efficacy in recruiting β-arrestin and in inducing internalization of the IP receptors compared to prostacyclin analogues (iloprost, treprostinil and beraprost). The potencies of the compounds in the cAMP assays were considerably shifted leftward versus the β-arrestin assay (free EC_{50} values for selexipag and ACT-333679 were: 0.58 nM and 0.031 nM in the cAMP assay, 13 nM and 1.4 nM in the ß-arrestin assay). It is hypothesized by the Applicant that due to the partial agonism in the desensitization pathway, ACT-333679 and selexipag might induce reduced tachyphylaxis in vivo.

IP receptor activation induces vascular smooth muscle relaxation through PKA-mediated myosin light-chain kinase (MLCK) phosphorylation (Merritt et al. 1991), and in cultured pulmonary arterial smooth muscle cells selexipag and metabolite ACT-333679 induced vascular smooth muscle relaxation with EC_{50} values of 157 and 4.3 nM, respectively (the re-calculated free EC_{50} values were 2.5 nM and 0.12 nM, respectively), via a stimulation of PKA-mediated MLCK phosphorylation.

PGI_2 analogues inhibit the proliferation of human pulmonary arteries via a cAMP-dependent pathway (Clapp et al. 2002), and cell cycle progression from G1-to S-phase is inhibited by block of CRE- and pocket protein-dependent cyclin A gene expression (Kothapalli et al. 2003). ACT-333679 inhibited the platelet-derived growth factor (PDGF)-mediated ^{3H}thymidine uptake in cultured human pulmonary artery smooth muscle cells (hPASMC) with an IC_{50} value of 400 nM and the platelet-derived growth factor-BB (PDGF-BB)-induced proliferation of human pulmonary arterial smooth muscle cells (PASMC) with an IC_{50} value of 2.9 nM (the re-calculated free IC_{50} value was 0.081 nM).

TGF-ß1 is a cytokine involved via a production of reactive oxygen species (ROS) in the process of pulmonary fibrogenesis (review in Todd 2012), and IP receptor activation via the PKA-dependent inhibition of Ras/MEK/ERK signaling inhibits synthesis of extracellular matrix proteins induced by pro-fibrotic mediators such as PDGF-BB and TGF-ß1 (Stratton et al. 2001 and 2002). ACT-333679 (0.1 - 10 µM) reduced TGF-ß1-stimulated up-regulation of collagen production on normal human lung fibroblast cells (NHLF) and had anti-fibrotic activity. Furthermore, ACT-333679 inhibited platelet-derived growth factor-BB (PDGF-BB)-induced and transforming growth factor-ß1 (TGF-ß1)-induced extracellular ^{3H}proline incorporation, a measure of extracellular matrix synthesis, in primary normal human lung fibroblasts (NHLF) with an IC_{50} value of 9.7 nM (the re-calculated free IC_{50} value was 0.27 nM).

The IC_{50}/EC_{50} values for free selexipag and ACT-333679 are lower compared to the K_i values obtained in binding experiments, indicating the presence of spare IP receptors. This hypothesis is supported by the observation that in humans, values for therapeutically effective free maximum plasma concentrations are 0.12 nM for selexipag and 0.28 nM for ACT-333679 following administration of the 1600 µg b.i.d. dose. These concentrations are in the range of the IC_{50}/EC_{50} values and, therefore, sufficient to stimulate the IP receptors. The existence of differences in spare IP receptors together with differences in the degrees of signal amplification of the IP receptor signaling cascade can explain the different potencies of selexipag/ACT-333679 in functional assays performed in different in-vitro test systems.

Mice were used in the carcinogenicity studies and rabbits in the reproductive and developmental toxicity studies performed with selexipag. There are marked species differences in the affinity/potency of selexipag and ACT-333679 at the IP receptor. In order to give an explanation for the findings observed in mouse carcinogenicity studies and in the rabbit reproductive and developmental toxicity studies, the Applicant has provided results from a new study in which in vitro potencies (EC_{50} values), as measured by cAMP accumulation, were determined in recombinant cells expressing similar levels of the mouse, rabbit, or human IP receptor. EC_{50} values for selexipag and ACT-333679 were: 22 uM and 960 nM, respectively, at the rabbit IP receptor, 25 uM and 730 nM, respectively, at the mouse IP receptor (based on total concentrations). Rabbit and mouse IP-receptors have 61and 69-fold lower potencies for selexipag and 74- and 56-fold lower potencies for ACT-333679, respectively, compared to humans (based on total concentrations).

In-vivo:

Selexipag decreased the mean arterial blood pressure and increased the heart rate (in normotensive rats at i.d. doses of 10 mg/kg for MAP and $\geq$ 3 mg/kg for HR; in conscious spontaneous hypertensive rats (SHRs) at oral doses of 1 - 10 mg/kg) and increased femoral skin blood flow in anaesthetized rats

(at i.d. doses of 1 - 10 mg/kg). No tachyphylaxis was observed after 4 weeks of administration in anaesthetized rats or after 10 days of administration in SHR.

Two models of PH in rats were used: (1) the rat monocrotaline (MCT) model of PH (Chesney 1973) is characterized by pulmonary hypertension (elevated right ventricular systolic pressure, cor pulmonale), medial thickening and endothelial dysfunction in the pulmonary artery and right ventricular hypertrophy (RVH) (Meyrick et al. 1980, review in Gomez-Arroyo 2012); MCT is activated to a reactive metabolite in the liver which is transported to the lung, where it initiates endothelial injury (review in Wilson et al. 1992); (2) the Sugen-hypoxia model of PH was developed from the observation that an inhibition of the VEGF receptor 2 with Sugen 5416 (a VEGF receptor 2 blocker) in combination with chronic hypoxia causes cell death-dependent pulmonary endothelial cell proliferation and severe pulmonary hypertension, since in this model chronic reduction of the alveolar oxygen pressure elicits pulmonary arterial vasoconstriction and vascular remodelling of the distal branches of pulmonary arteries leading to PH (Taraseviciene-Stewart 2011). In MCT-PH Wistar rats, selexipag had the following effects: 5 days of repeated selexipag administration (10 mg/kg, p.o., b.i.d.) decreased pulmonary arterial pressure (PAP) without affecting the HR, and the efficacy of selexipag was maintained over the 5-day treatment period; selexipag at 1 mg/kg twice daily for 19 days suppressed the increase of RVSP and RVH in MCT-induced PH rats; MCT-induced PH accompanied by hypertrophy of the pulmonary artery was suppressed by selexipag orally administered at 1 mg/kg twice daily for 19 days; oral administration of selexipag at 1 mg/kg twice daily for 19 days ameliorated the attenuated acetylcholine-induced relaxation of PGF2α-pre-contracted pulmonary arteries; right ventricular hypertrophy was suppressed by the oral administration of selexipag at doses of 1 and 3 mg/kg twice daily for 19 days; the survival of MCT-treated rats was prolonged by selexipag orally administered at a dose of 1 mg/kg twice daily for 45 days.

In conscious Sugen-hypoxia PH rats, selexipag at oral doses of 3, 10 and 30 mg/kg dose-dependently decreased mean pulmonary arterial pressure (MPAP), MAP and core body temperature, and increased HR and tail temperature. The effects of selexipag on pulmonary (MPAP decrease) and peripheral haemodynamics (peripheral vasodilation leading to tail temperature increase) correlated, which indicates that selexipag shows no selectivity for pulmonary vs. peripheral arteries.

Secondary pharmacodynamic studies

Neither selexipag nor ACT-333679 tested at concentrations of up to 10 µM had marked effects in 69 enzyme and radioligand binding assays.

Selexipag and ACT-333679 induced a concentration-dependent increase of intra-platelet cAMP in human platelets with EC_{50} values of 40 µM and 550 nM, respectively (the re-calculated free EC_{50} values were 120 nM and 2.2 nM, respectively). The maximal elevation of cAMP induced by both selexipag and ACT-333679 was lower compared to other IP receptor agonists, indicating that ACT-333679 is a partial agonist of the IP receptor. 10 µM ADP-induced platelet aggregation was inhibited with IC_{50} values of 4655 nM for selexipag and 121 nM for ACT-333679; at a lower ADP concentration of 3 µM, the potency of ACT-333679 was higher (IC_{50} value of 74 nM). Selexipag inhibited platelet aggregation induced by ADP in platelet-rich plasma from humans and monkeys with IC_{50} values of 5.5 and 3.4 µM, respectively (the re-calculated free IC_{50} values were 17 nM and 0.84 nM, respectively), but showed a very weak inhibition in dogs (IC_{50} value >100 µM), and ACT-333679 inhibited platelet aggregation in platelet-rich plasma from humans, monkeys, dogs and rats with IC_{50} values of 0.21, 0.21, 25 and 10 µM, respectively. The effects of a single i.d. dose of 10 mg/kg selexipag on thrombus formation in rat femoral artery induced by 10% (w/w) ferric chloride ($FeCl_3$) in vivo consisted of a prolongation of the average time to occlusion (TTO).

Safety pharmacology programme

In rats, selexipag had no effects on the central nervous system at doses of up to 30 mg/kg. At a dose of 10 mg/kg, selexipag did not affect respiratory function, whereas at higher doses of selexipag (≥ 30 mg/kg) transiently increased respiration rate, tidal volume and minute volume were observed.

No marked effects of selexipag and ACT-333679 at micromolar concentrations were observed on hERG channels expressed in CHO cells. Force and rate of contraction were not markedly affected by selexipag and ACT-333679 in isolated right atria from guinea pigs. In isolated guinea pig papillary muscles, selexipag shortened the action potential duration in a concentration-dependent manner at concentrations of 10 - 100 µM. After administration of single oral doses of selexipag to conscious male Beagle dogs, MAP decreased at doses ≥ 1 mg/kg and HR increased at doses of ≥ 3 mg/kg, and at doses of ≥ 1 mg/kg the QT interval shortened, which seemed to be caused by HR changes since QTcF intervals were not affected.

In male Sprague-Dawley rats, single oral administration of selexipag did not have marked effects on bleeding time, PT or APTT at doses of up to 100 mg/kg.

In the isolated rat uterus, ACT-333679 at concentrations of 30 and 100 µM decreased the frequency of spontaneous contractions.

In male Sprague-Dawley rats, oral administration of selexipag decreased urinary Cl^- secretion and Na^+/K^+ ratio dose-dependently at doses of 10 - 100 mg/kg, and urinary Na^+ excretion and urine volume slightly decreased at 30 and 100 mg/kg. These effects are known effects of IP receptor agonists.

Pharmacodynamic drug interactions

In fasted Sprague-Dawley rats, oral administration of single doses of 10, 30 and 100 mg/kg selexipag inhibited intestinal transport of charcoal, and i.d. doses of 10 - 100 mg/kg decreased the total acid output of gastric juice.

Contractile EP_3 receptors are implicated in emesis and diarrhoea (Kan et al. 2002) and are located on the rat gastric fundus (Morrison et al. 2010). Neither selexipag nor ACT-333679 at concentrations of 1 mM contracted rat fundus, whereas the nonselective PGI2 analogues iloprost, beraprost and treprostinil contracted rat fundal strips, which was antagonized by an EP3 receptor antagonist.

Selexipag and ACT-333679 did not have synergistic effects with contractile α1ARs in rat femoral arteries, whereas activation of EP3 receptors by non-selective analogues of PGI2 is enhanced by α1AR stimulation.

Both PGE_2 and PGI_2 reduce the threshold of nociceptor sensory neurons to stimulation (review in Smyth et al. 2009). IP prostacyclin receptor agonists have the potential to induce neurogenic pain (Bley et al. 1998, review in Rahman et al. 2011).

2.3.3 Pharmacokinetics

The pharmacokinetic profile of selexipag was mainly characterized in the rat and dog, the species used in the repeated dose toxicity studies.

Absorption

Selexipag was rapidly absorbed after oral administration in rats, dogs and monkeys with t_{max} values of 1 – 4 h. Selexipag exposure was lower than that to ACT-333679 in all species, and this difference was

2-fold in monkeys, 6-fold in rats and 13-fold in dogs. After administration of selexipag, the oral bioavailability of ACT-333679 was 57% in rats and 29% in monkeys. In rats, the pharmacokinetics of selexipag after oral administration was linear to doses of 0.3 - 3 mg/kg. In rats, food intake did not affect the extent of absorption of selexipag, and no sex differences in the pharmacokinetics were observed. ACT-333679 was rapidly absorbed in the rat with an oral bioavailability of 57%.

Distribution

The selexipag-related radioactivity distributed rapidly through the whole body and the highest concentrations were found in the liver followed by the gastro-intestinal tract, small intestine, stomach, kidney, lung, i.e. in organs involved in the absorption and elimination of the substance. Selexipag hardly passes the blood-brain-barrier. Tissue concentrations of radioactivity decreased in parallel with the decrease in the plasma concentrations. In pigmented rats, limited binding of ^{14}C-selexipag-related radioactivity to melanin was observed.

Placental transfer of selexipag/metabolites was shown with maximum fetal radioactivity concentrations of about 15% of maternal plasma concentrations representing altogether 0.01% of the dose.

Binding of selexipag and ACT-333679 in rat, dog, monkey and man sera was in a range of 97–99%. Both substances bind to human serum albumin and α1-acid glycoprotein. Equilibrium dialysis studies in mouse, rat, rabbit, dog, monkey, and man plasma gave free fractions of 0.3-0.6% for selexipag and 0.4-0.8% for ACT-333679. The volume of distribution at steady-state was 1.8-2.5 l/kg, i.e. in excess of total body water in rats and dogs, indicating good tissue penetration.

Metabolism

Selexipag undergoes five types of primary biotransformation reactions, and the main pathway is hydrolysis of the sulfonamide and formation of the pharmacologically active acid ACT-333679 via a carboxylesterase-mediated reaction. Formation of ACT-333679 is the major metabolic pathway of selexipag in all species, although some interspecies differences in terms of turnover as wells as of metabolic profiles were observed. Hepatic microsomes from all tested species including humans are able to form ACT-333679, whereas microsomes of the small intestines from all species including humans are not able to hydrolyse selexipag. Selexipag was hydrolysed to ACT-333679 in plasma of rat and mouse, whereas little or no degradation occurred in plasma of dog, rabbit, cynomolgus monkey and man. Metabolism of ACT-333679 was lower compared to selexipag in all tested species including human. Therefore, whereas ACT-333679 formation in rabbit, dog, cynomolgus monkey and human is mostly catalysed by hepatic microsomal enzymes, in the mouse and rat - in addition to hepatic microsomal enzymes - carboxylesterases present in plasma are also responsible for selexipag hydrolysis and formation of ACT-333679. CYP2C8 is mainly involved in the formation of MRE-6300 (a hydroxylated metabolite of ACT-333679), and CYP3A4 is also involved. Human UGT1A3 is involved in the glucuronidation of ACT-333679 to the acyl glucuronide P11 followed by UGT2B7.

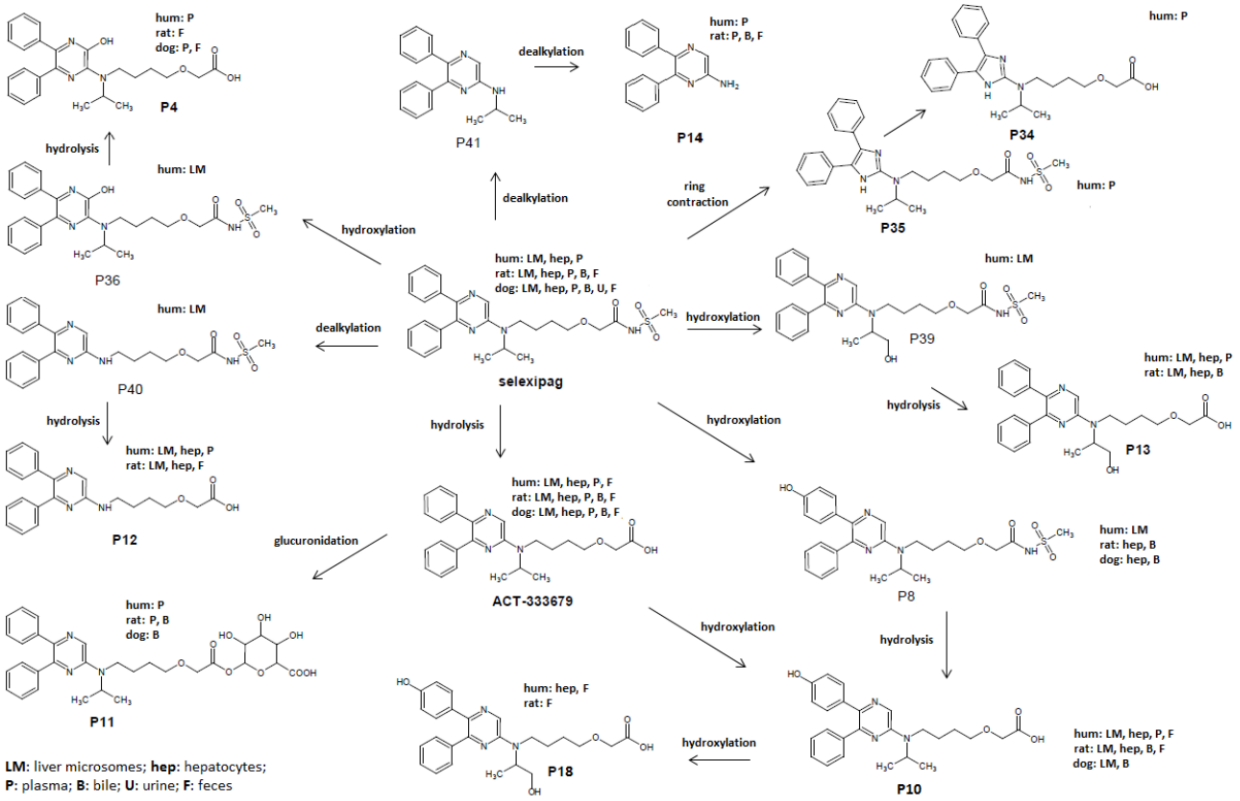


Figure 2: The proposed metabolic pathways of selexipag in rat, dog, and human.

Excretion

In rats, biliary excretion was the major elimination pathway of selexipag after either the oral or intravenous route of administration accounting for about 90-95% of the absorbed dose, and renal elimination of hydrophilic metabolites was much less important (0.9 - 4.7% of the dose). In dogs, biliary excretion was also the main excretion pathway (80 - 89% of total radioactivity), whereas renal excretion was much less important (< 2% of total radioactivity).

Selexipag and/or its metabolites transferred into milk. The exposure to radioactivity was 2.5-fold higher in milk than in plasma.

Pharmacokinetic drug interactions

Both selexipag and ACT-333679 possess good membrane permeabilities, and this behaviour seems to be primarily responsible for the tissue distribution of these substances. In rats, selexipag administered orally for 7 days at doses of 1 and 10 mg/kg/die had no effect on drug-metabolizing liver enzymes. Selexipag and ACT-333679 inhibited CYP2C8, CYP2C9, CYP2D6 and CYP3A4 activities at supra-therapeutic micromolar concentrations, and both substances did not affect the human multidrug resistance protein MDR-1 (ABCB1, P-gp). Selexipag is a weak substrate of human P-gp indicating that P-gp is involved in the transport of selexipag through the cell monolayers, whereas ACT-333679 is not a substrate of P-gp. Selexipag is a weak substrate for both OATP1B1 and OATP1B3 transporters, and ACT-333679 is also a weak substrate for OATP1B3. Selexipag and ACT-333679 inhibited the activities of both OATP1B1 and OATP1B3 transporters only at supra-therapeutic micromolar concentrations. Selexipag is not a BCRP substrate, whereas ACT-333679 is a BCRP substrate. At micromolar concentrations, both selexipag and ACT-333679 inhibited OAT1-, BCRP-, BSEP-, OAT3- and MATE1-transporters, and ACT-333679 also inhibited the MRP2-transporter. In human hepatocytes, both selexipag and ACT-333679 induced CYP isoenzyme mRNAs with the following free EC_{50} values: 20

nM/90 nM for CYP3A4, 6 nM/29 nM for CYP2C9. These free EC_{50} values are above therapeutically effective free plasma concentrations (0.12 nM selexipag, 0.28 nM ACT-333679). However, assuming a luminal selexipag concentration of 1.3 µM and a free selexipag concentration in enterocytes of 8 nM, clinically relevant induction of CYP3A4 and CYP2C9 in the gut cannot be excluded. Therefore, the administration of selexipag at the highest proposed dose in PAH patients (1600 µg b.i.d.) could be an inducer of both CYP3A4 and CYP2C9 in the intestine. Although in a study in healthy subjects, selexipag (400 µg b.i.d.) did not alter the exposure to S-warfarin (CYP2C9 substrate) or R-warfarin (CYP3A4 substrate) after a single dose of 20 mg warfarin, interactions with CYP2C9 and CYP3A4 in humans treated with the highest proposed dose have not been studied and thus potential interactions at clinically relevant concentrations cannot be ruled out.

In conclusion, based on the re-calculated free concentrations of selexipag and ACT-333679 in the in-vitro pharmacokinetic interaction studies, selexipag and its metabolite do not seem to have any relevant inhibitory potential on CYP P450 enzymes, on transport proteins or on BCRP in the gut. However, an induction of CYP3A4 and CYP2C9 by selexipag in the gut cannot be excluded.

2.3.4 Toxicology

Single dose toxicity

Single dose toxicity of selexipag was determined in Slc:ddY mice, Slc:SD rats and Beagle dogs. The maximum non-lethal i.v. dose of selexipag was 40 mg/kg in mice and rats. After oral dosing the maximum non-lethal dose of selexipag was 250 mg/kg in rats and 200 mg/kg in male dogs.

Repeat-dose toxicity

Repeat-dose toxicity of selexipag was determined in B6C3F1/Crlj mice, SD rats and Beagle dogs.

In mice, liver weight increased (at doses of 300 mg/kg/day in a 13 week study), correlating histologically with hypertrophy of centrilobular hepatocytes, and these alterations seemed to be related to the induction of drug-metabolizing enzymes.

In rats, selexipag-induced mortality occurred in repeated dose toxicity studies in rats after oral treatment at doses of ≥ 500 mg/kg/day and was related to marked vasodilation induced by selexipag. The primary clinical symptoms after oral administration of selexipag were flush, red discoloration of pinna/limbs/abdomen and flaccidity linked to IP receptor-dependent vasodilation and blood pressure decrease (at doses of ≥ 6 mg/kg/day). Selexipag increased urine volume accompanied by a decreased excretion of Na and K (at doses of ≥ 25 mg/kg/day), which might be explained by the vasodilating effects of selexipag which induced an increase in renal blood flow and an enhancement of urine production. Increased adrenal weight (at doses of ≥ 25 mg/kg/day) associated with cortical hypertrophy and hypertrophy of the zona glomerulosa seems to be a stress-related response. At high oral doses (≥ 100 mg/kg/day), the administration of selexipag induced increased liver weight associated with hypertrophy of centrilobular hepatocytes and proliferation of the smooth endoplasmatic reticulum of hepatocytes as demonstrated in electron microscopic examinations; these findings might be explained by an induction of hepatic drug-metabolizing enzymes by selexipag. These effects might also be responsible for the increased thyroid weights accompanied by hyperplasia of the follicular cells in the thyroid (≥ 25 mg/kg/day). Platelet count dose-dependently decreased at doses of ≥ 6 mg/kg/day in males and at doses of ≥ 20 mg/kg/day in females. The Applicant was not able to provide a mechanistic explanation for this effect observed in rats. Due to the minor effect, the reversibility of the effect and the absence of effects on coagulation times or bleeding, the rat finding of decreased platelet counts after administration of selexipag seems to have no human relevance. Furthermore, decreased platelet count has also been observed after administration of other IP receptor agonists in

rat repeated-dose toxicity studies (e.g. for treprostinil). Haemorrhage in the alveoli of lungs at doses of ≥ 20 mg/kg/day selexipag might be explained by the platelet-inhibitory effects of selexipag.

Dogs were the more sensitive species compared to rats in repeated dose toxicity studies performed with selexipag. In juvenile dogs, the major clinical findings were related to selexipag-induced disturbance of intestinal motility leading to the development of intussusception with changes in stool, prolapse of anus and dark red discoloration in the jejunum and intussusception (jejunum), which manifested histologically as haemorrhagic infarction (necrosis, haemorrhage and congestion of the intestinal mucosa; at doses of ≥ 2 mg/kg/day). Intussusception was the cause of death (3 animals at a dose of 20 mg/kg/day in the 14 day study, 2 animals at a dose of 4 mg/kg/day in the 39 week study).

The mechanism for the development of gastrointestinal alterations induced in dogs by selexipag has been discussed by the Applicant. In contrast to other prostaglandins, prostacyclin (PGI_2) prevents diarrhoea caused by other prostaglandins, PGI_2 inhibits gastric acid secretion and is cytoprotective for the stomach and the small intestine, and the antidiarrheal activity of PGI_2 may be due to its antipropulsive effects (Ruwart and Rush 1984). Administration of the prostacyclin analogue taprostene induced hypermotility of the gastrointestinal tract resulting in intestinal invagination (intussusception) in dogs (Wöhrmann et al. 1994). Intussusception is defined as prolapse of a proximal bowel segment into a distal segment and may result in luminal obstruction, mucosal congestion or infarction. Intussusception is more common in young dogs (< 6-8 month old; Merck Veterinary Manual), which is the age of affected dogs in repeated dose toxicity studies performed with selexipag. Intussusception is the most important cause of gastrointestinal obstruction in dogs (Mutasa et al. 1994). In humans, intussusception is rare in adults and mainly observed in association with cancer, but it is relatively common in children (Azar and Berger 1997, Duijff et al. 2007). The Applicant suggests that intussusception is a result of exaggerated pharmacodynamics of selexipag in dogs. The risk for humans to develop intussusception is considered low by the Applicant in view of the particular sensitivity of dogs to IP receptor agonist-induced effects on intestinal motility, the increased sensitivity of young dogs to develop intussusception and the safety margins for a human dose of 1600 µg b.i.d. According to the Applicant, no case of intestinal invagination was reported during the clinical studies with selexipag.

Intussusception did not occur in mouse or rat toxicity studies. However, in our view, safety margins at the NOEL of 1 mg/kg/day regarding the gastrointestinal findings in dogs as obtained in the 39 week study, corrected for species difference in receptor potency, are very low with values of 0.1 for selexipag and 1 - 1.6 for ACT-333679, respectively, in relation to human exposure at a dose of 1600 µg b.i.d.. Therefore, the possible induction of gastrointestinal disturbances denoting intestinal intususception (manifested as ileus or obstruction) induced by selexipag has been included as an important potential risk in the Risk Management Plan, and special caution is needed in the treatment of children, since children (and also young dogs) are more susceptible than adults to the induction of intussusception (Azar and Berger 1997, Duijff et al. 2007).

The second most marked effect aside from the gastrointestinal effects observed in repeated dose toxicity studies in dogs performed with selexipag were bone and bone marrow alterations. These consisted of increased ossification of the trabeculae and periosteum and bands of fibroblasts with collagen fibres ("fibrosis") in the femur and sternum (at doses of ≥ 6 mg/kg/day in the 14 day study, ≥ 3 mg/kg/day in the 4 weeks study and at all doses (≥ 1 mg/kg/day) in the 39 weeks study). Furthermore, the amount of hematopoietic tissue in the bone marrow of the femur and sternum was affected: it decreased at doses of ≥ 6 mg/kg/day in the 14 day study and ≥ 3 mg/kg/day in the 4 week study, but increased at all doses (≥ 1 mg/kg/day) in the 39 week study. Extramedullary haematopoiesis in the spleen was observed at a dose of 6 mg/kg/day in the 4 week study. In the 39 week repeated dose toxicity study in dogs, a NOAEL could not be established for bone/bone marrow findings. Increased bone mass was still observed after 4 weeks of recovery in the 4-week dog toxicity

study. The increased ossification was not associated with clinical signs indicative of pain or changes in blood chemistry. Increased ossification was associated with changes in the bone marrow, including bands of fibroblasts with collagen fibres ("fibrosis") and altered appearance of the hematopoietic tissue in femur or sternum (either decreased or increased haematopoiesis).

Increased ossification of femur and sternum was also reported in the juvenile dog study. In the juvenile study, no effects were noted on limb function or on growth measurements like tibia length and standing shoulder height.

The observation that ACT-333679 was similarly active at the dog EP_4 receptor (EC_{50} value of 18 nM) compared to the dog IP receptor (EC_{50} value of 14 nM), but was inactive at the human EP_4 receptor, plays a central role in the assessment of human relevance of the bone findings observed in dogs. Therefore, in repeated dose toxicity studies performed with selexipag in dogs both IP and EP_4 receptors are stimulated (the first by both selexipag and ACT-333679, the latter by ACT-333679).

PGE_2 can activate formation of the periosteal and endocortical surface of long bones in both the rat and dog, which involves the recruitment and proliferation of osteo-progenitor cells present in the periosteum and mesenchymal cells of the marrow cavity; furthermore, prostaglandins activate remodelling activity on the surface of trabeculae and in the cortex of long bones indicating that prostaglandins are involved with increases in both bone formation (stimulation of osteoblasts) and of bone resorption (stimulation of osteoclastic bone resorption; review in Norrdin et al. 1990). PGE_2 increases bone mass in animals and humans; stimulation of the EP_2 receptor stimulates formation, stimulation of the EP_4 receptor stimulates resorption (and possibly formation), and stimulation of the FP receptor produces new trabeculae (review in Hartke and Lundy 2001). The EP_4 prostanoid receptor is one of 4 receptor subtypes for prostaglandin E_2 and belongs to the family of G protein–coupled receptors, is coupled to G_{sa} and stimulates AC activity and cAMP production, but is also associated with G_i, phosphatidylinositol 3-kinase (PI3K), ß-arrestin and ß-catenin (review in Yokohama et al. 2013). The following observations indicate that the EP_4 receptor has a major role in bone biology: the administration of selective EP_4 receptor agonists has been demonstrated to reverse osteoporotic changes, enhances the bone-implant interface strength and has a synergistic effect when used with other bone cell targeting pharmacological agents such as BMP-2 and bisphosphonates (review in Pagkalos et al. 2012); PGE_2 promotes both bone resorption and bone formation, and these effects are mediated by EP_4 signalling (review in Yokohama et al. 2013); ONO-4819, which is a prostaglandin (PG) E_2 EP_4 receptor selective agonist (EP_{4A}), accelerates BMP-induced osteoblastic differentiation of the pluripotent stromal cell line ST2 by stimulating the commitment for osteoblastic lineage (Nakagawa et al. 2007); using a selective EP_4 receptor antagonist, it was demonstrated that PGE_2 stimulates osteoblastic commitment of rat bone marrow stromal cells (BMSC) via activation of the EP_4 receptor (Shamir et al. 2004); results from studies in EP_4 receptor knockout mice indicated that the EP_4 receptor resulted in an imbalance in bone resorption over formation leading to a negative bone balance and that the absence of the EP_4 receptor decreases bone mass and impairs fracture healing in aged male mice, leading to the conclusion that the EP_4 receptor is a positive regulator in the maintenance of bone mass and fracture healing (Li et al. 2005); osteoblasts and bone marrow adipocytes are derived from a common bone marrow mesenchymal progenitor, and a PGE_2 receptor subtype 4 agonist stimulated bone formation at skeletal sites with hematopoietic and fatty marrow and simultaneously decreased fatty marrow area and the number of adipocytes in the bone marrow (Aguierre et al. 2007). "Fibrosis", characterized by bands of fibroblasts with collagen fibres, observed at high doses of selexipag administered in the repeated dose toxicity studies in dogs resembles callus tissue during the process of fracture healing, and local infusion of PGE_2 has been demonstrated to cause stimulation of callus formation in rabbits (Keller et al. 1993). Therefore, "fibrosis" was induced by high doses of selexipag via activation of the EP_4 receptor and seems to be similar to bone fracture healing.

The observation that in the repeated dose toxicity studies performed in dogs with selexipag the amount of haematopoietic tissue in the bone marrow of the femur and sternum was affected (either increased or decreased) is in line with the finding that PGE_2 has both stimulatory and inhibitory effects on the differentiation of haematopoietic progenitors.

The following observations indicate that PGE_2 has inhibitory effects on the differentiation of haematopoietic progenitors: PGE_1 and PGE_2 inhibit the proliferation of committed myeloid stem cells (Kurland et al. 1978); prostaglandins inhibit the in-vitro growth of erythroid progenitor cells obtained from patients with chronic renal failure (Taniguchi et al. 1989); prostaglandin inhibitors may have a role in combination with hematopoietic growth factors in accelerating hematopoietic recovery following cytoreductive chemotherapy (O´Reilly and Gamelli 1990); the in vivo administration of IL-1 results in neutrophilia and generation of myelopoietic suppressive effects mediated by cyclooxygenase pathway products; blockade of PG synthesis abrogates the myelopoietic suppressive effects associated with IL-1 administration and optimizes its myelopoietic stimulatory capacity (Pelus 1989); intravenous injection of PGE_2 resulted in the suppression of nucleated bone marrow and splenic cellularity, total resident nucleated peritoneal cells and the number of granulocyte-macrophage progenitor cells (Gentile et al. 1983).

However, the following observations indicate that PGE_2 has also stimulatory effects on the differentiation of hematopoietic progenitors: using a murine bone marrow stem cell assay, it was demonstrated that lipoxygenase products stimulate myeloid colony formation and lymphoid stem cell proliferation (Vore et al. 1989); in the bone marrow, PGE_2 expands hematopoietic stem cells and affects the differentiation of haematopoietic progenitors, and PGE_2 treatment expands hematopoietic stem cells with no negative impact on haematopoietic progenitors (Frisch et al. 2009); PGE_2 regulates hematopoietic stem/progenitor cell (HSPC) activity and the EP_4 receptor was identified as the key receptor for PGE_2-mediated regulation of HSPCs via stimulation of PKA and ß-catenin (Ikushima et al. 2013). Furthermore, two mechanisms of prostanoid activation of erythropoiesis have been proposed: 1. Activation of the erythroid progenitor cells in the bone marrow by PGE_2 and PGD_2 to increase the responsiveness of erythroid cells to erythropoietin, and 2. stimulation of renal erythropoietin production by hypoxia via the prostacyclin pathway (review in Fisher and Hagiwara 1984).

In conclusion, as metabolite ACT-333679 is similarly active on both IP and EP_4 receptors from dogs, the bone/ bone marrow effects in dogs induced by selexipag in the repeated dose toxicity studies might be related to effects of ACT-333679 on the EP_4 receptor. Because both selexipag and its metabolite ACT-333679 have no affinity for the human EP_4 receptor, the bone/bone marrow effects induced by selexipag in dogs; this effect is species-specific and, therefore, not relevant to humans.

As observed in rats, decreased platelet counts (at doses of $\geq$ 6 mg/kg/day) have been found in dogs. This effect might be IP receptor mediated because in anaesthetized dogs the infusion of prostacyclin has been demonstrated to produce splenic dilation that leads via blood pooling to a decrease in circulating blood cell concentrations (Noguchi et al. 2006). For the assessment of possible effects of selexipag on the bone marrow, see also the clinical assessment of questions 131 and 132.

Reduced urinary excretions of Na, K and Cl (at doses of $\geq$ 6 mg/kg/day) induced by selexipag might be explained by the vasodilating effects of selexipag.

Toxicokinetic evaluation of repeated-dose studies

Binding of both unchanged selexipag and its metabolite ACT-333679 in rat, dog, monkey, and man sera was in a range between 97–99%, and equilibrium dialysis in mouse, rat, rabbit, dog, monkey, and man plasma gave free fractions of 0.3-0.6% for selexipag and 0.4-0.8% for ACT-333679. Therefore, both selexipag and ACT-333679 exhibited no marked species differences in the extent of serum protein

binding among rats, dogs, monkeys and humans, and no correction of the exposure ratios for plasma protein binding is necessary.

However, it should be taken into account that both selexipag and ACT-333679 have species differences at the target IP receptor, with sensitivity in the order human > rat > dog (the EC_{50} values for free substances at the human, rat and dog IP receptors were 4, 170 and 1100 nM for selexipag, respectively, and 0.17, 3.1 and 14 nM for metabolite ACT-333679, respectively). When the exposure ratios at the NOAEL of 6 mg/kg/day in rats and at the LOEL of 1 mg/kg/day in dogs are corrected for the species-dependent EC_{50} values at the IP receptor, values for the exposure ratios for rats at the NOAEL obtained in the 26 week study are 0.04 - 0.08 for selexipag and 0.6 - 1.4 for ACT-333679, and for dogs at the LOEL obtained in the 39 week study are 0.1 for selexipag and 1 - 1.6 for ACT-333679, respectively.

Genotoxicity

A standard battery of genotoxicity test was performed with selexipag and the active metabolite ACT-333679. In conclusion, selexipag and its metabolite ACT-333679 were tested in vitro in AMES and chromosome aberration assays and in vivo in mouse bone marrow micronucleus and rat liver Comet assays with no biologically relevant adverse observations.

Carcinogenicity

Two GLP-conform carcinogenicity studies were performed in B6CF1/Crlj mice and SD rats.

In the mouse study there was no treatment-related increase in either number of tumours or tumour bearing animals in either sex. Slightly higher incidence of thyroid follicular cell tumours (adenoma and carcinoma) were observed in 2 males each in the 250 and 500 mg/kg groups and in 3 females in the 500 mg/kg group, although there were no statistically significant differences in either trend analysis or pairwise comparison between the control and any dose group. This was paralleled by increased incidence and severity of hyperplasia/hypertrophy of the follicular cells. Follicular cell adenoma was also observed in 1 female each at doses of 125 and 250 mg/kg, respectively. A treatment related effect cannot be completely excluded, since increased incidence and severity of hyperplasia/hypertrophy of the follicular cells were also observed in these groups. Safety margins for neoplastic findings at the NOEL of 125 mg/kg/day of 172-fold for selexipag and 54-fold for ACT-333679 were calculated towards AUC exposure levels at the clinical dose of 1600 µg b.i.d.

A mechanistic study performed in mice (T-13.030) revealed that selexipag induces the expression and activity of hepatic metabolic enzymes and plasma levels of T3 and TSH, which explains a continuous stimulation of the thyroid and subsequent hyperplasia and adenoma. This mechanism is rodent specific (Klaassen 2001, De Sandro 1991, Hood 1999]. Even so an increase in TRH and prolactin levels have not directly been demonstrated in mice treated with selexipag, the mechanistic study implies a dysregulation of the hormonal axis of the thyroid induced by liver enzyme induction and compensatory increases in TSH and TRH. Given the fact that rodents are more susceptible to thyroid hormone imbalances (Capen 1996) and these mechanisms are often rodent specific (Klaassen 2001, De Sandro 1991, Hood 1999) and hepatic enzyme induction has not been observed in clinical trials, these findings are not of toxicological concern.

In female mice ovarian corpora luteal hypertrophy, mammary gland lobular hyperplasia, and vagina mucification was observed at doses of $\geq$ 125 mg/kg (low dose) which hint to elevated levels of prolactin. Yamada et al. (2006) have shown that thyrotropin-releasing hormone (TRH) knock-out mice display slightly reduced prolactin levels; prolactin suppression was more pronounced during lactation in knock-out animals. This indicates that increased TRH levels result in increased prolactin levels (reviewed in Ben-Jonathan N et al 2008). Increased TRH levels might be triggered by hepatic microsomal enzyme induction and is in line with observed increased centrilobular hepatocellular

hypertrophy at doses of ≥ 125 mg/kg. Enzyme induction in mouse livers by selexipag has been studied in the mechanistic study (T-13.030) and led to compensatory increased T3 and TSH levels in treated mice. However, TRH levels have not been measured in this study but are likely to be compensatory elevated.

The incidence of fibro-osseous lesions increased in high-dose males. This lesion frequently occurred in female mice in the control and all treatment groups, indicating that it is a background finding in aging animals. The mechanism of these findings in high-dose males is unclear, however occurred at sufficiently high safety margins (NOAEL 250 mg/kg) of > 100-fold for selexipag and ACT-333679, respectively.

In the rat study there were no effects of selexipag on survival rate of males. A statistically significant trend of an increase in the survival rate with increasing dose levels was observed in females, and the survival rate of the 100 mg/kg group was significantly higher than that of the control group.

There was no treatment-related increase in either number of tumours or tumour bearing animals in either sex. A decrease in the number of benign tumours was observed in males in the 30 and 100 mg/kg groups. Decreases in the total number of tumours, number of malignant tumour bearing animals and number of multiple tumour bearing animals were observed in males in the 100 mg/kg group.

Marginally increased incidence of Leydig cell tumour was observed in the 100 mg/kg group, and statistically significant positive trend was noted (rare tumour, $p<0.025$); however, there was no statistical significance in pairwise comparison between the control and 100 mg/kg groups. Additionally, slightly higher incidence in focal hyperplasia of Leydig cells was observed in this group. The tumour incidence of the 100 mg/kg group (5/60 animals, 8%) was marginally higher than that of historical data (0 to 4% in the incidence). In addition, there was no statistically significant positive trend in incidence of Leydig cell tumour in the control, 10 and 30 mg/kg groups.

In the pituitary, increased incidence of anterior adenoma was observed in males in the 10 mg/kg group with statistical significance (common tumour, $p<0.01$). However, it was not considered to be treatment related, since it was not dose-related.

Mechanistic studies performed with cultured rat Leydig cells (T-11.295) and in vivo in rats (T-11.460) gave no conclusive explanation for the occurrence of Leydig cell adenoma in the rat carcinogenicity study. Leydig cell hyperplasia and subsequent adenoma formation is usually a proliferative response to increased testosterone, LH and/or prolactin levels in rats (reviewed in Cook JC 1999). In the in vitro study with cultured Leydig cells, selexipag/ACT-333679 increased testosterone excretion at relevant concentrations close to the C_{max} in the rat carcinogenicity study. However, testosterone, LH and prolactin levels were decreased in the in vivo mechanistic study using similarly high doses (up to 150 mg/kg/day). The reason for the decrease is not clear and cannot explain adenoma formation.

To this end rats are more sensitive in their proliferative response to LH and their sensitivity to chemically induced Leydig cell tumours (Prentice 1995 and Cook 1999). Safety margins at the NOEL of 30 mg/kg/day based on AUC values are 19-fold for selexipag and 92-fold for ACT-333679 at the clinical dose of 1600 µg selexipag b.i.d.. Taken together, due to the rat specific mechanism and the high safety margins, Leydig cell tumours are not expected to occur in humans at the anticipated maximum recommended human dose of 1600 µg b.i.d.

At ≥ 30mg/kg/day (NOAEL 10 mg/kg/day) eye dilation and meandering (tortuosity) of the retinal arterioles were observed in the rat carcinogenicity which were not accompanied by histological lesions. Ophthalmological findings were not observed in the other (shorter) repeat-dose toxicity studies. Prostaglandins and prostacyclins have been described to dilate retinal arterioles and increase retinal and choroidal blood flow via IP and EP_2 receptors (Mori 2007a, Mori 2007b). Safety margins of 5.52-

fold and 34.5-fold for selexipag and ACT-333679 towards human exposure at 1600 µg b.i.d., respectively, were calculated. As ophthalmological findings are probably an exaggerated pharmacological effect mediated via the IP receptor, a correction factor of 29 for selexipag (EC_{50}: 250 nM for human, 7200 nM for rat) and 18 for ACT-333679 (EC_{50} at IP receptor: 6.1 nM for human, 110 nM for rat) should be applied. This results in safety margins of 0.2x and 2x for selexipag and ACT-333679, respectively. Therefore, ophthalmic findings might be of relevance for humans. However, ophthalmological assessments have been implemented in phase 2 and phase 3 clinical studies. No treatment-related findings of retinal vascular tortuosity by using fundus photography were observed. Nevertheless, due to the low safety margins and limited long-term data in humans, ophthalmological effects associated with retinal vascular system have been included as an important risk in the Risk Management Plan.

Various non-neoplastic findings were observed in the mouse and rat carcinogenicity studies. Alterations of the liver, thyroid and adrenal gland are consistent with those found in general toxicity studies. Adaptive changes (hyperplasia or atrophy) in the thymus, fibro-osseous lesion in the femur, erosion/ulcer, adhesion with surrounding tissues and/or mucosal regeneration in the glandular stomach and hyperplasia of acinar cells in the pancreas were observed in mice and rats. Additionally, treatment-related lesions in the female reproductive system (hypertrophy of corpora lutea, vaginal mucification, lobular hyperplasia in mammary glands), in the sublingual gland (hypertrophy/atrophy of the acinar cells), in the intestine/duodenum (perforation), in the spleen (increased pigment in the red pulp and atrophy) and in the kidney (tubular hypertrophy of the papilla, eosinophilic droplet in papillary epithelium, tubular basophilia in the cortex, tubular hypertrophy in outer medulla, hyperplasia of the papillary epithelium, tubular regeneration and urinary cast) were found in mice. Finally, dilation and tortuosity of retinal arterioles were observed only in rats at the end of the study.

The Applicant explained that the ovarian corpora lutea hypertrophy, mammary gland lobular hyperplasia, and vagina mucification could be a consequence of an elevated prolactin level that could be induced by a multistep process, starting with hepatic microsomal enzyme induction. Although these alterations could be a consequence of elevated prolactin levels as the Applicant stated, hormonal imbalance (increments in levels of prolactin and/or TRH and decrement in T3 levels) associated with hypertrophy of ovarian corpora lutea that could produce a shift towards a progesterone-like phase of the normal oestrus cycle and lead to vagina mucification have not been reported in animals treated with selexipag. Moreover, decrements in prolactin levels were reported in male rats after selexipag administration.

Reproductive and Developmental Toxicology

The reproductive and developmental toxicity of selexipag was studied according to ICH-S5 in GLP-compliant studies in the rat and rabbit. During these studies standard parameters were assessed.

Toxicokinetic parameters were obtained from satellite animals. Pregnant rats showed a slightly higher exposure towards selexipag and ATC-333679 compared to non-pregnant rats for the highest dose group of 20 mg/kg bw.

In the study on fertility and early embryonic development in the rat, time until copulation was significantly longer in the high dose group probably due to impaired oestrus of females. Although fertility index and other female reproductive parameters were not affected, general effects on the female reproductive system cannot be excluded.

An embryotoxicity study was performed in the rat, and the rabbit was chosen as non-rodent species for the second embryotoxicity study. An altogether higher incidence for visceral anomalies was observed in the rat study. However, the overall incidence was reported to be within the historical control range and there was no significant difference in the incidence of any abnormality between the

control and high-dose group. In the rabbit study, retrocarval ureter was observed with higher incidence in the high dose compared to the control group, but was also shown to be within the historical control range of the study facility. Receptor potency studies provided by the applicant showed much lower potency of selexipag and ACT-333679 at the rat and rabbit IP-receptor compared to the human receptor (refer to the pharmacology section above). Therefore, IP receptor mediated effects on reproduction will probably not become evident during the reproductive toxicity studies since exposure margins adapted to IP-receptor potency are usually below human therapeutic exposures. In conclusion, selexipag did not show any teratogenic effects in the studies on embryo-fetal development. Exposure margins, based on total exposure, were about 13-times for selexipag and 46-times for ACT-333679 towards human therapeutic exposures.

In the pre/-postnatal development study performed in the rat, a delay in the cleavage of the balanopreputial gland in males of the F1 generation was observed for all dose groups compared to controls. However, otherwise functional development and reproductive performance of the F1 generation was not affected.

Studies in which the offspring (juvenile animals) are dosed and/or further evaluated

Based on a dose-range finding study, a pivotal GLP compliant juvenile toxicity study was performed in Beagle dogs. Dogs were 28 days of age at the beginning of the study.

In juvenile dogs, selexipag exposure was 2- to 3- fold lower than in adult animals at comparable doses and remained constant after repeated dosing. Exposure towards ACT-333679 was only comparable to adult exposure at the first day of dosing and decreased towards the end of the treatment period.

Like in the repeat-dose toxicity studies in adult dogs, mortality due to intussusception was observed in juvenile animals. Other treatment-related changes mainly consisted of increased thickness of the compact bone of the femoral shaft with increased numbers/thickness of trabeculae in the medullary cavity which were noted in a time- and dose-related pattern. Similar bone effects and haematopoietic hypercellularity were reported from the repeat-dose studies in adult dogs and were discussed to be mediated through ACT-333579 species specific activation of the dog EP_4 receptor. (see above)

A dose-dependent delay in the closure of the femoral and/or tibia epiphyseal growth plate was observed in animals sacrificed at week 39, a finding which could affect growth of the skeleton. A NOAEL for bone effects was not established. Bone effects as well as intestinal invagination have to be carefully discussed as soon as selexipag will be considered for the treatment of the paediatric population. Sexual maturation was also observed to be delayed in female dogs. It could be shown that this delay was not due to a direct involvement of prostacyclin in uterine function, but was rather due to toxicity of selexipag leading to low food consumption and a massive reduction in body weight gain and low ovary and uterus weights. In conclusion, bone and intestinal effects are described in the SmPC (Section 5.3). Reduced food consumption and consecutive effects were observed only at very high doses so that the relevance is regarded low and inclusion in the SmPC is not warranted.

Local Tolerance

In rabbits after intravenous and paravenous application of selexipag, no local irritation was observed.

Other toxicity studies

All tested impurities were negative for revertant colonies in the performed Ames tests and can be considered as non-mutagenic.

2.3.5 Ecotoxicity / environmental risk assessment

The predicted concentration for surface water is correct based on the applicant's assumption of the number of patients. In addition, in 2015, the prevalence at orphan.net has even been reduced to 1.5/1,000,000. The assessor agrees that the PEC surface water is clearly below the action limit.

The test on the determination of the partition coefficient of ACT-293987 according to OECD 107 is valid and plausible. It is agreed that no Phase I PBT assessment is necessary. The CHMP also agrees with the applicant's conclusion that there are no indications requiring an experimental Phase II assessment irrespective of the action limit.

Table 1 Summary of main study results

Substance (INN / Invented Name):			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	Log Dow = 3.86 (pH 5) Log Dow = 2.26 (pH 7)	Potential PBT N
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.000024	µg/L	> 0.01 threshold N
Other concerns (e.g. chemical class)			N

In conclusion, the environmental risk assessment of selexipag ends in Phase I because the predicted concentration in surface water is lower than 0.01 µg/l and the log Dow is lower than 4.5.

Therefore selexipag is not expected to pose a risk for the environment.

2.3.6 Discussion on non-clinical aspects

Upon request, the Applicant has calculated the free concentrations of selexipag/ACT-333679 in in-vitro functional assays and in in-vitro pharmacokinetic interaction studies and compared these values to the free therapeutically effective plasma concentrations of both selexipag (0.12 nM) and ACT-333679 (0.28 nM) in order to assess the clinical relevance of the observed findings. The free EC_{50}/IC_{50} values for selexipag and ACT-333679 shift to markedly lower values (to the low nanomolar range for selexipag and to the picomolar range for ACT-333679). As a consequence of these re-calculations, the Applicant supports the suggestion that there are spare IP receptors, since the IC_{50}/EC_{50} values for free selexipag and ACT-333679 are lower compared to the K_i values obtained in binding experiments. The re-calculated free EC_{50}/IC_{50} values for selexipag and ACT-333679 correlate with selexipag and ACT-333679 free peak plasma concentrations of 0.12 nM and 0.28 nM, respectively, at 1600 µg b.i.d. in humans.

The existence of differences in spare IP receptors together with differences in the degrees of signal amplification of the IP receptor signaling cascade can explain the different potencies of selexipag/ACT-333679 in functional assays performed in different in-vitro test systems.

Mice were used in the carcinogenicity studies and rabbits in the reproductive and developmental toxicity studies performed with selexipag. In order to give an explanation for the findings observed in mouse carcinogenicity studies and in the rabbit reproductive and developmental toxicity studies, the Applicant provided results from a new study in which in vitro potencies (EC_{50} values), as measured by cAMP accumulation, were determined in recombinant cells expressing similar levels of the mouse,

rabbit, or human IP receptor. The rabbit and mouse IP-receptors showed 61- and 69-fold lower potencies for selexipag and 74- and 56-fold lower potencies for ACT-333679, respectively. For any pharmacological effect mediated via the IP receptor occurring in mouse and rabbit studies, correction factors for differences in potencies should be applied for the calculation of safety margins. Taking the correction factors for IP-receptor potency into account, these safety margins diminish to values below human therapeutic exposures. However, adverse effects in the mouse carcinogenicity study and the rabbit reproductive toxicology studies are probably not mediated via the IP receptor

Nevertheless, a general statement regarding those differences in IP receptor potency in animals used for toxicity assessment compared to humans has been included into section 5.3 of the SmPC.

IP prostacyclin receptor agonists have the potential to induce neurogenic pain, and headache, pain, arthralgia, myalgia, abdominal pain, pain in jaw and pain in extremities are mentioned in the SmPC under section 4.8 undesirable effects.

Based on the re-calculated free concentrations of selexipag and ACT-333679 in the in-vitro pharmacokinetic interaction studies, selexipag and its metabolite do not seem to have any relevant inhibitory potential on CYP P450 enzymes, on transport proteins and on BCRP. However, an induction of CYP3A4 and CYP2C9 by selexipag in the intestine cannot be excluded. This is therefore mentioned in the SmPC under section 4.5.

In repeated-dose toxicity studies performed in rats and dogs, platelet count dose-dependently decreased. The Applicant could not able to provide a mechanistic explanation for this effect observed in rats. Nevertheless due to the small magnitude of the effect, its reversibility and the absence of effects on coagulation times or bleeding, the rat finding of decreased platelet counts after administration of selexipag has no human relevance; furthermore, decreased platelet count has also been observed after administration of other IP receptor agonists in rat repeated-dose toxicity studies (e.g. for treprostinil). The decreased platelet counts observed in dogs after administration of selexipag might be IP receptor mediated because in anaesthetized dogs the infusion of prostacyclin has been demonstrated to produce splenic dilation that leads via blood pooling to a decrease in circulating blood cell concentrations. In conclusion, decreased platelet counts observed in repeated-dose toxicity studies performed in rats and dogs do not seem to be of therapeutic relevance.

Reproductive toxicity of selexipag was studied according to ICH-S5 in the rat and in the rabbit. Receptor binding studies showed a much lower potency for selexipag and ATC-333679 at the rat and rabbit IP receptor compared to the human receptor. Therefore, IP mediated effects will probably not become evident during the reproductive toxicity studies because exposures adapted for IP receptor potency are usually below human therapeutic exposures. The margins adapted for differences in receptor potencies are provided in section 4.6 of the SmPC.

In the fertility study performed in rats, estrus cycles were prolonged increasing the time until copulation in the high dose group. Lower food consumption was observed for those dams, but no changes in body weights. Therefore, lower maternal body weight was the cause of these findings. The observation of prolonged oestrus cycle is mentioned in sections 4.6 and 5.3 of the SmPC.

In the embryo-fetal development study in the rabbit, retrocaval ureter was observed with a higher incidence in the high dose compared to the control group. Historical control data covering different time frames of the study facility showed that the incidences were within the historical control range. The same could be shown for the higher incidence of visceral anomalies, in general, observed for the high dose group of the rat embryotoxicity study. Accordingly, selexipag did not show any teratogenic effects in the studies on embryo-fetal development with exposure margins, based on total exposures, of approximately 13-times for selexipag and 46-times for ACT-333678, respectively.

In the juvenile toxicity study performed in the dog, a delay in sexual maturation in female beagle dogs was observed. It could be shown that this delay was not due to a direct involvement of prostacyclin in uterine function, but was rather due to toxicity of selexipag leading to low food consumption and a massive reduction in body weight gain and low ovary and uterus weights. A delay in the closure of the femoral and/or tibia epiphyseal growth plate was observed in animals sacrificed at week 39, a finding which could affect growth of the skeleton. The applicant argues that the distribution of animals with closed versus open growth plates is still within the normal range. However, effects on the closure of growth plates were clearly dose dependent. A NOAEL for bone effects was not established. A respective statement is mentioned in section 5.3 of the SmPC.

2.3.7 Conclusion on non-clinical aspects

From a non-clinical point of view, a Marketing Authorization for selexipag can be granted. Amendments to sections 4.5, 4.6 and 5.3 of the SmPC have been implemented as required during the assessment. In conclusion, the SmPC reflects the non clinical finding of relevance for the prescriber.

2.4 Clinical aspects

2.4.1 Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study Reference	Study Title
PS003	An open-label study of the pharmacokinetics, safety and tolerability of a single microdose of MRE-304 in healthy volunteers
186933	A Phase I study to investigate the absorption, metabolism and excretion of [^{14}C] NS-304 following oral administration to healthy male volunteers
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
NS304/P1/01	Single- and multiple-dose study of NS-304 in healthy adult and elderly male Japanese volunteers
AC-065-101	A single-center, randomized, placebo-controlled, double-blind, multiple-period, multiple-ascending- dose study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of oral ACT-293987 in healthy male subjects
AC-065-102	A single-center, assessor-blind, randomized, placebo- and positive-controlled, parallel group study to evaluate the phototoxic potential, safety, tolerability, and pharmacokinetics of ACT-293987 in healthy male subjects
AC-065-104	A single-center, open-label, single-dose Phase 1 study to investigate the pharmacokinetics, tolerability, and safety of 400 µg selexipag (ACT- 293987) in subjects with mild, moderate, or severe hepatic impairment compared to healthy subjects
AC-065-105	Single-center, open-label study to investigate the pharmacokinetics, safety, and tolerability of a single oral dose of selexipag in subjects with renal function impairment
AC-065-106	A single-center, double-blind, randomized, placebo- and positive-controlled, parallel-group with nested cross-over, multiple-dose, up-titration study of the

	effects of selexipag and its metabolite ACT-333679 on cardiac repolarization in healthy male and female subjects
AC-065-108	A single-center, open-label, randomized, two- period, two-treatment, crossover study in healthy male subjects to demonstrate bioequivalence of 1600 µg selexipag administered as eight tablets of 200 µg (reference drug) or as single tablet of 1600 µg (test drug)
AC-065-109	A single-center, randomized, open-label, 2-treatment, 2-period, cross-over study to assess the effects of Kaletra® (lopinavir / ritonavir) on the pharmacokinetics of selexipag(ACT-293987) in healthy male subjects
AC-065-110	Single-center, open-label, Phase 1, randomized, two-way crossover, single-dose to investigate the absolute bioavailability of a single oral dose of selexipag in healthy male subjects.
NS-304/-02	A multicenter, multinational, open-label, single-dose, acute hemodynamic study followed by a multicenter, multinational, randomized, double- blind, parallel-group, placebo-controlled study to assess the safety, tolerability, pharmacokinetics, and preliminary efficacy (proof-of-concept) of ACT-293987 (NS-304) in the treatment of pulmonary arterial hypertension in subjects aged 18 years and over
AC-065A201	Clinical Study to assess the efficacy, safety and pharmacokinetics of selexipag in patients with pulmonary arterial hypertension (PAH)
AC-065B201	An exploratory study to assess the efficacy and Safety of selexipag in patients with chronic thromboembolic pulmonary hypertension (CTEPH)
AC-065B202	An open-label extension study of selexipag in patients with chronic thromboembolic pulmonary hypertension (CTEPH) who completed the exploratory evaluation study (AC-065B201)
AC-065A302	GRIPHON: Prostacyclin (PGI_2) receptor agonist in pulmonary arterial hypertension A multicenter, double-blind, placebo-controlled Phase 3 study assessing the efficacy and safety of selexipag (ACT 293987) on morbidity and mortality in patients with pulmonary arterial hypertension (PAH)
AC-065A303	Open label extension study of AC-065A302

2.4.2 Pharmacokinetics

Selexipag is an orally available, selective non-prostanoid agonist of the prostacyclin (IP) receptor. Selexipag and its active metabolite, ACT-333679, are active at the IP receptor. ACT-333679 has a 13-fold higher affinity than selexipag for the human IP receptor. It is present at 3- to 4-fold higher levels than the parent drug at steady-state in humans. ACT-333679 is the major contributor to the efficacy of selexipag.

In total, 12 studies were preformed that were classified as PK-studies. In addition, PK was measured in PD and phase III studies.

Methods

Bioanalytical methods studies (high performance liquid chromatography coupled to tandem mass spectrometry [LC-MS/MS]) enabled measurement of selexipag and ACT-333679 concentrations in human plasma samples. These methods were sensitive, precise, and linear in the concentration range of 0.01–20.00 ng/mL for both selexipag and ACT-333679. Five method validation reports were provided. The two most frequently used methods were cross validated. Standard PK parameters and statistical analyses were used.

Absorption

An intravenous (i.v.) formulation of selexipag, has been developed and an absolute bioavailability study has been conducted (AC-065-110). The geometric mean (90% CI) absolute bioavailability calculated for selexipag is 0.49 (0.43, 0.57).

Relative bioavailability after oral administration has been properly characterized. PK results with solution (study PS003) and tablet (study QGUY/2006/NS-304/01) were found to be comparable.

The Applicant has not investigated the absorption site of selexipag. However, based on surface-to-volume characteristics and pH (around 8), most of the absorption of selexipag (freely soluble at pH 8) is anticipated to occur in the duodenum.

Following single-dose administration (100 to 800 µg), the PK profile of selexipag is characterized by rapid absorption with C_{max} achieved within 1 h after drug administration and a $t_{1/2}$ of approximately 0.8–2.5 h. The active metabolite, ACT 333679, is formed rapidly and eliminated with a $t_{1/2}$ of approximately 6–13 h.

An in vitro study was conducted to compare the dissolution profiles of 400, 600, 800, 1000, 1200, 1400, and 1600 µg film-coated tablets with that of the dose strength of 200 µg, in dissolution media of four different pH values: 1.2, 4.5, 5.5, and 6.8. When the dissolution profile of multiple tablets of the 200 µg dose was compared to that of a single tablet of higher strengths (e.g., 2 × 200 µg tablets vs 1 × 400 µg tablet), the f2 value was above 50 for all dose strengths and at all dissolution pH values. In addition, bioequivalence between 1 tablet of 1600 µg and 8 tablets of 200 µg selexipag was demonstrated in study AC-065-108 (figure 3).

Linear scale **Semilogarithmic scale**

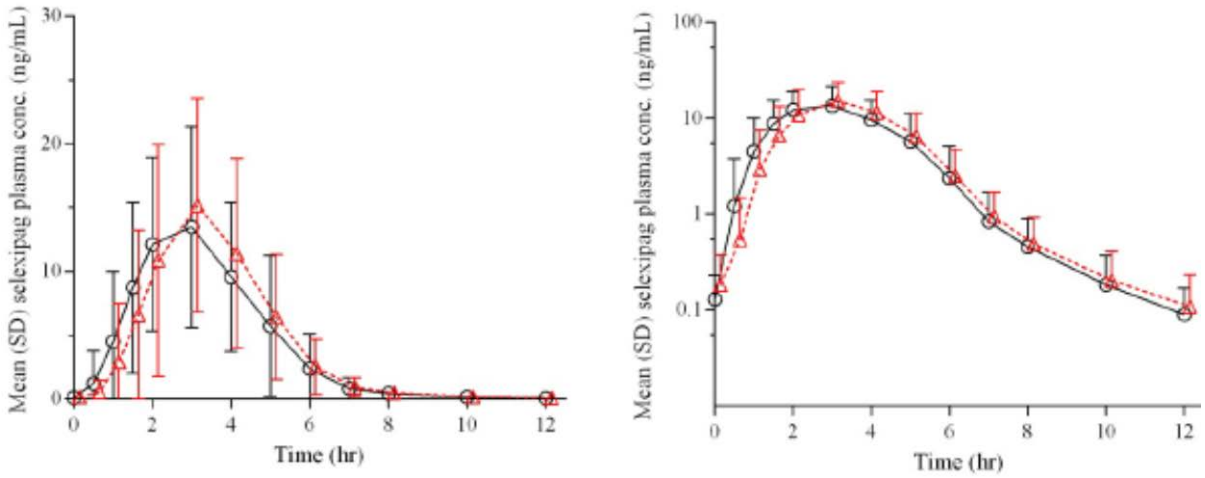


Figure 3: Selexipag arithmetic mean (± SD) plasma concentration-time profiles of selexipag over 12 h in healthy subjects (n = 65) at steady-state (Day 23) after treatment with 1600 µg selexipag in Treatment A (8 × 200 µg tablets; black) and Treatment B (1 × 1600 µg tablet; red)

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). 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. C_{max} and $AUC_{0-\infty}$ of ACT-333679 decreased by 48 and 27%, respectively, in the presence of food (figure 4).

Linear scale **Semilogarithmic scale**

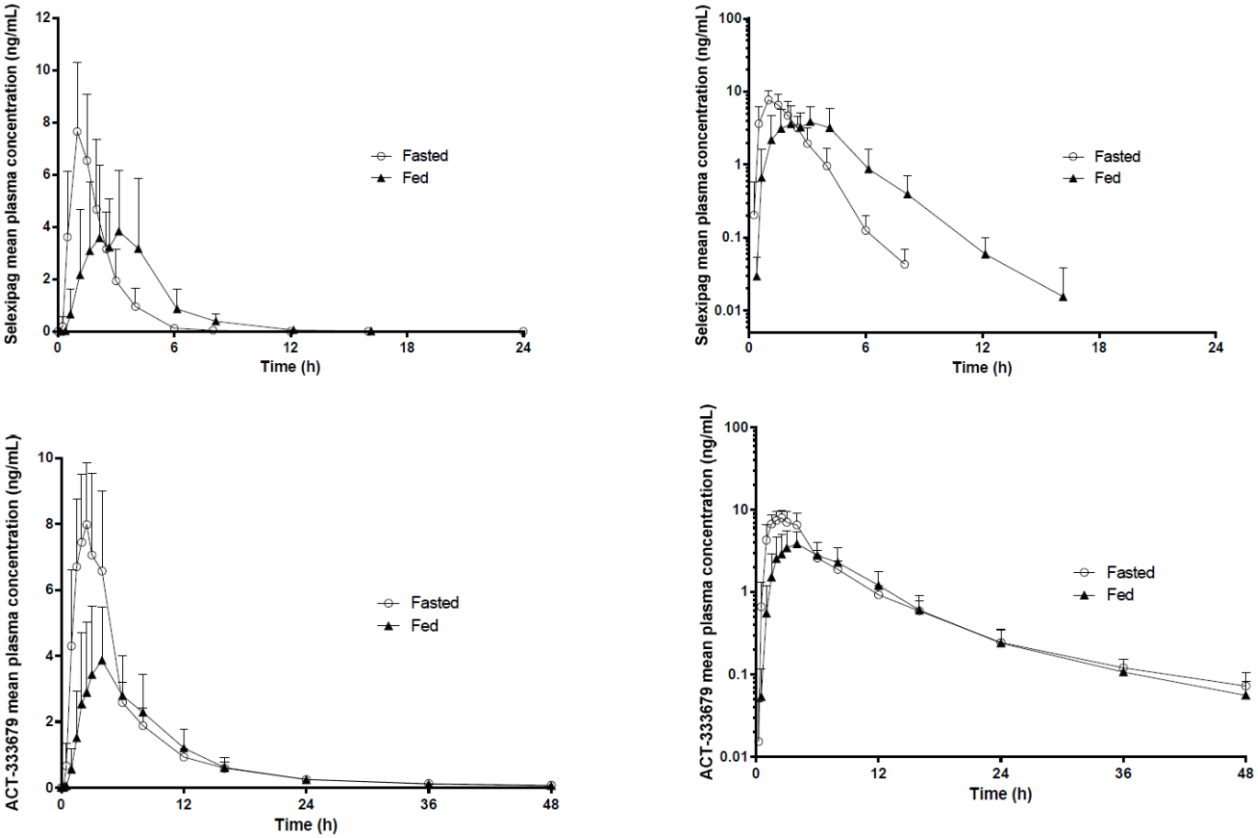


Figure 4: Mean (+SD) plasma concentration-time profiles of selexipag and ACT-333679 in healthy male subjects following single oral doses of 400 µg selexipag in the fasted (n = 11) and fed state (n = 12) (study QGUY/2006/NS304/-01 Part B)

Distribution

In vitro experiments showed that selexipag and ACT-333679 are highly bound to plasma proteins (> 99%), which was confirmed in phase 1 studies. Partitioning studies with selexipag and ACT-333679 indicated little or no binding of either compound to blood cells.

The geometric mean (95% CI) volume of distribution at steady-state (V_{ss}) of selexipag is 11.73 L (95% CI 10.55, 13.04; results from study AC-065-110), which is comparable to the volume of extracellular fluid (plasma plus interstitial fluid, around 15 L). This indicates that the distribution is limited mainly to the extracellular fluid and that selexipag does not accumulate in tissues.

Preclinical data indicate that selexipag and ACT-333679 permeate well through cell membranes and tissue distribution is mainly driven by passive diffusion.

Metabolism

Based on nonclinical findings, selexipag undergoes enzymatic hydrolysis by CES1 in the liver, to yield the active metabolite ACT-333679. Investigations in human liver microsomes (HLM) and with recombinant cytochrome P450 (CYP) enzymes indicate that the UGT enzymes UGT1A3 and UGT2B7 contribute 42% to the metabolism of ACT-333679, while CYP2C8 and CYP3A4 contribute to 46% and 12%, respectively.

Elimination

In a human ADME study with ^{14}C selexipag (study 186933), approximately 93% of radioactive drug material was eliminated in faeces at 168 h post-dose, none in the form of unchanged selexipag. A number of metabolites, including ACT-333679 (approximately 9–23%), were recovered in the faeces, indicating extensive metabolism of selexipag prior to biliary excretion.

ACT-333679 has the potential to undergo enterohepatic recirculation, but its extent is limited by the small amount of ACT-333679 present in bile.

Renal excretion was shown to be a minor route of elimination.

Dose proportionality and time dependency

Selexipag and ACT-333679 showed a dose-proportional increase in AUC and C_{max} after multiple-dose administration in healthy subjects. After multiple dosing (400 to 1800 µg b.i.d), steady-state conditions of selexipag and ACT-333679 were achieved within 3 days. Morning trough concentrations of both selexipag and ACT-333679 were somewhat higher than evening trough concentrations, which is thought to be due to the increased blood circulation and resulting increased metabolism during the day compared to the night, affecting the clearance of selexipag and ACT-333679. No accumulation of selexipag or ACT-333679 was observed.

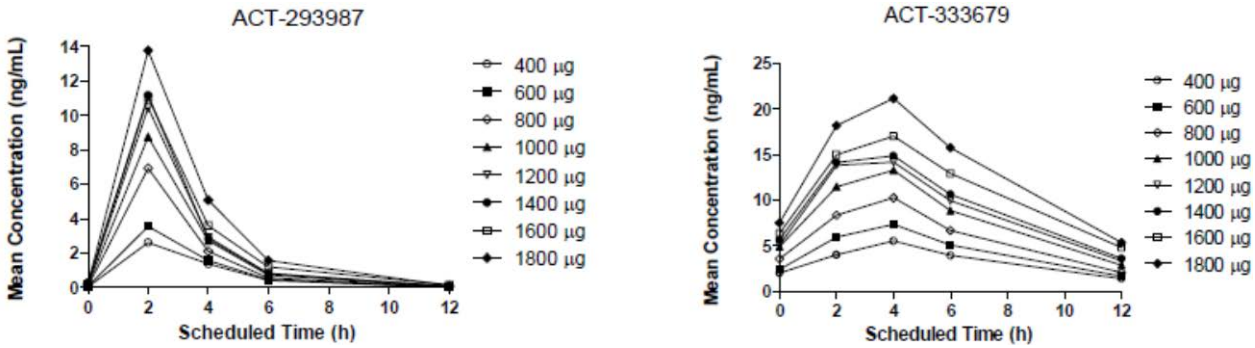


Figure 5: Arithmetic mean plasma concentration-time profiles of selexipag (ACT-293987) and ACT-333679 after multiple (Day 3) oral administrations of different dose levels of ACT-293987 in healthy male subjects (study AC-065-101)

Intra- and inter-individual variability

The **intra**-subject CVs of selexipag and ACT-333679 were about 25 % for AUC_T and $C_{max,ss}$. The **inter**-subject CVs of selexipag and ACT-333679 were about 40 % for AUC_T and $C_{max,ss}$.

Pharmacokinetics in target population

Exposure to selexipag and ACT 333679 were estimated to be 30% and 20%, respectively, higher in patients with PAH or CTEPH compared with healthy subjects.

Special populations

Gender, race and age are of minor importance for selexipag and ACT-333679 pharmacokinetics.

Body weight was identified as significant covariate for the volume of distribution as well as for drug exposure and clearance of selexipag and ACT-333679.

In the PK Study AC-065-105, the plasma concentrations of selexipag (~1.7-fold) and ACT-333679 (~1.5-fold) were higher in subjects with severe renal function impairment compared to healthy subjects (patients with mild or moderate renal impairment were not investigated). On the other hand,

in the confirmatory study AC-065A302 065A302/GRIPHON, CrCl was not identified as a significant covariate towards the PK of selexipag and ACT-333679.

In PK study AC-065-104, the exposure to selexipag generally increased with the severity of hepatic impairment. When compared to healthy subjects, the plasma concentrations of selexipag in subjects with mild hepatic impairment increased about 2-fold. Plasma concentrations of ACT-333679 and derived PK parameters were comparable with those for healthy subjects, except for $t_{1/2}$ (6.5 versus 12.6 h).

Plasma selexipag concentrations were markedly higher in subjects with moderate hepatic impairment (more than 4-fold increase in $AUC_{0-\infty}$). Median t_{max} (6.0 h) and mean $t_{1/2}$ (15.9 h) of ACT-333679 were longer in subjects with moderate hepatic impairment compared to healthy subjects (4.0 h and 12.6 h, respectively). Overall, this resulted in a 2.2-fold increase in exposure ($AUC_{0-\infty}$) to ACT-333679 in subjects with moderate hepatic impairment compared to healthy subjects. Only 2 subjects with severe hepatic impairment receiving a lower dose (200 vs 400 µg) were included and therefore, conclusions in this special population are limited. In study AC-065A302/GRIPHON, ALT and AST at baseline were not identified as significant covariates towards the PK of selexipag and ACT-333679. However, total bilirubin at baseline was identified as significant covariate for selexipag clearance.

The list of studies performed in elderly is detailed below. Age is of minor importance for selexipag and ACT-333679 pharmacokinetics.

Table 2: List of studies performed in elderly with breakdown on number of pstients per age group.

eCTD Module	Age 65–74 number / total number (all ages)	Age 75–84 number / total number (all ages)	Age 85+ number / total number (all ages)
Efficacy and Safety Studies[1]:	**218/1270**	**20/1270**	**0/1270**
NS-304-02	11/43	3/43	0/43
AC-065A201	4/37	0/37	0/37
AC-065A302	193/1156	13/1156	0/1156
AC-065B201	10/34	4/34	0/34
Human PK Studies:	**25/233**	**2/233**	**0/233**
PS003	0/5	0/5	0/5
186933	0/6	0/6	0/6
QGUY/2006/NS304/-01	0/96	0/96	0/96
NS-304P01/1	16/64	0/64	0/64
AC-065-104	1/26	0/26	0/26
AC-065-105	8/16	2/16	0/16
AC-065-109	0/20	0/20	0/20
Human PD Studies:	**0/227**	**0/227**	**0/227**
AC-065-101	0/16	0/16	0/16
AC-065-102	0/52	0/52	0/52
AC-065-106	0/159	0/159	0/159
Biopharmaceutical Studies:	**0/80**	**0/80**	**0/80**
AC-065-108	0/80	0/80	0/80
Controlled trials:	**214/1233**	**20/1233**	**0/1233**
NS-304-02	11/43	3/43	0/43
AC-065A302	193/1156	13/1156	0/1156
AC-065B201	10/34	4/34	0/34
Non controlled trials:	**4/37**	**0/37**	**0/37**
AC-065A201	4/37	0/37	0/37

[1]For AC-065A302, 4 randomized patients (in the placebo group) are included in the total number of patients although they were not treated. Open-label extension studies are not included as patients would be counted more than once.

Paediatric population

To date, no patients younger than 18 years have been treated with selexipag. The Applicant does not apply for use of selexipag in children or adolescents.

Interactions

Based on in vitro studies, the metabolism of selexipag was mostly driven by initial hydrolysis to the major metabolite ACT-333679, catalysed by hepatic CES1 in humans. No clinically relevant inhibition of CES1 by medicinal products has been reported.

The transformation of selexipag to other metabolites was catalysed by CYP2C8, CYP3A4, and CYP1A2. The UGT enzymes UGT1A3 and UGT2B7 contribute 42% to the metabolism of ACT-333679, while CYP2C8 and CYP3A4 contribute to 46% and 12%, respectively.

Selexipag and its active metabolite affecting the exposure of the patient to other drugs

The potential of selexipag and its metabolite, ACT-333679, to elicit CYP-mediated drug-drug-interactions (DDIs) was studied in vitro using human hepatic microsomes and CYP isoform-specific marker transformations. The lowest derived half maximal inhibitory concentration (IC_{50}) was 3.6 µM (selexipag on CYP2C8). The mean peak plasma concentrations of selexipag and ACT-333679 in human were 19.8 ng/mL and 28.7 ng/mL, i.e., about 0.04 µM and 0.07 µM, respectively. Although both compounds have shown an inhibitory potential against CYP2C8 and CYP2C9 activity in vitro, their potential for CYP-mediated DDIs appears negligible in light of the low unbound concentration of both selexipag and its metabolite, ACT-333679, in human plasma. However, assuming a luminal selexipag concentration of 1.3 µM and a free selexipag concentration in enterocytes of 8 nM, clinically relevant induction of CYP3A4 and CYP2C9 in the gut cannot be excluded.

Drugs affecting the exposure of the patient to selexipag and its active metabolite

Study QGUY/2006/NS304/-01 Part D was performed to investigate the potential PK (and PD) interactions between selexipag and **warfarin** in healthy male subjects. The geometric mean ratios (selexipag + warfarin vs selexipag alone) and their 90% CIs for AUC_T of selexipag (400 µg) and for AUC_T and C_{max} of ACT-333679 were within the bioequivalence range of 0.8 to 1.25. The lower boundary of the 90% CI for C_{max} was 0.77 (geometric mean ratio 0.94). Visual inspection of mean morning trough plasma concentrations of selexipag and ACT-333679 before (on Days 5–6) and after single dose administration of warfarin (measured on Days 9–11) showed that co-administration of warfarin on Day 8 had minor effect on the trough concentrations of selexipag and ACT-333679 at steady-state.

In **study AC-065-109** (a randomized, two-treatment, two-period crossover study), the effects of multiple doses of lopinavir/ritonavir (Kaletra) on the PK of selexipag (administered as a single 400 µg dose) and ACT-333679 were evaluated. The study was performed as selexipag and ACT-333679 have been identified in vitro as substrates of OATP transporters (OATP1B1 and OATP1B3) and lopinavir and ritonavir are inhibitors of these transporters. In addition, lopinavir/ritonavir is known to be a strong inhibitor of CYP3A4 and an inhibitor of P-gp. Plasma concentrations of selexipag were higher (almost 2-fold) in the presence of lopinavir/ritonavir than when it was administered alone. For ACT-333679, in the presence of lopinavir/ritonavir, C_{max} and $AUC_{0-\infty}$ were 1.3- and 1.1-fold higher, respectively. The results are adequately described in the SmPC.

Of note, no clinical DDI study was performed with a strong inhibitor of CYP2C8 (gemfibrozil), an inhibitor of UGTs (valproic acid), or an inducer of CYP2C8 and UGTs (rifampicin).

2.4.3 Pharmacodynamics

The clinical pharmacology data come from studies in healthy volunteers. The effect of selexipag and its metabolite on platelet aggregation, coagulation parameters, bone metabolism, cardiac repolarisation, and in-vivo drug-drug interactions was evaluated. Additionally, the phototoxic potential of selexipag was investigated.

Prostacyclin (PGI2) is a member of the prostaglandin family, which are endogenous, oxygenated fatty acid metabolites deriving from arachidonic acid. A dysregulation of the PGI2 pathway has been observed in patients with pulmonary arterial hypertension and in animal models of hypoxic pulmonary hypertension. Prostacyclin is a potent vasodilator and inhibitor of platelet aggregation. For example, the binding of PGI2 to the IP receptor, a G-protein coupled receptor on the surface of vascular smooth muscle cells, triggers an increase of intracellular cyclic adenosine monophosphate (cAMP), which leads to relaxation of vascular smooth muscle cells, and vasodilation of the pulmonary arteries. In this manner prostacyclin can counteract the vasoconstrictor activity of thromboxane and endothelin.

Selexipag acts as a selective, orally bioavailable, non-prostanoid IP receptor agonist. Selexipag undergoes an enzymatic hydrolysis of the sulfonamide by carboxylesterase 1 (CES1) in the liver, to yield the active metabolite ACT-333679. ACT-333679 has a 13-fold higher affinity than selexipag for the human IP receptor and it is at least 16-fold more potent than selexipag in cellular systems. *In vitro* experiments measuring cellular shape change using human pulmonary arterial smooth muscle cells showed that ACT-333679 is 37-fold more potent than selexipag in activating the human IP receptor. ACT-333679 is considered to be the major contributor to the efficacy of selexipag.

Primary and secondary pharmacology

Effects of selexipag on platelet aggregation, bleeding, and bone metabolism; identification of maximal tolerated dose

The relationship between plasma concentration and pharmacodynamic parameters of platelet aggregation and coagulation (*ex vivo* testing) was investigated in 16 healthy subjects in study AC-065-101 (placebo-controlled, multiple ascending dose study, 12 subjects on selexipag, 4 on placebo). Results after multiple-dose administrations of either selexipag or placebo indicated a high level of variability and no consistent differences in platelet aggregation test related PD parameters across the doses tested were observed. There was no obvious drug- or dose-dependent pattern. Mean % vWF measured on each third day after dose escalation was comparable between selexipag and placebo, albeit there was a trend for a decrease of vWF with selexipag, the vWF values remained above the lower limit of the normal range. Mean concentrations of the coagulation markers sTM and P-selectin after treatment with selexipag were not different from placebo. No changes from baseline were observed.

Increased bone ossification was reported in nonclinical studies in the Beagle dog with selexipag (studies T08/286 and T08/290). In humans no differences were observed between mean concentrations of bone formation PD markers (sOC, P1NP) or bone resorption markers (CTx, NTx; study AC-065-101) after treatment with selexipag or placebo.

The subjects were exposed to dose levels of Selexipag up to 1600 µg bid. The dose level of 1800 µg selexipag bid was less well tolerated due to an increase in moderate AEs (headache, myalgia, and nausea) that required concomitant medication. The maximum tolerated dose was determined as 1600 µg bid of selexipag. This dose was selected for further phase 3 testing.

Effects of selexipag on cardiac repolarisation: study AC-065-106 (thorough QT study)

The aim of this study was to demonstrate that selexipag and its metabolite do not have an effect on cardiac repolarisation measured by the QT interval at steady-state at 2 oral dose levels (800 and 1600µg bid) in 159 healthy male and female subjects. This was a double-blind, placebo controlled, parallel group with nested cross-over, multiple-dose, up-titration study with a positive control (single dose of moxifloxacin). Baseline characteristics were generally comparable between the selexipag group (treatment A) and the moxifloxacin group (treatment B).

Selexipag administration was associated with a mild increase in heart rate, with the largest placebo-corrected change from baseline heart rate reaching 6–7 bpm at 1.5 to 3 h after dosing with 800 µg selexipag and 9–10 bpm at the same time points after 1600 µg selexipag. There was no effect on mean blood pressure. Selexipag did not show an effect on cardiac repolarisation. Change from baseline QT interval corrected using the individualised formula QTcI (ΔQTcI) was small at all timepoints and the placebo-corrected ΔQTcI (ΔΔQTcI) did not exceed 1.4 ms (UB of 90% CI 3.9 ms) on selexipag 800µg and -0.7 ms (UB of 90% CI 2.1 ms) on 1600µg selexipag. There were no subjects with QTcI exceeding 480ms or ΔQTcI>30 ms on selexipag. Mean ΔΔQTcI peak effect for 400 mg moxifloxacin was 7.5 ms with a LB of the 90%CI of 4.8 msec. The LB of the 90% CI did not exceed 5.0 ms (the threshold indicated by the ICH E14 guidance) at any of the post-dose timepoints.

In this study no adverse experiences of Torsades de Pointes, sudden death, ventricular tachycardia, ventricular fibrillation or flutter, or seizures were reported.

Phototoxic potential of selexipag

In-vitro data suggested that selexipag and its active metabolite were potentially phototoxic. The photosensitizing potential of selexipag (800 and 1200 µg bid) was investigated in 52 healthy subjects, compared to placebo and ciprofloxacin (positive control; study AC-065-102). The photosensitizing potential of selexipag was assessed by evaluating the subject's cutaneous responses to UV irradiation (UV-A at 320–400 nm and UV-B at 290-320 nm) prior to and during the treatment period. Subjects were considered photosensitive if the Phototoxic Index (PI), defined as the ratio of baseline minimal erythema dose (MED) to post-dose MED (24 h after UV-irradiation) was greater than 1.66 for any waveband. The mean PI was below 1.66 for UV-A in all treatment groups, while it was greater than 1.66 for UV-B in each treatment group. No statistically significant differences in UV-A or UV-B PI between either selexipag dose and placebo or ciprofloxacin were observed. Overall, for UV-A and UV-B, administration of 800 µg and 1200 µg bid selexipag was not associated with clinically relevant phototoxic potential when compared to placebo or ciprofloxacin.

Substance P

As both selexipag and its metabolite are IP receptor agonists, substance P levels could increase in selexipag treated subjects and could increase pain perception. No effect of selexipag was observed on plasma substance P concentrations (study AC-065-102).

Relationship between plasma concentration and effect

The PK/ PD relationship between selexipag/ metabolite plasma levels and selected clinical safety and efficacy endpoints was evaluated using a population approach using data from the GRIPHON study AC-065A302. The main finding was a small but statistically significant increase in the 6MWT with increasing exposure, from 369 m with no exposure to 392 m with high exposure.

One phase 2 study (NS-304/02) investigated the relationship between hemodynamic parameters and the dose after individual up-titration. The primary endpoint was pulmonary vascular resistance (PVR). The study included 43 patients with PAH which were randomized in a 3:1 fashion to selexipag or placebo. The hemodynamic efficacy of selexipag, individually up-titrated to a maximum dose of 800 µg bid, versus placebo was evaluated at week 17. At this time, PVR (geometric mean and 95% CI) was

80.7% (72.8, 89.6; n = 29) and 115.9% (106.5, 126.1; n = 6) of the baseline values in the selexipag and placebo groups, respectively. The percent decrease (vs placebo) in geometric mean PVR of 30.3% on selexipag treatment was statistically significant (95% CI: -44.7, -12.2; p = 0.0045, Wilcoxon rank-sum test). There was no clear relationship between change in PVR and the patient`s optimized dose in this study. The PK data indicated that the mean exposure to selexipag and its metabolite at week 17 were in a similar range across all dose groups.

In-vivo interaction studies

In-vivo interaction studies were performed with warfarin and with lopinavir/ritonavir.

Selexipag given as multiple doses of 400 µg bid had no effect on the exposure to R-warfarin (CYP3A4 substrate) or S-warfarin (CYP2C9 substrate) after administration of a single dose of 20 mg warfarin (study NS304/-01). The pharmacodynamic effect of warfarin on the International Normalized Ratio was not affected by selexipag. The PK of selexipag and its active metabolite were not affected by warfarin.

Genetic differences in PD response

No DNA samples were collected during clinical development of selexipag.

2.4.4 Discussion on clinical pharmacology

Pharmacokinetics

Methods

Analytical methods used for determination of selexipag and ACT-333679 concentrations in human plasma samples are considered suitable and properly validated.

Absorption

An absolute bioavailability study has been conducted (AC-065-110) and indicated an absolute bioavailability for selexipag of 0.49 (0.43, 0.57). However, the results for the metabolite ACT-333679 suggest selexipag to be subject to a first pass effect leading to underestimation of the bioavailability. The AUC-value for ACT-333679 after a single oral dose of 400 µg selexipag was approximately 2.55 times higher compared with 200 µg selexipag i.v. indicating an almost complete absorption of selexipag.

Relative bioavailability after oral administration has been properly characterized. PK results with solution (study PS003) and tablet (study QGUY/2006/NS-304/01) were found to be comparable.

The Applicant has not investigated the absorption site of selexipag. However, based on surface-to-volume characteristics and pH (around 8), most of the absorption of selexipag (freely soluble at pH 8) is anticipated to occur in the duodenum. In study AC-065A302/GRIPHON, 142 (28%) out of the 510 patients included in the population PK (PopPK) analysis received at least one gastric pH-modifying drug. The results suggest no relevant difference with respect to exposure or absorption between patients receiving compared to those not receiving gastric pH-modifying drugs.

Selexipag and ACT-333679 showed a dose-proportional increase in AUC and C_{max} after multiple-dose administration in healthy subjects. Steady state conditions were achieved within 3 days.

Bioequivalence between 1 tablet of 1600 µg and 8 tablets of 200 µg selexipag has been demonstrated. A biowaiver for the intermediate dose strengths (400, 600, 800, 1000, 1200, and 1400 µg film-coated tablets) is considered justified because the manufacturing process is the same, the qualitative and quantitative composition is the same (except for the filler D-mannitol which compensates for differences in active substance) and the comparison of dissolution profiles gave f2 values above 50 for

all dose strengths and dissolution pH tested. Overall, bioequivalence between equimolar doses of different dose strengths can be assumed.

The influence of food on the pharmacokinetics of selexipag is characterised properly. Due to improved tolerability and to avoid changes in exposure when switching from fasting to fed intake or vice versa, it is recommended to take selexipag in the fed state only.

Distribution

Except for protein binding and whole blood / plasma distribution, only few data are available on distribution. The volume of distribution of selexipag at steady state is 11.7 L. Taken together, the data indicate that drug distribution is most prominent in the extracellular fluid and that selexipag does not accumulate in tissues outside the plasma and interstitial fluid.

Metabolism / Elimination

Selexipag undergoes enzymatic hydrolysis by CES1 in the liver to yield the active metabolite ACT-333679. The UGT enzymes UGT1A3 and UGT2B7 contribute 42% to the metabolism of ACT-333679, while CYP2C8 and CYP3A4 contribute to 46% and 12%, respectively.

Special populations

Gender, race and age are of minor importance for selexipag and ACT-333679 pharmacokinetics.

Body weight was identified as significant covariate for selexipag and ACT-333679 exposure. However, effect on ACT-333679, the major contributor to the efficacy of selexipag, is limited and since selexipag dosage will be based on individual tolerability, PK-dependency of weight is not considered an issue.

Pharmacokinetics in patients with renal or hepatic impairment is characterised properly. The applicant suggests warnings in the SmPC that, in patients with moderate hepatic impairment the starting dose of 200 micrograms once daily (instead of twice daily) and increase at weekly intervals by increments of 200 micrograms given once daily (instead of twice daily) is recommended. In patients with severe hepatic impairment, selexipag should not be used.

In patients undergoing dialysis, Uptravi should not be used. For patients with severe renal impairment, caution should be excerciced during dose titration.

No adjustment in dose regimen is needed in patients with mild or moderate renal impairment and in patients with mild hepatic impairment.

The respective wording in the proposed SmPC is in agreement with the results of the studies and is acceptable.

Interactions

Effects of selexipag and ACT-333679 on enzymes and transporters in the plasma and accordingly possible PK interaction with other drugs are considered negligible. However, assuming a luminal selexipag concentration of 1.3 µM and a free selexipag concentration in enterocytes of 8 nM, clinically relevant induction of CYP3A4 and CYP2C9 in the gut cannot be excluded. To address this point the applicant will conduct a clinical drug-drug interaction (DDI) study with midazolam as a post-approval commitment.

No effect of warfarin on the PK of selexipag or ACT-333679 was observed. The effect of lopinavir/ritonavir is considered clinically not relevant because, although plasma concentrations of selexipag increased almost 2-fold in the presence of lopinavir/ritonavir, the increase in exposure (1.1-fold) and C_{max} (1.3-fold) of the active metabolite (which is the major contributor to efficacy) was small. The lopinavir/ritonavir interaction study suggests minor importance of OATP1B1, OATP1B3, CYP3A4

and P-gp, however simultaneous inhibition of several compounds limit the interpretation to some extent as effects may counterbalance each other.

No data were provided in respect to a possible influence of transporter / enzyme inhibition or induction on the PK of selexipag or ACT-333679. This appears most important in respect to CYP2C8. A warning in respect to the combination of selexipag with CYP2C8, UGT1A3, and UGT2B7 modulators with an explicit listing of the drugs known to modulate these enzymes is included in the SmPC. The applicant is planning to undertake, as a post-approval commitment, a clinical DDI study with gemfibrozil, a strong inhibitor of CYP2C8. The extent of increased drug elimination by induction of CYP2C8 cannot be predicted and might result in a relevant loss of efficacy. To address this point, the applicant is planning to conduct a clinical DDI study with rifampicin as a post-approval commitment in addition to the DDI study with gemfibrozil. If it cannot be concluded that CYP2C8 is the major enzyme involved in the elimination of selexipag further studies may be needed to characterize the elimination *in vivo*.

Pharmacodynamics

The effect of selexipag and its metabolite on platelet aggregation, coagulation parameters, bone metabolism, cardiac repolarisation, and interaction with concomitantly administered drugs was investigated in healthy volunteers. In addition, the potential of selexipag to cause phototoxic reactions was investigated.

Prostacyclin is a potent inhibitor of platelet aggregation. Selexipag inhibited platelet aggregation induced by ADP in platelet-rich plasma from humans and monkeys with IC_{50} values of 5.5 and 3.4 µM, respectively (for details please refer to Nonclinical section). In study AC-065-101 pharmacodynamic Platelet Aggregation Test parameters (Emax, Etrough, AUE0-12, and tmax) after multiple-dose administration of either ACT-293987 or placebo twice daily (b.i.d) indicated a high level of variability presumably due to the limited number of subjects. There was no obvious drug- or dose-dependent pattern. In vitro data indicated that the mean maximal and trough plasma ACT-333679 concentrations in humans at 1600 µg b.i.d. are 3- and 16-fold lower than the IC50 of ADP-induced platelet aggregation, respectively; at these concentrations, platelet aggregation is inhibited by 1-15%. Overall, at therapeutic plasma levels an inhibitory effect on platelet aggregation is considered unlikely.

Because prostaglandin I2 receptors play a role in bone remodelling and because increased ossification was reported in a toxicity study in dogs, the effect of selexipag on bone formation markers and bone resorption markers was investigated. No differences to placebo were observed for any marker. However, in view of the low subject number and high variability a firm conclusion of a neutral effect of selexipag on bone metabolism cannot be drawn.

Selexipag did not affect cardiac repolarisation based on the thorough QT study (AC-065-106) conducted in accordance with Guideline ICH E14.

Selexipag was not associated with a clinically relevant phototoxic potential (study AC-065-102).

Selexipag seems not to increase Substance P which is involved in pain perception.

In-vivo interaction studies in healthy subjects were performed with warfarin and lopinavir/ritonavir. Selexipag (400 µg twice a day) did not alter the exposure to S-warfarin (CYP2C9 substrate) or R-warfarin (CYP3A4 substrate). Selexipag did not influence the pharmacodynamic effect of warfarin on the international normalized ratio. The pharmacokinetics of selexipag and its active metabolite are not affected by warfarin. Thus, selexipag can be used in combination with warfarin without dose adjustment. Based on similar metabolism, this conclusion is considered valid also for other vitamin K antagonists, such as phenprocoumon and acenocoumarol.

Potential drug-drug interactions between PAH co-medication (ERA and/or PDE inhibitor) and selexipag and its active metabolite were investigated in the phase 3 program by PopPK/PD analyses. PAH co-

medications (ERAs, PDE-5 inhibitors, and both) did not affect the PK of selexipag but statistically significantly increased the elimination rate constant of ACT-333679. The concomitant use of both an ERA and a PDE-5 inhibitor was predicted to result in a 30% lower exposure to ACT-333679 (please refer to section on PopPK/PD).

The SmPC reflects the findings of the PopPK analysis. However, the clinical relevance of the lower exposure determined in the PopPK analysis may be limited in light of the high intra-individual (87% for selexipag, 70% for the metabolite) and inter-individual variability (30%) found in the PopPK analysis.

The relationship between plasma concentration and effect was explored within the clinical development program (study NS-304/02) and by population PK/PD modelling using data from the phase 3 study. The population PK/PD analysis found a small increase (by 23m) in efficacy (6MWT) with increasing dose. A proof-of-concept study NS-304/02 supported the efficacy of selexipag in patients with PAH over the proposed dose range of 200 µg to 800 µg bid. PVR was significantly reduced by about 30% compared to placebo. A dose-proportional effect on PVR could not be found in this study, which is likely due to the low patient numbers studied and high variability.

Based on the data available, no conclusion on a positive relationship between dose and effect can be drawn. This is considered of limited clinical importance since an individual up-titration regimen based on individual tolerability is proposed for selexipag. Gradual up-titration to the individual patient`s tolerated dose is the general accepted regimen for prostaglandin receptor agonists. Based on tolerability in healthy male subjects (study ACT-065-101), 1600µg bid was selected as the maximal tolerated dose for further phase 3 testing.

2.4.5 Conclusions on clinical pharmacology

Pharmacokinetics

In general, the evaluation of pharmacokinetics is considered appropriate.

Limited data were provided in respect to a possible influence of transporter / enzyme inhibition or induction on the PK of selexipag or ACT-333679. This appears most important in respect to CYP2C8. In addition a clinically relevant induction of CYP3A4 and CYP2C9 in the gut by selexipag cannot be excluded. The applicant has committed to conduct post-marketing studies to address these issues, which is considered acceptable.

Pharmacodynamics

Based on the clinical pharmacology data selexipag does not affect cardiac repolarisation. Selexipag has no phototoxic potential.

No relevant in-vivo drug-drug interactions were found. No clear dose-response relationship was demonstrated. However, this is considered without clinical relevance since an individual dose up-titration according to tolerability is proposed. The dose range selected for the phase 3 study is considered justified based on the pharmacology data.

2.5 Clinical efficacy

2.5.1 Dose response studies

Summary of main efficacy results

The clinical phase 2 and 3 studies relevant for dose finding, efficacy and safety are summarised in table 1.

Table 1 Clinical studies in patients with PAH

Study	Phase	Study objectives	Patients enrolled	Treatment duration	Treatment/dose	Type of control/blinding
Completed studies in patients with PAH						
NS-304/-02	2	Safety, tolerability, pharmacokinetics, and preliminary efficacy (proof-of-concept) of selexipag in patients with PAH	Acute hemodynamic period			
			43	Single dose	Selexipag 200 µg or 400 µg	Uncontrolled, open-label
			Double-blind, placebo-controlled period			
			43	21 weeks	Selexipag 200 µg b.i.d. up to 800 µg b.i.d. Placebo b.i.d.	Placebo-controlled, double-blind
AC-065A302 (GRIPHON)	3	Efficacy and safety of selexipag in patients with PAH	1156	Up to 70 weeks	Selexipag 200 µg b.i.d. up to 1600 µg b.i.d. Placebo b.i.d.	Placebo-controlled, double-blind Event-driven (morbidity/mortality events)
Ongoing studies in patients with PAH						
AC-065A201	2	Efficacy, safety and pharmacokinetics (Japanese registration study)	37	N/A	Selexipag 200 µg b.i.d. up to 1600 µg b.i.d.	Uncontrolled, open-label
NS-304/-03	2	Long-term safety of selexipag in patients with PAH	39	N/A	Selexipag 200 µg b.i.d. up to 1600 µg b.i.d.	Uncontrolled, open-label extension
AC-065A303 (GRIPHON OL)	3	Long-term safety of selexipag in patients with PAH	218	N/A	Selexipag 200 µg b.i.d. up to 1600 µg b.i.d.	Uncontrolled, open-label extension

b.i.d. = twice daily; N/A = not applicable; OL = open-label; PAH = pulmonary arterial hypertension

The application also contains information from Phase 2 studies conducted in other indications, i.e., a controlled study and its open-label extension in patients with chronic thromboembolic pulmonary hypertension (CTEPH) and an ongoing controlled study in patients with arteriosclerosis obliterans (Table 2).

Table 2 Clinical studies in other indications

Study	Phase	Study objectives	Patients enrolled	Treatment duration	Treatment/dose	Type of control/blinding
Completed studies in other indications						
AC-065B201	2	Efficacy and safety of selexipag in Japanese patients with CTEPH	34	17 weeks	Selexipag 100 µg b.i.d. up to 800 µg b.i.d. Placebo b.i.d.	Placebo-controlled, double-blind
AC-065B202	2	Long-term safety of selexipag in Japanese patients with CTEPH	27	106 weeks	Selexipag 100 µg b.i.d. up to 800 µg b.i.d. p.o.	Uncontrolled, open-label extension
Ongoing studies in other indications						
NS-304C-P2OE	2	Long-term safety of selexipag in Japanese patients with CTEPH	2	N/A	Selexipag up to 800 µg b.i.d.	Uncontrolled, open-label extension
NS-304AP2-1	2	Efficacy and safety of selexipag in Japanese patients with arteriosclerosis obliterans with intermittent claudication	40	N/A	Selexipag 200 µg b.i.d. up to 800 µg b.i.d.	Placebo-controlled double-blind,

b.i.d. = twice daily; CTEPH = chronic thromboembolic pulmonary hypertension; N/A = not applicable; OL = open-label

Dose-response studies

Doses in the range of 200 – 1600 µg b.i.d. were administered in the pivotal study (GRIPHON study)As with other IP receptor agonists, dosing of selexipag aimed at achieving the maximum individually tolerated dose for maintenance treatment. In the pivotal GRIPHON study, this was achieved through a 12-week up-titration program, allowing a highest dose of 1600 µg b.i.d. (the dose defined as the maximum well-tolerated dose in healthy subjects).

The selection of the dose regimen and titration scheme used in the phase 3 study was based mainly on data from the PK/PD study NS-304/02. Phase I studies indicated that single doses of selexipag 100, 200, and 400 µg given after overnight fasting were well tolerated. Single doses of selexipag 600 and 800 µg led to adverse events like headache, nausea, dizziness, and vomiting. Multiple doses of selexipag 200, 400, and 400/600 µg twice daily (b.i.d.) were better tolerated. Improved tolerability after repeated dosing was suggested by the poor tolerability of a single 600-µg dose, whereas 600 µg b.i.d. was better tolerated when it followed administration of 400 µg b.i.d. during multiple dosing.

A b.i.d. application was selected in order to attain an acceptable exposure (AUC) of both the parent compound and the active metabolite ACT-333679 over the course of 24 h. In selexipag Phase 1 studies AC-065-101, AC-065-106 and AC-065-108 in which “forced” up-titrations were performed (as opposed to titration-by-tolerability), a trend for an increase in treatment emergent AEs typical for prostacyclin therapy was observed with increasing dose. This was also accompanied by a premature discontinuation rate (ranging between 19–38%) that was higher than that observed in Phase 2/3 studies. The use of weekly intervals between titration steps in study AC-065A302 was based on practical considerations. The starting dose of 200 µg b.i.d. in the pivotal study AC-065A302 was based on safety and tolerability data from study QGUY/2006/NS304/-01, a comparable tolerability profile of multiple doses of both 200 µg and 400 µg b.i.d. was demonstrated on initiation with the lower dose to account for potential inter-individual differences. Titration steps of 200 µg b.i.d. were introduced based on the understanding that the first up-titration step to 400 µg b.i.d. would result in a dose that had shown acceptable tolerability

as a starting dose in study QGUY/2006/NS304/-01. The highest allowed dose in AC-065A302 of 1600 µg b.i.d. was based on the observation from the Phase 1 study AC-065-101, in which the incidence of AEs of moderate severity requiring administration of concomitant medication was greater on the highest tested dose of 1800 µg b.i.d. compared to the 1600 µg b.i.d. and lower doses. No severe AEs were reported on any highest dose. The concept of gradual dose uptitration according to individual patient tolerability was further supported by data from studies in Japanese patients with PAH Dana class 1 (AC-065A201, individual dose titration from 200 to 1600 µg b.i.d.) and in patients with CTEPH (AC-065B202, individual dose titration from 100 to 800 µg b.i.d.) Albeit no clear dose relation for PVR was seen in study AC-065A201, efficacy on PVR appeared to be higher at the highest maintenance doses (1400 and 1600 µg bid).

The approach of an individual dose titration guided by tolerability is based on an assumption of a relationship between maximally tolerated and efficacious doses in the individual patient. As discussed below, the assumption seemed to be supported by the result for the primary efficacy endpoint in the pivotal GRIPHON trial. There was no correlation between maintenance dose and primary efficacy outcome.

Study NS-304/-02 was important for the selection of the doses used in phase 3. It was a multicenter, multinational, prospective, Phase 2a study of ACT-293987 treatment in PAH patients conducted in two periods: an open-label, single-dose acute period evaluating the effect of the drug on the hemodynamic parameters, followed by a randomized, double-blind, parallel-group, placebo-controlled 21-week treatment period investigating change in PVR, 6 MWT, Borg dysponea scale and other parameters. In the double blind treatment patients were uptitrated from 200 µg b.i.d. to a maximally tolerated individual dose but not above 800 µg b.i.d. 43 patients were enrolled and randomized 3:1 selexipag vs. placebo. The interpretation of the data is hampered by the low number of patients included and by the exclusion of 8 patients from the per-protocol set, leaving only 6 patients in the placebo group. There was an effect on PVR, on 6- MWT, a small effect on other haemodynamic parameters and on plasma NT pro-BNP concentrations. However, no conclusions can be drawn, whether there was a dose relation or not. No treatment effects were seen on NYHA functional class and Borg dyspnea score, and echocardiographic parameters. For 6-MWT there was even a negative result in patients receiving the lowest maintenance dose of 200 µg b.i.d. (n=4). This result was consistent with the result in the pivotal GRIPHON study. In GRIPHON, patients on a maximally tolerated dose <500 µg bid also had a negative effect on the 26 week 6 MWT as compared to placebo (see below).

The applicant has discussed the limitations of the assessment of the 6 MWD in relation to attained individual maintenance dose. In GRIPHON (see below), patients with down-titration due to prostacyclin related AEs had a sufficient efficacy for the primary endpoint. This supports the assumption that individual tolerability is linked to individual efficacy. For the other patients in the low dose range sufficient efficacy could not been demonstrated. Therefore, for the low dose group without dose limiting prostacyclin related AEs, it should be considered to try to up-titrate again at a later time point.

Taken together, a bid dosing and the approach of an individual uptitration of the dose based on tolerability is considered appropriate. Also, a dose range to be investigated in the pivotal GRIPHON trial (200 – 1600 µg bid) is justified based on studies 304/02 (tolerability, hemodynamic endpoints and efficacy endpoints for 200 and 400 µg single dose and 200 – 800 µg bid) and AC-065-101 (acceptable tolerability of 200 – 1600 µg bid with a lower tolerability of 1800 µg bid).

2.5.2 Main study

The application is mainly based on one pivotal trial, the AC-065A302 "GRIPHON" study. Overall the following studies contributed to the efficacy assessment as shown in Table 1-4:

Table 1-4 Overview of studies contributing efficacy assessments

		6MWD/WHO FC	Hemo-dynamics	MM	NT pro-BNP	QoL
AC-065A302	PAH	✓		✓	✓	✓
AC-065A303	PAH					
NS-304/-02	PAH	✓	✓		✓	
AC-065A201	PAH	✓	✓		✓	
AC-065B201	CTEPH	✓	✓		✓	

6MWD = 6-minute walk distance, CTEPH = Chronic thromboembolic pulmonary hypertension, MM = morbidity and/or mortality, NT pro-BNP = N-terminal pro-brain natriuretic peptide, PAH = pulmonary arterial hypertension, QoL = Quality of life, WHO FC = World Health Organization functional class.

Pivotal trial

Study title: AC-065A302/GRIPHON: Prostacyclin (PGI2) receptor agonist in pulmonary arterial hypertension. A multicenter, double-blind, placebo-controlled Phase 3 study assessing the efficacy and safety of selexipag (ACT-293987) on morbidity and mortality in patients with pulmonary arterial hypertension (PAH)

The study comprised the following periods: - Treatment period: Patients were uptitrated from 200 µg b.i.d. to a maximally tolerated individual dose but not above 1600 µg b.i.d. (12 weeks) and patients were kept on the maximally tolerated dose over 14 additional weeks. - Post-treatment observation period. - Post-treatment safety follow-up, and - double blind treatment Extension period.

Patients who had an end of study (EOS) visit following a morbidity event confirmed by the CEC were eligible to enter the extension study **AC-065A303**, in which all patients received open-label selexipag**.**

GRIPHON - study AC-065A302

Methods

The study was conducted at 181 sites in 39 countries (Asia, Australia, Europe, Latin America, and North America), with 171 sites in 34 countries participating also in the extension study AC-065A303/GRIPHON OL.

The following committees were involved in the conduct of the study: Steering Committee / Scientific Advisory Board (study design and conduct of the study), Critical Event Committee (CEC, blinded to treatment allocation and to prostacyclin- associated adverse events (AEs): adjudication of all reported morbidity/mortality (MM) events, initially, event-adjudication was only performed to confirm the occurrence of an MM event. Following Global Protocol Amendment 6, the process was adjusted to adjudicate the following details: i) the presence of an MM even tii) the type of endpoint component, iii) the MM event onset date, and iv) any PAH-association with a fatal outcome), Expert medical PAH review committee (blinded review of baseline PAH-related characteristics), and the Ophthalmology Safety Board (blinded to treatment allocation, reviewed ophthalmology data available from patients enrolled in the ophthalmology sub-study), Data Monitoring Committee (DMC, unblinded efficacy, safety and tolerability data approximately every 3 months to ensure patient safety in AC-065A302 and AC-065A303). The DMC conducted a planned unblinded interim efficacy and safety analysis on 29 April 2013 after 206 CEC-confirmed MM events were reported and recommended the continuation of the study.

AC-065A302/GRIPHON study design:

This was a multicenter, randomized, double-blind, parallel group, placebo-controlled, event-driven Phase 3 study to compare the effects (efficacy, safety, tolerability, pharmacokinetics/pharmacodynamics [PK/PD]) of selexipag (administered orally at an individualized dose in the range of 200- 1600 µg b.i.d.) versus placebo (1:1 randomization) in patients with symptomatic PAH. In case of typical prostacyclin-associated AEs the dose was reduced by 200 µ bid (MTD).

The study comprised the following periods [Figure 9-1]:

- Screening period

- Treatment period: first dose on the evening of day 1 (200 µg or placebo), uptitration in weekly increments in 200 µg bid steps until maximally tolerated individual maintenance dose (MTD) up to week 12. At Week 12, the MTD for each patient was determined, and this dose was to be kept stable for the next 14 weeks. After Week 26, for patients with study drug dose < 1600 µg b.i.d., investigators were allowed to further up-titrate the dose, if needed, by 200 µg increments up to the maximum of 1600 µg b.i.d., only at scheduled visits. Dose reduction for tolerability was allowed.

- Post-treatment observation period (PTOP[4] - refer to Figure 9-1) (added in study design following Protocol Amendment 6): patients who discontinued study drug with or without an MM event prior to Study closure announcement had an option to enter a post-treatment observation period to collect additional clinical data. A post-treatment observation closure visit (PTOCV) was to be performed within 4 weeks of Study closure announcement.

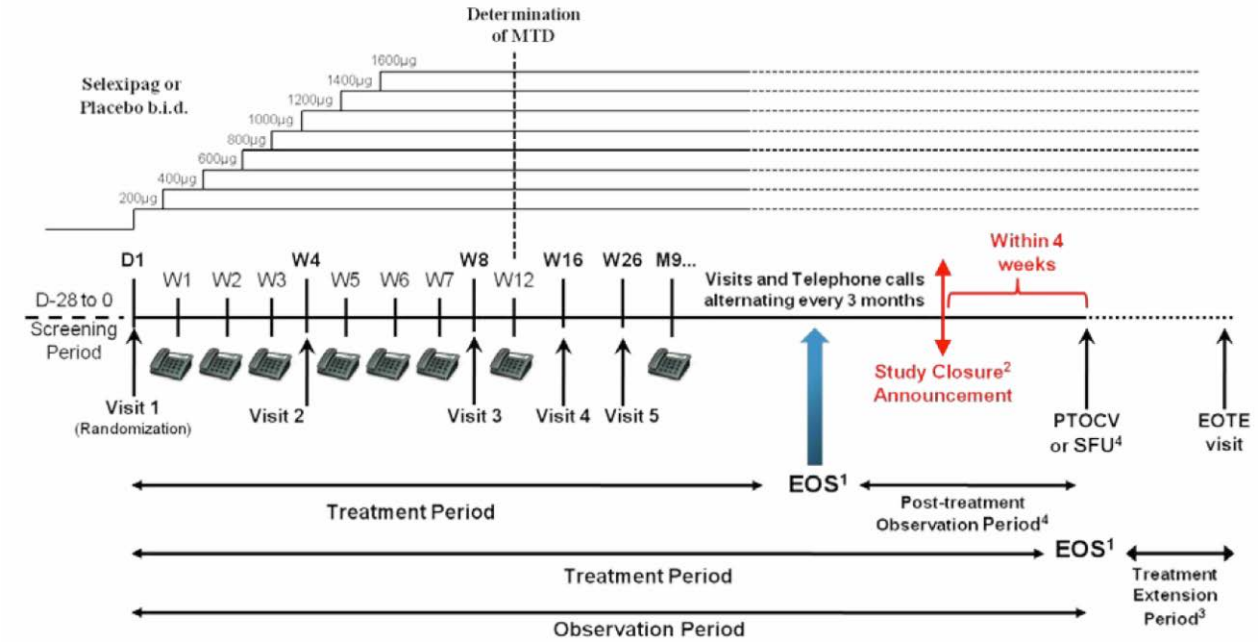
- Post-treatment safety follow-up for serious adverse event (SAEs) up to 30 days after the last intake of study drug or until administration of the first dose of selexipag in extension study AC-065A303, whichever occurred first.

- Survival follow-up phone call[4] (refer to Figure 9-1): All patients (except those who had withdrawn consent from all study components) were contacted at the time of study closure to ascertain vital status. Survival data up to study closure (overall study) includes patients from different phases of the study.

- Treatment Extension period[3] (refer to Figure 9-1): for patients who were receiving AC-065A302 study drug at the time of Study closure, a double blind treatment extension period was offered that was planned to be up to 3 months. Patients who had an EOS visit following a morbidity event confirmed by the CEC were eligible to enter the extension study AC-065A303, if the extension study was approved by the national Health Authority in the country.

End of study (EOS) was reached a) after an MM event or at the time of premature discontinuation of study medication (for an individual patient), b) at the time when 331 MM events were achieved (for the remainining patients). EOS analysis does not include the extension study AC-065A303.

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



[1.] EOS Visit was to be performed within 4 weeks of Study closure announcement. For patients who had a CEC-confirmed MM event or discontinued study drug before Study closure, the EOS Visit was performed following the morbidity event or following premature discontinuation. A Post-treatment safety follow-up phone call was performed for all patients who discontinued treatment.

[2.] Study closure was announced when the target number of CEC-confirmed MM events was achieved.

AC-065A303/GRIPHON OL study design:
It was an open-label, uncontrolled study following the double-blind study AC-065A302 to assess long-term safety and tolerability of selexipag in patients with PAH. Patients from study AC-065A302 who had a CEC-confirmed morbidity event or who completed study AC-065A302 as scheduled, and who met the eligibility criteria were eligible to be enrolled in AC-065A303. All patients receive selexipag during AC-065A303. The study is still ongoing.

- **Study participants**

Inclusion criteria

- Male and female patients aged from 18 to 75 (*following Protocol Amendment 1)* years inclusive with PAH in modified NYHA/WHO FC I- IV with symptomatic PAH, both naïve to or receiving PAH specific treatment (ERAs and/or PDE-5i, except for prostacyclin and prostacyclin analogs) were included. A single administration of i.v./inhaled prostacyclin or analogs during a right heart catheter procedure was allowed.

- Patients with PAH were included (Idiopathic (IPAH), Heritable (HPAH),Drug or toxin induced or Associated (APAH) with one of the following (Connective tissue disease, Congenital heart disease with simple systemic-to-pulmonary shunt at least 1 year after surgical repair, HIV infection.

· Documented hemodynamic diagnosis of PAH by right heart catheterization

· 6-MWD between 50 and 450 m (inclusive) at Screening

· refrain from prolonged exposure to sun during the study

For study AC-065A303: (extension study) · Patients who had a CEC-confirmed morbidity event during study AC-065A302 for most countries involved.

Key exclusion criteria

- Patients with pulmonary hypertension that were not covered by the inclusion criterion

- Scheduled to receive or Intake of prostacyclin (epoprostenol) or prostacyclin analogs up to 1 month prior to the Baseline visit

- moderate or severe obstructive lung disease: FEV1/FVC < 70% and FEV1 < 65% of predicted value after bronchodilator administration or moderate or severe restrictive lung disease: Total Lung Capacity < 70% of predicted value

- moderate or severe hepatic impairment

- documented left ventricular dysfunction (i.e., ejection fraction < 45%, clarified by amendment 1)

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

- BMI < 18.5 kg/m2 (modified by amendment 1)

- Lactating or pregnant

- Following Protocol Amendment 1, exclusion criterion on hypotensive patients was removed.

• **Treatments**

Film-coated tablets containing 200 μg selexipag or matching placebo (AC-065A302).

The first dose was taken on the evening of day 1 (200 µg or placebo), uptitration in weekly increments in 200 µg bid steps until maximally tolerated individual maintenance dose (MTD) up to week 12 and up to 1600 m (8 tablets).

Objectives

Primary objective

· To demonstrate the effect of selexipag on time to first MM event in patients with PAH.

Secondary objectives

· To evaluate the effects of selexipag on exercise capacity and other secondary and exploratory efficacy endpoints in patients with PAH.

· To evaluate the safety and tolerability of selexipag in patients with PAH.

• **Outcomes/endpoints**

Primary efficacy endpoint

The primary efficacy endpoint was the Time to first CEC-confirmed MM event up to 7 days after the last study drug intake in the AC-065A302 treatment period (i.e., end of treatment [EOT] + 7 days). MM events included • Death (all-causes) • Hospitalization for worsening of PAH based on predefined criteria • Worsening of PAH resulting in need for lung transplantation or balloon atrial septostomy • Initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH •

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

Key secondary endpoints were :

. change from baseline to Week 26 in

- 6MWD measured at trough
- Absence of worsening in NYHA/WHO FC

. Time from randomization to

- first of CEC-confirmed death due to PAH or CEC confirmed hospitalization due to PAH up to 7 days after end of treatment
- death of all causes up to Study closure

- **Sample size**

It was initially estimated that a total of 202 MM events confirmed by the CEC were needed to obtain an overall power of 90% for rejection of the null hypothesis (at two sided alpha 0.01), assuming a hazard ratio of 0.5729 for selexipag versus placebo over the estimated maximum study duration of 3.5 years. The originally assumed hazard ratio of 0.5729 was largely based on previous monotherapy studies in patients in WHO FC III/IV and was later amended to 0.65, taking into account the predominant enrolment of patients in GRIPHON in FC II and III, and on background PAH therapy. To detect this amended treatment effect without changing the protocol requirements for the Type I and Type II error rates, and within the study timelines, an increase of the number of primary events to 332 and of the sample size to 1150 patients was required. At the same time a group-sequential design with one interim analysis to be conducted by the Independent Data Monitoring Committee after the originally projected 202 confirmed MM events (an information fraction of f = 202/331 = 0.61) was introduced. Based on Protocol Amendment 6 there were further changes to calculation of the sample size and assumptions: A total of 331 confirmed MM events were needed in order to obtain an overall power of 90% for rejection of the null hypothesis. With the recruitment of up to 1150 patients randomized 1:1 to active treatment and placebo over a period of 3.1 years, the number of events was expected within a maximum of 4.3 years.

Randomisation

In study AC-065A302 eligible patients were randomized in a 1:1 ratio to selexipag or placebo using a centralized randomization system via IVRS.

Blinding (masking) Study AC-065A302 was performed in a double-blind fashion.

- **Statistical methods**

The null hypothesis was that there was no difference between selexipag and placebo for time to first confirmed MM event. The primary statistical analysis was performed on the Full Analysis Set (FAS) by a one-sided unstratified log-rank test in a group-sequential setting. A number of supportive analyses to the primary endpoint were performed using different tests and models.

A group-sequential design with one interim analysis to be conducted by the Independent Data Monitoring Committee after the originally projected 202 confirmed MM events (an information fraction of 202/331 = 0.61) was introduced by amendment. The group-sequential design used a one-sided overall type I error level of 0.005, maximum information was specified as 331 first MM events, and the one-sided type I error level at the interim analysis was fixed to 0.00005. The change in the target hazard ratio was initially discussed with the FDA (Amendment 4 of the protocol). In order to eliminate any concern that the protocol changes based on global Amendment 4, submitted on August 16th 2011 to the FDA, could be considered informed, MM events with a confirmed onset date up to August 16th 2011 were censored and were not considered in the primary analysis.

Hierarchical testing was stipulated in the protocol following the list of secondary endpoint as described below. This procedure controls the family-wise type I error rate on a one-sided alpha level of 0.005 (two-sided alpha of 0.01).

Confirmed MM events, including those with onset date up to August 16th 2011 were included as events in the secondary analyses and additional analyses.

The analyses of the primary endpoint including or excluding components up to study closure used a one-sided unstratified log-rank test (at the corresponding one-sided overall type I error level defined by the group-sequential design).

The first secondary endpoints analysed in a hierarchical procedure were (1) the absolute change from baseline in 6MWD at trough at Week 26 analyzed by a non-parametric analysis of covariance (ANCOVA), (2) absence of worsening from baseline to Week 26 in WHO FC was analysed by 2-sided Cochran-Mantel-Haenszel test stratified by WHO FC at baseline, (3) time from randomization to first of confirmed death due to PAH or confirmed hospitalization due to PAH worsening up to 7 days after last study drug intake was analyzed by a one-sided unstratified log-rank test and (4) time to death up to study closure using a one-sided unstratified log-rank test.

The analyses of changes in 6MWD and WHO FC over time were performed descriptively.

GCP

Generally, there were no indications that the studies were not conducted appropriately. One inspection report from DCGI India regarding the Site #6501 Dr. Kohli, Delhi was requested. The applicant stated that no report was to be expected from DCGI. The issue is not considered relevant for the overall conclusions since only 1 patient was randomised in this center. After additional explanations, an initial concern related to partial unblinding for 280 patients in 27 centres to the clinical supply manager and unblinding due to typical AEs was not considered to be relevant for the reliability of the data or the integrity of the study.

Results

AC-065A302

Baseline characteristics and study discontinuations

A total of 1156 patients were randomized in a 1:1 ratio to selexipag (N = 574) or placebo (N = 582). A total of 27.0% and 41.6% of patients in the selexipag and placebo groups, respectively, discontinued with a CEC-confirmed Morbidity/Mortality (MM) event up to EOT + 7 days. The proportion of patients who discontinued prior to Study closure with no CEC-confirmed MM event up to EOT + 7 days was

22.6% in the selexipag group and 15.1% in the placebo group. 113 and 137 patients in the selexipag and placebo groups, respectively, consented to participate in the post-treatment observation period (PTOP). The disposition of patients is summarized in Table 15-1 and in Figure 10-1.

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

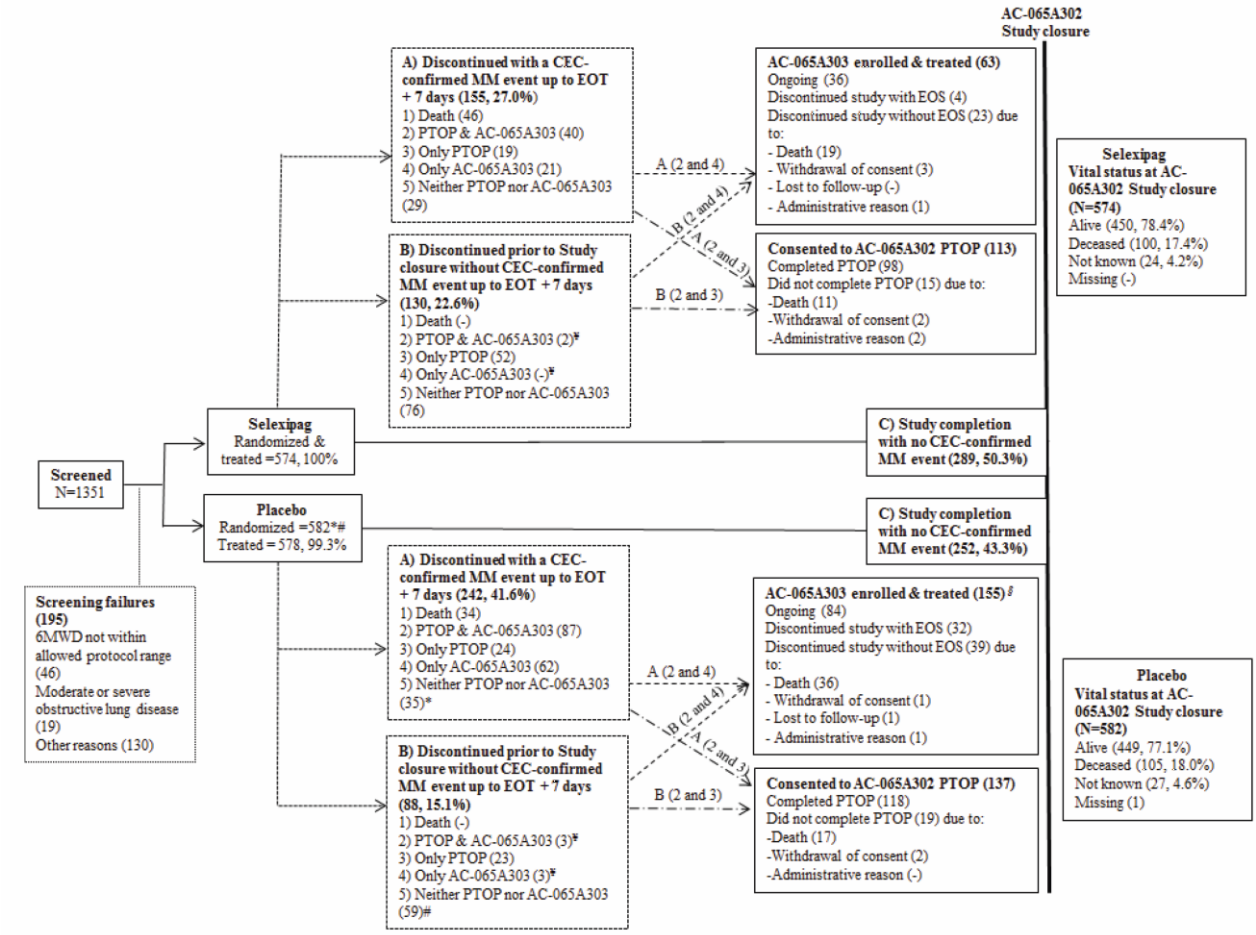
ACT-293987, Protocols AC-065A302/AC-065A303
Disposition of patients in studies AC-065A302 and AC-065A303
Set: Full analysis set

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

PTOP=post-treatment observation period.
* denominator is number of patients who consented to AC-065A302 PTOP.
** denominator is number of patients enrolled in AC-065A303. Patients summarized under "placebo" were
randomized to placebo in AC-065A302 and treated with selexipag in AC-065A303.
Table TDISP_F - Produced by milotjel on 19JUN14 - Data dump of 12JUN2014

(Page 1/1)

Figure 10-1 Disposition of patients



A total of 218 patients (63 previously randomized to selexipag, 155 previously randomized to placebo) were enrolled into the extension study AC-065A303. All 218 patients received selexipag in study AC-065A303.

The study population was predominantly female (79.8%). Median age at screening was 49.0 years, and approximately 18% of the patients were elderly (≥ 65 years). Most of the patients were Caucasian/White (65.0%) or Asian (21.2%). Median time from PAH diagnosis was 1.0 year. The most common PAH etiology was idiopathic (56.1%), followed by PAH associated with connective tissue disease (28.9%) or congenital heart disease (9.5%). Only few patients with heritable, drug or toxin induced, or HIV infection mediated PAH were included (0.9 – 2.3% with 10 – 27 patients of the total number of subjects randomized). At baseline, patients were predominantly in NYHA/WHO FC II (45.8%) and FC III (52.5%). Only 9 patients in FC I and only 11 in FC IV were randomized. The median 6MWD of 372.0 m and the median Borg dyspnea index of 3.0 at baseline correspond to this FC distribution. Similar proportions of patients in each treatment group (80.5% selexipag, 78.7% placebo) were receiving background PAH-specific therapy at baseline, mainly PDE-5 inhibitor monotherapy (32.9% selexipag, 31.8% placebo) or combination therapy with ERA and PDE-5 inhibitor (31.2% selexipag, 33.8% placebo). Patients entering study AC-065A303 tended to have more severe disease.

Maintenance doses of selexipag

The individual maintenance dose in the selexipag group and in the placebo group are shown in Table 11-1

Table 11-1 Individual maintenance dose (IMD) of selexipag and placebo in AC-065A302, FAS

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

IMD is defined as the selexipag or placebo b.i.d. dose to which each patient was exposed for the longest duration in the maintenance period, or, for patients who did not enter maintenance, as the highest tolerated selexipag or placebo b.i.d. dose to which each patient was exposed during the titration period.
Source: Table 15-38

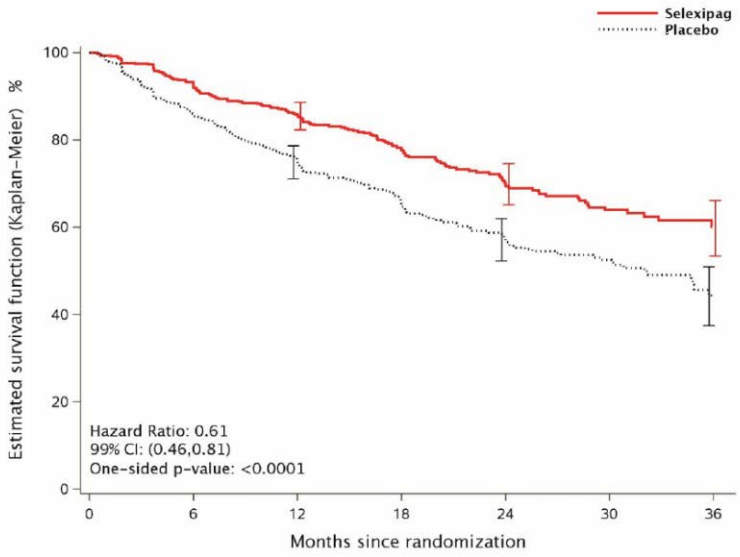
28.4% of the patients reached the maximal dose level with selexipag, 67.5% with placebo. The placebo data indicate that in some of the patients dose titration by tolerability may not lead to the optimal dose because non-specific events are a reason not to increase the dose further. . In clinical practice, trying to increase the dose again at a later time point may be appropriate for such patients.

Efficacy results

The median double-blind on-treatment period was 70.7 weeks in the selexipag and 63.7 weeks in the placebo group, respectively. The proportion of patients who experienced a CEC-confirmed MM event up to 7 days after last study drug intake was 24.4% (140 patients) in the selexipag group compared to 36.4% (212 patients) in the placebo group (Figure 11-1). The primary efficacy endpoint showed a clear and significant effect favoring selexipag. There was a numerical difference of 72 events between the groups favoring selexipag.

Figure 11-1 Kaplan-Meier estimates of time from randomization to first CEC-confirmed MM event up to 7 days after last study drug intake in AC-065A302 treatment period, FAS

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



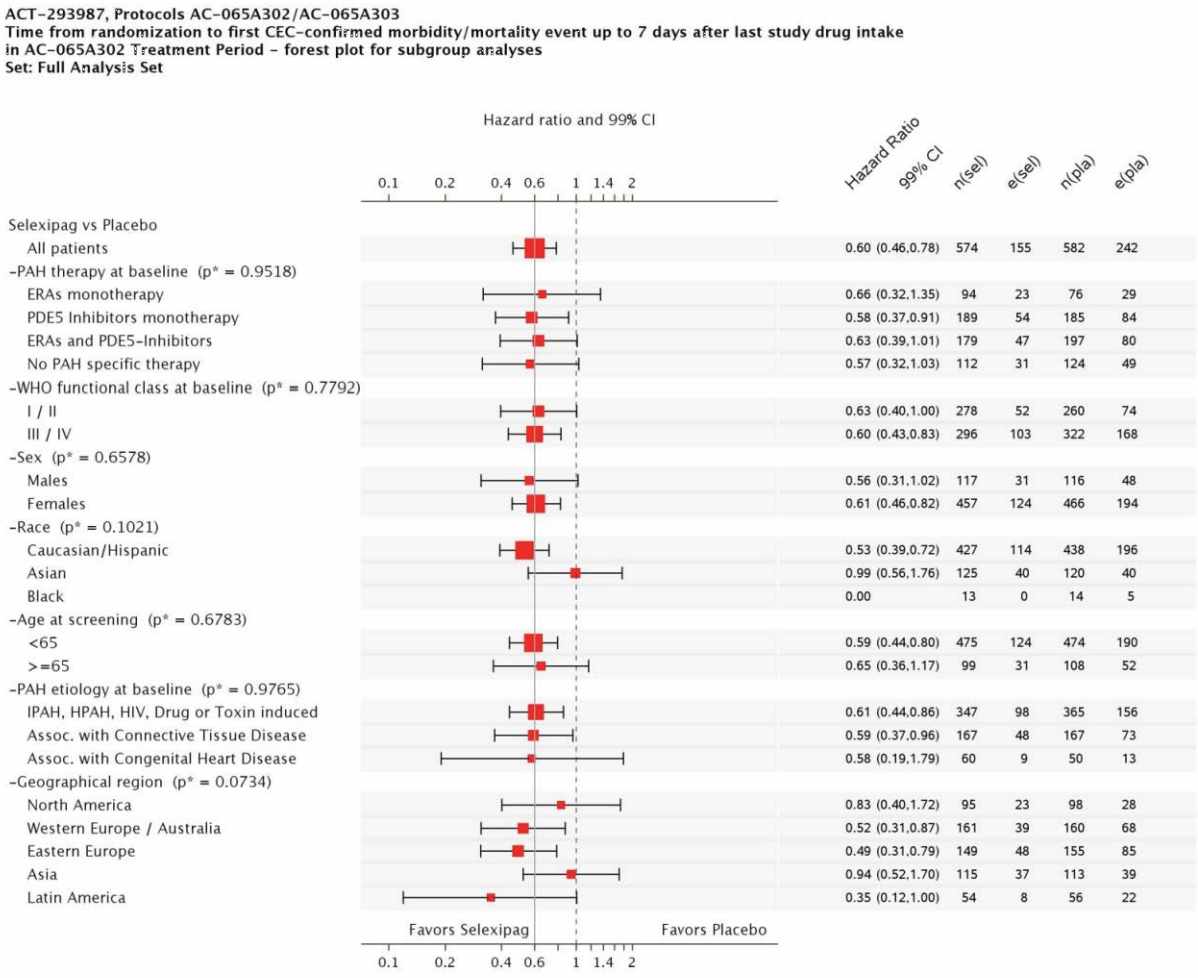
Selexipag patients:							
at risk	574	455	361	246	171	101	40
event(s)	0	36	70	99	121	134	138
censored	0	83	143	229	282	339	396

Placebo patients:							
at risk	582	433	347	220	149	88	28
event(s)	0	76	128	167	191	202	211
censored	0	73	107	195	242	292	343

Events with CEC-confirmed onset date up to 16 Aug 2011 are not included as events.
Note: Bars on the graph show 95% confidence intervals of the estimates.
Figure FMMT_F - Produced by zeeja1 on 18JUN14 - Data dump of 12JUN2014

Source: Figure 15-2

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



** = Interaction p-value. n(sel) = No. patients in Selexipag. e(sel) = No. patients with event in Selexipag. n(pla) = Number of patients in Placebo e(pla) = No. patients with event in Placebo.*
Note: Race group Other is not displayed in analysis, as the population is less than 20. The vertical solid line references the overall treatment effect
Events with CEC-confirmed onset date up to 16 Aug 2011 are included as events.
Figure FMMTGRP_F - Produced by zeeja1 on 28JUL14 - Data dump of 12JUN2014

Source: Figure 15-14

The observed treatment effect was consistent across subgroups (Figure 11-7). Only for the Asian race and the subgroups of Asia and North America (geographical region), the hazard ratio for selexipag versus placebo was close to 1.

For the overall primary analysis shown above according to amendment 5 (the assumed hazard ratio was increased from 0.5729 to 0.650 and consecutively the planned sample size was increased from 670 to 1150 patients) events up to 16 Aug 2011 were not counted in order to eliminate any concern that the protocol change could be considered informed. Overall, the results were consistent for the analyses including these events. When events up to August 16 2011 were included the proportion of patients who experienced a CEC-confirmed MM event up to 7 days after last study drug intake was 27.0% (155 patients) in the selexipag group compared to 41.6% (242 patients) in the placebo group. .

Table 11-4 summarizes the first CEC-confirmed MM event up to EOT + 7 days excluding events up to August 16, 2011.

Table 11-2 Summary of type of first CEC-confirmed MM event up to 7 days after last study drug intake in AC-065A302 treatment period, FAS

	Selexipag N=574 n	%	Placebo N=582 n	%
Patients with morbidity/mortality event	140	24.4%	212	36.4%
First morbidity/mortality event:				
Death	25	4.4%	16	2.7%
DEATH	25	4.4%	15	2.6%
HOSPITALIZATION-PAH / DEATH	0		1	0.2%
Hospitalization for PAH worsening	71	12.4%	96	16.5%
HOSPITALIZATION-PAH	51	8.9%	68	11.7%
DIS. PROGR. / HOSPITALIZATION-PAH	15	2.6%	19	3.3%
INIT. OF CHRONIC OXY. THERAPY / HOSPITALIZATION-PAH	4	0.7%	5	0.9%
INIT. OF PARENTERAL PROST. THERAPY / HOSPITALIZATION-PAH	1	0.2%	2	0.3%
DIS. PROGR. / INIT. OF CHRONIC OXY. THERAPY / HOSPITALIZATION-PAH	0		2	0.3%
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	11	1.9%	14	2.4%
INIT. OF PARENTERAL PROST. THERAPY	7	1.2%	8	1.4%
INIT. OF CHRONIC OXY. THERAPY	4	0.7%	4	0.7%
DIS. PROGR. / INIT. OF CHRONIC OXY. THERAPY	0		2	0.3%
Disease Progression	32	5.6%	84	14.4%
DIS. PROGR.	32	5.6%	84	14.4%

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 not included as events.
Source: Table 15-42

Table 11-4 summarizes the first CEC-confirmed MM event up to EOT + 7 days including events up to August 16, 2011.

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

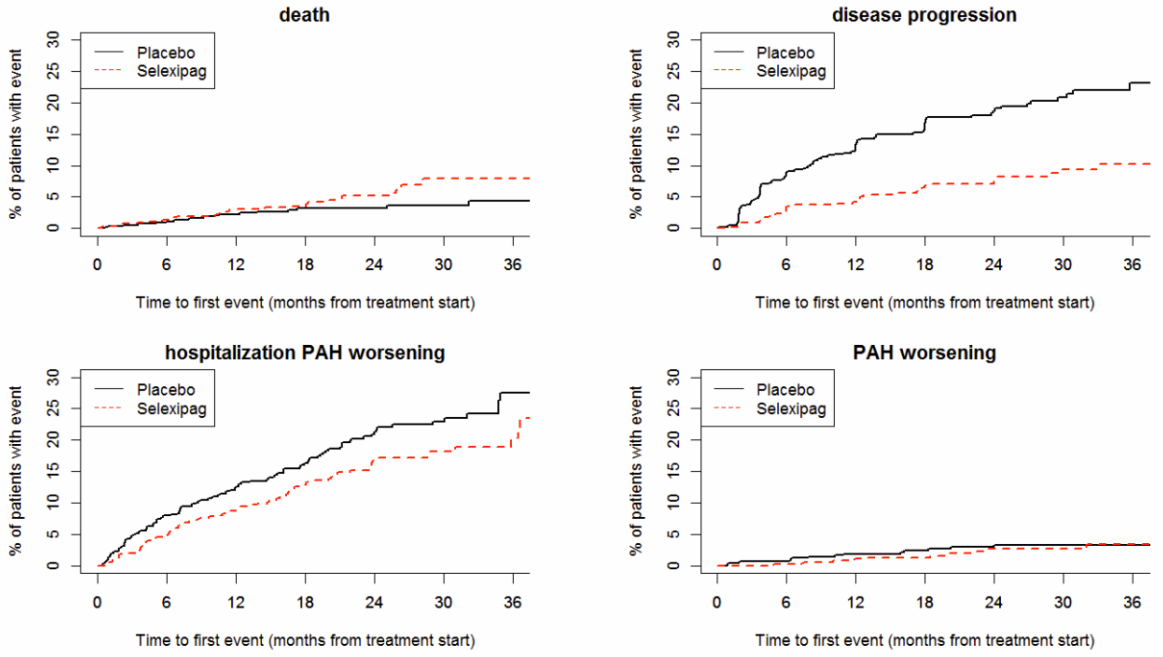
	Selexipag N=574 n	%	Placebo N=582 n	%
Patients with morbidity/mortality event	155	27.0%	242	41.6%
First morbidity/mortality event:				
Death	28	4.9%	18	3.1%
DEATH	28	4.9%	17	2.9%
HOSPITALIZATION-PAH / DEATH	0		1	0.2%
Hospitalization for PAH worsening	78	13.6%	109	18.7%
HOSPITALIZATION-PAH	54	9.4%	78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

When more than one event have the same onset date, all event components are displayed.
CEC=Critical Event Committee.
Events with CEC-confirmed onset date up to 16 Aug 2011 are included as events.
Source: Table 15-48

A competing risk analysis showed that all 4 components of the primary efficacy endpoint components competed with each other during the treatment period since the occurrence of one prevented the observation of the others up to 7 days after last study drug intake. Patients in the selexipag group showed a lower risk of disease progression ($p < 0.0001$) and hospitalization for PAH worsening ($p = 0.0402$) than patients in the placebo group. No significant difference was observed between selexipag and placebo for the risk of PAH worsening ($p = 0.5342$).

(Fig. 11-8).

ACT-293987, Protocols AC-065A302/AC-065A303
Competing risk analysis for Time from randomization to first CEC-confirmed morbitity / mortality event up to 7 days after last study drug intake in AC-065A302 treatment period.
Supportive analysis counting CEC-confirmed events with onset date up to 16 August 2011 as events
Cumulative Incidence Function - Gray's Method, by event
Analysis set: Full analysis set



Graph FMMTICRGRAYEV_F - Produced by krackhi on 23JUL14 - Data dump of 12JUN2014

The number of patients who experienced, as a first event, death due to PAH or hospitalisation for PAH up to end of treatment was 102 (17.8%) in the selexipag group and 137 (23.5%) in the placebo group. Death due to PAH as a component of the endpoint was observed in 16 (2.8%) patients on selexipag and 14 (2.4%) on placebo. Hospitalisation for PAH was observed in 86 (15.0%) patients on selexipag and 123 (21.1%) patients on placebo. Selexipag reduced the risk of hospitalisation for PAH as a first outcome event compared to placebo (HR 0.67, 99% CI: 0.46, 0.98; one sided log rank p = 0.04).

Effect of selexipag on mortality

Death as a first event was in favour of placebo (4.9 vs. 3.1%, 28 vs. 18 events) (censored analysis: 4.4 vs. 2.7%, 25 vs. 16 events) almost reaching statistical significance (p = 0.0827). The unfavourable trend emerged after about 18 months of treatment. Median treatment duration was different in the selexipag (70.7 weeks) vs. the placebo (63.7 weeks) group. Adjustment for this difference reduced but did not remove the numerical difference in mortality at EOT: taking into account the treatment duration, mortality rate (deaths per 100 patient years) was 5.45 in the selexipag and 4.64 in the placebo group, yielding a hazard ratio (HR) of 1.17.

The GRIPHON trial was event-driven and designed to stop treatment of an individual patient after their first primary outcome event, which was usually a disease progression (morbidity) event. Experiencing a morbidity event was associated with a higher risk of dying.

Up to EOT, more morbidity events occurred in patients on placebo than in patients on selexipag (205 vs. 109 respectively). Consistently, in the post-treatment observation period (PTOP), more patients entering from the placebo group (17/137, 12.4%) died than patients entering from the selexipag group (11/113, 9.7%). Not all patients entered the subsequent extension study (in which all patients received open-label selexipag). Death rate was generally higher in patients not participating vs. those

participating in the extension study: for patients having already received selexipag in the parent study, the difference in death rate was 0.41 vs. 0.33 per patient year, respectively; (patients after a CEC confirmed M&M event). For patients coming from the placebo group, the difference in death rate was 0.37 vs. 0.22 per patient year, respectively.

A number of additional analyses were performed to address aspects of the results for the mortality component of the primary endpoint.

According to the analyses, death rates up to EOT are biased by informative censoring. Informative censoring occurs when events are not counted in the analysis due to reasons related to the study design.

Since more morbidity events occurred in the placebo group, more patients at high risk were excluded from further follow-up in the placebo group than in the selexipag group with a consequence that follow-up is shorter in the placebo group and follow-up from more patients that are at higher risk is excluded from the placebo group, resulting in bias. Observation of the patient is 'censored' when follow-up is discontinued according to the protocol definition and because the risk for those patients is probably increased, the censoring is termed 'informative' for outcome (patients at increased risk are more likely to be censored). In other words, due to the study design, the risk profile of the patients changed during the course of the study, favouring placebo group at the end of the trial despite of randomization. This is consistent with the observation that the imbalance did not emerge before month 18.

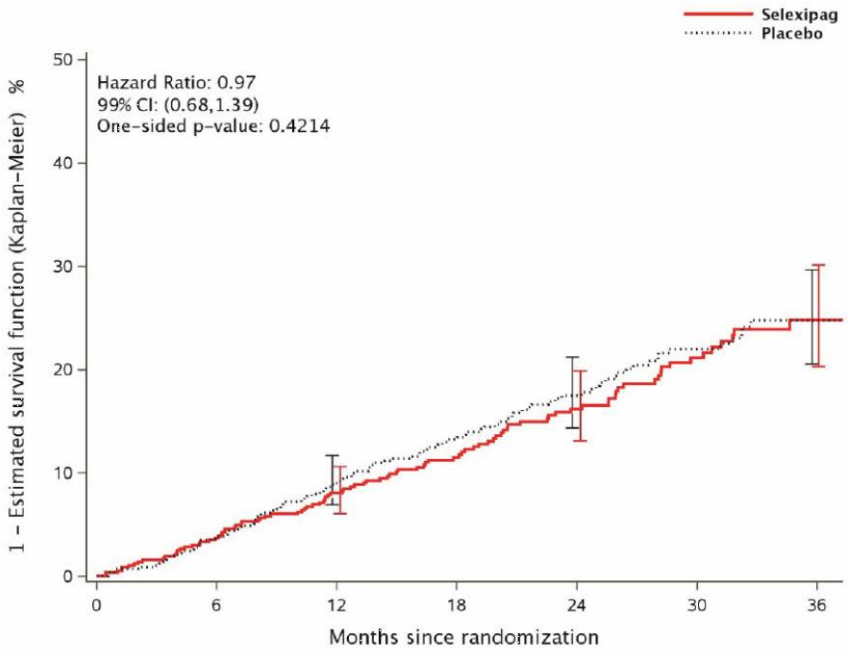
In order to further evaluate the overall effect of informative censoring on the treatment comparison for survival, an analysis as proposed by Denne et al. 2013 was conducted by the applicant. The method compares the event rates in the study arms prior to censoring with the follow-up period after EOT +7 days up to study closure. If the censoring would be non-informative (i.e. if morbidity and mortality events would be independent from one another), the ratio of the event rates (censoring event rate ratio, CERR) would be expected to be 1.0. The observed CERR was 4.8 in the placebo group and 4.2 in the selexipag group indicating that patients censored are at a considerably greater risk of death compared to patients not censored in both treatment arms.

Additionally, a "landmark analysis" as proposed by Anderson et al 1983 was performed. This analysis compares survival between patients with and without a morbidity event prior to the landmark time points 3, 6, 12 and 18 months. In both treatment arms, the hazard ratio for death was significantly increased for patients with a morbidity event compared to patients without a morbidity event at all time points. In the selexipag group, the hazard ratio decreased slightly over time. This analysis supports the view that a morbidity event is associated with an increased risk of death.

Up to study closure a total of 100 and 105 patients in the selexipag and placebo groups died, respectively (Fig. 10-1, and Fig. 11-13). In this analysis patients were included that, after the first M&M event, either remained on selexipag, discontinued treatment or switched from placebo to selexipag in the extension study. This implies that patients on placebo could cross over to treatment with selexipag and this cross-over could have an impact the mortality estimates.

Figure 11-13 Kaplan-Meier estimates of time to death up to Study closur

ACT-293987, Protocols AC-065A302/AC-065A303
Time to death up to Study Closure - Kaplan-Meier estimates.
Set: Full Analysis Set



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

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

Note: Bars on the graph show 95% confidence intervals of the estimates.
Death with onset date up to 16 Aug 2011 are included as death.
Figure FTDSTI_F - Produced by zeeja1 on 29SEP14 - Data dump of 12JUN2014

Source: Figure 15-46

The applicant presented two analyses to explore the impact of cross-over from the placebo arm and treatment discontinuations in the selexipag arm on the mortality up to study closure. These are a Rank Preserving Structural Accelerated Failure Time Model (RPSFT Model) and an approach using a Marginal Structural Cox Proportional Hazards Model with time-dependent weights according to the Inverse Probability of Censoring Weighting (IPCW) scheme. For both approaches, the RPSFT and Structural Proportional Hazards Model analyses, patients were considered on “active treatment” if they were treated with selexipag or with an agent targeting the same pathway as selexipag. The number of patients in both treatment arms receiving prostacyclin and analogues with the same target as selexipag after study drug discontinuation was similar (40 in the selexipag arm, 44 in the placebo arm). Considering selexipag and agents targeting the same pathway as selexipag as “active treatment”, patients in the selexipag arm were about 85% of their observation time on active treatment and patients in the placebo arm were about 16% on active treatment.

The results RPSFT Model provide a valuable estimate of relative survival on active treatment compared to no treatment of 1.19 with a quite wide 95% confidence interval of (0.56, 2.05).

Using the Structural Proportional Hazards Model with IPCW weighting the estimate for the hazard ratio for death as if all patients had received active treatment compared to the situation if all patients had never received active treatment was 0.92 with a 95% confidence interval of (0.58, 1.47) for the 1 month time intervals, showing a slight advantage for treatment with selexipag. Both estimations with models with longer time intervals show non-significant lower hazard ratios (0.79 and 0.75).

A subgroup analysis for mortality indicated that the imbalance favouring placebo was restricted to patients in WHO FC I/ÌI (HR 1.70, (99% CI 0.59, 4.91), death up to EOT + 7 days, p=0.28). The analysis up to study closure showed a significant treatment by subgroup interaction for NYHA/WHO FC at baseline (p=0.0346) with a HR for FC I/II of 1.69 (0.80; 3.56) favouring placebo.

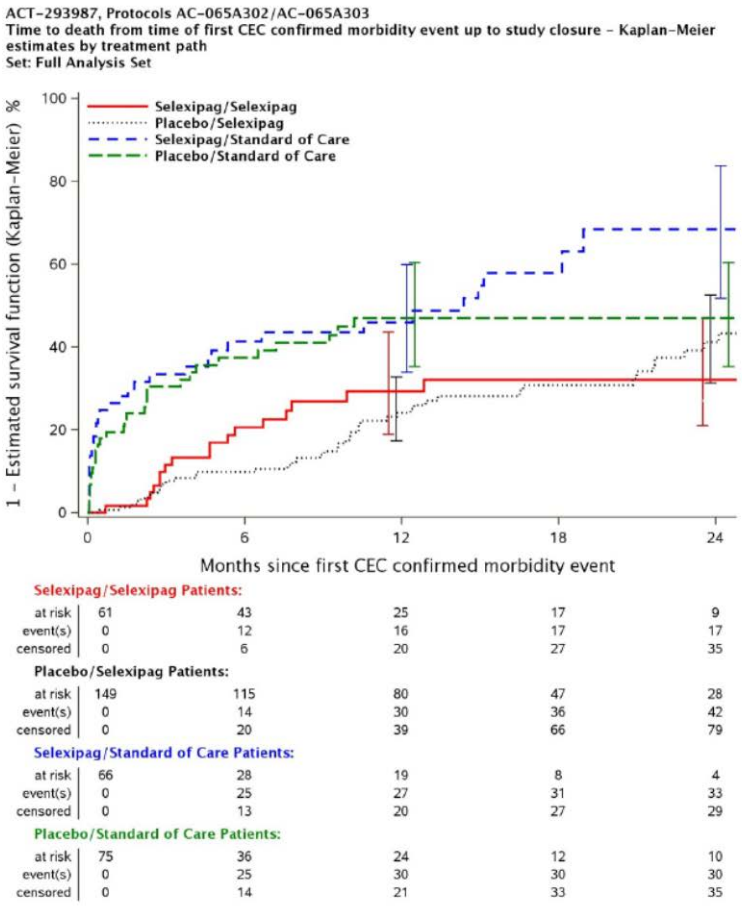
The Applicant submitted two independent mathematical simulations in order to model the observed pattern of mortality. The observed data could be fitted well with two assumptions: First, selexipag has a neutral effect on mortality, i.e. mortality is neither increased nor reduced by selexipag intake. Second, selexipag reduces non-fatal but not fatal endpoint events during treatment. This assumption was needed to explain the higher proportion of mortality among the endpoint events with selexipag as compared to placebo.

The simulations showed that the probability to observe a large imbalance for death as first event of 10 (or more) is in the range of 30% to 51% and for death up to EOT+7d of 9 (or more) is in the range of 26% to 47%. The probability to observe any imbalance with more deaths as first event for selexipag would be typically higher than 70%.

Additional discussion is provided in section 2.6.1 Discussion on clinical safety.

A post-morbidity event survival analysis by treatment path was conducted [Figure 4]. The Kaplan-Meier survival estimate was better in patients treated with selexipag in the OL extension study (AC-065A303/GRIPHON OL), than in patients treated with standard of care (SoC) outside GRIPHON OL, irrespective of their original treatment allocation. Of note, patients were not randomly allocated in this analysis and it cannot be clarified whether deteriorating patients may have preferentially received selexipag or standard of care. Since pre-treatment status (selexipag or placebo) did not appear to have a major impact on outcome during the open label phase, the data do not suggest selexipag to have a beneficial disease modifying effect beyond treatment time.

Figure 4 **Kaplan-Meier estimates of time to death from time of first CEC-confirmed morbidity up to Study closure by treatment path; Full Analysis Set**



CEC = Critical Event Committee.
Studies AC-065A302
Source: Annex 2, Figure 118

The Applicant also provided a post-hoc analysis using the primary endpoint as proposed by the CHMP guideline on PAH.

Notably, the composite endpoint recommended in the respective CHMP guideline includes right-sided heart failure, which was not part of the primary composite endpoint in GRIPHON. With this analysis, death as an overall first event was essentially balanced between the selexipag and placebo groups (2.4% vs. 2.1%, see table below).

Table 51 Components of the first CHMP-defined MM event up to EOT + 7 days in GRIPHON, Full Analysis Set

	Selexipag N=574 n	%	Placebo N=582 n	%
Patients with morbidity/mortality event	268	46.7%	343	58.9%
First morbidity/mortality event:*				
Death	14	2.4%	12	2.1%
Hospitalization for PAH worsening	21	3.7%	42	7.2%
Signs or symptoms of right-sided heart failure	97	16.9%	162	27.8%
Increase in WHO FC from baseline	43	7.5%	38	6.5%
>=15% drop in 6MWD from baseline	93	16.2%	89	15.3%

When more than one event have the same onset date, the most severe event type is displayed.
6MWD = 6-minute walk distance; EOT = end of treatment; MM = morbidity/mortality; PAH = pulmonary arterial hypertension.
Events with onset date up to 16 Aug 2011 are included as events.
Annex 1, Table 66

The incidence of the components of the CHMP-defined endpoint are displayed in the table below (first event in each category analysis, a patient may be counted in more than one category).

Table 52 Individual primary endpoint component event analysis up to EOT + 7 days according to CHMP endpoint, Full Analysis Set

	Selexipag N = 574		Placebo N = 582		Hazard Ratio [99% CI]	p-value
	N	%	N	%		
Component						
Death	46	8.0	37	6.4	1.17 [0.66, 2.07]	0.7656
Hospitalization for PAH worsening	86	15.0	124	21.3	0.65 [0.46, 0.94]	0.0011
Signs or symptoms of right-sided heart failure	160	27.9	247	42.4	0.60 [0.47, 0.78]	<0.0001
Increase in WHO FC from baseline	122	21.3	178	30.6	0.65 [0.48, 0.88]	0.0001
Drop ≥ 15% in 6MWD from baseline	198	34.5	284	48.8	0.66 [0.52, 0.84]	<0.0001

6MWD = 6-minute walk distance; CI = confidence interval, EOT = end of treatment; FC = functional class; PAH = pulmonary arterial hypertension
Percentages are derived based on the total number of patients randomized to each treatment arm.
For each endpoint component, the first event for all patients who had such an event was counted. As a result, patients may have been included in more than one first component category.
Source: modified from Annex 1, Table 63, Table 97

When using the CHMP proposed primary composite endpoint, the results in all predefined subgroups were consistently in favour of selexipag (HR between 0.26 and 0.89) with the exception of patients on previous ERA monotherapy (HR 1.29 (0.74; 2.22 99% CI) and the geographical region North America (HR 1.18 (0.79; 1.98)).

6-MWD

Median absolute change from Baseline to Week 26 in 6MWD measured at trough was 4.0 m in the selexipag group and −9.0 m in the placebo group. The difference was statistically significant (1-sided Wilcoxon-Mann-Whitney p = 0.0027). The treatment effect (location shift using Hodges-Lehmann method) versus placebo in the selexipag group was 12.0 m (99% CI: 1, 24). Mean change was -52.00 m and -66.26 m, respectively. There was a significantly lower incidence of patients in the selexipag group (198 patients, 34.5%) compared to the placebo group (284 patients, 48.8%) who experienced a drop (deterioration) in 6MWD ≥ 15% during the GRIPHON treatment period (see Table 52 below). The treatment effect on the 6MWD was larger in treatment naïve patients (difference of +34 m vs. placebo at the pre-defined timepoint of 6 months (99% CI: 10.0; 63.0, 1-sided Wilcoxon-Mann-Whitney p = 0.0002)) compared to patients pretreated with ERA, PDEi or ERA+ PDEi (location shift -1 (-38.0; 28.0 m), +12.0 (-8.0; 33.0m), and +6.0 (-14.0; 24.0 m), respectively). It was larger in patients with FC III/(IV) (+17.0 (-1.0; 36m) compared to patients with FC (I)/II (+5.0 (-8.0; 19.0 m).

Change from baseline in NYHA/WHO FC

At all time points, the proportion of patients with non-missing values who had improved FC compared to Baseline was greater in the selexipag group than in the placebo group. The proportion of patients with non-missing values who had worsened FC compared to Baseline was lower in the selexipag group than in the placebo group except for week 4, month 6 and month 24.

Quality of life (Cambridge Pulmonary Hypertension Outcome Review)

For the overall symptom score, the treatment effect (median absolute change from Baseline to Week 26) of selexipag versus placebo was 0.0 (99% CI: −1.0, 1.0, p = 0.2185). For the sub-scale 'Breathlessness' the treatment effect of selexipag versus placebo was 0.0 (99% CI: −0.4, 0.0, p = 0.1700).

Plasma NT pro-BNP

The absolute change from Baseline to end of treatment (corresponding to individual patients end of study visit) in median plasma NT pro-BNP was 5.5 ng/L (range: −4790 to 10873) in the selexipag group compared to 75.0 ng/L (range: −7309 to 41586) in the placebo group, mean absolute changes from baseline were 271.7 (SD 1337.6) vs. 659.6 (SD 2976.3) ng/mL, respectively.

Efficacy by individual maintenance dose

For the primary efficacy endpoint there was no clear correlation between dose and treatment effect. The hazard ratios versus placebo for the occurrence of an MM event in the selexipag IMD categories were:

• selexipag IMD category 200–500 µg b.i.d.: 0.60 (95% CI: 0.41, 0.88, 1-sided unstratified log-rank p = 0.0038),

• selexipag IMD category 600–1100 µg b.i.d.: 0.53 (95% CI: 0.38, 0.72, 1-sided unstratified log-rank p < 0.0001), and

• selexipag IMD category 1200–1600 µg b.i.d.: 0.64 (95% CI: 0.49, 0.82, 1-sided unstratified log-rank p = 0.0002).

For the 6-MWT

median/mean absolute changes from Baseline to Week 26 in 6MWD measured at trough in the selexipag IMD categories were

• selexipag IMD category 200–500 µg b.i.d.: −20.0 m/ -115.68 m

• selexipag IMD category 600–1100 µg b.i.d.: 8.5 m/-43.66 m

• selexipag IMD category 1200–1600 µg b.i.d.: 15.0 m/-7.75 m

• placebo: −9.0 m/-66.26

Table 1: Summary of efficacy for trial AC-065A302/GRIPHON

The following table summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Study identifier	**AC-065A302/GRIPHON including data from AC-065A302 post treatment observation period**		
Design	Multicenter, randomized, double-blind, parallel group, placebo-controlled, event-driven Phase 3 study to compare the effects (efficacy, safety, tolerability, pharmacokinetics/pharmacodynamics [PK/PD]) of selexipag (administered orally at an individualized dose in the range of 200–1600 µg b.i.d.) versus placebo (1:1 randomization) in patients with symptomatic PAH		
	median duration of double-blind study treatment:		selexipag: 70.7 weeks (range: 0.3–216.7 weeks) placebo: 63.7 weeks (range: 0.7–192.0 weeks)
	Duration of Extension phase:		ongoing
Hypothesis	Superiority selexipag vs. placebo		
Treatments groups	Selexipag		Selexipag individual dose titration 200 µg bid – 1600 µg bid in 200 µg bid steps until maximally tolerated individual maintenance dose, number randomized 574
	Placebo		Placebo, number randomized 582
Endpoints and definitions	time from randomization to first CEC-confirmed MM event up to 7 days after last study drug intake	composite	- Death (all causes) or - Hospitalization for worsening of PAH based on predefined criteria - Worsening of PAH resulting in need for lung transplantation or balloon atrial Septostomy - Initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH - Disease progression: Decrease in 6MWD from Baseline and a) Worsening of NYHA/WHO FC (patients in FC II-III) b) Need for additional PAH-specific therapy (patients in FC III-(patients in FC III-IV)

	Secondary endpoint	6-MWT	- Absolute change from Baseline to Week 26 in 6MWD measured at trough
		No worsening	- Absence of worsening from Baseline to Week 26 in NYHA/WHO FC
		PAH death or PAH hosp	- Time from randomization to first of CEC-confirmed death due to PAH or CEC confirmed hospitalization due to PAH worsening up to 7 days after last study drug intake in the AC-065A302 treatment period.
		All-cause death	- Time from randomization to death of all causes up to Study closure.
		Breathlessness	- Absolute change from Baseline to Week 26 in the sub-scale 'Breathlessness' of CAMPHOR (Cambridge Pulmonary Hypertension Outcome Review) 'Symptoms
		CAMPHOR	- Absolute change from Baseline to Week 26 in CAMPHOR 'Symptoms' score
	exploratory		NT pro-BNP And others
Database lock	First patient, first visit: 30 Dec 2009 Last patient, last visit (in AC-065A302 treatment period): 27 Apr 2014		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	The primary statistical analysis for the primary composite endpoint was performed on the Full Analysis Set for the time to the first primary endpoint event excluding data up to August 16, 2011 (a) (amendment 5). Results including all data are also listed (b).		
Descriptive statistics and estimate variability	Treatment group	Selexipag	Placebo
	Number of subject	574	582
Effect estimate per comparison	Primary endpoint	a) 140 patients (24.4%) p < 0.0001 b) 155 patients (27.0%)	a) 212 patients (36.4%) b) 242 patients (41.6%)
	Primary endpoint components		
	Death	a) 25 (4.4%) b) 28 (4.9%)	a) 16 (2.7%) b) 18 (3.1%)
	Hospitalization for worsening of PAH	a) 71 (12.4%) b) 78 (13.6%)	a) 96 (6.5%) b) 109 (18.7%)
	Worsening of PAH (lung transplantation or atrial septostomy)	a) 1 (0.2%) b) 1 (0.2%)	a) 2 (0.3%) b) 2 (0.3%)
	Prostanoid or oxygen therapy due to worsening of PAH	a) 11 (1.9%) b) 10 (1.7%)	a) 14 (2.4%) b) 13 (2.2%)
	Disease progression	a) 32 (5.6%) b) 38 (6.6%)	a) 84 (14.4%) b) 100 (17.2%)

	6-MWT Baseline values mean (SD) median	358.5 (76.3) m 376.0 m	348.0 (83.2) m 369.0 m
	median change	4.0 m	-9.0 m
	mean change (SD) no worsening	-53 (150.24) m	- 66 (148.23) m
		77.8%	74.9%
	PAH death or PAH hosp.	102 (17.8%)	137 (23.5%)
	All-cause death	100 (17.4%)	105 (18.0%)
	Breathlessness	0.0	0.0
	CAMPHOR	−1.0	0.0
Notes	According to analyses the higher rate in mortality events as a primary endpoint component may be due to informative censoring.		

Clinical studies in special populations

No studies in special populations were conducted. The pivotal GRIPHON study included a wide variety of patients with PAH.

Analysis performed across trials (pooled analyses AND meta-analysis)

No pooled analyses or meta-analyses were provided by the applicant for efficacy evaluation.

Supportive studies

Study AC-065A201

An interim report of a multicentre, uncontrolled, phase 2 open label clinical study in Japanese patients with PAH was provided. The interim report includes the results up to Week 16 of treatment with selexipag. Albeit uncontrolled, treatment of 37 patients with PAH over 16 weeks with selexipag was associated with small – moderate beneficial effects on pulmonary haemodynamics, as decreases in pulmonary vascular resistance, pulmonary artery pressure, and small increases in cardiac output and cardiac index. The mean performance in the 6-MWT test improved, but without a placebo control the data cannot be considered as a measure of a true treatment effect. No beneficial effect was seen on the Borg dyspnea index.

Study AC-065B201

Study AC-065B201 was an exploratory controlled, double blind, multicentre study in 34 Japanese patients with chronic thromboembolic pulmonary hypertension (CTEPH).

Selexipag was associated with small – moderate beneficial effects on pulmonary haemodynamics, as decreases in pulmonary vascular resistance, pulmonary artery pressure, and small increases in cardiac index.

There was no beneficial effect on the 6 MWT: The mean treatment effect (95% CLs of difference in mean) selexipag was lower than with placebo: -9 m (-57 to 39 m). No beneficial effect was seen on the Borg dyspnea index.

Study **AC-065B202** was an open label extension study of study AC-065B201.

28 patients were treated open label with selexipag. There were small changes in the 6-MWT, the BORG dyspnea scale and WHO function class. The data do not indicate a detrimental effect on efficacy parameters with selexipag in the long term treatment of patients with CTEPH.

2.5.3 Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical program was mainly based on 1 controlled pivotal phase III study, the GRIPHION trial, in patients with PAH of different origin.

Prior to initiation of the GRIPHON trial (AC-065A302, 1156 patients) Study NS-304/02 was conducted, containing 2 parts, a multicenter, open-label, single-dose, acute hemodynamic study (43 patients) followed by a multicenter, randomized, double-blind, parallel-group, placebo-controlled study over 21 weeks in 43 patients with PAH. Dose selection for the phase III study based on these studies was considered appropriate.

The design of the pivotal study (GRIPHON trial) was largely in agreement with the requirements of the relevant EMA guideline EMEA/CHMP/EWP/356954/2008. The applicant used a combined endpoint (death, hospitalization for worsening of PAH based on predefined criteria, worsening of PAH resulting in need for lung transplantation or balloon atrial septostomy, initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH, and disease progression). Signs or symptoms of right heart failure have not been included in the primary endpoint as opposed to the proposal of the guideline. The Applicant provided a post-hoc analysis using the composite endpoint suggested by the Guideline in PAH. The results were largely consistent with the results of the predefined primary efficacy endpoint. After inclusion of right heart failure as a first event, the difference in primary mortality events between selexipag and placebo decreased.

The choice of the primary endpoint in combination with the decision to discontinue selexipag in patients after the first primary endpoint event with the possibility to switch placebo patients to selexipag after the first event turned out to be a relevant drawback of the design. A large difference between the groups for “disease progression (as a component of the primary endpoint)” was a major obstacle to reliably assess all-cause mortality.

The primary efficacy endpoint was accompanied by relevant secondary endpoints including the single components of the primary endpoint and 6- MWT, quality of life, Borg dyspnea scale, and biomarkers.

Generally, there were no indications that the studies were not conducted appropriately.

At study closure (i.e., when the overall target number of 331 CEC confirmed MM events was achieved), vital status of 24 patients (4.2%) and 27 patients (4.6%) in the selexipag and placebo groups, respectively, was reported as not known. However, the impact on the overall study results is limited, as has been demonstrated by additional analyses provided.

Study population

The number of patients included was overall appropriate (selexipag: 574, placebo: 582). In fact up to now, GRIPHON is the largest trial conducted in patients with PAH. The median duration of double-blind study treatment was 70.7 weeks in the selexipag group compared to 63.7 weeks in the placebo group, with 63.8% and 62.6% of patients in the respective groups receiving study treatment for at least 1 year. The data are sufficient to support long term maintenance of efficacy.

The patient populations were well characterized based on accepted clinical and haemodynamic criteria, mainly patients in WHO II and III. Overall the patient population included in the clinical trials is

representative of the population of the intended indication. More than 50% of patients had idiopathic PAH, almost 30% connective tissue disease, around 10% congenital heart disease. Other groups of patients (heritable, drug or toxin induced, HIV infection) had a low representation (0.9 – 3.0%, 5 – 17 patients). Similarly, only few patients in NHYA I and IV (3 – 8 per group) were included. Therefore, only patient with idiopathic PAH and connective tissue disease in stages II – III were sufficiently represented in the study in order to be reflected in the wording of an indication. Efficacy data were provided separately for IPAH, HPAH, and HIV associated and drug induced PAH. The representation of heritable and idiopathic PAH in GRIPHON was similar to SERAPHIN (Opsumit, macitentan).

The wording of the indication for Opsumit (macitentan) includes both heritable and idiopathic PAH as follows: “Efficacy has been shown in a PAH population including idiopathic and heritable PAH, PAH associated with …”. A consistent wording including IPAH and HPAH is acceptable for selexipag. Patients in FC I and in FC IV are not included in the final wording of the indication due to the limited data available in this patient population.

The treatment groups were generally balanced regarding demographics and disease characteristics. However, a slightly higher proportion of patients in NYHA/WHO FC III/IV and a somewhat lower mean baseline 6MWD was noted in the placebo group, compared to selexipag. According to a sensitivity analysis this was not of relevance for the overall study result.

Most patients (80.5% selexipag, 78.7% placebo) were receiving PAH-specific medication at baseline consisting of ERA monotherapy (16.4/13.1%), PDE5 inhibitor monotherapy (32.9/31.8%) or both (31.2/33.8%). The use of placebo as a comparator in the GRIPHON study is considered to be ethically acceptable in patients receiving background therapy with approved specific PAH medication. The Applicant ensured that patients who were not receiving PAH-specific medications at baseline were not unduly exposed to any increased risk due to their participation in GRIPHON.

Statistical methods

The statistical methods used were well described in all studies and generally considered appropriate. The issue of missing values is handled appropriately by providing sensitivity analyses. Post hoc, additional analyses were performed in order to assess if the issue of increased mortality with selexipag in the first event analysis and whether this finding could be explained by informative censoring. Overall, the methods appear to have been appropriately applied. An additional analysis relating to grouping of selexipag with other drugs with the same presumed pathway of action confirmed the initial analysis.

The blinded expert medical review revealed that 6.7% of the patients had baseline characteristics atypical for PAH, 76.4% typical and 17.0% consistent baseline characteristics. The applicant to provided data supporting consistency of the results for 3 groups.

Maintenance dose

With respect to dose some patients may have not been uptitrated appropriately due to non-specific AES. In clinical practice, trying to increase the dose again at a later time point in patients initially not tolerating the maximal dose may be appropriate.

Efficacy data and additional analyses

The results on the primary efficacy endpoint showed a clear and significant effect favoring selexipag. The proportion of patients who experienced a CEC-confirmed MM event up to 7 days after last study drug intake (EOT+ 7d) was 24.4% in the selexipag group compared to 36.4% in the placebo group. There was a numerical difference of 72 events between the groups favoring selexipag. The overall

effect on the primary endpoint was consistent for hospitalization for PAH, parenteral prostanoid or oxygen therapy. It was mainly driven by “disease progression” (decrease in 6 MWD accompanied either by a decrease in FC or by the need for additional PAH therapy): Selexipag 71 (12.4%) vs. placebo 96 (16.5%). On the other hand there was an imbalance for all-cause mortality favoring placebo (Selexipag 25 (4.4%), Placebo 16 (2.7%)). A similar numerical imbalance in deaths was observed for other secondary survival endpoints in the FAS and safety analysis sets EOT +7 days and EOT+30 days.

The Applicant conducted a number of additional analyses to address aspects of the results for the mortality component of the primary endpoint. In subgroup analyses the difference was attributable to an imbalance in patients with NYHA II and not with NYHA III. Similarly, the difference was observable in patients with better cardiac function but not in patients with poor cardiac function (reference is made to the safety section of this report). The analysis of time to death until study closure showed no difference in mortality between selexipag and placebo for the whole group of patients However, in the subgroup of patients with FC I/II, mortality was still increased at study closure (HR 1.69). Additional analyses indicated that the analysis at end of treatment +7 days underestimates the risk of death in both arms and that the degree of underestimation is higher in the placebo group. The analyses are hampered by the fact that some patients from the placebo group switched to selexipag in the extension study, whereas other patients from the selexipag group did not enter the open label extension period on selexipag. Two models accounting for cross-over (i.e. a Rank Preserving Structural Accelerated Failure Time Model and a Marginal Structural Cox Proportional Hazards Model (with IPCW)) indicated that treatment with selexipag might in the best case even be associated with an improvement in mortality by up to about 25%. Two additional simulations were performed which indicated that an imbalance for death as first event up to EOT or EOT+7d is not an unexpected result under the assumption that selexipag decreases non-fatal but not fatal events. The results showed that the probability to observe a large imbalance for death as first event of 10 (or more) is in the range of 30% to 51% and for death up to EOT+7d of 9 (or more) is in the range of 26% to 47%. The probability to observe any imbalance with more deaths as first event for selexipag would be typically higher than 70%.

Taken together, the mortality data are complex to assess. At the primary analysis timepoint EOT+7d, selexipag appeared to have a negative effect on mortality as the primary endpoint component, whereas the analysis up to study closure in the full analysis set (FAS) suggested a neutral effect and mathematical models which take into account cross-over even indicated an up to 25% reduction in mortality. These models should however be interpreted with caution because in any such model assumptions have to be made.

Exclusion of a detrimental effect on survival is a key aspect for a new drug in this therapeutic field (EMEA/CHMP/EWP/356954/2008). The additional analyses provided supported the assumption that the increase in mortality after month 18 can be explained by informative censoring. i.e., since selexipag was effective in reducing morbidity events, more patients in the placebo arm were taken off study medication after a first morbidity event. Since these are patients at increased risk to die, an imbalance developed during the study favouring placebo with respect to the risk of dying.

Simulations indicated that there was a high probability for an imbalance with more deaths as first event for selexipag in case the overall effect on mortality was neutral.

In addition, when signs and symptoms of right heart failure are taken into account, as proposed by the respective CHMP guideline, the difference for death as a first event is small (14 vs. 12 events selexipag vs. placebo). No difference in mortality was observed when patients were analysed according to Benza disease severity category, a key predictor of survival in patients with PAH (Benza RL et al. Circulation 2010).

Mortality as a first overall event up to EOT+7 days was mainly due to an increase in MACE events which may also be explained by study design. The same statistical considerations apply for MACE events for all-cause mortality. Some patients with sudden death on treatment had underlying cardiovascular risk factors. It was pointed out that the intermittent increase in heart rate about 2 – 4 hours after drug intake might be of concern for patients at increased cardiovascular risk due to coronary artery disease (see safety section below). Albeit the changes in heart rate were generally modest and similar to those seen with other medicinal products approved for PAH the applicant agreed to include contraindications in place for prostacyclin analogues (e.g. severe coronary artery disease, status post myocardial infarction, unstable angina).

The main study result was consistent in all of the subgroups investigated. Only in Asian patients and in Asia as a geographical region there was no treatment effect. In North America the treatment effect was numerically lower than in the other regions. Irrespectively of the regional differences, the results do not raise concerns for an application in the EU. Only few Black patients were included. Albeit numerically in favour of selexipag, only limited conclusions can be drawn on B/R in black patients.

The clinical relevance of the effect on the primary endpoint can further be assessed based on the results of the secondary endpoints. **6 MWT**: There was a mean decrease from baseline to week 26 by 53 m in the selexipag group and by 66 m in the placebo group. Median change was + 4.0 vs. – 9.0 m, respectively, indicating that many patients were largely in a stable condition over 26 weeks. The treatment effect on the 6MWD in treatment naïve patients (difference of +34 m vs. placebo at the pre-defined timepoint of 6 months (99% CI: 10.0; 63.0, p = 0.0002)) was within the range of what has been observed with other medicinal products previously approved in the EU. As expected, the effect was smaller in patients pretreated with ERA, PDEi or ERA+ PDEi (location shift -1 (-38.0; 28.0 m), +12.0 (-8.0; 33.0m), and +6.0 (-14.0; 24.0 m), respectively). In patients with FC III/(IV) the difference was larger (+17.0 (-1.0; 36m) than in patients with FC (I)/II (+5.0 (-8.0; 19.0 m)).

Taking into consideration the clinically relevant effect in treatment naive patients that was in the range of other medicinal products approved for PAH and the well known observation that the effect on the 6 MWD is less pronounced in pretreated patients, the moderate mean overall effect on 6-MWD observed in the study is mainly related to the high number of pretreated patients included in the study .

Due to low numbers one should be cautious not to over interpret the negative results in the elderly (≥ 65 years), in North America, and in Black patients.

For the reasons of internal consistency, it should be demonstrated that an improvement in 6MWD is correlated with not developing the main study outcome "morbidity/mortality". In this respect, the applicant was requested to provide: An analysis of responders in 6MWD, defined in absolute and relative terms as: i) Improvement > 30 m from baseline at study endpoint; ii) Improvement > 15% from baseline at study endpoint. The applicant has provided the analysis. The effect compared to baseline depended largely on the imputation of missing values, but the effect as compared to placebo was unaffected.

There was no clinically relevant effect of selexipag on overall **quality of life** and on **breathlessness** as measured by the CAMPHOR scale. This finding is not fully understood since the clear benefit with regard to morbidity events would be expected to translate into improved QoL However, although the CAMPHOR scale has been validated in small populations in different regions, it is currently not known whether it is sensitive to changes in QoL. Therefore, the lack of impact of selexipag on QoL as measured by the CAMPHOR questionnaire does not invalidate the beneficial effects of selexipag on morbidity events.

For **NT-proBNP** levels median improvements on therapy vs. placebo were small.

There was no correlation between maintenance dose and the primary endpoint outcome at least for patients with typical AEs. This is consistent with the assumption that, on an individual level, tolerability correlates with efficacy. For patients without AEs typical for prostacyclin analogues efficacy was questionable for the lowest dose range. It may be appropriate that these patients try to increase their dose during therapy.

2.5.4 Conclusions on clinical efficacy

In summary, a statistically significant and clinically relevant benefit as measured by the primary endpoint has been demonstrated for patients with PAH in FC II and III, on baseline therapy or treatment naïve. The result was consistent for almost all of the relevant subgroups, except Asian patients and Asia and North America as region. Patients with idiopathic/hereditary PAH or connective tissue disease in FC stages II – III and patients with PAH associated with simple corrected congenital heart disease were sufficiently represented in the study to be reflected in the wording of an indication.

The analysis of the results for all-cause mortality is challenging. At the primary analysis timepoint EOT+7d, selexipag appeared to have a negative effect on mortality as the primary endpoint component. This finding can be explained statistically by informative censoring. On the other hand, the analysis up to study closure in the FAS suggested a neutral effect and mathematical models which take into account cross-over even indicated an up to 25% reduction in mortality.These models have limitations due to assumptions that have to be made and should be interpreted with caution.

The finding of increased all-cause mortality as primary endpoint event was mainly observed in patients in FC II and in those with better cardiac functioning and was paralleled by an increase in MACE events that also may be related to informative censoring. The safety data did not indicate a specific concern related to patients in FC II and there was no plausible explanation for a risk in patients in FC II and better cardiac functioning that would not be relevant for more vulnerable patients at a more advanced stage of PAH. Cross study comparisons, albeit to be taken with caution, indicated that the mortality rate in the selexipag arm in FC II was largely within the expected range, whereas mortality in the placebo arm (FCII) was low.

Overall, CHMP considered that the finding of increased mortality as a primary endpoint event is most likely due to informative censoring and/or a chance finding. This assumption is supported by the following considerations: a) selexipag exerted beneficial effects on morbidity endpoints in patients with PAH and morbidity events were shown to increase the risk of dying, b) selexipag is an IP receptor agonist with the typical adverse event profile of the prostacyclin/prostacyclin analogues known class of PAH medications; prostacyclins are not suspected to be associated with an increased risk of mortality c) the increase in heart rate after each dose is generally modest and transient and in the range of other vasodilatory drugs approved for PAH, d) no specific/unique safety issue could be identified that could explain an increase in mortality, e) any putative safety issue leading to increased mortality would be more likely to become evident in PAH patients with deteriorated health condition as opposed to patients in FCII and better cardiac functioning. Reference is also made to the safety section of this report.

The overall effect of selexipag on the 6 MWT appeared to be moderate when compared to the effects observed with non-prostacyclin medicinal products in a cross study comparison. However, the effect in treatment naïve patients was in the range of what has previously been observed and accepted as clinically relevant. Therefore, the mean effect was largely driven by the high number of patients (about 80%) on baseline therapy. It is well known that only smaller effects can be expected in these patients.

There was no improvement in quality of life as measured by the CAMPHOR scale. At present, it cannot be finally decided whether this is due to a low sensitivity of the test used or indicates that the clinically

relevant benefits of selexipag on morbidity events do not translate into improvements in the categories investigated by the test.

Although the beneficial effects might be regarded as moderate, they are clinically relevant. As most patients (about 80%) in GRIPHON received selexipag on top of baseline therapy with ERAs and/or PDE5-inhibitors, a second line indication is considered appropriate in order not to withhold therapeutic use of these drugs that have an established clinical benefit demonstrated over years in large numbers of patients.

2.6 Clinical safety

Safety information is mainly contributed by completed pivotal Phase 3 study AC-065A302 (GRIPHON) in the PAH indication. This study has 1152 patients in its safety data set. Beside this pivotal trial, only a few small Phase 2 trials with 26 to 43 patients per study were performed, in the PAH and also in the CTEPH (chronic thromboembolic pulmonary hypertension) indication. Thus, safety evaluation is mostly based on the GRIPHON trial. GRIPHON has an ongoing, uncontrolled extension phase (i.e. all patients are treated with selexipag, no comparator is included).

An independent Critical Event Committee (CEC) adjudicated all reported morbidity/mortality (MM) events. The CEC was blinded to the patient's study treatment allocation and to the occurrence of typical prostacyclin-associated adverse events (AEs). The CEC comprised 3 clinical experts who had experience and expertise in the management of patients within this disease area, and experience in the monitoring of randomized clinical trials. The CEC members were not involved as investigators in the GRIPHON study.

Patient exposure

Exposure is described below for the double-blind period of the GRIPHON study. In the phase 1 and phase 2 studies patient exposure was comparably low. In study AC-065A303 (open-label extension of GRIPHON), median duration of study treatment (up to 10 March 2014) was 37.2 weeks (range: 0.9–160.0 weeks), with 34.4% of patients (75/218) receiving study treatment for a cumulative duration of at least 1 year.

GRIPHON study, double blind period

Median duration of study treatment in study AC-065A302 was 70.7 weeks (range: 0.3–216.7 weeks) in the selexipag group compared to 63.7 weeks (range: 0.7–192.0 weeks) in the placebo group, with 63.8% and 62.6% of patients in the respective groups receiving study treatment for a cumulative duration of at least 1 year. 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.

Thus, the mean duration of treatment was close to one and a half year in the selexipag group, and the majority of patients were treated for more than one year. For further details see table below.

Table 12-1 of Study Report: Duration of study treatment in AC-065A302, SAF

	Selexipag	Placebo
	N=575	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 8 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%)	0

Of the 575 selexipag-treated patients in study AC-065A302, 28.3% received selexipag at an individual maintenance dose (IMD) of 1600 µg bid (i.e., the maximum selexipag dose allowed in the study). In the placebo group, the highest number of tablets corresponding to the 1600 µg bid IMD was achieved by 67.5% of patients. For details see table below.

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

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

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

Adverse events

GRIPHON study, double blind period (AC-065A302)

A total of 98.3% and 96.9% of patients in the selexipag and placebo groups, respectively, had at least 1 AE in study AC-065A302 (i.e. GRIPHON, double blind period). The Applicant defined certain AEs as

"prostacyclin-associated AEs" which included pain in various defined locations, flushing and several gastrointestinal effects. These AEs were also defined as AEs of special interest. These prostacyclin-associated AEs, together with the related AEs abdominal pain and neck pain, were the most frequently reported AEs and had markedly higher frequencies in the selexipag group compared to the placebo group. Other salient AEs reported more frequently on selexipag compared to placebo included hypotension (5.0% vs 3.1%), anaemia (8.3% vs 5.4%), hyperthyroidism (1.4% vs. 0%) and acute renal failure (2.4% vs 1.2%).

On the level of SOC (System Organ Class), skin and subcutaneous tissue disorders revealed an imbalance. Respective events were reported for 19.7% of patients in the selexipag group compared to 15.8% in the placebo group. This difference was mainly driven by rash (4.5% selexipag, 2.8% placebo) and erythema (2.3% vs. 1.4%). Furthermore, Eye disorders were reported for 11.0% of patients in the selexipag group compared to 8.0% in the placebo groups. This difference was mainly driven by the PT "Eye Pain" (1.6% vs. 0.3%).

On the other hand, PAH (worsening) and right ventricular failure were reported less frequently in the selexipag group (21.9% and 8.0% of patients, respectively) compared to the placebo group (35.7% and 10.1%, respectively). Similarly, other manifestations of underlying PAH disease were also reported less frequently in the selexipag group compared to placebo: dyspnoea (16.0% vs 21.0%), peripheral oedema (13.9% vs 18.0%), and syncope (6.4% vs 8.8%).

Taken together, most of the AEs which were more frequent in the selexipag group are most likely related to the PD effect of selexipag (the so-called prostacyclin-associated AEs as well as hypotension). Beside these, salient differences between selexipag and placebo were observed for anaemia, hyperthyroidism and acute renal failure. These conditions are further discussed as AEs of special interest below.

Nasopharyngitis and influenza were also more frequent with selexipag, but infections and infestations in total were well balanced between selexipag and placebo. Thus, there is no hint that selexipag affects the immune system.

Table 12-4 of Study Report: Treatment-emergent AEs in study AC-065A302 sorted by difference in incidence (at least 1.0%) between selexipag and placebo, SAF

	Selexipag		**Placebo**		**Selexipag minus Placebo**
Preferred Term	N=575		N=577		
	n	%	n	%	
Patients with at least one AE	**565**	**98.3%**	**559**	**96.9%**	**1.4%**
HEADACHE	375	65.2%	189	32.8%	32.5%
DIARRHOEA	244	42.4%	110	19.1%	23.4%
PAIN IN JAW	148	25.7%	36	6.2%	19.5%
NAUSEA	193	33.6%	107	18.5%	15.0%
MYALGIA	92	16.0%	34	5.9%	10.1%
VOMITING	104	18.1%	49	8.5%	9.6%
PAIN IN EXTREMITY	97	16.9%	46	8.0%	8.9%
FLUSHING	70	12.2%	29	5.0%	7.1%
ARTHRALGIA	62	10.8%	44	7.6%	3.2%
ANAEMIA	48	8.3%	31	5.4%	3.0%
ABDOMINAL PAIN	48	8.3%	33	5.7%	2.6%
DECREASED APPETITE	34	5.9%	19	3.3%	2.6%
PAIN	18	3.1%	3	0.5%	2.6%
NASOPHARYNGITIS	75	13.0%	63	10.9%	2.1%
HYPOTENSION	29	5.0%	18	3.1%	1.9%
DYSPEPSIA	25	4.3%	14	2.4%	1.9%
RASH	26	4.5%	16	2.8%	1.7%

WEIGHT DECREASED	17	3.0%	8	1.4%	1.6%
NECK PAIN	15	2.6%	6	1.0%	1.6%
HYPERTHYROIDISM	8	1.4%	0		1.4%
ASTHENIA	31	5.4%	24	4.2%	1.2%
ABDOMINAL DISCOMFORT	21	3.7%	14	2.4%	1.2%
RENAL FAILURE ACUTE	14	2.4%	7	1.2%	1.2%
BONE PAIN	9	1.6%	2	0.3%	1.2%
EYE PAIN	9	1.6%	2	0.3%	1.2%
PYREXIA	23	4.0%	17	2.9%	1.1%
INFLUENZA	20	3.5%	14	2.4%	1.1%
MUSCULOSKELETAL PAIN	18	3.1%	12	2.1%	1.1%
NASAL CONGESTION	17	3.0%	11	1.9%	1.1%
HOT FLUSH	14	2.4%	8	1.4%	1.0%
BURNING SENSATION	6	1.0%	0		1.0%

Intensity of the AEs

In study AC-065A302, AEs of mild and moderate intensity were reported for 8.2% and 41.0% of patients, respectively, in the selexipag group and 8.8% and 42.8% of patients, respectively, in the placebo group. Severe intensity AEs were reported for 49.0% and 44.9% of patients in the selexipag and placebo groups, respectively. The most frequently reported severe AE was PAH (14.4% selexipag, 21.0% placebo).

Investigator-attributed relationship of adverse events to study treatment

In study AC-065A302, 89.6% of patients in the selexipag group had at least 1 AE which was considered by the investigator to be treatment-related compared to 56.7% in the placebo group. Prostacyclin-associated AEs were the events most frequently considered by the investigator to be treatment-related. Other individual PT AEs considered treatment-related and reported more frequently in the selexipag group compared to the placebo group included decreased appetite (3.5% vs 1.4%), pain (2.4% vs 0.5%), and decreased weight (1.0% vs 0%).

GRIPHON study, open label period (AC-065A303)

Of the 218 patients who were enrolled and received selexipag in study AC-065A303, 209 (95.9%) had at least 1 AE. Similar to AC-065A302, prostacyclin-associated AEs (i.e., headache, diarrhoea, jaw pain, nausea, vomiting, pain in extremity, myalgia, arthralgia, and flushing) were the most frequently reported AEs in AC-065A303. PAH (worsening) and right ventricular failure were reported for 25.7% and 16.5% of patients, respectively. Other frequently reported AEs included peripheral oedema (11.5%), anaemia (5.5%), hypotension (4.6%), and decreased appetite (4.1%). For further AEs see table below. No placebo arm was included in this open-label period.

Thus, AEs probably related to prostacyclin physiology were also frequent in the uncontrolled extension period of the GRIPHON study. Other events can be related to the underlying disease or accompanying medication. This study period gives no hint for undesired effects of selexipag that were not yet detected in the double blind period.

Table 12-5: Treatment-emergent AEs in study AC-065A303 sorted by PT incidence (at least 3%), SAF (subset treated in study AC-065A303)

	Selexipag	
Preferred Term	N=218	
	n	%
Adverse events		
Patients with at least one AE	**209**	**95.9%**
HEADACHE	119	54.6%
DIARRHOEA	78	35.8%

PULMONARY ARTERIAL HYPERTENSION	56	25.7%
PAIN IN JAW	46	21.1%
NAUSEA	44	20.2%
RIGHT VENTRICULAR FAILURE	36	16.5%
VOMITING	31	14.2%
OEDEMA PERIPHERAL	25	11.5%
PAIN IN EXTREMITY	25	11.5%
MYALGIA	22	10.1%
ARTHRALGIA	21	9.6%
DIZZINESS	18	8.3%
DYSPNOEA	18	8.3%
FLUSHING	18	8.3%
COUGH	14	6.4%
UPPER RESPIRATORY TRACT INFECTION	14	6.4%
NASOPHARYNGITIS	13	6.0%
ANAEMIA	12	5.5%
BRONCHITIS	12	5.5%
FATIGUE	10	4.6%
HYPOTENSION	10	4.6%
ABDOMINAL PAIN UPPER	9	4.1%
DECREASED APPETITE	9	4.1%
SYNCOPE	9	4.1%
ASCITES	8	3.7%
PNEUMONIA	8	3.7%
URINARY TRACT INFECTION	8	3.7%
ABDOMINAL PAIN	7	3.2%
CONSTIPATION	7	3.2%
EPISTAXIS	7	3.2%
HAEMOPTYSIS	7	3.2%
HYPOKALAEMIA	7	3.2%
PALPITATIONS	7	3.2%
PYREXIA	7	3.2%

AEs of special interest

The AEs of special interest included those expected to be observed with selexipag based on its mechanism of action i.e., prostacyclin-associated AEs, hypotension, and haemorrhage (also of increased risk in PAH, particularly in patients receiving anticoagulants and anti-platelet agents) and AEs of potential risk identified from preclinical studies with selexipag i.e., eye disorders (retinal vasculature impairment). Furthermore, malignancies and signs of drug-induced liver injury were regarded as AEs of special interest. In addition, AEs which were found to be more frequent with selexipag than with placebo were discussed by the Applicant in further detail, namely anaemia, renal failure (including other renal disorders for completeness) and hyperthyroidism.

In case of hypotension, a mechanistic link is likely based on theoretical considerations (prostacyclin-mediated vasodilation). Reassuringly, the incidence of serious hypotension events was balanced between selexipag and placebo.

For renal failure, a causal relationship to selexipag treatment remained unclear. Not all events were regarded serious; e.g. temporal worsening of chronic renal failure was considered non-serious. For serious events of acute renal failure, the imbalance was smaller (10 patients with selexipag vs. 7 patients with placebo).

Malignancies and MACE are described in more detail in the following. For the other AEs of special interest the closer analysis did not reveal new insights and is therefore not presented. No relevant differences between selexipag and placebo were detected for haemorrhage.

Malignancies

Malignancy AEs were reported for 11 patients (14 AEs) in the selexipag group versus 4 patients (4 AEs) in the placebo group. All events were considered by the investigator to be unrelated to study drug. The events were reported as serious in 7 patients (8 events) in the selexipag group and 4 patients (4 events) in the placebo group. There was a salient imbalance in light-dependent skin tumours (basalioma and keratoacanthoma) in the selexipag vs. placebo group (five tumours in four patients of the selexipag group, none in the placebo group).

PAH can be associated with autoimmune disease so that some patients received immunosuppressant medication prior or during the study. However, no relevant differences between the selexipag and the placebo group become obvious.

It is known that sunlight exposure can play a role in the formation of the types of skin tumours which were observed in the selexipag group. Simultaneously, selexipag was found to be potentially phototoxic in an *in-vitro* screening test (see Non-clinical AR). The Applicant aimed to confirm or exclude phototoxicity of selexipag in a dedicated Phase 1 study AC-065-102 (see Pharmacology section for details).

However, this study is not informative since the positive control did not yield the expected results.

Cardiovascular events

There was a numerical imbalance in serious and total Major Adverse Cardiovascular Events (MACE) in the selexipag vs. the placebo group in the GRIPHON study (double blind period), in disfavour of selexipag. A mechanistic link to selexipag action is not immediately obvious since prostacyclin inhibits platelet aggregation which could even have a protective effect. The analysis of MACE is summarized in the table below. The overall proportion of patients with such events was 2.4% in the selexipag group and 1.4% in the placebo group. Corrected for exposure, the average annualized event rate was 0.015 and 0.010 for selexipag and placebo, respectively. No specific leading cause of MACE was identified; see the two following tables for details.

Table 57 : Summary of MACE AEs in the DOUBLE BLIND, placebo-controlled PAH safety analysis set from study AC-065A302 (Pool 1)

	Selexipag (N=575)		Placebo (N=577)	
	n	%	n	%
Patients with at least one AESI	14	**2.4%**	8	**1.4%**
Patients with at least one AESI leading to discontinuation	8	1.4%	2	0.3%
Patients with at least one serious AESI	14	2.4%	7	1.2%
Patients with at least one AESI with a fatal outcome	10	1.7%	6	1.0%
Average annualized event rate	0.016		0.010	
Number of recurrent AESI	14		8	
Patient-years of observation	851.529		794.505	

Serious adverse events and deaths

Deaths

The numbers of fatal events as a component of the primary endpoint were 25 (4.4%) and 16 (2.7%) in the selexipag and placebo groups, respectively. However, due to the competing nature of morbidity/mortality events considered for the primary endpoint, informative censoring takes place, and these numbers should be interpreted with caution (see Efficacy and B/R part of this report for detailled explanation and discussion of informative censoring).

Overall, a total of 46 deaths (8.0%) and 37 deaths (6.4%) in the selexipag and placebo groups, respectively, were reported up to EOT + 7 days. Among these, a similar proportion (71.7% vs 73.0%) in the selexipag and placebo group, respectively, were adjudicated as PAH-related by the CEC. At Study closure, the number of deaths was similar in the selexipag and placebo groups (100 [17.4%] and 105 [18.0%] respectively). The proportion of patients who died due to PAH was 12.2% and 14.3% in the selexipag and placebo groups, respectively. For further details see table below.

Table 12-7 of study report: Summary of deaths in AC-065A302 Full analysis set

	Selexipag N = 574 n (%)	**Placebo N = 582 n (%)**
Deaths as the first event up to EOT + 7 days	**28 (4.9)**	**18 (3.1)**
All deaths up to EOT + 7 days	**46 (8.0)**	**37 (6.4)**
Death due to PAH	33 (71.7)	27 (73.0)
Death not due to PAH	13 (28.3)	10 (27.0)
All deaths up to Study closure	**100 (17.4)**	**105 (18.0)**
Death due to PAH	70 (12.2)	83 (14.3)
Death not due to PAH	30 (5.2)	22 (3.8)

The treatment duration was somewhat longer in selexipag vs. placebo patients (mean 76.4 vs. 71.2 weeks, see Section 4.2 “Patient exposure” above). The hazard ratio for mortality for the treatment period was **1.17**, as stated in the Kaplan-Meier plot below.

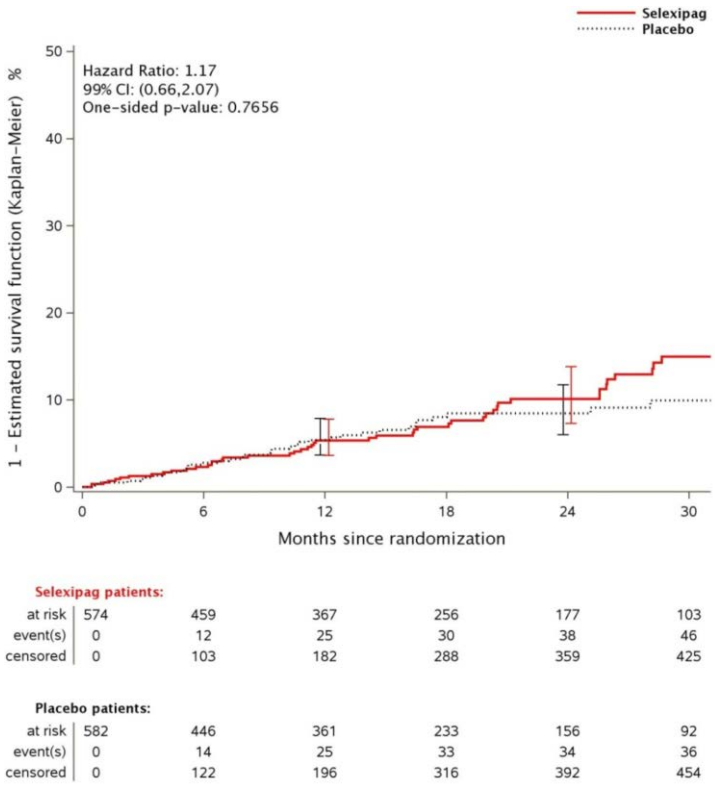


Figure 1-87 Appendix 2: Kaplan-Meier estimates of time from randomization to CEC confirmed death up to AC-065A302 EOT + 7 days, FAS

Most of the fatal events were regarded as **cardiac death** (38 of 46 in the selexipag group and 29 of 37 in the plc group).

The imbalance in overall mortality and cardiac deaths was restricted to patients in FC I/II, see table below.

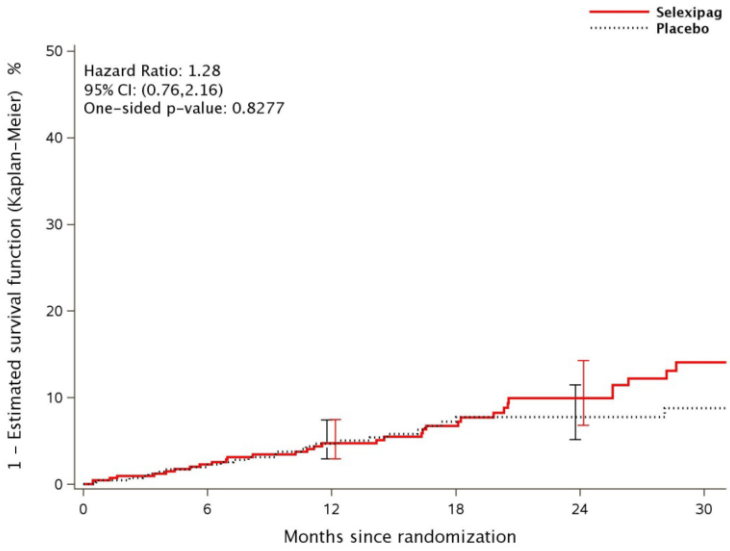
Table 3 of Response Document: Adjudicated cause of death up to EOT + 7 days (blinded adjudication by independent cardiologist and CEC) by WHO FC at baseline, AC-065A302, FAS

	WHO FC I/II			WHO FC III/IV		
	Selexipag N = 278	Placebo N = 260	Total N = 538	Selexipag N = 296	Placebo N = 322	Total N = 618
Cardiac death	**15**	**6**	**21**	**23**	**23**	**46**
Sudden death	7	0	7	5	6	11
Myocardial infarction	0	0	0	0	1	1
Heart failure	8	6	14	18	16	34
Non-cardiac death	**2**	**3**	**5**	**6**	**5**	**11**
Total	**17**	**9**	**26**	**29**	**28**	**57**

CEC = Critical Event Committee; EOT = End of treatment; FAS = Full analysis set; FC = functional class

Otherwise, major deviations of a subgroup HR from the all patient HR were only observed for small subgroups in which, due to the low patient number, a high degree of uncertainty resulted.

The Applicant also provided a Kaplan-Meier plot (see below) of survival restricted to patients with "typical PAH", whereby *Typical PAH* is defined as PAH in patients who had no co-morbidity that might have introduced a doubt on the aetiology of PAH. It turned out that this large subgroup of patients also had a higher mortality in the selexipag group; the HR was 1.28 and thereby numerically even higher than in all patients (HR 1.17).



Selexipag patients:						
at risk	439	352	282	194	131	77
event(s)	0	9	17	22	28	33
censored	0	78	140	223	280	329

Placebo patients:						
at risk	444	356	289	182	123	71
event(s)	0	9	17	23	24	25
censored	0	79	138	239	297	348

Figure 1-112 Appendix 2: Time from randomization to CEC-confirmed death up to 7 days after last study drug intake in the AC-065A302 Treatment Period in patients with typical PAH according to the blinded expert review - Kaplan-Meier estimates, FAS patients with typical or consistent PAH

An independent analysis investigated the influence of several baseline factors on mortality. A significant association was found for cardiac index (CI), whereby the interaction was complex. The Kaplan-Meier plot below visualises mortality over time for patients with low (25th percentile, marked "Q1" in the figure) and high (75th percentile, marked "Q3" in the figure) CI, having received selexipag or placebo. The placebo group meets the expectations in that mortality was higher with low cardiac index (Q1) than with high CI (Q3). With selexipag, mortality decreased in the low-CI group but clearly increased in the high-CI group. The reason for this effect in the high-CI-group is not clear.

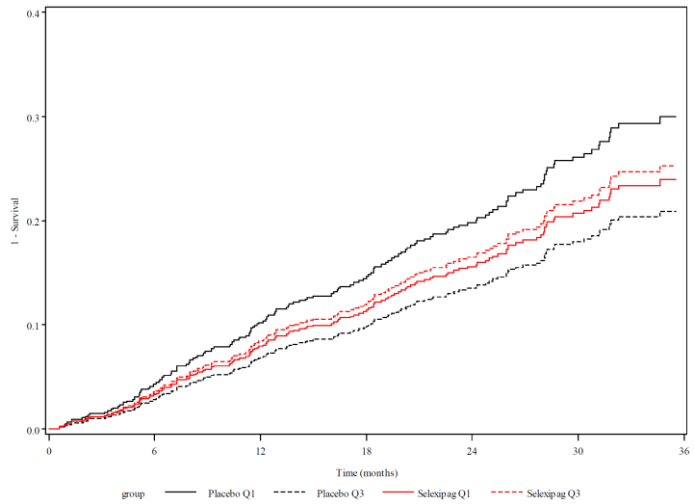
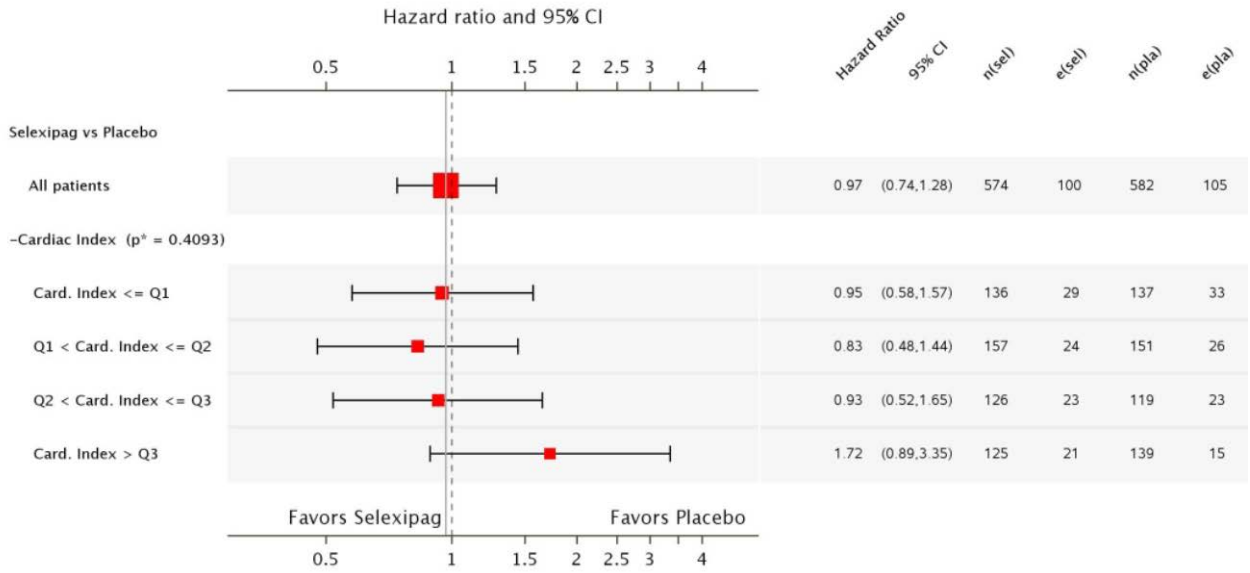


Figure 4 -response Document: Estimated mortality up to Study closure by treatment group

Increased mortality with higher CI (>Q3) is also clearly visible in the Forest plot analysis shown below.

Figure 3 of the Response Document: Time to death up to EOS, selexipag vs placebo, by quartiles of cardiac index at baseline, AC-065A302, FAS



In search for potential explanations of the observed numerically higher mortality with selexipag up to EOT+7d, the applicant performed two independent **mathematical modelling** approaches (for details see section 3.4.5 Clinical Efficacy). Assuming selexipag to have a beneficial effect non-fatal events and a neutral effect on mortality, the results of the mathematic models fitted the observed difference in deaths very well. In particular, the simulation in the first model showed on average 38 deaths for placebo and 46 deaths for selexipag, compared to the observed 37 and 46 deaths, respectively. The probability of observing more deaths with selexipag compared to placebo was **79%** and of observing an excess of 9 or more deaths was **45%**. In the second model, the likelihood of observing more deaths in the selexipag arm up to EOT+7d was also high, ranging from **60–81%**. The expected difference ranged from 3.0 to 7.8, and the probability of observing a difference of 9 or more deaths between treatment arms up to EOT+7d was **26–47%**. This model considered three scenarios of acceleration of the death process by an endpoint event. Hence, the probabilities are given as ranges covering the three scenarios.

SAEs

In AC-065A302, 43.8% and 47.1% of patients in the selexipag and placebo groups, respectively, had at least 1 SAE (see table below), i.e. SAEs were numerically lower with selexipag than with placebo. PAH worsening and right ventricular failure were the most frequently reported SAEs, and both were reported at lower frequencies in the selexipag group (14.4% and 5.9%, respectively) compared to the placebo group (22.0% and 7.1%, respectively). Other SAEs reported at lower frequencies in the selexipag group included pneumonia (3.0% selexipag, 4.3% placebo) and syncope (1.7% selexipag, 3.5% placebo). The SAE “right ventricular failure” was less frequent in the selexipag group which is well in line with the efficacy finding of slowing of PAH progression

Table 12-8: Treatment-emergent SAEs in study AC-065A302 sorted by PT incidence, SAF

	Selexipag		**Placebo**	
Preferred Term	N=575		N=577	
	n	%	n	%
Adverse events				
Patients with at least one SAE	**252**	**43.8%**	**272**	**47.1%**
Number of SAEs	513		515	
PULMONARY ARTERIAL HYPERTENSION	83	14.4%	127	22.0%
RIGHT VENTRICULAR FAILURE	34	5.9%	41	7.1%
PNEUMONIA	17	3.0%	25	4.3%

DYSPNOEA	17	3.0%	13	2.3%
SYNCOPE	10	1.7%	20	3.5%
ATRIAL FIBRILLATION	7	1.2%	4	0.7%
CHEST PAIN	6	1.0%	6	1.0%
RENAL FAILURE ACUTE	6	1.0%	6	1.0%
BRONCHITIS	6	1.0%	4	0.7%
HAEMOPTYSIS	5	0.9%	5	0.9%
ABDOMINAL PAIN	5	0.9%	4	0.7%
SUDDEN DEATH	5	0.9%	4	0.7%
ANAEMIA	5	0.9%	3	0.5%
SYSTEMIC LUPUS ERYTHEMATOSUS	5	0.9%	1	0.2%
EPISTAXIS	4	0.7%	4	0.7%
LOWER RESPIRATORY TRACT INFECTION	4	0.7%	4	0.7%
PULMONARY EMBOLISM	4	0.7%	3	0.5%
RESPIRATORY TRACT INFECTION	4	0.7%	3	0.5%
UPPER RESPIRATORY TRACT INFECTION	4	0.7%	3	0.5%
LUNG INFECTION	4	0.7%	2	0.3%
ROAD TRAFFIC ACCIDENT	4	0.7%	2	0.3%

The percentage of patients with AEs with fatal outcome was larger in the selexipag than in the placebo group (on-treatment), see table below. This is in line with the numerically increased mortality described above, subsection “Deaths”. PAH or cardiopulmonary failure as causes of death were more frequently reported with selexipag than with placebo, despite an overall slowed disease progression.

Table 15-199 (shortened): Treatment-emergent SAEs in study AC-065A302 with fatal outcome sorted by PT incidence in the selexipag group, SAF (EOT + 7 days)

	Selexipag		Placebo	
Preferred Term	N=575		N=577	
	n	%	n	%
Patients with fatal SAE	49	**8.5%**	41	**7.1%**
Number of fatal SAEs	73		64	
PULMONARY ARTERIAL HYPERTENSION	19	3.3%	16	2.8%
RIGHT VENTRICULAR FAILURE	7	1.2%	6	1.0%
SUDDEN DEATH	5	0.9%	4	0.7%
CARDIOPULMONARY FAILURE	3	0.5%	1	0.2%
ACUTE RIGHT VENTRICULAR FAILURE	2	0.3%	3	0.5%
RENAL FAILURE ACUTE	2	0.3%	3	0.5%
CARDIO-RESPIRATORY ARREST	2	0.3%	2	0.3%
PNEUMONIA	2	0.3%	2	0.3%
CARDIAC ARREST	2	0.3%	1	0.2%
ROAD TRAFFIC ACCIDENT	2	0.3%	1	0.2%
VENTRICULAR FIBRILLATION	2	0.3%	0	

The adjudication of death cases was made separately by the CEC and by an external expert cardiologist. Combining the adjudications identified 7 cases of sudden cardiac death (6 selexipag, 1 placebo) not related to PAH (up to EOT + 7 days). Most of the six patients in the selexipag group had pre-existing CV disease beyond PAH.

Laboratory findings

Haematology

Mean absolute changes from baseline to regular visits in haemoglobin ranged from −3.4 to −0.6 g/L in the selexipag group compared to −0.6 to 3.0 g/L in the placebo group of the GRIPHON study. Mean absolute change from baseline to regular visits in platelet count ranged from 3.1 to 9.7 GI/L in the selexipag group compared to −4.6 to 2.2 GI/L in the placebo group. There were no changes from baseline in mean haematocrit, erythrocyte and leukocyte counts in the two groups. However, markedly decreased Hb was more frequently reported as an AE in the selexipag as compared to the placebo group (<80 g/L, 1.3% vs.0.7%; <100 g/L, 8.8% vs. 5.0%). There was also an increased frequency of reported decreases in leukocyte count in the selexipag group (<2.0 G/L, 0.9% vs. 0.2%; <3.0 G/L, 5.0% vs. 2.0%).

Serum Chemistry

There were 2.5% of patients in the selexipag group and 1.4% in the placebo group reporting decreased potassium to <3.0 mmol/L. No relevant differences between selexipag and placebo in mean potassium level were observed. There was one patient in the selexipag group who had study drug dose reduction due to hypokalaemia. Otherwise no relevant imbalances between the groups disfavouring selexipag were observed.

Vital signs

Heart rate and ECG

At the Month 12 visit, an ECG at 2 and 4 h post-dose was performed. Median HR was 74.0 and 72.0 bpm in the selexipag and placebo groups, respectively, at pre-dose at Month 12. The mean change from pre-dose in HR at 2 h post-dose was 5.4 bpm and 2.1 bpm for selexipag and placebo, respectively. At 4 h post-dose, the mean change from pre-dose value was smaller than after 2 hours for selexipag, 3.7 bpm. Changes in the PR interval were consistent with the observed HR changes. No meaningful changes in QRS duration and the QTcF interval were observed at 2 and 4 h post-dose ECG recordings.

Categorical heart rate analysis of the GRIPHON trial data (see table below) revealed a higher percentage of patients with a HR increase of >10, >15 or >20 bpm 2 hours after dosing in the selexipag compared to the plc group (see Table 18 below).

Table 18 from the Response Document: Categorical change in heart rate post-dose vs pre-dose at Month 12 (ECG), AC-065A302, SAF

	Selexipag N=575 n	%	Placebo N=577 n	%	Odds Ratio* 95% CI
Increase from Month 12 pre-dose to 2hours post-dose					
No increase or increase <= 10 bpm	208 /287	72.5%	227 /265	85.7%	2.35
Increase > 10 - 15 bpm	32 /287	11.1%	23 /265	8.7%	(1.53, 3.60)
Increase > 15 - 20 bpm	30 /287	10.5%	9 /265	3.4%	
Increase > 20 bpm	17 /287	5.9%	6 /265	2.3%	
Increase from Month 12 pre-dose to 4hours post-dose					
No increase or increase <= 10 bpm	214 /275	77.8%	219 /257	85.2%	1.60
Increase > 10 - 15 bpm	39 /275	14.2%	20 /257	7.8%	(1.02, 2.49)
Increase > 15 - 20 bpm	11 /275	4.0%	9 /257	3.5%	
Increase > 20 bpm	11 /275	4.0%	9 /257	3.5%	

*Selexipag vs. placebo for increased heart rate

Blood pressure

A higher percentage of patients in the selexipag than in the placebo group of GRIPHON (double blind period) revealed low SBP (<90 mmHg), 9.7% vs. 6.7%, in line with the observed increased incidence in hypotension. No meaningful changes in mean blood pressure were observed in GRIPHON. In the selexipag group, mean changes from baseline in SBP ranged from -2.0 to 1.5 mmHg compared to -1.3 to 0.0 mmHg in the placebo group; DBP: -1.6 to -0.1 mmHg vs. -1.1 to 0.3 mmHg.

Bone turnover markers

Because of bone findings in animals (increased ossification in dogs, characterized by periosteal bone formation and increased thickness and numbers of trabeculae), bone turnover markers were assessed in study AC-065A302 (i.e. double blind period of GRIPHON). Mean absolute changes from baseline in bone specific alkaline phosphatase and carboxyterminal telopeptide showed no consistent pattern in either group. Thus, no hints for bone effects in humans were detected. The Applicant also had performed mechanistic studies in animals which make a dog-specific effect likely.

Safety in special populations

Age: The safety analysis set comprised 476 patients aged < 65 years treated with selexipag (709 patient-years) vs 470 treated with placebo (638 patient-years), and 91 patients aged 65–74 years treated with selexipag (116 patient-years) vs 102 treated with placebo (137 patient-years). The number of patients ≥ 75 years old was low (8 selexipag, 5 placebo) and insufficient to allow meaningful evaluation of AEs in this age group. The overall AE frequency was 97.5% and 100% in the selexipag group and 97.0% and 96.1% in the placebo group for patients aged < 65 years and 65–74 years, respectively. The pattern of AEs was generally similar in patients aged < 65 years and in those aged 65–74 years, although some differences in the frequency of individual AEs was observed. A

higher frequency of prostacyclin AEs leading to discontinuation of selexipag treatment was reported for patients aged between 65 and 75.

Regarding other special populations, the Applicant provided AE listings for several demographic factors, type of PAH and background medication. No special concerns became obvious. No safety information on patients with liver or kidney disease was provided.

Patients with relevant renal or hepatic impairment were rare in the GRIPHON study so that safety evaluation of these subgroups is not possible.

Immunological events

In the GRIPHON study, double blind period, there were three cases (0.5%) of hypersensitivity reported in the selexipag group vs. four cases (0.7%) in the placebo group. In total, immune system disorders were reported in 1.9% vs. 3.8% of patients (selexipag vs. placebo) in this study.

Safety related to drug-drug interactions and other interactions

The Applicant provided AE listings stratified for the different accompanying PAH treatments. No marked differences according to accompanying PAH medication can be detected. The AE profile was similar under all conditions, with an increase of gastrointestinal AEs, pain in various locations and rash/flushing increased in the selexipag groups vs. placebo. Interaction was more closely studied for hypotension. The triple combination of selexipag, ERA and PDE5i produced the highest rate of hypotension.

Discontinuation due to AES

A total of 31.7% of patients in the selexipag group had at least 1 AE leading to discontinuation of study drug in study AC-065A302 compared to 37.1% in the placebo group. The most frequently reported AE leading to discontinuation of study drug was PAH worsening (13.6% selexipag, 23.4% placebo). The proportion of patients who discontinued due to right ventricular failure was 2.4% in the selexipag group and 4.0% in the placebo group. Hence, a marked difference in discontinuation due to PAH was observed in favour of selexipag. This again indicates that selexipag can influence PAH progression positively. Conversely, more patients in the selexipag group than in the placebo group discontinued due to presumably prostacyclin-related effects. The total discontinuation rate was higher in the placebo group.

2.6.1 Discussion on clinical safety

The safety information is mainly based on the double-blind, placebo-controlled treatment period of the pivotal phase 3 study GRIPHON. Nearly all patients had at least one AE in the selexipag as well as in the placebo group. However, there was a set of characteristic AEs which were markedly more frequent with selexipag than with placebo. These AEs included various gastrointestinal (GI) symptoms, pain at various locations and flushing. Furthermore, mean heart rate was increased for a few hours after each administration of selexipag (mean 3.3 bpm vs. placebo) whereas mean systemic blood pressure was hardly affected; however, events of hypotension were more frequent with selexipag than with placebo. All these mentioned signs and symptoms are in line with the PD action of selexipag, i.e. activation of the IP receptor. The Applicant therefore used the term “prostacyclin-associated AEs” to describe this set of AEs.

Furthermore, a slight imbalance of acute renal failure, disfavouring selexipag, was observed. Renal and urinary disorders reported as previous or concomitant diseases higher in the selexipag group (13.1%) than in the placebo group (10.3%). However, it cannot fully be excluded that the prostacyclin-like action of selexipag could worsen renal function because of the complex effects of prostaglandins on

various organs. Thus, "renal function impairment" / "acute renal failure" have been listed as important potential risks in the RMP.

Regarding SAEs, the total percentage of patients with at least one serious AE was numerically lower in the selexipag than in the placebo group. This was mainly driven by the markedly lower incidence of (worsening of) PAH in the selexipag group and was in line with the findings of the efficacy analysis. An analysis of MACE events revealed an increase of them in the selexipag group. The imbalance in MACE is essentially due to the imbalance in CV deaths because most of the MACE were fatal. Sudden death and death due to heart failure were most frequent. MACE have been listed as important potential risks in the RMP.

Until the end of treatment (EOT)+7 days, mortality was numerically higher in the selexipag group compared to the placebo group (46 vs. 37 cases, HR 1.17). The imbalance was due to cardiovascular death; non-CV death was fairly balanced between the groups. Notably, the difference between selexipag and placebo was largest for deaths as part of the primary endpoint. This means that in the selexipag group more often than in the placebo group death occurred without prior signs of PAH worsening. This could indicate a merely symptomatic improvement by selexipag treatment without affecting mortality. However, in their response the Applicant submitted a further analysis which also included worsening of right heart function as a parameter for PAH progression as suggested in the relevant CHMP guideline and with this analysis the number of deaths as first event decreased in the selexipag group so that no relevant difference between selexipag and placebo remained (see efficacy part of this report).

Analysis of mortality (as first event) is biased by informative censoring (see Efficacy and B/R part of this report). Since presence of informative censoring does not rule out a true increase, a careful search for mechanisms by which selexipag could potentially adversely affect mortality was performed. It was observed that increased mortality with selexipag as compared to placebo was limited to patients with FC II at baseline and with a cardiac index (CI) in the highest quartile. Cardiac index (CI) was found to be significantly correlated with survival under selexipag treatment. Analyses suggested that selexipag increases survival in low-CI patients but decreases survival in the high-CI patients, which is an implausible biological and clinical finding. Furthermore, cross study comparisons suggested that the mortality rate on selexipag in patients with FCII was not higher than expected, whereas the mortality rate in FC II on placebo was remarkably low. No safety signal, overall or specifically related to FC II, was detected and there is no clinical rationale why patients in functional class II with better cardiac function should be more sensitive to a putative harmful effect of selexipag than patients in FC III/IV with deteriorated cardiac function making a causal relationship between the observed increased mortality and selexipag in the first event analysis is highly unlikely.The numerical increase in deaths up to end of treatment + 7 days but not up to study closure was further investigated by mathematical modelling, showing that the imbalance in deaths is consistent with the assumption of a neutral effect on PAH mortality and reduction of non-fatal events (reference is made to section 3.4.5 Clinical Efficacy).

Regarding vital signs, a transient and small increase in mean **heart rate** (HR; around 3 bpm vs. plc) was noted after dosing of selexipag compared to placebo in the pivotal GRIPHON trial. Correspondingly, higher percentages of patients had increases in HR >10, > 15 or > 20 bpm with selexipag compared to placebo. Although changes in heart rate were generally modest and similar to those seen with other medicinal products approved for PAH, HR increases could be relevant in vulnerable patients. Therefore, patients at high risk of experiencing cardiovascular events have been excluded from treatment by including the iloprost contraindications (e.g. severe coronary artery disease, status post myocardial infarction, unstable angina) into the SmPC of selexipag.

Malignancies were found to be numerically more frequent in the selexipag group of the GRIPHON trial (11 vs. 4 patients, selexipag vs. placebo). The surplus in the selexipag group is mainly due to skin tumours which did not occur at all in the placebo group. Phototoxicity of selexipag and its metabolite ACT-333679 was observed in non-clinical in-vitro screening tests and could not be excluded in a dedicated trial. However, the Applicant pointed out that no signs of phototoxicity were observed in the patients suffering skin tumours and that the incidence observed in the selexipag group is well within the expectations based on the frequency of these tumours in the general population. Thus, a chance finding is likely as the absolute number of cases was low. Of note, light-dependent non-melanoma skin malignancies are listed as important potential risks in the RMP.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2 Conclusions on clinical safety

The applicant has provided mathematical models and simulations that can explain the finding of a numerically higher rate of deaths in the first overall event analysis as a result of informative censoring. These show that the finding of an imbalance for death as first event up to EOT or EOT+7d is not unexpected under the assumption that selexipag decreases non-fatal but not fatal events. For further details see efficacy part of this report.

No specific/unique safety issue could be identified that could explain an increase in mortality with selexipag. In addition, any putative safety issue leading to increased mortality would be more likely to become evident in PAH patients with poor health condition as opposed to patients in FCII and better cardiac functioning. Therefore, the observed increased mortality in the primary MM endpoint analysis is most likely due to informative censoring and/or a chance finding and lacks biological or clinical plausibility. Hence, CHMP considered the mortality issue as satisfactorily addressed.

The CHMP considered acceptable to further monitor the safety profile as mentioned in the RMP, in the clinical use setting as a post authorisation study included in the RMP.

In reference to the safety profile it is also agreed with the implementation of risk minimisation activities as proposed by the applicant and reflected into the Marketing Authorisation (see below for details).

2.7 Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 4 is acceptable. In addition, minor revisions were recommended to be taken into account before opinion. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The applicant implemented the changes in the RMP as requested by PRAC.

The CHMP endorsed the Risk Management Plan version 5 with the following content:

Safety concerns

Important identified risks	• Hypotension • Anaemia
Important potential risks	• Pulmonary oedema associated with pulmonary veno-occlusive disease • Hyperthyroidism • Major adverse cardiovascular events • Renal function impairment / 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) • Medication error • Off-label use
Missing information (or limited)	• Use in paediatric patients • Use in elderly over 75 years old • Use during pregnancy and lactation • Use in patients with severe hepatic impairment • Use in patients undergoing dialysis • Concomitant use with strong inhibitors of CYP2C8, UGT1A3 and UGT2B7 or inducers of CYP2C8, UGT1A3, and UGT2B7 • Concomitant use with substrates of intestinal CYP3A4 and CYP2C9

Pharmacovigilance plan

Study/activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
PASS: observational cohort study of PAH patients exposed and unexposed to Uptravi® (selexipag) in routine clinical practice Category 3	1. To describe demographics, disease characteristics and clinical course in PAH patients who either initiated treatment with Uptravi < 3 months prior to or at enrolment or during observation (Uptravi exposed patients), or were never treated with Uptravi (Uptravi unexposed patients), overall and in the subset of patients > 75 years old	- Hypotension - Anaemia / decreased haemoglobin concentration - Pulmonary oedema associated with pulmonary veno-occlusive disease - Hyperthyroidism - Major adverse cardiovascular events, i.e., PTs denoting cardiovascular death, sudden death, MI, ischaemic or hemorrhagic	Planned	Final study report 2023

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
	2. To further characterise the Uptravi safety profile and estimate the incidence rates during the observation period of all-cause death and the important identified or potential risks [see list in column 'Safety concerns addressed'] 3. To compare rates of MACE and all-cause death between Uptravi exposed patients and Uptravi unexposed patients, stratified using a propensity score analysis.	cerebrovascular disorder - Renal function impairment / acute renal failure - Bleeding events - Light-dependent non-melanoma skin malignancies - Ophthalmological effects associated with retinal vascular system - GI disturbances denoting intestinal intussusception (manifested as ileus or obstruction)		
PASS to evaluate medication error risk minimisation measures for the Uptravi titration phase Category 3	To evaluate medication error risk minimisation measures during the Uptravi titration phase. To record the occurrence of 'wrong dose' medication errors self-reported by the patient.	Occurrence of medication errors during the Uptravi titration phase	Planned	Final study report 2020

Risk minimisation measures

Important identified risks		
Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Hypotension	**Proposed SmPC** Hypotension is described in section 4.4: 'Hypotension Uptravi has vasodilatory properties that may result in lowering of blood pressure. Before prescribing Uptravi, physicians should carefully consider whether patients with certain underlying conditions could be adversely affected by vasodilatory effects (e.g., patients on antihypertensive therapy or with resting hypotension, hypovolaemia, severe left ventricular outflow obstruction or autonomic dysfunction).' Hypotension is included in section 4.8 Undesirable effects in the ADR table as a common adverse reaction. **Other routine risk minimisation measures** None	None proposed
Anaemia	**Proposed SmPC** Anaemia and haemoglobin decreased are included in section 4.8 Undesirable effects in the ADR table as common adverse events. Changes in haemoglobin in PAH patients in the GRIPHON study are included in section 4.8 Undesirable effects under the ADR table under Description of selected adverse reactions: '*Haemoglobin decrease* In a Phase 3 placebo-controlled study in patients with PAH, mean absolute changes in haemoglobin at regular visits compared to baseline ranged from −0.34 to −0.02 g/dL in the selexipag group compared to −0.05 to 0.25 g/dL in the placebo group. A decrease from baseline in haemoglobin concentration to below 10 g/dL was reported in 8.6% of selexipag-treated patients and 5.0% of placebo-treated patients.' **Other routine risk minimisation measures**	None proposed

	None	
Important potential risks		
Pulmonary oedema associated with pulmonary veno-occlusive disease	**Proposed SmPC** PVOD is described in section 4.4: 'Pulmonary veno-occlusive disease Cases of pulmonary oedema have been reported with vasodilators (mainly prostacyclins) when used in patients with pulmonary veno-occlusive disease. Consequently, if signs of pulmonary oedema occur when Uptravi is administered in patients with PAH, the possibility of pulmonary veno-occlusive disease should be considered. If confirmed, treatment with Uptravi should be discontinued.' **Other routine risk minimisation measures** None	None proposed
Hyperthyroidism	**Proposed SmPC** Hyperthyroidism is listed in section 4.4: 'Hyperthyroidism Hyperthyroidism has been observed with Uptravi. Thyroid function tests are recommended as clinically indicated in the presence of signs or symptoms of hyperthyroidism.' Hyperthyroidism is included in section 4.8 Undesirable effects in the ADR table as a common adverse event. Values of thyroid function tests in the GRIPHON study are included in section 4.8 Undesirable effects under the ADR table: '*Thyroid function tests* In a Phase 3 placebo-controlled study in patients with PAH, hyperthyroidism was reported for 1.6% of patients in the selexipag group, compared to no case in the placebo group (see section 4.4). A reduction (up to −0.3 MU/L from a baseline median of 2.5 MU/L) in median thyroid-stimulating hormone was observed at most visits in the selexipag group. In the placebo group, little change in median values was apparent. There were no mean changes in triiodothyronine or thyroxine in either group.'	None proposed

	Other routine risk minimisation measures None	
Major adverse cardiovascular events	**Proposed text in SmPC** Relevant contraindications listed in section 4.3 '• 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 (e.g., 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.' **Other routine risk minimisation measures** None	None proposed
Renal function impairment / acute renal failure	None	None proposed
Bleeding events	None	None proposed
Light-dependent non-melanoma skin malignancies	None	None proposed
Ophthalmological effects associated with retinal vascular system	**Proposed text in SmPC** Nonclinical data described in section 5.3: 'Tortuosity of retinal arterioles was noted after 2 years of treatment only in rats. Mechanistically, the effect is considered to be induced by life-long vasodilation and subsequent changes in ocular haemodynamics. Additional histopathological findings of selexipag were observed only at exposures sufficiently in excess of the maximum human exposure, indicating little relevance to humans.' **Other routine risk minimisation measures** None	None proposed
Gastrointestinal disturbances denoting intestinal intussusception	**Proposed text in SmPC** Administration in paediatric population not recommended in section 4.2:	None proposed

(manifested as ileus or obstruction)	'*Paediatric population (< 18 years)* The safety and efficacy of Uptravi in children aged 0 to less than 18 years have not yet been established. No data are available. Administration of selexipag in the paediatric population is not recommended. Animal studies indicated an increased risk of intussusception, but the clinical relevance of these findings is unknown (see section 5.3).' Description of nonclinical data in section 5.3: 'In juvenile dogs, intussusception due to prostacyclin-related effects on intestinal motility was observed sporadically. Safety margins adapted for IP receptor potency for the active metabolite were 2-fold (based on total exposure) in relation to human therapeutic exposure. The finding did not occur in mouse or rat toxicity studies. Because of the species-specific sensitivity of dogs to develop intussusception, this finding is considered not relevant for adult humans.' **Other routine risk minimisation measures** None	
Medication error	**Proposed text in SmPC** Under section 4.2 Posology and method of administration: 'Treatment should only be initiated and monitored by a physician experienced in the treatment of PAH.' **Other routine risk minimisation measures** Product information clear and understandable to the HCP and patients Maximise easy identification and maximum differentiation by choice of colour of the two dosage strengths to be used during the titration phase (light yellow and green) Packaging design of strengths used during the titration process: the non-transparent alu/alu foil of the blister is maximally visually differentiated, matching the colour of the tablet and that used for the outer carton	Controlled Access System Educational material in a prescriber kit containing: Cover letter to the HCP and pharmacist A4 laminated card HCP titration guide SmPC Package leaflet and patient titration guide Patient titration guide included in the titration pack

Off-label use	**Proposed SmPC** Clear indication of target population is detailed in the indication section 4.1 of the SmPC: 'Uptravi is indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients with WHO functional class (FC) II–III. Uptravi may be used as combination therapy in patients insufficiently controlled on treatment 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. Efficacy has been shown in a PAH population including idiopathic and heritable PAH, PAH associated with connective tissue disorders, and PAH associated with corrected simple congenital heart disease (see section 5.1).' **Other routine risk minimisation measures** None	None proposed

Missing information (or limited)		
Use in paediatric patients	**Proposed SmPC** SmPC section 4.2: '*Paediatric population (< 18 years)* The safety and efficacy of Uptravi in children aged 0 to less than 18 years have not yet been established. No data are available. Administration of selexipag in the paediatric population is not recommended. Animal studies indicated an increased risk of intussusception, but the clinical relevance of these findings is unknown (see section 5.3).' Description of nonclinical data in section 5.3: 'In juvenile dogs, intussusception due to prostacyclin-related effects on intestinal motility was observed sporadically. Safety margins adapted for IP-receptor potency for the active metabolite were 2-fold (based on total exposure) in relation to human therapeutic exposure. The finding did not occur in mouse or rat toxicity studies. Because of the species-specific sensitivity of dogs to develop intussusception, this finding is considered not relevant for adult humans.' **Other routine risk minimisation measures** None	None proposed
Use in elderly over 75 years old	**Proposed SmPC** Section 4.2: '*Elderly (≥ 65 years)* No adjustment to the dosing regimen is needed in elderly people (see section 5.2). There is limited clinical experience in patients over the age of 75 years, therefore Uptravi should be used with caution in this population (see section 4.4).' Caution in section 4.4: 'Elderly (≥ 65 years) There is limited clinical experience with selexipag in patients over the age of 75 years, therefore Uptravi should be used with caution in this population (see section 4.2).' **Other routine risk minimisation measures**	None proposed

	None	
Use during pregnancy and lactation	**Proposed SmPC** Section 4.4: Women of childbearing potential Women of childbearing potential should practise effective contraception while taking selexipag. Section 4.6: Women of childbearing potential / Contraception in males and females Women of childbearing potential should practise effective contraception while taking selexipag. Pregnancy There are no data from the use of selexipag in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Selexipag and its main metabolite showed 20- to 80-times lower prostacyclin (IP) receptor potency *in vitro* in animal species used in reproductive toxicity testing compared to humans. Therefore, safety margins for potential IP receptor-mediated effects on reproduction are accordingly lower than for non-IP-related effects (see section 5.3). Uptravi is not recommended during pregnancy and in women of child-bearing potential not using contraception. Breast-feeding It is unknown whether selexipag or its metabolites are excreted in human milk. In rats, selexipag or its metabolites are excreted in milk (see section 5.3). A risk to the suckling child cannot be excluded. Uptravi should not be used during breast-feeding.' **Other routine risk minimisation measures** None	None proposed
Use in patients with severe hepatic impairment	**Proposed SmPC** Dosage recommendation in section 4.2: '*Hepatic impairment* Uptravi should not be administered in patients with severe liver impairment (Child-Pugh class C; see section 4.4). For patients with moderate hepatic	None proposed

	impairment (Child-Pugh class B), the starting dose of Uptravi should be 200 micrograms once daily, and increased at weekly intervals by increments of 200 micrograms given once dailyuntil adverse reactions, reflecting the mode of action of selexipag, that cannot be tolerated or medically managed, are experienced. No adjustment to the dosing regimen is needed in patients with mild hepatic impairment (Child-Pugh class A).' Caution in section 4.4: 'Patients with hepatic impairment There is no clinical experience with selexipag in patients with severe liver impairment (Child-Pugh class C), thereforeUptravi should not be administered in these patients. The exposure to selexipag and its active metabolite is increased in subjects with moderate hepatic impairment (Child-Pugh class B; see section 5.2). In patients with moderate hepatic impairment, Uptravi should be dosed once daily (see section 4.2).' PK described in section 5.2: 'Hepatic impairment In subjects with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment, exposure to selexipag was 2- and 4-fold higher, respectively, when compared to healthy subjects. Exposure to the active metabolite remained almost unchanged in subjects with mild hepatic impairment and was doubled in subjects with moderate hepatic impairment. Only two subjects with severe (Child-Pugh class C) hepatic impairment were dosed with selexipag. Exposure to selexipag and its active metabolite in these two subjects was similar to that in subjects with moderate (Child-Pugh class B) hepatic impairment. Based on modelling and simulation data from a study in subjects with hepatic impairment, the exposure to selexipag at steady state in subjects with moderate hepatic impairment (Child-Pugh class B) after a once-daily regimen is predicted to be approximately 2-fold higher than that in healthy subjects during a twice-daily	

	regimen. The exposure to the active metabolite at steady state in these patients during a once-daily regimen is predicted to be similar to that in healthy subjects during a twice-daily regimen. Subjects with severe hepatic impairment (Child-Pugh class C) showed similar predicted exposure at steady state as subjects with moderate hepatic impairment during a once-daily regimen.' **Other routine risk minimisation measures** None	
Use in patients undergoing dialysis	**Proposed SmPC** Dosage recommendation in section 4.2: '*Renal impairment* No adjustment to the dosing regimen is needed in patients with mild or moderate renal impairment. No change in starting dose is required in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2); dose titration should be done with caution in these patients (see section 4.4).' Caution in section 4.4: 'Patients with renal impairment In patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) caution should be exercised during dose titration. There is no experience with Uptravi in patients undergoing dialysis (see section 5.2), therefore Uptravi should not be used in these patients.' **Other routine risk minimisation measures** None	None proposed
Concomitant use with strong inhibitors of CYP2C8, UGT1A3 and UGT2B7 or inducers of CYP2C8, UGT1A3, and UGT2B7	**Proposed SmPC** Listed in section 4.5 under Effect of other medicinal products on selexipag: 'Inhibitors or inducers of CYP2C8, UGT1A3, and UGT2B7 The effect of inhibitors of CYP2C8 (gemfibrozil), inhibitors of UGT1A3 and UGT2B7 (valproic acid, probenecid, and fluconazole), inducers of CYP2C8 (rifampicin, rifapentine), or inducers of UGT1A3, and UGT2B7 (rifampicin) on the exposure to selexipag and its active metabolite has not been studied. Caution	None proposed

	is required when administering these medicinal products concomitantly with Uptravi. A potential pharmacokinetic interaction with strong inhibitors or inducers of these enzymes cannot be excluded.' **Other routine risk minimisation measures** None	
Concomitant use with substrates of intestinal CYP3A4 enzyme	**Proposed SmPC** Listed in section 4.5 under Effect of selexipag on other medicinal products: 'Selexipag and its active metabolite do not inhibit cytochrome P450 enzymes at clinically relevant concentrations. Selexipag and its active metabolite do not inhibit transport proteins. Selexipag and its active metabolite are not expected to induce cytochrome P450 enzymes in the liver and kidney at clinically relevant concentrations. *In vitro* data indicate that selexipag could be an inducer of both CYP3A4 and CYP2C9 in the intestine.' **Other routine risk minimisation measures** None	None proposed

2.8 Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9 Product information

2.9.1 User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2 Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Uptravi (selexipag) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that

this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

Benefits

The application is based on one pivotal clinical study (GRIPHON) which was an endpoint-driven trial that investigated the effect of selexipag on morbidity and mortality with onset date up to 7 days after last study drug intake in patients with PAH. The primary composite endpoint included the components death (all causes), hospitalization for worsening of PAH based on predefined criteria, worsening of PAH resulting in need for lung transplantation or balloon atrial septostomy, initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH and confirmed disease progression. Disease progression was defined by a decrease in the 6 Minute Walk Test (MWT) by at least 15% that is accompanied either by a) Worsening of NYHA/WHO Functional Class (FC) (patients in FC II-III) or by b) Need for additional PAH-specific therapy (patients in FC III-(patients in FC III-IV). Right heart failure, an endpoint component proposed in the relevant CHMP PAH guideline, was not part of the composite endpoint. Median duration of double-blind study treatment was 70.7 weeks for the selexipag and 63.7 weeks for the placebo group. After a primary morbidity/mortality event, patients could enter an extension phase and either remain on selexipag, discontinue treatment or switch from placebo to selexipag.

Beneficial effects

A statistically significant and clinically relevant benefit of selexipag vs. placebo has been demonstrated for the composite primary morbidity and mortality endpoint (24.4% vs. 36.4%, 140 vs. 212 patients with morbidity and mortality endpoint event. This beneficial effect was driven by a positive effect on “disease progression” and “hospitalization due to PAH worsening”. There was no beneficial effect on all-cause mortalityor quality of life.

A small beneficial effect was also observed for the 6 Minute Walk Test (-53 m vs. -66m). This effect was more pronounced in patients with Functional Class III than in those with Functional Class II and in treatment naïve patients comparedwas estimated to be larger [difference of +34 m vs. placebo at the pre-defined timepoint of 6 months (99% CI: 10.0; 63.0, p = 0.0002)] than in patients pretreated with ERA, PDEi or ERA+ PDEi (Point estimate and two-sided 99% CI for location shift, Hodges-Lehman method -1 (-38.0; 28.0 m), +12.0 (-8.0; 33.0m), and +6.0 (-14.0; 24.0 m), respectively)]. In patients with FC III/(IV) the difference was larger (+17.0 (-1.0; 36m) than in patients with FC (I)/II (+5.0 (-8.0; 19.0 m)).

Overall, a benefit has been shown in adult patients with IPAH or PAH due to connective tissue disease, in PAH associated with simple corrected congenital heart disease in WHO Functional Class II and 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. Maintenance of the effect has been sufficiently demonstrated over time since it was a long-term endpoint-driven trial.

Selexipag will be the first orally available prostacyclin (PGI_2) receptor agonist in the EU.

Uncertainty in the knowledge about the beneficial effects

The GRIPHON trial was not designed to investigate whether selexipag has disease modifying activity with maintenance of an effect after cessation of therapy.

Due to low numbers of patients in Functional Class I and IV included in GRIPHON study, efficacy in these functional classes cannot be reliably assessed. Thus, these patients are not included in the indication.

The individual components of the primary endpoint were assessed as secondary endpoints. Results were all in favour of selexipag except for mortality, which was numerically increased with selexipag compared to placebo (4.9% vs. 3.1%, 28 vs. 18 events at EOT+7 days follow up).

The observation of increased mortality in this analysis is prone to bias, and in consequence the event rates above are potentially misleading, firstly the trial was event-driven and patient follow-up contributing to the primary assessment of mortality ceased after their first primary outcome event, which was usually a disease progression (morbidity) event. After a first morbidity event, patients were allowed to cross over to another treatment: patients could remain on selexipag, discontinue treatment or switch from placebo to selexipag. Experiencing a morbidity event was associated with a higher risk of dying. Since more morbidity events occurred in the placebo group, more patients at high risk were excluded from further follow-up in the placebo group than in the selexipag group with a consequence that follow-up is shorter in the placebo group and follow-up from more patients that are at higher risk is excluded from the placebo group, resulting in bias. Observation of the patient is 'censored' when follow-up is discontinued according to the protocolled definition, and because the risk for those patients is probably increased, the censoring is termed 'informative' for outcome (patients at increased risk are more likely to be censored). In other words, due to the study design, the risk profile of the patients changed during the course of the study, favouring placebo group at the end of the trial despite of randomization. This is consistent with the observation that the imbalance did not emerge before month 18.

To explore the impact of these phenomena, mathematical simulations were conducted simulating the trial design under scenarios assuming a beneficial effect of treatment on morbidity and a neutral effect on mortality. These simulations indicated that, in a scenario where the placebo arm has increased 'informative censoring', there is a chance of at least a 70% to observe more deaths on selexipag and a chance of 26% to 47% to observe a large difference of 9 or more deaths.

As stated above, the follow-up time on treatment was longer in the selexipag vs. the placebo group (median 70.7 vs. 63.7 weeks, respectively. Adjustment for the difference in follow-up time ('at risk period') reduces but does not remove the numerical difference in mortality: estimated mortality rate (deaths per 100 patient years) is 5.45 in the selexipag and 4.64 in the placebo group, yielding a hazard ratio (HR) of 1.17. However, this adjustment assumes a constant risk over time, whereas in fact it can be understood that risks changed over time to a different degree in both arms.

The observed unfavourable effect on mortality as a primary endpoint event was less prominent when signs and symptoms of right heart failure were also taken into account as proposed by the relevant CHMP guideline on development of PAH medication (2.4% vs. 2.1%, 14 vs. 12 events, selexipag vs. placebo, respectively). At study closure, mortality was comparable between treatment groups (100 vs. 105 cases for selexipag vs. placebo, respectively) but this comparison is hampered by the possibility of open label cross-over to another treatment after the first morbidity event.

Of note, subgroup analyses for mortality indicated that the imbalance favouring placebo at EOT+7d analysis was restricted to patients in Functional Class I/II (HR 1.7 [99% CI 0.59,4.91] and to patients with cardiac index in the highest quartile as opposed to patients in Functional Class III/IV and patients with low cardiac index. This is hence not suggestive of a true effect of selexipag on mortality due to lack of biological or clinical plausibility. No safety issues were identified for selexipag that could explain an increased mortality. (see safety section).

Risks

Unfavourable effects

The safety information is mainly based on the double-blind, placebo-controlled treatment period of the pivotal phase 3 study GRIPHON. The safety dataset of this study encompassed **1152 patients**. Around 63% of patients were treated for at least one year.

Nearly all patients of the selexipag and of the placebo group had at least one AE during the double-blind period of the GRIPHON study. There was a set of characteristic AEs which were markedly more frequent with selexipag than with placebo. These AEs included various **gastrointestinal** (GI) symptoms, **pain** at various locations and **flushing**. Furthermore, mean **heart rate** was increased after administration of selexipag whereas mean systemic blood pressure was hardly affected; however, events of **hypotension** were more frequent with selexipag than with placebo. All these events are in line with the pharmacodynamic action of selexipag, i.e. activation of the IP receptor, and with the AE profile of other prostacyclin (analogues). Beside these, a slight imbalance in **anaemia**, acute **renal failure** and **hyperthyroidism**, both disfavouring selexipag, was observed.

Serious AEs (SAEs) during the double-blind treatment period were numerically lower in the selexipag than in the placebo group (43.8% vs. 47.1%). The difference was mainly due to the lower incidence of (worsening of) PAH in the selexipag group, which was in line with the findings of the efficacy analysis. Within the SAE analysis, **SAEs with fatal outcome** were reported more frequently in the selexipag than in the placebo group (8.5% vs. 7.1%). The imbalance was mainly due to increased reports of PAH-related fatal events in the selexipag group (e.g. worsening of PAH, right ventricular failure or cardiopulmonary failure); this reflects the mortality findings at EOT+7 days in the efficacy analysis. Major Cardiovascular Events (**MACE**) were also increased in the selexipag group as compared to placebo (7.1% vs. 5.7%, up to End of Treatment + 7 days). Most of the observed MACE were fatal; sudden death and death due to heart failure were the most frequent categories.

Laboratory findings (vital signs) included an increased **heart rate** (HR) for about 3 hours after each injection (i.e. twice daily). The increase was 5.4 bpm in the selexipag group vs. 2.1 bpm in the placebo group. Correspondingly, the number of patients with transient HR increases >10, >15, or >20 bpm was higher on selexipag than on placebo (10.5% vs. 3.1% for HR increase between >15 and 20 bpm, 5.9% vs. 2.3% for HR increase >20 bpm, selexipag vs. plc, measured 2h post-dose).

Uncertainty in the knowledge about the unfavourable effects

All-cause mortality was numerically higher in the selexipag group during the on-treatment period (median 70.7 and 63.7 weeks for the selexipag and placebo group, respectively). The treatment difference was largest for deaths that were considered as primary endpoint event (4.9% vs. 3.1%, Full Analysis Set). Due to study design and endpoint definition, the mortality results are prone to bias. For details see efficacy section above and discussion section below.

Only few patients aged 75 or above were present in the main safety database (GRIPHON study, double-blind period). Therefore, safety information on this population is limited. Limited data are also provided in patients with hepatic insufficiency.

Hypotension was more frequent with selexipag. Data on the influence of accompanying PAH medication is not fully conclusive.

The significance of the observed imbalance in acute renal failure is not clear. Further investigation of the individual cases did not suggest an underlying mechanism; however, a direct effect of selexipag on the kidney via its prostacyclin-like mode of action cannot be excluded. Therefore, "renal function impairment / acute renal failure" are listed in the RMP as important potential risks.

Benefit-risk balance

Importance of favourable and unfavourable effects

There is a **medical need** for new medicinal products for the treatment of PAH, in particular in the add-on treatment. Despite of available treatment options, PAH continues to be a life-threatening and debilitating disease. Currently, only parenteral or inhaled prostacyclin (analogues) are available and difficulties and undesired effects associated with their administration frequency and/or route of administration are stated to result in under treatment (Lang IM, Eur Respir Rev 2015). Therefore, an **orally available prostacyclin (IP) receptor agonist** such as selexipag would be a valuable addition to the armamentarium of medicinal products for the treatment of PAH.

Selexipag was shown to provide a statistically significant and clinically relevant reduction of **morbidity events** in patients with PAH. An improvement in **survival** has not been demonstrated. However, a mortality benefit is not a requirement for approval and has not been demonstrated for any of the approved specific PAH medications (except for i.v. epoprostenol in a small short-term study, Barst RJ, New Eng J Med 1996). Cross study comparisons, although to be interpreted with caution due to different patient populations, study designs, study durations and endpoints in most of these studies, suggest that efficacy of selexipag may be somewhat lower than that of non-prostacyclin PAH-specific medications. However, the treatment benefit of selexipag in itself as determined in GRIPHON is statistically significant and clinically relevant.

The overall effect of selexipag on the **6MWD** appears moderate. However, taking into consideration the clinically relevant effect in treatment naive patients that was in the range of other medicinal products approved for PAH and the well known observation that the effect on the 6 MWD is much less pronounced in pretreated patients (about 80% of patients in GRIPHON were pretreated with one or two PAH medications), the moderate mean overall effect on 6-MWD observed in the study is mainly related to the high number of pretreated patients included in the study but does not indicate an overall lack of efficacy.

Despite a clear effect on morbidity, no improvement in **quality of life** (QoL**)** could be shown for selexipag compared to placebo. This lack of association is difficult to explain since even a merely symptomatic effect would be expected to result in an improved QoL scale. Although the CAMPHOR (Cambridge Pulmonary Hypertension Outcome Review) questionnaire used in GRIPHON has been validated in mainly small populations with PAH in different regions, it is unclear at present whether it is sensitive to changes in QoL. Therefore, the lack of impact of selexipag on QoL as measured by the CAMPHOR questionnaire does not invalidate the beneficial effects on morbidity events.

The observed increased **mortality** as a primary endpoint event on selexipag compared to placebo was the most serious concern raised during the review of this application and for the conclusion on benefit risk. The observation is plausibly explained by differences in duration of exposure and (as demonstrated in the simulations) by informative censoring. Based on statistical analyses and simulations, analyses of the safety characteristics and supported by cross study comparisons, a true negative effect on mortality was considered highly unlikely.

Indeed, even if the difference in mortality as first endpoint event would not be fully explained by informative censoring, a detrimental effect of selexipag on mortality appears highly unlikely due the following considerations: a) selexipag exerted a beneficial effect on morbidity events in patients with PAH, which in turn were shown to be predictive for mortality events, b) selexipag is a prostacyclin analogue with the typical adverse event profile of this known class of PAH medications; prostacyclins are not suspected to be associated with an increased risk of mortality, c) the increase in heart rate after each dose is generally modest and transient and in the range of other vasodilatory drugs approved for PAH, d) There was no obvious explanation for the observed pattern that the imbalance

was limited to patients with FC II and better cardiac functioning. These patients should be less vulnerable to adverse effects than patients in FC III (and IV) and deteriorated cardiac function and there was no other unfavourable pattern seen in FC II. In a cross study comparison, mortality rate on selexipag in FC II was within the expected range, whereas the rate in the placebo arm was lower than expected. E.g. patients with PAH included in the REVEAL Registry (Farber et al., Chest. 2015 Oct 1;148(4):1043-54) had an estimated 5-year survival rate of 88.0%, 75.6%, 57.0%, and 27.2% in FC I, II, III, and IV, respectively, if they were diagnosed previously. For newly diagnosed patients, 5-year survival rates were 72.2%, 71.7%, 60.0%, and 43.8%, respectively. The about 11% 3-year mortality rate in FC II on selexipag in the GRIPHON study does not indicate an increased risk. The result on selexipag fits better to these published survival rates than the < 4% 3-year mortality rate observed in the placebo arm.

Taken together, the CHMP concluded that the observed increase in all cause mortality in the first event analysis was most likely an artefact due to informative censoring and/or a chance finding.

Selexipag was generally well tolerated and exhibited the **typical AE profile** known for the class of prostacyclin (analogues).

The transient and, on average, mild increase in **heart rate** after each administered dose of selexipag is of similar magnitude as reported for other vasodilatory PAH medication. However, in some patients the increase may be more pronounced and harmful, e.g. in patients at high risk for cardiovascular events.

There was an imbalance in events of acute **renal failure** in the GRIPHON study (double-blind period), disfavouring selexipag. Not all of these events were considered serious because they reflected a transient decrease in renal function in patients with known chronic kidney disease. The number of cases was small (14 vs. 7) so that a chance finding cannot be excluded. There is no clear mechanistic link although prostacyclin (and thereby selexipag) may theoretically affect renal function, e.g. by affecting renal perfusion. However, since the number of events was small and the imbalance of serious events was less pronounced (10 vs. 7) the impact of this observation on B/R is considered low.

Hypotension was more frequent with selexipag, which can be explained by a systemic vasodilatory effect of selexipag via the IP receptor. This finding is also in accordance with the observation of slightly increased heart rate after each administration. The incidence of serious hypotension was low and was balanced between the selexipag and the placebo group so that the impact on Benefit/Risk is considered minimal. Mentioning in the SmPC is considered sufficient. A more pronounced imbalance (selexipag vs. placebo) in hypotension was observed in patients receiving concomitant ERA and PDE5i. This is mechanistically a plausible explanation however the number of patients and events in this subgroup was too low for definite conclusions.

Benefit-risk balance

The B/R balance for selexipag in the proposed second-line indication is considered favourable.

Discussion on the benefit-risk balance

Selexipag clearly reduced morbidity events in patients with PAH, which is a clinically relevant benefit.

The beneficial effect on the 6-MWT in treatment naïve patients was within the range of other approved medicinal products and is considered clinically meaningful. It is also expected to observe a less pronounced effect in pretreated patients as observed with other treatments in PAH. Overall, the efficacy of selexipag appears to be moderate mainly related to the high number (80%) of pretreated

patients in the study and may potentially be lower than that of approved non-prostacyclin PAH medications, which are usually considered as first-line treatments in PAH.

Selexipag is the first orally available prostacyclin (IP) receptor agonist with proven long-term efficacy, compared to the currently approved prostacyclin analogues that have to be administered parenterally or by inhalation and are associated with risks such as embolism and thrombosis (continuous i.v. administration), local reactions (s.c. administration) or are time consuming (frequent inhalation).

Considering all analyses and arguments, the CHMP concluded that the finding of increased mortality in the primary morbidity and mortality endpoint analysis is an artefact, which could be due to the study design and explained by informative censoring and/or a chance finding.

Furthermore, no specific/unique safety issue could be identified that could explain the observed increase in mortality in patients with FC II as opposed to more severe patients in FC III and FC IV, thus providing additional reassurance that the observed increase in mortality is likely not attributable to selexipag.

In view of the efficacy demonstrated together with an acceptable safety profile, the CHMP concluded by majority on a positive benefit-risk balance. Selexipag is considered to provide a valuable orally available treatment alternative for patients with PAH. Based on these considerations and since selexipag was primarily assessed as an add-on treatment in the GRIPHON study, a second line indication is considered appropriate as follows :

Uptravi is indicated for 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.

Efficacy has been shown in a PAH population including idiopathic and heritable PAH, PAH associated with connective tissue disorders, and PAH associated with corrected simple congenital heart disease (see section 5.1).

Although there is no strong evidence from the trial data that the vasodilatory and heart rate effects of selexipag are harmful for patients with a high risk of CV events, contraindications for approved prostacyclin analogues (specifically iloprost) have been included in the product information of selexipag as a precautionary measure.

Table on Uptravi (selexipag)

Effects		Description	Units	Selexipag	Placebo	Uncertainties/Limitations
Favourable Effects	Composite endpoint	- Death (all causes) or - Hospitalization for worsening of PAH based on predefined criteria - Worsening of PAH resulting in need for lung transplantation or balloon atrial Septostomy - Initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH - Disease progression: Decrease in 6MWD from Baseline <u>and</u> a) Worsening of NYHA/WHO FC (patients in FC II-III) b) Need for additional PAH-specific therapy (patients in FC III-(patients in FC III-IV)	First events/% of patients	a) 140/ 24.4% (b) 155/ 27.0%	212/ 36. 4% 42/41.6%	Most components of the primary endpoint were in favour for selexipag. The analysis of the single components was hampered by informative censoring *(a) Analysis excluding events before Aug 16 2011* (selexipag vs. placebo: Hospitalization for PAH worsening 12.4% vs. 16.5%, 71 vs. 96 events; PAH worsening resulting in need for lung transplantation or balloon atrial septostomy 0.2% vs. 0.3%, 1 vs. 2 events; initiation of parenteral prostanoid therapy or chronic oxygen therapy 1.9% vs. 2.4%, 11 vs. 14 events; disease progression 5.6% vs. 14.4%, 32 vs. 84 events). Only all-cause mortality was numerically in favour of placebo (on treatment analysis: 4.4% vs. 2.7%, 25 vs. 16 events). *(b) Analysis including events before Aug 16 2011* (selexipag vs. placebo: Hospitalization for PAH worsening 13.6% vs. 18.7%, 78 vs. 109 events; PAH worsening resulting in need for lung transplantation or balloon atrial septostomy 0.2% vs. 0.3%, 1 vs. 2 events; initiation of parenteral prostanoid therapy or chronic oxygen therapy 1.7% vs. 2.7%, 10 vs. 13 events; disease progression 6.6 vs. 17.2%, 38 vs. 100 events). Only all-cause mortality was numerically in favour of placebo (on treatment analysis: 4.9% vs. 3.1%, 28 vs. 18 events).

Effects		Description	Units	Selexipag	Placebo	Uncertainties/Limitations
	6-MWT	Median Mean (SD) No worsening	m m %	4.0 -53 (150.24) 77.8%	-9.0 -66 (148.23) 74.9%	
	PAH death or PAH hosp.		events	102 (17.8%)	137 (23.5%)	
	CAMPHOR Quality of life Breathlessness subscore		scale	-1.0 0.0	0.0 0.0	
	Composite endpoint as proposed by CHMP guideline	- Death (all causes) or - Hospitalization for worsening of PAH based on predefined criteria - Signs or symptoms of right sided heart failure - Increase in WHO FC from baseline - Decrease in 6MWD from Baseline by at least 15%	First events/% of patients	268/46.7 %	343/58.9 %	All components of the primary endpoint were in favour of selexipag except for all-cause mortality, which was numerically slightly in favour of placebo on treatment (2.4% vs. 2.1%, 14 vs. 12 events). The analysis of the single components was hampered by informative censoring.
Unfav	TEAEs	Headache Diarrhoea Pain in Jaw Nausea	%	65.2 42.4 25.7 33.6	32.8 19.1 6.2 18.5	Selexipag exhibited the typical AE profile of prostacyclin (analogues)

Effects	Description	Units	Selexipag	Placebo	Uncertainties/Limitations
	Myalgia		16.0	5.9	
	Vomiting		18.1	8.5	
	Pain in extremity		16.9	8.0	
	Flushing		12.2	5.0	
	Arthralgia		10.8	7.6	
	Anaemia		8.3	5.4	
	Abdominal pain		8.3	5.7	
	Decreased appetite		5.9	3.3	
	Pain		3.1	0.5	
	Nasopharyngitis		13.0	10.9	
	Hypotension		5.9	3.8	
	Anaemia or decreased haemoglobin		10.4	8.0	Renal toxicity is included as potential risk in the RMP
	acute renal failure		2.4	1.2	
	renal impairment		0.7	0	
	hyperthyroidism		1.6	0	
	Malignancies	Patients	11	4	
	MACE	%	2.4%	1.4%	Death as a first event was possibly biased in favour of placebo due to informed censoring
	Death (first event up to EOT + 7 days)	n (%)	28 (4.9%)	18 (3.1)	
	All deaths up to EOT + 7 days		46 (8.0) 33 (71.7)	37 (6.4) 27 (73.0)	Interpretation of death up to study closure is hampered due to the possibility of cross-over after the first morbidity event.
	Death due to PAH		100 (17.4)	105 (18.0)	
	All deaths up to study closure		70 (12.2)	83 (14.3)	

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that selexipag is not similar Volibris, Opsumit and Adempas within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the risk-benefit balance of Uptravi for the following indication: "l*ong 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.*

Efficacy has been shown in a PAH population including idiopathic and heritable PAH, PAH associated with connective tissue disorders, and PAH associated with corrected simple congenital heart disease (see section 5.1)"

is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch of UPTRAVI in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the Controlled Access System with the National Competent Authority.

The Controlled Access System is aimed to facilitate the identification of prescribers, to approach them with the appropriate information on the safe and effective use of UPTRAVI, and to provide them with risk minimisation tools, especially regarding the potential risk of medication error. The Controlled Access System should include three key principles that will be incorporated within each system in all Member States. These are:

- The identification and maintenance of a list of all UPTRAVI prescribers
- The distribution of kits to all identified prescribers to minimise the risks of medication error in particular
- Tracking of the receipt of the kits by prescribers

The MAH shall ensure that in each Member State where UPTRAVI is marketed, all healthcare professionals who are expected to prescribe and/or dispense UPTRAVI are provided with a Prescriber Kit containing the following:

- The Summary of Product Characteristics for UPTRAVI
- Cover letter to the HCP
- HCP A4 laminated titration guide
- Patient titration guide

The cover letter to the HCP should explain that the purpose of the educational materials is to reduce the risk of medication error due to the availability of multiple tablets and dose strengths, and it should provide a list of the content of the prescriber kit.

The HCP A4 laminated titration guide is intended to reduce the risk of medication error due to the titration phase at treatment initiation with UPTRAVI and it should contain the following key elements:

- the dosing and titration concept
- the move to the maintenance dose (titration phase)
- expectations and management of adverse events during the titration phase
- encouragement and guidance for HCP to communicate clearly with the patient during their first visit, as well as to take responsibility to contact the patient during the titration phase, facilitating communication between HCP and the patient (need for contact and to schedule telephone calls)

The Patient titration guide to be used by the HCP during discussions with the patient should contain the following key elements:

- lay language version of the HCP A4 laminated titration guide
- diary to facilitate UPTRAVI use and serve as a reminder for the patients (e.g., to contact her/his doctor), and a place to record intake of tablets
- information about the safe and effective use of UPTRAVI in lay language

The patient titration guide along with the Patient Information Leaflet should be given to the patient after the demonstration.

- **Obligation to complete post-authorisation measures**

Not applicable

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that selexipag is qualified as a new active substance.

Divergent position(s) to the majority recommendation are appended to this report.

APPENDIX 1

DIVERGENT POSITION DATED 1 April 2016 Rev 1

The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the marketing authorisation of Uptravi indicated for 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.

Efficacy has been shown in a PAH population including idiopathic and heritable PAH, PAH associated with connective tissue disorders, and PAH associated with corrected simple congenital heart disease (see section 5.1).

The overall benefit-risk balance for Uptravi in the claimed indication is considered negative due to:

- A detrimental effect on mortality and major adverse cardiac events (MACE) and transient ischemic attack (TIA) in the long-term cannot be ruled out.
- An increase in all-cause death with selexipag cannot be excluded (selexipag 46 events vs. placebo 37 events; HR: 1.17; 95%CI: 0.66 to 2.07) and an increase in CV death cannot be excluded (selexipag 38 events vs. placebo 29 events; HR: 1.24; 95%CI: 0.77 to 2.02) [Full analysis set (FAS) up to End of Treatment plus seven days (EoT+7d). An increase in CV mortality in the patients with a better prognostic at baseline (FCII, preserved cardiac index) cannot be excluded (selexipag 15 events vs. placebo 6 events; HR: 2.24; 95%CI: 0.87 to 5.77) (FAS, EoT+7d). In addition, there were 7 cases of blindly adjudicated sudden cardiac death (6 selexipag vs. 1 placebo) not related to PAH, in which a causal relationship with selexipag cannot be ruled out (FAS, EOT+7d). Statistical artifacts, like informative censoring cannot fully explain the imbalances observed in mortality.
- The same trend was noticed for the combination of fatal and non fatal MACE+TIA, for which an increase be excluded (selexipag 43 events vs. placebo 33 events; HR: 1.24; 95%CI: 0.79 to 1.96) (FAS, EoT+7d).
- In the context of a disease with several specific medications available of different pharmacological classes, including other prostacyclin agonists, the approval of a drug with such uncertainties in CV safety and mortality is not endorsed.

Overall, for these reasons, I consider that the benefit/risk ratio is negative for Uptravi in the above claimed indication.

DIVERGENT POSITION

Uptravi EMEA/H/C/003774/0000

……..	……	……...
Andrea Laslop	Fatima Ventura	Concepcion Prieto Yerro
…….	……	…….
Daniela Melchiorri	Karsten Bruins Slot	Pieter De Graeff

……

Sol Ruiz