**Report on the Deliberation Results**

September 14, 2016

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

| | |
|---|---|
| **Brand Name** | Uptravi Tablets 0.2 mg,<br>Uptravi Tablets 0.4 mg |
| **Non-proprietary Name** | Selexipag (JAN*) |
| **Applicant** | Nippon Shinyaku Co., Ltd. |
| **Date of Application** | January 7, 2016 |

**Results of Deliberation**

In its meeting held on September 7, 2016, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 10 years. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug, and the drug product is not classified as a biological product or a specified biological product.

**Conditions of Approval**

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Since only an extremely limited number of Japanese patients participated in clinical studies of the product, the applicant is required to conduct a use-results survey covering all Japanese patients treated with the product after the market launch until data from a certain number of patients have been gathered, in order to understand the characteristics of patients using the product, and to promptly collect safety and efficacy data so that necessary measures are taken to ensure proper use of the product.

**Japanese Accepted Name (modified INN)*

**Review Report**

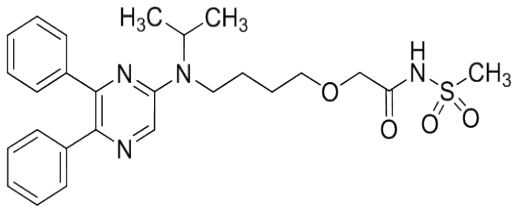
August 16, 2016

Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency.

| | |
|---|---|
| **Brand Name** | Uptravi Tablets 0.2 mg,<br>Uptravi Tablets 0.4 mg |
| **Non-proprietary Name** | Selexipag |
| **Applicant** | Nippon Shinyaku Co., Ltd. |
| **Date of Application** | January 7, 2016 |
| **Dosage Form/Strength** | Each film-coated tablet contains 0.2 or 0.4 mg of Selexipag |
| **Application Classification** | Prescription drug (1) Drug with a new active ingredient |

**Chemical Structure**



Molecular formula: $C_{26}H_{32}N_4O_4S$
Molecular weight: 496.62
Chemical name:
2-{4-[(5, 6-Diphenylpyrazin-2-yl)(propan-2-yl)amino]butoxy}-*N*-(methanesulfonyl)acetamide

| | |
|---|---|
| **Items Warranting Special Mention** | Orphan drug (Drug Designation No. 347 of 2014 [*26 yaku*], PFSB/ELD Notification No. 0917-6 dated September 17, 2014, by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare) |
| **Reviewing Office** | Office of New Drug II |

**Results of Review**

The Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the data submitted demonstrate the efficacy of the product in the treatment of pulmonary arterial hypertension and acceptable safety in view of the benefits indicated by the data submitted, as shown in Attachment.

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration as shown below, with the following conditions. Blood pressure decreased, haemorrhage, headache, etc., in patients receiving the product and the safety in patients with hepatic or renal impairment should be further investigated.

**Indication**
Pulmonary arterial hypertension

**Dosage and Administration**
The usual starting dose for adults is 0.2 mg of Selexipag administered orally twice daily after a meal. Based on individual tolerability, the dose is increased by 0.2 mg increments at ≥7-day intervals to a maximum tolerated dose, to determine the maintenance dose. The maximum dose per administration is 1.6 mg. Selexipag is administered orally twice daily after a meal regardless of dose level.

**Conditions of Approval**
1. The applicant is required to develop and appropriately implement a risk management plan.
2. Since only an extremely limited number of Japanese patients participated in clinical studies of the product, the applicant is required to conduct a use-results survey covering all Japanese patients treated with the product after the market launch until data from a certain number of patients have been gathered, in order to understand the characteristics of patients using the product, and to promptly collect safety and efficacy data so that necessary measures are taken to ensure proper use of the product.

**Attachment**

**Review Report (1)**

June 14, 2016

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency.

**Product Submitted for Approval**

| | |
|---|---|
| **Brand Name** | Uptravi Tablets 0.2 mg,<br>Uptravi Tablets 0.4 mg |
| **Non-proprietary Name** | Selexipag |
| **Applicant** | Nippon Shinyaku Co., Ltd. |
| **Date of Application** | January 7, 2016 |
| **Dosage Form/Strength** | Each film-coated tablet contains 0.2 or 0.4 mg of Selexipag |
| **Proposed Indication** | Pulmonary arterial hypertension |
| **Proposed Dosage and Administration** | Dose titration period:<br>The starting dose for adults is 0.2 mg of Selexipag administered orally twice daily. Based on individual tolerability, the dose is up-titrated by 0.2 mg at ≥3-day intervals to an individual maximum tolerated dose.<br>The maximum dose is 1.6 mg twice daily and, if the elevated dose is not tolerated, the dose is decreased to the previous level.<br><br>Dose maintenance period:<br>The dose is maintained at an individual maximum tolerated dose determined during the dose titration period.<br>The dose is decreased if the patient cannot tolerate the dose. |

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**List of Abbreviations**

| | |
|---|---|
| ACC | American College of Cardiology |
| ADP | Adenosine 5'-diphosphate |
| ALP | Alkaline phosphatase |
| ALT | Alanine aminotransferase |
| APD | Action potential duration |
| $APD_{30}$ | Action potential duration at 30% repolarization |
| $APD_{90}$ | Action potential duration at 90% repolarization |
| APTT | Activated partial thromboplastin time |
| AST | Aspartate aminotransferase |
| AUC | Area under the time-plasma concentration curve |
| $AUC_{0-t}$ | AUC from time 0 to t after administration |
| BA | Bioavailability |
| BCRP | Breast cancer resistance protein |
| BSEP | Bile salt export pump |
| cAMP | Cyclic adenosine 5'-monophosphate |
| CES | Carboxylesterase |
| CI | Confidence interval |
| CK | Creatine Kinase |
| CL | Total clearance |
| CL/F | Apparent clearance |
| $C_{max}$ | Maximum plasma concentration |
| Cu/C | Ratio of free (unbound) to total plasma concentrations |
| CYP | Cytochrome P450 |
| DBTSA | (2E)-3-(3',4'-dichlorobiphenyl-2-yl)-*N*-(2-thienylsulfonyl)acrylamide |
| DNA | Deoxyribonucleic acid |
| DP receptor | Prostaglandin $D_2$ receptor |
| $EC_{50}$ | 50% Effective concentration |
| eGFR | Estimated glomerular filtration rate |
| EOS | End of study |
| EP receptor | Prostaglandin $E_2$ receptor |
| ERA | Endothelin receptor antagonist |
| ESC/ERS Guidelines | Guidelines for the diagnosis and treatment of pulmonary hypertension by the European Society of Cardiology and the European Respiratory Society |
| FAS | Full analysis set |
| FP receptor | Prostaglandin $F_{2\alpha}$ receptor |
| GC | Gas chromatography |
| GPCR | G protein-coupled receptor |
| hERG | Human ether-a-go-go related gene |
| HIV | Human immunodeficiency virus |
| HPAH | Heritable pulmonary arterial hypertension |
| HPLC | High performance liquid chromatography |
| IBMX | 3-Isobutyl-1-methylxanthin |
| ICH | International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use |
| ICH Q1E Guideline | "Guideline on Evaluation of Stability Data" (PFSB/ELD Notification No. 0603004 dated June 3, 2003) |
| $IC_{50}$ | 50% Inhibitory concentration |
| INR | International normalized ratio |
| IP receptor | Prostacyclin receptor |
| IPAH | Idiopathic pulmonary arterial hypertension |
| IR | Infrared absorption spectrum |
| $k_a$ | Absorption rate constant |

| | |
|---|---|
| $K_i$ | Kinetics of inhibition |
| $K_m$ | Michaelis-Menten constant |
| $k_m$ | Elimination rate constant of MRE-269 |
| $k_{met}$ | Rate constant for the metabolism of selexipag to MRE-269 |
| LC-MS/MS | Liquid Chromatography and tandem Mass Spectrometry |
| LDH | Lactate dehydrogenase |
| L-NAME | NG-nitro-L-arginine methyl ester hydrochloride |
| LOCF | Last observation carry-forward |
| LV + S | Left ventricle + septum |
| MATE | Multidrug and toxin extrusion |
| MC solution | Aqueous solution of methylcellulose |
| MDR | Multidrug resistance protein |
| MDRD | Modification of Diet in Renal Disease |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mPAP | Mean pulmonary artery pressure |
| MPP | 1-Methyl-4-phenylpyridinium iodide |
| mRNA | Messenger ribonucleic acid |
| MRP | Multidrug resistance-associated protein |
| NADPH | Nicotinamide adenine dinucleotide phosphate |
| NMR | Nuclear magnetic resonance spectrum |
| NT-proBNP | N-terminal pro-brain natriuretic peptide |
| OAT | Organic anion transporter |
| OATP | Organic anion transporting polypeptide |
| OCT | Organic cation transporter |
| PAH | Pulmonary arterial hypertension |
| PCWP | Pulmonary capillary wedge pressure |
| PDE-5 | Phosphodiesterase type 5 |
| PDGF | Platelet derived growth factor |
| $PGE_2$ | Prostaglandin $E_2$ |
| $PGF_{2\alpha}$ | Prostaglandin $F_{2\alpha}$ |
| $PGI_2$ | Prostacyclin |
| $PGI_2$ preparation | Drug consisting of prostacyclin or its derivative |
| P-gp | P-glycoprotein |
| PPK | Population pharmacokinetic |
| PPS | Per-protocol set |
| PT | Prothrombin time |
| PTP | Press through packaging (blister pack) |
| PVR | Pulmonary vascular resistance |
| PVRI | Pulmonary vascular resistance index |
| PXR | Pregnane X receptor |
| QTc | Corrected QT |
| RV | Right ventricle |
| SD | Sprague-Dawley |
| sGC | Soluble guanylate cyclase |
| SMQ | Standardised MedDRA queries |
| SOC | System organ class |
| $t_{max}$ | Time for maximum plasma concentration |
| $t_{1/2}$ | Half-life |
| $T_3$ | Triiodothyronine |
| $T_4$ | Thyroxine |
| TP receptor | Thromboxane $A_2$ receptor |
| TSH | Thyroid stimulating hormone |
| UGT | Uridine diphosphate glucuronosyltransferase |
| UV-VIS | Ultraviolet-visible spectrum |

| | |
|---|---|
| $V_m$ | Distribution volume of the central compartment of MRE-269 |
| $V_m/F$ | Apparent distribution volume of the central compartment of MRE-269 |
| $V_p$ | Distribution volume of the central compartment of selexipag |
| $V_p/F$ | Apparent distribution volume of the central compartment of selexipag |
| $V_{ss}$ | Volume of distribution at steady state |
| 6MWD | 6-minute walk distance |
| BE Guideline for Different Contents | Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms (PMSB/ELD Notification No. 64 dated February 14, 2000, partially revised by PFSB/ELD Notification No. 0229-10 dated February 29, 2012) |
| PMDA | Pharmaceuticals and Medical Devices Agency |
| Uptravi | Uptravi Tablets 0.2 mg, 0.4 mg |

## 1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Selexipag is a non-prostanoid prostacyclin receptor (IP receptor) agonist discovered by the applicant. Similar to existing prostacyclin ($PGI_2$) preparations, selexipag and its main metabolite MRE-269 are expected to improve the conditions of pulmonary arterial hypertension (PAH) through their vasodilating and anti-platelet aggregating effects. In Japan, the following $PGI_2$ preparations are approved for the treatment of PAH: Epoprostenol sodium (continuous intravenous administration), treprostinil (continuous intravenous or continuous subcutaneous administration), iloprost (inhalation), and beraprost sodium (oral administration). For the administration of epoprostenol sodium or treprostinil, the patient has to wear a dedicated medical device. Iloprost has a short elimination half-life, requiring 6 to 9 inhalations a day. Beraprost sodium is approved as an oral $PGI_2$ preparation in Japan but not in the US or Europe; it has only a low level of evidence and is not highly recommended by Japanese and foreign clinical practice guidelines. Uptravi tablets (hereinafter referred to as Uptravi), an oral IP receptor agonist with a long half-life, was developed to overcome these drawbacks.

The development of Uptravi in foreign countries was initiated in 2008 by Actelion Pharmaceuticals (Switzerland), resulting in the approval of Uptravi for the indication of "Pulmonary arterial hypertension" in the US (December 2015) and in Europe (May 2016). As of May 2016, Uptravi is approved in 6 countries or regions.

In Japan, the applicant initiated the development of Uptravi in 20[redacted]. Based on the results from Japanese and foreign clinical studies, the applicant has submitted a marketing application for Uptravi with the proposed indication of "pulmonary arterial hypertension." Selexipag has been designated as an orphan drug with the intended indication of "Pulmonary arterial hypertension" (Drug Designation No. 347 of 2014 [*26 yaku*]).

## 2. Data Relating to Quality and Outline of the Review Conducted by PMDA

### 2.1 Drug substance

#### 2.1.1 Characterization

The drug substance is pale yellow to yellow crystals or crystalline powder. The following general properties of the drug substance have been determined: description, melting point, distribution coefficient, solubility, dissociation constant, hygroscopicity, and crystalline polymorphism. The drug substance exists in 3 crystalline forms (I, II, III), but only crystalline form I is produced in the manufacturing process under the commercial scale and is stable under room temperature conditions.

The chemical structure of the drug substance has been elucidated by elemental analysis, infrared absorption spectrum (IR), nuclear magnetic resonance spectrum (NMR) ($^{1}$H-NMR, $^{13}$C-NMR), mass spectrometry, and ultraviolet-visible spectrum (UV-VIS).

#### 2.1.2 Manufacturing process

The drug substance is synthesized through 5 steps using the following starting materials: [redacted], [redacted], [redacted], and [redacted]

[redacted] ([redacted]), [redacted] ([redacted]), and [redacted] are identified as the critical steps. In-process control parameters and action limits have been established for the critical steps and [redacted] ([redacted]). In order to constantly ensure the quality of the drug substance, [redacted], [redacted], [redacted], and [redacted] are controlled as the critical intermediates.

#### 2.1.3 Control of drug substance

The proposed specifications for the drug substance include content, description (visual inspection), identification (UV-VIS, IR), purity (heavy metals, related substances [high performance liquid chromatography (HPLC)], residual solvents [gas chromatography (GC)]), loss on drying, residue on ignition, crystalline form (X-ray powder diffraction), particle size (laser diffractometry), and assay (HPLC).

### 2.1.4 Stability of drug substance

Table 1 shows the main stability studies performed on the drug substance. A photostability testing showed that the drug substance was photostable.

**Table 1. Stability studies of drug substance**

| Study | Primary batches | Temperature | Humidity | Storage form | Storage period |
|---|---|---|---|---|---|
| Long-term | 3 commercial-scale batches | 25ºC | 60%RH | Double-layered polyethylene bag + high-density polyethylene drum | 36 months |
| Accelerated | | 40ºC | 75%RH | | 6 months |

Based on the above, a retest period of 48 months has been proposed for the drug substance when stored at room temperature in the double-layered polyethylene bag placed in a high-density polyethylene drum, in accordance with the Guideline on Evaluation of Stability Data (ICH Q1E Guideline). Long-term testing will be continued for 60 months.

## 2.2 Drug product

### 2.2.1 Description and composition of the drug product, and formulation development

The drug product is film-coated tablets, each containing 0.2 or 0.4 mg of the drug substance. The drug product contains the following excipients: D-mannitol, corn starch, low substituted hydroxypropylcellulose, hydroxypropylcellulose, magnesium stearate, hypromellose, propylene glycol, titanium oxide, yellow ferric oxide, red ferric oxide (0.4 mg tablets), and carnauba wax.

### 2.2.2 Manufacturing process

The drug product is manufactured through blending, granulating, lubricant mixing, size granulating, granule mixing, tableting, and film-coating. [redacted], [redacted], and [redacted] have been identified as the critical steps. In-process control parameters and action limits have been established for [redacted], [redacted], and [redacted].

### 2.2.3 Control of drug product

The proposed specifications for the drug product include content, description (visual inspection), identification (UV-VIS), purity (related substances [HPLC]), uniformity of dosage unit (content uniformity), dissolution (HPLC), and assay (HPLC).

### 2.2.4 Stability of drug product

Table 2 shows the main stability studies performed on the drug product. A photostability test showed that the drug product was photostable.

**Table 2. Stability studies of drug product**

| Study | Primary batches | Temperature | Humidity | Storage form | Storage period |
|---|---|---|---|---|---|
| Long-term | 3 commercial-scale batches | 25ºC | 60%RH | PTP[a] or bottle[b] | 24 months |
| Accelerated | | 40ºC | 75%RH | | 6 months |

[a] A PTP sheet is made of polyvinyl chloride film and aluminum foil. Several PTP sheets and a desiccant (calcium chloride) are packaged in a bag made of aluminum/polyethylene terephthalate/polyethylene laminate film.
[b] Polyethylene bottles with a polypropylene cap containing a desiccant (silica gel)

Based on the above, the shelf life of 24 months has been proposed for the drug product when stored at room temperature (a) in a press through packaging (PTP) sheet packaged together with a desiccant (calcium chloride) in a bag made of aluminum/polyethylene terephthalate/polyethylene laminate film, or (b) in a polyethylene bottle with a polypropylene cap containing a desiccant (silica gel). Long-term testing will be continued for 36 months.

## 2.R Outline of the review conducted by PMDA

Based on the results of the reviews on the submitted data, PMDA has concluded that the quality of the drug substance and the drug product is controlled in an appropriate manner.

## 3. Non-clinical pharmacology and Outline of the Review Conducted by PMDA

### 3.1 Primary pharmacodynamics

#### 3.1.1 Effect of selexipag and MRE-269 on the binding of $^{3}$H-labeled iloprost to IP receptors of rats (CTD 4.2.1.1-1)

Unlabeled selexipag (30-100,000 nmol/L), MRE-269 (demethylsulfonyl amide of selexipag; 10-30,000 nmol/L), or beraprost sodium (1-3000 nmol/L) was added to cell membranes prepared from CHO cells stably expressing rat IP receptors together with $^{3}$H-labeled iloprost (10 nmol/L), to evaluate the binding affinity of each drug to rat IP receptors. Selexipag, MRE-269, and beraprost sodium inhibited the binding of iloprost to IP receptors in a concentration-dependent manner, with kinetics of inhibition ($K_i$) of 4098.4, 394.3, and 40.4 nmol/L, respectively.

#### 3.1.2 Effect of selexipag and MRE-269 on the binding of $^{3}$H-labeled iloprost to human IP receptors (CTD 4.2.1.1-2)

Unlabeled selexipag (100-30,000 nmol/L), MRE-269 (3-3000 nmol/L), beraprost sodium (3-3000 nmol/L), or limaprost (1-300 nmol/L) was added to cell membranes prepared from CHO cells stably expressing human IP receptors together with $^{3}$H-labeled iloprost (5 nmol/L), to evaluate the binding affinity of each drug to human IP receptors. Selexipag, MRE-269, beraprost sodium, and limaprost inhibited the binding of iloprost to IP receptors in a concentration-dependent manner, with $K_i$ of 263.0, 19.8, 39.0, and 10.4 nmol/L, respectively.

#### 3.1.3 Effect of selexipag and MRE-269 on cAMP formation, β-arrestin, and IP receptor internalization in CHO cells expressing human IP receptors (CTD 4.2.1.1-4)

Selexipag (0.32-1000 nmol/L), MRE-269 (0.0064-100 nmol/L), beraprost sodium (0.0064-100 nmol/L), treprostinil (0.0064-100 nmol/L), or iloprost (0.0064-100 nmol/L) was incubated with CHO cells stably expressing human IP receptors for 30 minutes in the presence of 3-Isobutyl-1-methylxanthin (IBMX) (0.5 mmol/L). Cyclic adenosine 5'-monophosphate (cAMP) level in the cells was determined by enzyme immunoassay. Selexipag, MRE-269, beraprost sodium, treprostinil, and iloprost all increased cAMP formation in a concentration-dependent manner, with the 50% effective concentration ($EC_{50}$) of 36, 1.1, 0.23, 0.57, and 0.068 nmol/L, respectively.

CHO cells stably expressing human IP receptors were engineered to express enzyme-fused β-arrestin that allows the detection of β-arrestin binding to IP receptors by luminescence. The cells were incubated for 90 minutes in the presence of selexipag, MRE-269, beraprost sodium, treprostinil, or iloprost at a concentration of 0.51 to 10,000 nmol/L, to evaluate recruitment of β-arrestin to IP receptors. All the drugs caused the maximum level of β-arrestin recruitment at or below 10,000 nmol/L. Compared with the maximum response to iloprost (taken as 100%), the maximum response to selexipag, MRE-269, beraprost sodium, and treprostinil was 24%, 40%, 90%, and 67%, respectively.

Selexipag, MRE-269, beraprost sodium, treprostinil, or iloprost at 100, 1000, or 10,000 nmol/L was incubated with CHO cells stably expressing human IP receptors for 20 hours, to evaluate internalization of IP receptor using anti-human IP receptor antibody. No clear internalization of IP receptors was observed in the presence of selexipag or MRE-269. Internalization of IP receptors was observed in the presence of ≥1000 nmol/L beraprost sodium, ≥1000 nmol/L treprostinil, or ≥100 nmol/L iloprost.

#### 3.1.4 Effect of selexipag and MRE-269 on morphological change of primary cultured human pulmonary artery smooth muscle cells (CTD 4.2.1.1-5)

An increased cAMP level caused by the activation of Gs-coupled G protein-coupled receptors (GPCR) induces changes in cellular morphology, leading to a decrease in impedance (*J Pharmacol Sci.* 2014;126:302-9). Selexipag (1-1000 nmol/L), MRE-269 (1-1000 nmol/L), beraprost sodium (1-1000 nmol/L), treprostinil (1-1000 nmol/L), or iloprost (0.1-1000 nmol/L) was incubated with primary cultured human pulmonary artery smooth muscle cells for 24 hours, to evaluate changes in cellular morphology by measuring impedance. Selexipag, MRE-269, beraprost sodium, treprostinil, and iloprost all decreased impedance in a concentration-dependent manner, with $EC_{50}$ of 157, 4.3, 2.1, 3.6, and 0.12 nmol/L, respectively.

In order to investigate whether relaxation of actomyosin contributed to the above change in cell morphology, MRE-269, treprostinil, or iloprost at 0.1 to 100 nmol/L was incubated with primary cultured human pulmonary artery smooth muscle cells for 90 minutes, to evaluate phosphorylation of myosin light chain kinase by Western blotting. All drugs increased the level of phosphorylated myosin light chain kinase in a concentration-dependent manner.

### 3.1.5 Effect of selexipag and MRE-269 on ligand binding to human prostanoid receptor subtypes (CTD 4.2.1.1-6)

Unlabeled selexipag or MRE-269 at 1 μmol/L, together with $^{3}H$-labeled receptor ligands, were added to cell membranes prepared from cells expressing human prostanoid receptors (IP, prostaglandin $D_2$ [DP], prostaglandin $E_2$ [$EP_1$, $EP_2$, $EP_3$, $EP_4$], prostaglandin $F_{2\alpha}$ [FP], or thromboxane $A_2$ [TP] receptors), to evaluate binding affinities of the ligands to the receptors. Selexipag and MRE-269 inhibited ligand binding to human IP receptors by 59% and 85%, respectively, whereas they had no clear effect on the ligand binding to other human prostanoid receptors.

### 3.1.6 Effect of selexipag and MRE-269 on human, rat, and dog IP, $EP_2$, and $EP_4$ receptors (CTD 4.2.1.1-7)

HEK293 cells stably expressing human, rat, or dog IP, $EP_2$, or $EP_4$ receptors were incubated for 30 minutes, in the presence of IBMX (0.5 mmol/L), with selexipag or MRE-269 (1-10,000 nmol/L in IP receptor-expressing cells, 20-10,000 nmol/L in $EP_2$ or $EP_4$ receptor-expressing cells) or with the positive control (iloprost [0.01-100 nmol/L] in IP receptor-expressing cells, prostaglandin $E_2$ [$PGE_2$] [1-10,000 nmol/L] in $EP_2$ receptor-expressing cells, $PGE_2$ [0.001-10 nmol/L] in $EP_4$ receptor-expressing cells). Then, intracellular cAMP level was determined by enzyme immunoassay.

Selexipag, MRE-269, and iloprost all increased cAMP level in cells expressing human, rat, or dog IP receptors in a concentration-dependent manner. $EC_{50}$ for human, rat, and dog receptors was as follows: (a) selexipag, 250, 7200, and 19,000 nmol/L, respectively; (b) MRE-269, 6.1, 110, and 500 nmol/L, respectively; (c) iloprost, 0.13, 0.17, and 0.18 nmol/L, respectively.

Selexipag did not affect the amount of cAMP formed in cells expressing $EP_2$ receptors. MRE-269 and $PGE_2$ increased the amount of cAMP formed in cells expressing human, rat, or dog $EP_2$ receptors in a concentration-dependent manner. MRE-269 had $EC_{50}$ of 8700, 11,000, and 31,000 nmol/L for human, rat, and dog $EP_2$ receptors, respectively. $PGE_2$ had $EC_{50}$ of 2.6, 4.4, and 4.9 nmol/L for human, rat, and dog $EP_2$ receptors, respectively.

Selexipag did not affect the amount of cAMP formed in cells expressing $EP_4$ receptors. MRE-269 increased the amount of cAMP formed in cells expressing dog $EP_4$ receptors in a concentration-dependent manner with $EC_{50}$ of 660 nmol/L, but had no effect on the amount of cAMP formed in cells expressing human or rat $EP_4$ receptors. $PGE_2$ increased the amount of cAMP formed in cells expressing human, rat, or dog $EP_4$ receptors in a concentration-dependent manner with $EC_{50}$ of 0.051, 0.021, and 0.24 nmol/L, respectively.

### 3.1.7 Relaxant effect of selexipag and MRE-269 on isolated intralobar pulmonary artery preparation of rats (CTD 4.2.1.1-8)

Artery specimens were prepared by removing the endothelium from intralobar pulmonary artery isolated from rats. The artery specimens were contracted with prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) (10 μmol/L). Selexipag or MRE-269 (0.01-30 μmol/L) was then added to the specimens, to evaluate their relaxant effect against $PGF_{2\alpha}$-induced contraction. The relaxant effect of selexipag and MRE-269 was evaluated by ratio to that of papaverine hydrochloride 100 μmol/L (taken as 100%). Selexipag and MRE-269 suppressed $PGF_{2\alpha}$-induced contraction in a concentration-dependent manner, with the 50% inhibitory concentration ($IC_{50}$) of 11 and 2.7 μmol/L, respectively.

### 3.1.8 Effect of MRE-269, beraprost sodium, iloprost, epoprostenol sodium, and treprostinil on $PGF_{2\alpha}$-induced contraction of pulmonary artery specimens isolated from rats (CTD 4.2.1.1-9 to 4.2.1.1-13, Reference data)

Intra- and extra-lobar pulmonary arteries were isolated from rats, and artery specimens were prepared by removing the endothelium from the isolated arteries or leaving them intact. The artery specimens were contracted with $PGF_{2\alpha}$ (10 μmol/L). MRE-269 (0.001-30 μmol/L), beraprost sodium (0.001-30 μmol/L), iloprost (0.001-30 μmol/L), epoprostenol sodium (0.01-10 μmol/L), or treprostinil (0.001-30 μmol/L) was then added to the contracted specimens, to evaluate their relaxant effect against $PGF_{2\alpha}$-induced contraction. In addition, the relaxant effect of MRE-269, beraprost sodium, epoprostenol sodium, and treprostinil was evaluated in the presence of NG-nitro-L-arginine methyl ester hydrochloride (L-NAME; an inhibitor of nitric oxide synthase [10 or 100 μmol/L]) using the extralobar pulmonary artery specimens with intact endothelium (intralobar pulmonary artery specimens were also used for MRE-269 and epoprostenol sodium). The relaxant effect of these IP receptor agonists was evaluated by ratio to that of 100 μmol/L papaverine hydrochloride (taken as 100%).

Table 3 shows the maximum relaxation effect (ratio to that of papaverine hydrochloride) of the IP receptor agonists. MRE-269 suppressed $PGF_{2\alpha}$-induced contraction of extra- and intra-lobar pulmonary arteries to a similar extent, and neither removal of the endothelium nor addition of L-NAME had any detectable effect on the action of MRE-269. Epoprostenol sodium had maximum relaxation at 1 μmol/L in both extra- and intra-lobar pulmonary arteries, while the relaxant effect was attenuated at concentrations higher than 1 μmol/L. The relaxant effect of epoprostenol sodium on extra- and intra-lobar pulmonary arteries was attenuated both by endothelium removal and by L-NAME treatment. The relaxant effect of beraprost sodium and treprostinil was attenuated both by endothelium removal and by L-NAME treatment in the extra-lobar pulmonary artery specimens, but not by endothelium removal in the intralobar pulmonary artery specimens. The relaxant effect of iloprost was not affected by endothelium removal either in extra- or intra-lobar pulmonary artery specimens.

**Table 3. Relaxant effect of IP receptor agonists on pulmonary artery specimens**

| | Extralobar pulmonary artery | | | Intralobar pulmonary artery | | |
|---|---|---|---|---|---|---|
| | With endothelium | Without endothelium | With endothelium + L-NAME | With endothelium | Without endothelium | With endothelium + L-NAME |
| MRE-269 | 96.7 | 96.3 | 90.1 | 93.5 | 100.1 | 92.6 |
| Beraprost sodium | 76.6 | 50.5 | 47.6 | 34.3 | 30.5 | - |
| Iloprost | 80.6 | 91.0 | - | 75.5 | 74.1 | - |
| Treprostinil | 78.6 | 62.4 | 63.7 | 52.6 | 51.0 | - |
| Epoprostenol sodium | 58.8 | 26.2 | 27.1 | 39.8 | 15.5 | 22.8 |

Maximum relaxation effect (%); -, Not determined

### 3.1.9 Effect of selexipag, MRE-269, beraprost sodium, iloprost, and treprostinil on gastric fundus preparation isolated from rats (CTD 4.2.1.1-14)

Selexipag (0.01-100 μmol/L), MRE-269 (0.01-100 μmol/L), beraprost sodium (0.001-100 μmol/L), iloprost (0.001-10 μmol/L), or treprostinil (0.001-100 μmol/L) was added to gastric fundus preparation isolated from rats, to evaluate their contractile effect, in the absence and presence of the IP receptor antagonist CAY10441 (3 μmol/L) or the $EP_3$ receptor antagonist (2E)-3-(3',4'-dichlorobiphenyl-2-yl)-N-(2-thienylsulfonyl)acrylamide (DBTSA) (10 μmol/L). The contractile effect of these IP receptor agonists was evaluated by ratio to that of carbachol 10 μmol/L (taken as 100%).

Beraprost sodium, iloprost, and treprostinil contracted the gastric fundus preparation. The contractile effect was not affected by CAY10441 but suppressed by DBTSA. Neither selexipag nor MRE-269 had a contractile effect on the gastric fundus preparation.

### 3.1.10 Effect of MRE-269 on the growth of primary cultured human pulmonary artery smooth muscle cells (CTD 4.2.1.1-15)

Platelet derived growth factor (PDGF) (10 ng/mL) was added to primary cultured human pulmonary artery smooth muscle cells to enhance cell growth. MRE-269 (3-3000 nmol/L) was then added to the

mixture to evaluate uptake of $^{3}$H-labeled thymidine. MRE-269 at ≥10 nmol/L suppressed PDGF-induced thymidine uptake in a concentration-dependent manner.

### 3.1.11 Effect of MRE-269 on ADP-induced aggregation in rat and human platelet-rich plasma (CTD 4.2.1.1-16, 4.2.1.1-17)

MRE-269 or beraprost sodium was added to the whole blood collected from rats and humans (MRE-269, 0.3-100 μmol/L in rat blood, 3-1000 nmol/L in human blood; beraprost sodium, 0.003-1 μmol/L in rat blood, 0.3-100 nmol/L in human blood). Platelet-rich plasma was then prepared from the whole blood. Adenosine 5'-diphosphate (ADP) was added to the plasma (10 μmol/L in rat plasma, 2.5 μmol/L in human plasma) to evaluate platelet aggregation.

Both MRE-269 and beraprost sodium suppressed ADP-induced aggregation in rat and human platelet-rich plasma preparations in a concentration-dependent manner. $IC_{50}$ of MRE-269 was 8.3 μmol/L (rat plasma) and 69 nmol/L (human plasma). $IC_{50}$ of beraprost sodium was 0.063 μmol/L (rat plasma) and 5.8 nmol/L (human plasma).

### 3.1.12 Effect of repeated oral administration of selexipag on right heart hypertrophy in rats with monocrotaline-induced pulmonary hypertension (CTD 4.2.1.1-18)

Monocrotaline (40 mg/kg) was administered subcutaneously to male Sprague-Dawley (SD) rats (6 week old), followed by repeated oral administration of vehicle (0.5% methylcellulose [MC] solution), selexipag (1 mg/kg/dose), or beraprost sodium (0.1 mg/kg/dose) twice daily for 19 days (n = 12/group). At 20 days after the start of the treatment, the heart was isolated. Wet weight of (a) right ventricle (RV) and (b) left ventricle + septum (LV + S) was measured, and right heart hypertrophy was evaluated based on the wet weight ratio of RV to LV + S (the RV/[LV + S] ratio). The RV/(LV + S) ratio in rats receiving monocrotaline and vehicle was 2.04 times that in untreated rats. Compared with vehicle, selexipag and beraprost sodium significantly suppressed monocrotaline-induced right heart hypertrophy; RV/(LV + S) ratio in rats receiving selexipag and beraprost sodium was 1.57 and 1.60 times, respectively, that in untreated rats.

### 3.1.13 Effect of repeated oral administration of selexipag on thickening of small pulmonary artery in rats with monocrotaline-induced pulmonary hypertension (CTD 4.2.1.1-19, Reference data)

Monocrotaline (40 mg/kg) was administered subcutaneously to male SD rats (6 week old), followed by repeated oral administration of vehicle (0.5% MC solution) or selexipag (1 mg/kg/dose) twice daily for 19 days (n = 8-10/group). At 20 days after the start of the treatment, the left pulmonary tissue was isolated, to measure the outer diameter of the small pulmonary artery and the thickness of the arterial wall. The thickening of the small pulmonary artery was evaluated based on the ratio of the wall thickness to the outer diameter ([wall thickness × 2]/outer diameter of the blood vessel). In rats receiving monocrotaline and vehicle, the ratio of the vascular wall thickness to the outer diameter was 1.99 times that in untreated rats. Compared with vehicle, selexipag significantly suppressed the monocrotaline-induced thickening of the small pulmonary artery; the vascular wall thickness/outer diameter ratio in rats receiving selexipag was 1.45 times that in untreated rats.

### 3.1.14 Effect of repeated oral administration of selexipag on the survival of rats with monocrotaline-induced pulmonary hypertension (CTD 4.2.1.1-20, Reference data)

Monocrotaline (60 mg/kg) was administered subcutaneously to male SD rats (8 week old), followed by repeated oral administration of vehicle (0.5% MC solution) or selexipag (1 mg/kg/dose) twice daily for 46 days (n = 30/group). At 45 days after monocrotaline administration, the survival rate was significantly higher in the selexipag group (53% [16 of 30 animals]) than in the vehicle group (27% [8 of 30 animals]).

### 3.1.15 Effect of a single intraduodenal administration of selexipag on the right ventricular pressure during systole in rats with U46619-induced pulmonary hypertension (CTD 4.2.1.1-21)

U46619, a thromboxane $A_2$ receptor (TP receptor) agonist, was intravenously administered continuously to male SD rats (8 week old), to adjust the right ventricular pressure during systole at around 50 mmHg, followed by a single intraduodenal administration of vehicle (0.5% MC solution) or selexipag (3 mg/kg).

Then, the right ventricular pressure during systole, systemic blood pressure, and heart rate were measured over 90 minutes (n = 8/group). Compared with vehicle, selexipag significantly decreased the right ventricular pressure, resulting in up to a 13.8% decrease from the value before selexipag administration. Selexipag had no clear effect on either systemic blood pressure or heart rate.

#### 3.1.16 Effect of repeated oral administration of selexipag on pulmonary artery pressure in rats with monocrotaline-induced pulmonary hypertension (CTD 4.2.1.1-22)

Male Wistar rats (4 months old) received a single subcutaneous dose of monocrotaline (60 mg/kg). Four to five weeks later, the rats received repeated oral administration of vehicle (0.5% MC solution) or selexipag (10 mg/kg/dose) twice daily for 5 days, during which pulmonary artery pressure and heart rate were measured over time (n = 7-8/group). Selexipag decreased pulmonary artery pressure at all time points of administration, resulting in up to a 2 to 16 mmHg decrease from baseline to each time point of administration. No clear attenuation of the effect was observed throughout the administration period. Selexipag had no clear effect on heart rate.

### 3.2 Secondary pharmacodynamics

#### 3.2.1 Effect of selexipag and MRE-269 on enzyme activities and on binding activities of other receptors (CTD 4.2.1.2-1 to 4.2.1.2-5, Reference data)

Tissues or cells expressing various enzymes, receptors, ion channels, or transporters were treated with their respective substrates or ligands, together with selexipag or MRE-269 at 0.1, 1, 10, or 100 nmol/L, to evaluate the binding affinity of the drugs. Neither selexipag nor MRE-269 at the concentrations tested inhibited the binding of the substrate or ligand by ≥50%, except for prostanoid receptor binding.

#### 3.2.2 Effect of repeated oral administration of selexipag on systemic blood pressure in spontaneously hypertensive rats (CTD 4.2.1.1-22, 4.2.1.1-23)

Male spontaneously hypertensive rats (6-10 month old) received oral vehicle (0.5% MC solution) or selexipag (10 mg/kg/dose) twice daily for 5 days, during which systemic blood pressure and heart rate were measured over time (n = 4-6/group). Selexipag decreased systemic blood pressure at all time points of administration, resulting in up to an 11 to 21 mmHg decrease from baseline to each time point of administration. No clear attenuation of the effect of selexipag was observed throughout the administration period. Selexipag had no clear effect on heart rate.

Male spontaneously hypertensive rats (5-15 month old) were fed with the usual diet or the diet mixed with selexipag (10, 30, 100, 300 mg/kg/day) for 4 days, and systemic blood pressure and heart rate were measured over time (n = 7-8/group). In the selexipag group, the starting dose was 10 mg/kg/day, which was increased every 4 days, after which the diet without selexipag was given for 2 days. Selexipag at ≥30 mg/kg/day decreased systemic blood pressure in a dose-dependent manner. The systemic blood pressure in the selexipag 30, 100, and 300 mg/kg/day groups was 4, 14, and 29 mmHg lower, respectively, than that in the vehicle group. (These figures represent the maximum difference from vehicle.) After the end of selexipag administration, systemic blood pressure increased to baseline level. Selexipag had no clear effect on heart rate.

Male spontaneously hypertensive rats (4-5 month old) intravenously received vehicle (phosphate buffer containing dimethylformamide) or treprostinil (30 μg/kg/h) for 48 hours continuously at a speed of 5 μL/h, during which systemic blood pressure and heart rate were measured over time (n = 10-15/group). Treprostinil decreased systemic blood pressure, with the maximum decrease of approximately 30 mmHg compared with vehicle. The systemic blood pressure-decreasing effect of treprostinil was attenuated gradually and, at 48 hours after the start of the continuous administration, the systemic blood pressure in the treprostinil group reached a level similar to that in the vehicle group.

### 3.3 Safety pharmacology

Table 4 shows the results of safety pharmacology studies.

**Table 4. Outline of the results of safety pharmacology studies**

| Organ system | Test system | Endpoints and methods | Dose | Route of administration | Findings | CTD |
|---|---|---|---|---|---|---|
| Central nervous system | SD rats (6 males/ group) | Modified Irwin's method | Single dose of selexipag (0, 10, 30, 100 mg/kg) | Oral | 100 mg/kg: Flashing of skin, hunchback position, decreased passivity, tiptoe gait, decreasing tendency of body temperature, abnormal righting reflex, abnormal posture, deep respiration, loose stool, abnormality in wire-hanging test, and reduced body weight gain. | 4.2.1.3-1<br>4.2.1.3-2 |
| | SD rats (6 males/ group) | Body temperature, hexobarbital-induced sleep, nociceptive response | | | ≥30 mg/kg: Body temperature decreased.<br><br>100 mg/kg: Sleep duration prolonged and nociceptive response decreased. | 4.2.1.3-3 |
| Cardiovascular system | CHO-K1 cells stably expressing hERG channel | hERG current | Selexipag (0, 3, 10, 30, 100 μmol/L) | *in vitro* | 30 μmol/L: hERG current decreased to 85.2% of the level before selexipag administration.<br><br>100 μmol/L: Impossible to retain whole cell condition, precluding current measurement. | 4.2.1.3-4 |
| | | | MRE-269 0, 3, 10, 30 μmol/L | *in vitro* | No effect observed | 4.2.1.3-5 |
| | Isolated guinea pig papillary muscle preparation | Myocardial action potential | Selexipag (0, 10, 30, 100 μmol/L) | *in vitro* | ≥10 μmol/L: $APD_{30}$ decreased.<br><br>≥30 μmol/L: $APD_{90}$ decreased.<br><br>100 μmol/L: Resting membrane potential increased and action potential amplitude decreased. | 4.2.1.3-7 |
| | Isolated guinea pig right atrium preparation | Contractile force and beating rate | Selexipag (0, 3, 10, 30, 100 μmol/L) | *in vitro* | 100 μmol/L: Contractile force and beating rate increased. | 4.2.1.3-8 |
| | | | MRE-269 0, 3, 10, 30, 100 μmol/L | *in vitro* | ≥30 μmol/L: Contractile force increased or tended to increase. | 4.2.1.3-9 |
| | Beagle dogs (4 males/ group) | ECG, blood pressure, heart rate, clinical observations | Single dose of Selexipag (0, 1, 3, 10 mg/kg) | Oral | ≥1 mg/kg: QT interval, mean blood pressure, and diastolic blood pressure decreased.<br><br>≥3 mg/kg: Systolic blood pressure decreased and heart rate increased.<br><br>Clinical observations:<br>≥1 mg/kg: Vomiting<br><br>≥3 mg/kg: Decreased food intake and loose stool<br><br>10 mg/kg: Diarrheal stool | 4.2.1.3-6 |
| Respiratory system | SD rats (6 males/ group) | Respiratory rate, tidal volume, minute ventilation | Single dose of Selexipag (0, 10, 30, 100 mg/kg) | Oral | ≥30 mg/kg: Respiratory rate, tidal volume, and minute ventilation increased. | 4.2.1.3-10 |
| | Beagle dogs (4 males/ group) | Respiratory rate, hemoglobin oxygen saturation | Single dose of Selexipag (0, 1, 3, 10 mg/kg) | Oral | ≥3 mg/kg: Respiratory rate increased. | 4.2.1.3-6 |
| Renal/ urinary system | SD rats (4-6 males/ group) | Urine volume, osmotic pressure, urinary electrolyte excretion | Selexipag (0, 10, 30, 100 mg/kg) administered as a single dose | Oral | ≥10 mg/kg: Urinary $Cl^-$ excretion and $Na^+/K^+$ ratio decreased, and osmotic pressure tended to increase.<br><br>≥30 mg/kg: Urine volume and urinary $Na^+$ excretion decreased. | 4.2.1.3-11 |

| Organ system | Test system | Endpoints and methods | Dose | Route of administration | Findings | CTD |
|---|---|---|---|---|---|---|
| Gastrointestinal system | SD rats (5-6/ group) | Charcoal transfer rate in small intestine | Single dose of Selexipag (0, 10, 30, 100 mg/kg) | Oral | ≥10 mg/kg: Charcoal transfer rate decreased. | 4.2.1.3-12 |
| | | Gastric fluid volume, total acidity of gastric fluid, pH of gastric fluid | | Intraduodenal | ≥10 mg/kg: Gastric fluid volume and total acidity of gastric fluid decreased.<br><br>100 mg/kg: pH of gastric fluid increased. | |
| Somatic nervous system | Hartley guinea pigs (6 males/ group) | Corneal reflex | Single dose of MRE-269 0, 10, 30, 100 μg/mL | Ocular instillation | No effect observed. | 4.2.1.3-13 |
| Blood coagulation system | SD rats (6 males/ group) | Bleeding time, PT, APTT | Single dose of Selexipag (0, 10, 30, 100 mg/kg) | Oral | No effect observed. | 4.2.1.3-14 |
| Uterine smooth muscle | Isolated rat uterus preparation | Amplitude of spontaneous movement, contraction frequency | MRE-269 (0, 10, 30, 100 μmol/L) | *in vitro* | ≥30 μmol/L: Frequency of spontaneous contractile movement decreased. | 4.2.1.3-15 |

## 3.R Outline of the review conducted by PMDA

The applicant's explanation on the improvement of pulmonary hypertension by selexipag:

In *in vitro* studies, selexipag and MRE-269 showed selective binding affinity to IP receptors, increased cAMP formation, relaxed isolated pulmonary artery smooth muscles, suppressed cell growth, and inhibited platelet aggregation. In *in vivo* studies in various pulmonary hypertension models of rats, selexipag suppressed right heart hypertrophy, suppressed the increase in right ventricular pressure, decreased pulmonary arterial pressure, suppressed thickening of small pulmonary arteries, and prolonged survival. These results suggest that selexipag contributes to the improvement of pulmonary hypertension.

*In vitro* studies show that the binding affinity of MRE-269 to rat IP receptors is approximately 10 times that of selexipag. Also, the exposure to selexipag is less than one tenth of the exposure to MRE-269 in rats [see 4.1 Absorption]. These results suggest that the pharmacological effects observed in the rat models of pulmonary hypertension are due to MRE-269. In humans also, MRE-269 has an approximately 13 times higher affinity to IP receptors than selexipag, according to *in vitro* studies. In addition, the exposure to selexipag is approximately one third of the exposure to MRE-269 in humans [see 6.2.2.1 Single-dose and multiple-dose studies in Japanese healthy adults]. These results suggest that, as in rats, MRE-269 is responsible for the pharmacological effect observed in humans receiving selexipag.

PMDA's view:

In *in vitro* studies, selexipag and MRE-269 selectively bound to human IP receptors, thereby exhibiting activities that may contribute to the improvement of pulmonary hemodynamics (e.g., relaxation of pulmonary arterial smooth muscles). In *in vivo* studies, selexipag decreased pulmonary arterial pressure and prolonged the survival of animals of pulmonary hypertension models. In light of these findings, selexipag is expected to contribute to the improvement of pulmonary hypertension in humans. However, the pharmacological effect of selexipag and MRE-269 may cause adverse events such as a decrease in systemic blood pressure and haemorrhage. Appropriate cautionary statements for the safe use of selexipag should be discussed, in view also of the results of clinical studies [see 7.R.4 Safety].

## 4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

Plasma concentrations of selexipag and MRE-269, the active metabolite of selexipag, were measured by HPLC. The lower limits of quantitation of plasma concentrations of selexipag and MRE-269 in rats and dogs were all 0.05 μg/mL. Radioactivity after administration of $^{14}$C-selexipag and $^{14}$C-MRE-269 was measured using a liquid scintillation counter.

Pharmacokinetic parameters are expressed in mean or mean ± standard deviation (SD) unless specified otherwise.

## 4.1 Absorption

### 4.1.1 Single-dose administration (CTD 4.2.2.2-1, 4.2.2.2-3 – 4.2.2.2-5, 4.2.2.2-8, 4.2.2.2-11)

Table 5 shows the pharmacokinetic parameters of radioactivity following a single oral administration of $^{14}$C-selexipag to rats.

**Table 5. Pharmacokinetic parameters of radioactivity following a single oral administration of $^{14}$C-selexipag**

| Dose (mg/kg) | Sex | Fed or Fasted | n | $C_{max}$ (ng eq/mL) | $t_{max}$[a] (h) | $t_{1/2}$ (h) | $AUC_{0-\infty}$ (ng eq·h/mL) |
|---|---|---|---|---|---|---|---|
| 0.3 | M | Fed | 3 | 21.5 ± 3.2 | 2 | 17.2 ± 5.6 | 504 ± 129 |
| 1 | M | Fed | 3 | 92.1 ± 31.3 | 2 | 11.2 ± 1.3 | 1550 ± 210 |
| | M | Fasted | 3 | 587 ± 50 | 0.25 | 12.5 ± 1.1 | 1930 ± 320 |
| | F | Fed | 3 | 103 ± 21 | 1 | 13.4 ± 2.3 | 1370 ± 100 |
| 3 | M | Fed | 3 | 313 ± 136 | 2 | 13.0 ± 1.5 | 5530 ± 790 |

[a] Median

Table 6 shows the pharmacokinetic parameters of selexipag and MRE-269 following a single oral administration of selexipag or $^{14}$C-selexipag to rats, dogs, and cynomolgus monkeys.

**Table 6. Pharmacokinetic parameters of selexipag and MRE-269 following a single oral administration of selexipag or $^{14}$C-selexipag**

| Animal species | Dose (mg/kg) | Sex | n | Analyte | $C_{max}$[a] (ng eq/mL) | $t_{max}$[b] (h) | $t_{1/2}$ (h) | $AUC_{0-\infty}$[c] (ng eq·h/mL) |
|---|---|---|---|---|---|---|---|---|
| Rats | 1[d] | M | 3[f] | Selexipag | 5.84 | 8 | 9.54 | 113 |
| | | | 3[f] | MRE-269 | 117 | 1 | 4.27 | 766 |
| Dogs | 0.25[e] | M | 4 | Selexipag | 590 ± 298 | 1 | 8.31 ± 7.87 | 1100 ± 440 |
| | | | 4 | MRE-269 | 958 ± 59 | 3 | 8.66 ± 1.73 | 14,600 ± 3300 |
| Cynomolgus monkeys | 0.25[d] | M | 3 | Selexipag | 15.2 ± 11.9 | 1 | 7.31 ± 2.85 | 68.6 ± 18.7 |
| | | | 3 | MRE-269 | 16.1 ± 6.7 | 2 | 10.7 ± 5.5 | 213 ± 128 |

[a] ng/mL in dogs; [b] median (the figures for rats were calculated from changes in mean concentration); [c] ng·h/mL in dogs; [d] $^{14}$C-selexipag; [e] unlabeled selexipag; [f] number of animals at time point

### 4.1.2 Repeat-dose administration (CTD 4.2.3.2-5, 4.2.3.2-8)

The applicant submitted the pharmacokinetic data following repeated oral administration of selexipag (toxicokinetics data in repeat-dose toxicity studies).

Table 7 shows the pharmacokinetic parameters of selexipag and MRE-269 following repeated oral administration of selexipag to male and female rats for 26 weeks.

**Table 7. Pharmacokinetic parameters of selexipag and MRE-269 following repeated oral administration of selexipag to rats for 26 weeks**

| Dose (mg/kg) | Time point | $C_{max}$ (μg/mL) | | $AUC_{0\text{-}24h}$ (μg·h/mL) | |
|---|---|---|---|---|---|
| | | Male | Female | Male | Female |
| Selexipag | | | | | |
| 6 | Day 1 | 0.204 | 0.181 | 0.137 | 0.126 |
| | Week 26 | 0.398 | 0.405 | 0.229 | 0.286 |
| 25 | Day 1 | 1.27 | 2.08 | 1.73 | 1.72 |
| | Week 26 | 0.498 | 2.77 | 1.43 | 2.81 |
| 100 | Day 1 | 4.89 | 5.51 | 13.1 | 12.4 |
| | Week 26 | 2.07 | 10.1 | 5.33 | 18.8 |
| MRE-269 | | | | | |
| 6 | Day 1 | 1.12 | 0.904 | 6.43 | 3.10 |
| | Week 26 | 1.26 | 1.78 | 4.77 | 6.79 |
| 25 | Day 1 | 7.06 | 6.85 | 38.5 | 33.2 |
| | Week 26 | 4.46 | 11.9 | 22.7 | 45.7 |
| 100 | Day 1 | 22.3 | 20.0 | 192 | 190 |
| | Week 26 | 12.7 | 43.7 | 76.3 | 202 |

n = 3/sex/time point

Table 8 shows the pharmacokinetic parameters of selexipag and MRE-269 following repeated oral administration of selexipag to male and female dogs for 39 weeks.

**Table 8. Pharmacokinetic parameters of selexipag and MRE-269 following repeated oral administration of selexipag to dogs for 39 weeks**

| Dose (mg/kg) | Time point | $C_{max}$ (μg/mL) | | $AUC_{0\text{-}24h}$ (μg·h/mL) | |
|---|---|---|---|---|---|
| | | Male | Female | Male | Female |
| Selexipag | | | | | |
| 1 | Day 1 | 0.977 ± 0.332 | 1.53 ± 0.34 | 2.55 ± 0.53 | 3.36 ± 1.47 |
| | Week 26 | 1.83 ± 0.63 | 0.974 ± 0.479 | 3.49 ± 0.47 | 2.85 ± 1.01 |
| | Week 39 | 1.03 ± 0.22[a] | 1.36 ± 0.71[a] | 2.55 ± 0.50[a] | 2.88 ± 0.42[a] |
| 2 | Day 1 | 2.54 ± 1.10 | 2.87 ± 0.95 | 8.44 ± 4.17 | 7.30 ± 2.00 |
| | Week 26 | 4.50 ± 2.34 | 3.26 ± 1.18 | 10.2 ± 3.7 | 9.15 ± 2.97 |
| | Week 39 | 3.10 ± 0.67[a] | 1.79 ± 1.02[a] | 8.15 ± 2.54[a] | 6.54 ± 1.83[a] |
| 4 | Day 1 | 5.77 ± 2.23 | 5.21 ± 1.78 | 17.4 ± 3.7 | 17.6 ± 7.3 |
| | Week 26 | 5.66 ± 3.26 | 5.03 ± 2.08[b] | 18.1 ± 11.9 | 16.2 ± 6.1[b] |
| | Week 39 | 8.62 ± 1.06[a] | 6.88 [c] | 21.3 ± 1.4[a] | 18.0 [c] |
| MRE-269 | | | | | |
| 1 | Day 1 | 2.50 ± 0.15 | 3.05 ± 0.76 | 24.6 ± 1.5 | 33.2 ± 11.7 |
| | Week 26 | 3.29 ± 0.52 | 2.52 ± 0.69 | 28.8 ± 6.4 | 24.6 ± 5.8 |
| | Week 39 | 2.60 ± 0.89[a] | 3.26 ± 0.70[a] | 23.1 ± 2.2[a] | 35.7 ± 12.1[a] |
| 2 | Day 1 | 5.27 ± 0.74 | 5.56 ± 0.98 | 49.9 ± 5.4 | 54.0 ± 10.9 |
| | Week 26 | 6.40 ± 1.30 | 6.13 ± 1.89 | 55.8 ± 22.6 | 52.2 ± 11.1 |
| | Week 39 | 5.29 ± 1.46[a] | 5.87 ± 1.69[a] | 40.5 ± 4.9[a] | 58.9 ± 22.0[a] |
| 4 | Day 1 | 9.17 ± 1.68 | 8.62 ± 1.03 | 94.4 ± 19.9 | 104 ± 15 |
| | Week 26 | 6.89 ± 2.10 | 10.4 ± 1.6[b] | 58.4 ± 17.7 | 90.8 ± 9.0[b] |
| | Week 39 | 9.54 ± 1.23[a] | 12.5[c] | 109 ± 31[a] | 120[c] |

n = 6/sex; [a] n = 3; [b] n = 4; [c] n = 2

## 4.2 Distribution

### 4.2.1 Protein binding and distribution in blood cells (CTD 4.2.2.3-1, 5.3.2.1-1, 5.3.2.1-2)

$^{14}$C-selexipag or $^{14}$C- MRE-269 (0.1, 1 μg/mL [final concentration]) was added to the serum of rats, dogs, and cynomolgus monkeys, to investigate serum protein binding. In rat serum, binding of MRE-269 alone was investigated because selexipag was rapidly hydrolyzed. Neither selexipag nor MRE-269 showed concentration-dependent change in the protein binding rate. The serum protein binding rate of selexipag was 97.3% to 97.8% in dogs and 97.8% to 97.9% in cynomolgus monkeys. The binding rate of MRE-269 was 96.6% to 97.2% in rats, 97.3% to 98.0% in dogs, and 97.2% to 97.3% in cynomolgus monkeys.

$^{14}$C-selexipag or $^{14}$C-MRE-269 (0.1-50 μg/mL [final concentration]) was added to plasma of mice, rats, rabbits, dogs, and cynomolgus monkeys, to investigate plasma protein binding. In mouse and rat plasma, binding of MRE-269 alone was investigated because selexipag was rapidly hydrolyzed. Neither

selexipag nor MRE-269 showed concentration-dependent change in the protein binding rate within the concentration range tested. The binding rate of selexipag was 99.1% to 99.6% in rabbits, 99.5% to 99.8% in dogs, and 98.8% to 99.7% in cynomolgus monkeys. The binding rate of MRE-269 was 99.3% to 99.4% in mice, 99.1% to 99.3% in rats, 98.9% to 99.5% in rabbits, 98.9% to 99.7% in dogs, and 99.1% to 99.5% in cynomolgus monkeys.

$^{14}$C-selexipag (1 mg/kg) was administered orally as a single dose to male rats. The amount of covalently bound radioactivity at 2 and 168 hours after administration was 0.179 and 0.011 pmol/mg of protein, respectively, in serum; and 0.858 and 0.062 pmol/mg of protein, respectively, in the liver. These results confirmed the covalent binding of radioactivity with serum and hepatic proteins, but only at a slight level.

$^{14}$C-selexipag and $^{14}$C-MRE-269 (0.1, 20 μg/mL [final concentration]) were added to the blood samples of mice, rats, rabbits, dogs, and cynomolgus monkeys, to investigate distribution of selexipag and MRE-269 in blood cells. Since selexipag was rapidly hydrolyzed in mouse and rat blood, binding of only MRE-269 was investigated in these blood samples. The blood/plasma ratio of selexipag was 0.72 to 0.75 in rabbits, 0.54 in dogs, and 0.61 to 0.64 in cynomolgus monkeys. The blood/plasma ratio of MRE-269 was 0.59 to 0.63 in mice, 0.68 in rats, 0.77 in rabbits, 0.54 to 0.55 in dogs, and 0.62 to 0.68 in cynomolgus monkeys, showing only a low distribution of both selexipag and MRE-269 in blood cells.

### 4.2.2 Tissue distribution (CTD 4.2.2.3-2 to 4.2.2.3-5, 4.2.2.3-7)

$^{14}$C-selexipag (1 mg/kg) was administered orally as a single dose to male and female albino rats and to male pigmented rats. Radioactivity concentration at 1, 8, 24, 72, 168, and 504 hours after administration was measured by quantitative whole-body autoradiography. Albino and pigmented rats showed similar tissue distribution of radioactivity; in most tissues, the radioactivity concentration peaked at 1 hour after administration (particularly high in the gastrointestinal tract, bile duct, liver, pancreas, kidneys, and adrenals). The tissue radioactivity concentration decreased over time in a manner similar to plasma radioactivity concentration and, at 72 hours after administration, fell close to or below the lower detection limit.

$^{14}$C-selexipag (1 mg/kg) was administered orally as a single dose to male and female albino rats. Tissues were isolated from the rats at 1, 2, 4, 8, 24, 48, and 72 hours after administration to measure radioactivity. No clear trend of sex difference was observed in the distribution of radioactivity. In most tissues, radioactivity concentration peaked at 1 hour after administration (particularly high in the liver, small intestine, stomach, kidneys, and lung). The tissue radioactivity concentration decreased over time in a manner similar to plasma radioactivity concentration. At 72 hours after administration, radioactivity was detected only in the liver and kidneys. $^{14}$C-selexipag (1 mg/kg) was administered orally as a single dose to male pigmented rats. At 1, 4, 8, 24, and 48 hours after administration, tissues were isolated from the rats to measure radioactivity. The radioactivity in melanin-containing tissues (eyes and skin) in pigmented rats tended to decrease more gradually compared with albino rats. At 48 hours after administration, radioactivity concentration in the eye balls (2.03 ng eq/g) and skin (3.12 ng eq/g) of pigmented rats slightly exceeded the lower detection limit (1.4 ng eq/g), whereas radioactivity concentration in both tissues of albino rats was below the lower detection limit (3 ng eq/g).

$^{14}$C-selexipag (1 mg/kg) was orally administered once daily for 14 days to male albino rats. The radioactivity distribution profile at 1 hour after the last dose was similar to that after the first dose. After the last dose of the repeated administration, tissue radioactivity concentration decreased more gradually than after the single-dose administration but, at 168 hours after the last dose, radioactivity concentration decreased to levels close to or below the lower detection limit in all tissues tested, except for the liver, kidneys, and adrenals. At 408 hours after the last dose, radioactivity concentration decreased to levels close to the lower detection limit in the liver, kidneys, adrenals, and blood as well. The repeated administration thus showed no retention of radioactivity in tissues.

### 4.2.3 Placental transfer (CTD 4.2.2.3-2, 4.2.2.3-6)

$^{14}$C-selexipag (1 mg/kg) was administered orally as a single dose to albino rats on Gestation Day 17. Radioactivity concentration at 1, 8, 24, and 72 hours after administration was measured by quantitative

whole-body autoradiography. At 1 hour after administration, the ratio of fetal radioactivity concentration to maternal plasma radioactivity concentration was approximately 0.08, showing that part of the radioactivity had crossed the placenta after $^{14}$C-selexipag administration. Radioactivity concentration in fetuses decreased below the lower limit of quantitation at 8 hours after administration. $^{14}$C-selexipag (1 mg/kg) was administered orally as a single dose to albino rats on Gestation Day 19, and tissues were isolated and measured for radioactivity. As a result, tissue radioactivity distribution was similar to that observed with the whole-body autoradiography.

#### 4.2.4 Excretion in milk (CTD 4.2.2.3-7)

$^{14}$C-selexipag (1 mg/kg) was administered orally as a single dose to lactating rats. Radioactivity concentration in milk and plasma of maternal animals was measured at 0.5, 1, 2, 4, 8, 24, 48, and 72 hours after administration. Radioactivity concentration in milk peaked at approximately 4 hours after administration and, at 48 hours after administration, decreased below the lower detection limit. $AUC_{0-\infty}$ of radioactivity in milk was approximately twice that of plasma radioactivity, but half-life ($t_{1/2}$) of radioactivity was similar in milk and plasma, showing that radioactivity was eliminated from milk in a similar manner as from plasma.

### 4.3 Metabolism

#### 4.3.1 *In vitro* metabolism (CTD 5.3.2.2-1)

Liver microsomes of mice, rats, rabbits, dogs, minipigs, and cynomolgus monkeys were incubated at 37°C with $^{14}$C-selexipag (10 μmol/L [final concentration]). As a result, only MRE-269 was formed in the absence of nicotinamide adenine dinucleotide phosphate (NADPH). In the presence of NADPH, the main metabolite was MRE-269, and other metabolites were P12 (de-methylsulfonyl amidated form of P40 [*N*-dealkylated at aminopyrimidine group of selexipag]) in mice, rabbits, and cynomolgus monkeys; P21 (chemical structure unidentified) in rats and minipigs; and MRE-6300 (hydroxylated at phenyl group of MRE-269) in dogs.

Liver microsomes of mice, rats, rabbits, dogs, minipigs, and cynomolgus monkeys were incubated at 37°C with $^{14}$C-MRE-269 (10 μmol/L [final concentration]). The main metabolites were P12 in mice, rabbits, and cynomolgus monkeys; P21 in rats and minipigs; and P25 (chemical structure unidentified) in dogs.

Hepatocytes of mice, rats, dogs, minipigs, and cynomolgus monkeys were incubated at 37°C with $^{14}$C-selexipag or with $^{14}$C-MRE-269 (10 μmol/L [final concentration]). In the presence of $^{14}$C-selexipag, MRE-269 was the main metabolite in all animal species, and other main metabolites were P7 (chemical structure unidentified) in mice and rats, P23 (chemical structure unidentified) in dogs, P12 in minipigs, and MRE-6300 in cynomolgus monkeys. In the presence of $^{14}$C-MRE-269, the main metabolites were P7 in mice, P13 (de-methyl sulfonyl amidated form of P39 [hydroxylated at isopropyl group of selexipag]) in minipigs, and P20 (chemical structure unidentified) in cynomolgus monkeys. MRE-269 was scarcely metabolized by rat or dog hepatocytes.

#### 4.3.2 *In vivo* metabolism

##### 4.3.2.1 Metabolites in plasma (CTD 4.2.2.4-1, 4.2.2.4-3)

$^{14}$C-selexipag (20 mg/kg) was administered orally as a single dose to male rats. At 30 minutes after administration, MRE-269 was detected as the main metabolite in plasma; other metabolites were MRE-6001 (acyl glucuronide conjugate of MRE-269) and P14 (*N*-dealkylated form of P41 [*N*-dealkylated selexipag]). The abundance ratio in plasma (expressed as a percentage of total radioactivity in plasma) of MRE-269, MRE-6001, and P14 was 74%, 15%, and 9%, respectively. Unchanged selexipag was not detected in plasma.

Bile duct-cannulated male dogs were given a single dose of $^{14}$C-selexipag 2 mg/kg (oral) or 1 mg/kg (intravenous), to investigate metabolites in plasma. Following the oral administration, mainly MRE-269 and unchanged selexipag were observed in plasma, with the abundance ratio of MRE-269 and unchanged selexipag in plasma being ≥75% up to 4 or 8 hours after administration. Intravenous administration showed a metabolic profile similar to that of oral administration.

#### 4.3.2.2 Metabolites in urine, feces, and bile (CTD 4.2.2.4-1 to 4.2.2.4-3)

Bile duct-cannulated male rats received oral $^{14}$C-selexipag (20 mg/kg) as a single dose. As a result, 0.9% (expressed as a percentage of the administered radioactivity) was excreted in bile in the form of unchanged selexipag within 96 hours after administration; main metabolites in bile were MRE-6001 (20.7%), P8 (hydroxylated at phenyl group of selexipag, 17.1%), MRE-269 (15.3%), and P9 (chemical structure unidentified, 12.4%). Mainly unchanged selexipag (7.09%) and MRE-269 (5.54%) were observed in feces within 96 hours after administration. Unchanged selexipag was not excreted but P27 (chemical structure unidentified, 4.01%) was detected as the main metabolite in urine within 96 hours after administration. When bile duct-cannulated male rats received intravenous $^{14}$C-selexipag (0.9 mg/kg) as a single dose, the profiles of metabolites excreted in urine and bile were similar to those observed after oral administration.

Bile duct-cannulated male dogs received oral $^{14}$C-selexipag (2 mg/kg) as a single dose. Unchanged selexipag (33.7%) was excreted in bile within 96 hours after administration. This suggests that the contribution of metabolism to the elimination of selexipag is minor in dogs compared with rats. Main metabolites detected in bile were MRE-269 (24.5%), P8 (13.5%), MRE-6001 (3.76%), and P9 (3.76%). MRE-269 (8.83%) was the main metabolite detected in feces within 96 hours after administration. Only a slight amount of unchanged selexipag was detected and MRE-269 was undetectable in urine within 96 hours after administration. When bile duct-cannulated male dogs received intravenous $^{14}$C-selexipag (1 mg/kg) as a single dose, the profiles of metabolites excreted in urine and bile were similar to those observed after oral administration.

When bile duct-cannulated male dogs received intravenous $^{14}$C-MRE-269 (1 mg/kg) as a single dose, mainly P8 (16.3%), MRE-6001 (12.3%), and P9 (6.98%) were detected in bile within 96 hours after administration.

#### 4.3.2.3 Effect on drug-metabolizing enzymes (CTD 4.2.2.4-4)

Selexipag (1 or 10 mg/kg) was administered orally to male rats once daily for 7 days. Rats receiving selexipag showed no significant change in the amounts or activities of the following proteins or enzymes, compared with control rats receiving vehicle (0.5% MC solution): Amount of liver microsomal proteins, cytochrome P450 (CYP) content, cytochrome b5 content, NADPH-cytochrome c reductase activity, aminopyrine-*N*-demethylase activity, aniline hydroxylase activity, 7-ethoxycoumarin-*O*-deethylase activity, testosterone-6β-hydroxylase activity, and 4-methylumbelliferone UDP-glucuronosyltransferase activity. These results suggested that selexipag did not induce drug-metabolizing enzymes in rats at the doses tested.

### 4.4 Excretion

#### 4.4.1 Excretion in urine and feces (CTD 4.2.2.2-7, 4.2.2.2-9, 4.2.2.2-11, 4.2.2.5-1, 4.2.2.5-2)

Male rats received oral $^{14}$C-selexipag (1 mg/kg) or $^{14}$C-MRE-269 (0.845 mg/kg) as a single dose. The urinary excretion rate of radioactivity (expressed as a percentage of the administered radioactivity) within 168 hours after administration was 5.8% ($^{14}$C-selexipag) and 5.6% ($^{14}$C-MRE-269), and the fecal excretion rate was 89.3% ($^{14}$C-selexipag) and 89.7% ($^{14}$C-MRE-269). Male rats received intravenous $^{14}$C-MRE-269 (0.845 mg/kg) as a single dose. The urinary and fecal excretion rates of radioactivity within 168 hours after administration were 4.9% and 94.2%, respectively.

Male dogs received a single dose of $^{14}$C-selexipag at 2 mg/kg (oral) or 1 mg/kg (intravenous). The urinary excretion rate of radioactivity within 192 hours after administration was 5.3% (oral) and 3.4% (intravenous), and the fecal excretion rate was 78.8% (oral) and 90.9% (intravenous).

Male cynomolgus monkeys received a single dose of oral $^{14}$C-selexipag (0.25 mg/kg) or intravenous $^{14}$C-MRE-269 (0.211 mg/kg). Within 168 hours after administration, the urinary excretion rate of radioactivity was 16.1% ($^{14}$C-selexipag) and 15.5% ($^{14}$C-MRE-269) and the fecal excretion rate was 77.0% ($^{14}$C-selexipag) and 76.7% ($^{14}$C-MRE-269).

Male rats received oral $^{14}$C-selexipag (1 mg/kg) once daily for 14 days. The urinary and fecal excretion rates of radioactivity within 24 hours after administration were similar regardless of the number of doses.

The cumulative urinary and fecal excretion rates of radioactivity within 168 hours after the last dose were 6.4% and 93.1%, respectively, showing that the radioactivity did not remain in the body.

### 4.4.2 Excretion in bile (CTD 4.2.2.4-1, 4.2.2.4-3, 4.2.2.5-3)

Bile duct-cannulated male rats received intravenous $^{14}$C-MRE-269 (0.845 mg/kg) as a single dose. Biliary, urinary, and fecal excretion rates of radioactivity (expressed as a percentage of the administered radioactivity) within 24 hours after administration were 90.17%, 4.54%, and 3.60%, respectively.

Bile duct-cannulated male rats received a single dose of $^{14}$C-selexipag at 20 mg/kg (oral) or 0.9 mg/kg (intravenous). The excretion rates (individual values) of radioactivity within 96 hours after oral administration were 54.9% and 77.9% in bile, 4.72% and 6.34% in urine, and 18.1% and 39.5% in feces. The excretion rates (individual values) of radioactivity within 96 hours after intravenous administration were 88.9% and 95.5% in bile, 0.87% and 4.66% in urine, and 2.39% and 5.53% in feces.

Bile duct-cannulated male dogs received a single dose of oral $^{14}$C-selexipag 2 mg/kg, intravenous $^{14}$C-selexipag 1 mg/kg, or intravenous $^{14}$C-MRE-269 1 mg/kg. The excretion rates (individual values) of radioactivity within 96 hours after administration were as follows: oral $^{14}$C-selexipag, 80.1% and 86.7% (bile), 0.5% and 1.5% (urine), and 7.3% and 10.2% (feces); intravenous $^{14}$C-selexipag, 81.4% and 87.5% (bile), 0.7% and 1.2% (urine), and 4.9% and 10.3% (feces); intravenous $^{14}$C-MRE-269, 82.4% and 88.9% (bile), 1.5% and 2.0% (urine), and 10.7% and 11.6% (feces).

### 4.4.3 Enterohepatic circulation (CTD 4.2.2.5-4)

Bile duct-cannulated male rats received intravenous $^{14}$C-MRE-269 (0.845 mg/kg) as a single dose, and bile collected from these animals was administered intraduodenally to other bile duct-cannulated male rats. The biliary, urinary, and fecal excretion rates of radioactivity (expressed as a percentage of the administered radioactivity) within 24 hours after administration were 52.63%, 1.88%, and 16.26%, respectively. This suggests that part of the radioactivity excreted in bile underwent enterohepatic circulation.

### 4.R Outline of the review conducted by PMDA

PMDA asked the applicant to explain the safety of selexipag in tissues in which radioactivity was distributed at a high concentration and in tissues from which radioactivity was eliminated only gradually, as observed in tissue distribution studies.

The applicant's explanation:

Tissue distribution studies showed that radioactivity was detected at a high concentration in the gastrointestinal tract, liver, and kidneys and that radioactivity was eliminated more gradually from the liver and kidneys than from other tissues. Also, elimination of radioactivity from the adrenals and blood (blood cells) was slow after repeated administration. As for the safety in these tissues, the repeat-dose toxicity study in mice showed increased liver weight and centrilobular hypertrophy of hepatocytes, and the repeat-dose toxicity study in rats also showed these findings and increased adrenal weight, adrenocortical hypertrophy, hypertrophy of adrenal glomerulosa, decreased platelet count, and increased fibrinogen level. Jejunal and ileal intussusceptions were observed in the repeat-dose toxicity study in dogs. In addition, an effect on the kidneys was observed in the carcinogenicity study in mice, and an increased incidence of gastric erosion or ulcer was observed in carcinogenicity studies in mice and rats.

Thus, toxicity findings were observed in the gastrointestinal tract, liver, kidneys, and adrenals after oral administration of selexipag. Haematology did not show any effect on blood cells, but showed decreased platelet count and increased fibrinogen level. Intussusceptions observed in dogs are probably irrelevant to humans [see "5.R.4 Intussusceptions"], but the other events (toxicity findings) may occur in humans as well, given the mechanism of the action of selexipag. In the carcinogenicity study in mice and rats, the increased incidence of gastric erosion or ulcer was probably due to stress, and these events occurred only in animals receiving a higher dose than the clinical dose; therefore, the incidence of gastric erosion or ulcer is unlikely to increase in humans. In contrast, there are no sufficient safety margins against the events related to the kidneys, liver, adrenals, fibrinogen, and platelet count. Therefore, the safety of selexipag was investigated in view of the incidences of these events in clinical studies. In the foreign phase III study (Study AC-065A302) in patients with PAH, gastrointestinal disorders occurred slightly

more frequently in the selexipag group (65.4% [376 of 575 of patients]) than in the placebo group (48.9% [282 of 577 patients]). This is probably due to a higher incidence of nausea and diarrhoea (adverse events caused by the pharmacological effect of selexipag) in the selexipag group, and is not due to the accumulation of selexipag or its metabolites into tissues. The incidences of other tissue-related adverse events (hepatobiliary disorders, renal and urinary disorders, endocrine disorders, and blood and lymphatic system disorders) did not differ significantly between the selexipag and placebo groups. The incidences of these events in the Japanese phase II study (Study AC-065A201) and the foreign extension study (Study AC-065A303), both involving patients with PAH, were similar to those observed in the selexipag group of Study AC-065A302.

Based on the above, the applicant considers that the distribution of selexipag or its metabolites in the gastrointestinal tract, liver, kidneys, adrenals, or blood (blood cells) is unlikely to pose clinical problems.

PMDA's view:
Tissue distribution studies showed that selexipag or its metabolites were distributed in the gastrointestinal tract, liver, kidneys, adrenals, and blood (blood cells). However, the distribution of selexipag or its metabolites at high concentration in these tissues is unlikely to pose clinical problems, judging from the incidences of adverse events in clinical studies.

## 5. Toxicology and Outline of the Review Conducted by PMDA

The following toxicology studies were conducted: Single-dose toxicity studies, repeat-dose toxicity studies, genotoxicity studies, carcinogenicity studies, reproductive and developmental toxicity studies, local tolerance studies, and other toxicity studies (study on the mechanism of toxicity, studies on the toxicity of metabolites, studies on the toxicity of impurities, phototoxicity studies).

### 5.1 Single-dose toxicity (CTD 4.2.3.1-1 to 4.2.3.1-4)

As single-dose toxicity studies, oral dose toxicity studies in rats and dogs, and intravenous dose toxicity studies in mice and rats were conducted.

The approximate lethal dose of selexipag was 500 mg/kg in rats and 2000 mg/kg in dogs after a single oral administration, and >40 mg/kg both in mice and rats after a single intravenous administration. The following symptoms were observed after selexipag administration: flushing (due to the vasodilating effect); decreased activity, hypotonia, prone position, and lateral position (all suggestive of decreased blood pressure due to vasodilation); and darkening or loss of the tail. In dogs, vomiting, abnormal feces (e.g., diarrheal or watery stools), and death due to intussusception were observed. The applicant considered that the intussusception in dogs was caused by selexipag, but determined that this finding is not directly linked to the risk in humans given the high sensitivity of dogs to IP receptor agonist-induced intussusception.

### 5.2 Repeat-dose toxicity

Repeated oral dose toxicity studies were conducted in mice (4 and 13 weeks), rats (4 and 26 weeks), and dogs (2, 4, and 39 weeks). The animals showed findings (e.g., flushing, decreased activity, hypotonia) probably due to the vasodilating effect, the pharmacological action of selexipag. The applicant considered that flushing was not a toxicity of selexipag, but decreased activity and hypotonia (suspected to be caused by decreased blood pressure) were toxicities of selexipag. Changes observed in both mice and rats were flushing, hypotonia, centrilobular hypertrophy of hepatocytes due to enzyme induction. Changes observed in rats were darkening or loss of the tail, increased urine volume, hyperplasia of thyroid follicular epithelial cells, hypertrophy of adrenal cortex (zona glomerulosa), hyperplasia of mammary acinar cells, and hypertrophy of submandibular acinar cells. In dogs, abnormal stools (e.g., loose, diarrheal, or bloody stool) and intussusception were observed. In addition, increased bone formation in the femur and sternum, fibrosis of myelopoietic tissue, and a decrease or increase in myelopoietic tissue were observed in dogs. The applicant determined that the changes observed with bones and bone marrow were due to $EP_4$ receptor-mediated effects of MRE-269 unique to dogs and were not relevant to humans. In the 26-week oral dose toxicity study in rats, $AUC_{0\text{-}24h}$ of selexipag and its active metabolite MRE-269 after administration of selexipag at the no observed adverse effect level (NOAEL) (6 mg/kg/day) was 2.93 and 20.9 times, respectively, that observed at the maximum clinical dose in humans (1.6 mg/dose twice daily). In contrast, the NOAEL in the 39-week oral dose toxicity

study in dogs was determined to be <1 mg/kg/day by the applicant, with the safety margin being unknown.

### 5.2.1 Thirteen-week repeated oral dose toxicity study in mice (CTD 4.2.3.2-2)

Selexipag (0 [0.5% MC solution], 100, 300, 500 mg/kg/day) was administered orally for 13 weeks to male and female B6C3F1 mice (n = 10/sex). One female in the 500 mg/kg/day group for the toxicokinetics study died due to the effect of selexipag administration. Adverse events were flushing, hypotonia, increased total cholesterol, and centrilobular hypertrophy of hepatocytes in the ≥300 mg/kg/day groups; and crawling position, eye discharge, and increases in creatine kinase (CK) and alanine aminotransferase (ALT) in the 500 mg/kg/day group. Based on the above, the applicant determined the NOAEL to be 100 mg/kg/day.

### 5.2.2 Four-week repeated oral dose toxicity study in rats (i) (CTD 4.2.3.2-3)

Selexipag (0 [0.5% MC solution], 20, 60, 180 mg/kg/day) was administered orally for 4 weeks to male and female SD rats (n = 10/sex). Adverse events were flushing of the pinna, limbs, or whole body, piloerection, lacrimation, salivation, soiled fur, decreased platelet count, and intra-alveolar haemorrhage in the ≥20 mg/kg/day groups; inanimation, hypotonia, prone position, decreased body weight, increased water intake, decreased triglycerides, decreased blood glucose, increased total cholesterol, increased calcium, increased urine volume, low chloride, and adrenocortical hypertrophy in the ≥60 mg/kg/day groups; and depilation, loose stool, decreased or no feces, discoloration (darkening) and loss of tail tip, increased total protein, increased albumin, increased α-globulin, increased β-globulin, decreased potassium, centrilobular hypertrophy of hepatocytes in the liver, and increased subcutaneous fibrous tissue (in animals with lost tail tip) in the 180 mg/kg/day group. In animals with centrilobular hypertrophy of hepatocytes, electron microscopy showed hyperplasia of smooth endoplasmic reticulum. Based on the above, the applicant determined the NOAEL to be <20 mg/kg/day.

### 5.2.3 Four-week repeated oral dose toxicity study in rats (ii) (CTD 4.2.3.2-4)

Selexipag (0 [0.5% MC solution], 2, 6, 60 mg/kg/day) was administered orally for 4 weeks to male and female SD rats (n = 10/sex). Animals in the ≥6 mg/kg/day groups showed flushing of the pinna, limbs, or whole body, and animals in the 60 mg/kg/day group showed piloerection, lacrimation, reddish tear, salivation, inanimation, hypotonia, prone position, soiled fur (perioral, submaxillary), decreased faecal volume, decreased body weight, decreased food consumption, increased water intake, decreased platelet count, decreased blood glucose, increased calcium, increased urine volume, decreased potassium, increased weight or organ-to-body-weight ratio of the adrenals, thyroid, and liver, decreased weight or organ-to-body-weight ratio of prostatic gland and seminal vesicle, and adrenocortical hypertrophy. All changes were reversible or tended to be reversible after a 4-week recovery period. Based on the above, the applicant determined the NOAEL to be 6 mg/kg/day.

### 5.2.4 Twenty six-week repeated oral dose toxicity study in rats (CTD 4.2.3.2-5)

Selexipag (0 [0.5% MC solution], 6, 25, 100 mg/kg/day) was administered orally for 26 weeks to male and female SD rats (n = 12/sex). Animals in the ≥6 mg/kg/day groups showed flushing of pinna and limbs. Animals in the ≥25 mg/kg/day groups showed flushing of whole body, increased water intake, increases in urine volume and potassium, decreased urinary osmotic pressure, increased weight or organ-to-body-weight ratio of the adrenals and liver, increased frequency and intensity of adrenal glomerulosa hypertrophy, increased frequency of acinar cell hypertrophy of salivary gland (submandibular gland), and diffuse hyperplasia of thyroid follicular epithelial cells. Animals in the 100 mg/kg/day group showed lacrimation, salivation, hypotonia, crawling position, depilation, loose stool, decreased body weight, increased fibrinogen level, decreased platelet count, increases in alkaline phosphatase (ALP) and total cholesterol, decreases in triglycerides, blood glucose, and potassium, increased weight or organ-to-body-weight ratio of salivary gland, centrilobular hypertrophy of hepatocytes, and increased intensity of diffuse hyperplasia of mammary acinar cells. The applicant determined that the decreased platelet count observed in the 6 and 25 mg/kg/day groups was of little toxicological significance for the following reasons: (1) It was a very slight change; (2) no changes were observed in other blood coagulation-related parameters; and (3) no haemorrhagic changes were observed on histopathological examination. All changes were reversible or tended to be reversible after a 4-week recovery period. Based on the above, the applicant determined the NOAEL to be 6 mg/kg/day.

### 5.2.5 Two-week repeated oral dose toxicity study in dogs (CTD 4.2.3.2-6)

Selexipag (0 [gelatin capsule]), 2, 6, 20 mg/kg/day) was administered orally for 2 weeks to male and female beagle dogs (n = 3/sex). Two males and 1 female in the 20 mg/kg/day group died or were euthanized because of intussusception due to selexipag. Surviving animals in the ≥6 mg/kg/day groups showed loose stools (including reddish brown, dark brown, and brown stools), diarrheal stools (including bloody stool, reddish brown, dark brown, and brown stools), watery stools, decreased faecal volume, inanimation, decreased body temperature, increased frequency of vomiting and jelly like stool, decreased body weight or reduced body weight gain, decreased food consumption, decreases in platelet count, white blood cell count, and neutrophil count, increases in α-globulin and ALT, urinary occult blood, decreased urine potassium, increased bone formation, and decreased myelopoietic tissue and its fibrosis. Surviving animals in the 20 mg/kg/day group showed exhaustion, emaciation, lateral position, hypotonia, soiled fur (perianal), no feces, bradypnea, vocalization and cage scratching, decreased water intake, QRS and corrected QT (QTc) prolongation, activated partial thromboplastin time (APTT) prolongation, increased total bilirubin, decreased inorganic phosphate, decreased blood and urine electrolytes, ileal intussusception, thymic atrophy, dark red foci in the lung (accompanied by histological changes such as congestion, haemorrhage, and enhanced megakaryocyte production), salivary (sublingual) stromal edema and bleeding as well as necrosis of acinar cells, and decreased glycogen granules in hepatocytes. As for loose stools and diarrheal stools observed in the 2 mg/kg/day group, the applicant determined that these findings were of little toxicological significance for the following reasons: (1) There was no clear relationship between the findings and administration of the test substance, and (2) the decreased urine potassium level was within the range of physiological variation. Based on the above, the applicant determined the NOAEL to be 2 mg/kg/day.

### 5.2.6 Four-week repeated oral dose toxicity study in dogs (CTD 4.2.3.2-7)

Selexipag (0 [gelatin capsule], 1.5, 3, 6 mg/kg/day) was administered orally for 4 weeks to male and female beagle dogs (n = 3/sex). Animals in the ≥3 mg/kg/day groups showed vomiting, loose stool, diarrheal stool, jelly like stool, dark brown feces, bloody stool, decreased faecal volume, decreased urinary sodium and potassium, increased bone formation, and fibrosis of myelopoietic tissue. Animals in the 6 mg/kg/day group showed inanimation, intussusception, decreases in platelet count, white blood cell count, neutrophil count, and fractional neutrophil count, decreased urine chloride, increased adrenal weight, decreased myelopoietic tissue, and increased extramedullary haemopoiesis in the spleen. Animals with intussusception also showed the following changes: Emaciation, decreases in body weight, food consumption, and water intake, decreases in blood electrolytes, calcium, and inorganic phosphate, congestion in the jejunum and mesenteric lymph nodes, deposition of brown pigment on the ileal lamina propria, muscle layer, and Peyer's patch. They also showed various histopathological findings that may be associated with aggravation of nutritional conditions and systemic conditions. All changes were reversible or tended to be reversible after a 4-week recovery period. Based on the above, the applicant determined the NOAEL to be 1.5 mg/kg/day.

### 5.2.7 Thirty-nine-week repeated oral dose toxicity study in dogs (CTD 4.2.3.2-8)

Selexipag (0 [gelatin capsule], 1, 2, 4 mg/kg/day) was administered orally for 26 or 39 weeks to male and female beagle dogs (n = 6/sex; 3 each were necropsied at Week 26 and 3 each at Week 39). Two females in the 4 mg/kg/day group were euthanized because of anal prolapse due to selexipag administration. Surviving animals in the ≥1 mg/kg/day groups showed increased bone formation and myelopoietic tissue, those in the ≥2 mg/kg/day groups showed bloody stool, and those in the 4 mg/kg/day group showed black stool, yellow-green stool, no-feces, flushing, conjunctival hyperaemia, and fibrosis of myelopoietic tissue. Based on the above, the applicant determined the NOAEL to be <1 mg/kg/day.

## 5.3 Genotoxicity (CTD 4.2.3.3.1-1, 4.2.3.3.1-2, 4.2.3.3.2-1, 4.2.3.3.2-2)

The following genotoxicity studies were conducted: bacterial reverse mutation assay, chromosomal aberration assay using cultured mammalian cells (Chinese hamster lung-derived fibroblasts), micronucleus assay using mouse bone marrow, and comet assay using rat liver.

Cytotoxicity was observed in the chromosomal aberration assay using cultured mammalian cells. Under the conditions where the prescribed number of the cells (200) could not be examined, i.e., in the absence of the metabolic activating system at selexipag concentration of 250 μg/mL, structural changes of chromosomes were induced in 40.5% of the cells. However, the applicant determined that selexipag is not genotoxic *in vivo* for the following reasons: (1) Gene mutation was not induced in the bacterial reverse mutation assay, (2) micronuclei were not induced in the micronucleus assay using mouse bone marrow, and (3) no deoxyribonucleic acid (DNA) damage was induced in hepatocytes in the comet assay using rat liver.

### 5.4 Carcinogenicity

As carcinogenicity studies, 104-week carcinogenicity studies in mice and rats were conducted. The studies showed a tendency of increase in thyroid follicular cell-derived tumor in mice and a slight increase in testicular Leydig cell tumor in rats as neoplastic changes. The applicant considered that these tumors are probably irrelevant to humans and therefore do not suggest carcinogenic risk in humans. The ratio of selexipag exposure ($AUC_{0\text{-}24h}$) at the non-carcinogenic dose to that at the maximum clinical dose in humans was 172 in mice and 19.2 in rats. The ratio of exposure to the active metabolite MRE-269 ($AUC_{0\text{-}24h}$) at the non-carcinogenic dose to that at the clinical dose in humans was 54.3 in mice and 92.0 in rats.

#### 5.4.1 Long-term carcinogenicity study in mice (CTD 4.2.3.4.1-1)

Selexipag (0 [0.5% MC solution], 125, 250, 500 mg/kg/day) was administered orally to male and female B6C3F1 mice for 104 weeks (n = 55/sex). In the 500 mg/kg/day group, many females died, and surviving animals in the same group were necropsied at the end of Week 99. A tendency of increase in thyroid follicular cell adenoma or adenocarcinoma was observed as a selexipag-associated neoplastic change in the ≥250 mg/kg/day groups. Non-neoplastic changes observed were increased incidences of the following findings: Hyperplasia or hypertrophy of thyroid follicular cells, centrilobular hypertrophy or necrosis of hepatocytes in the liver, polynuclear hepatocytes, hypertrophy of ovarian corpora lutea, vaginal mucification, hyperplasia of mammary lobules, hyperplasia of pancreatic acinar cells, hypertrophy of salivary (sublingual) acinar cells, hypertrophy of renal papillary tubules, eosinophilic droplets in papillary epithelial cells, renal tubule regeneration, renal tubule dilatation, basophilic changes of cortical renal tubules, hyaline casts, hypertrophy of outer medullary renal tubules, hyperplasia of papillary epithelial cells, increased pigment in splenic red pulp, and fibrotic lesion of femur (bone marrow).

#### 5.4.2 Long-term carcinogenicity study in rats (CTD 4.2.3.4.1-2)

Selexipag (0 [0.5% MC solution], 10, 30, 100 mg/kg/day) was administered orally to male and female SD rats for 104 weeks (n = 60/sex). An increase in testicular Leydig cell adenoma was observed in the 100 mg/kg/day group as the selexipag-associated neoplastic change. Non-neoplastic changes observed were increased incidences of hyperplasia of testicular Leydig cells, centrilobular hypertrophy of hepatocytes, enostosis of femur/sternum, atrophy of pancreatic acinar cells, hyperplasia of acinar cells, hyperplasia of thymic epithelium, and gastric erosion or ulcer, as well as tortuosity and dilatation of retinal arterioles in ophthalmological examination.

### 5.5 Reproductive and developmental toxicity

The following reproductive and developmental toxicity studies were conducted: a study of fertility and early embryonic development to implantation in rats, studies of embryo-fetal development in rats and rabbits, a study of effects on pre- and postnatal development, including maternal function, in rats, and a 39-week repeated oral dose toxicity study in juvenile dogs. Selexipag-associated changes include hypotonia, decreased food consumption, reduced body weight gain or decreased body weight, prolonged estrous cycle, increased respiratory rate, inanimation, soiled perianal fur, and death in parental animals; and decreased mean body weight in surviving fetuses. The studies of embryo-fetal development showed that, at the NOAEL for fetuses (6 mg/kg/day in rats, 30 mg/kg/day in rabbits), $AUC_{0\text{-}24h}$ of selexipag was 1.77 (rats) and 17.7 (rabbits) times the $AUC_{0\text{-}24h}$ at the clinical dose in humans, and $AUC_{0\text{-}24h}$ of the active metabolite MRE-269 was 12.1 (rats) and 49.6 (rabbits) times the $AUC_{0\text{-}24h}$ at the clinical dose in humans. This suggests that selexipag crosses the placenta and is excreted in milk [see “4.2.3 Placental transfer” and “4.2.4 Excretion in milk”].

**5.5.1 Study of fertility and early embryonic development to implantation (CTD 4.2.3.5.1-1)**

Selexipag (0 [0.5% MC solution], 6, 20, 60 mg/kg/day) was administered orally to male and female SD rats (n = 20/sex). Males received the solution for 2 weeks before mating, throughout the mating period, and until 1 day before necropsy. Females received the solution for 2 weeks before mating, throughout the mating period, and until Gestation Day 7. Changes observed were flushing of pinna and limbs in parental animals in the ≥6 mg/kg/day groups, hypotonia and decreased food consumption in parental animals in the ≥20 mg/kg/day groups, and reduced body weight gain in males and prolonged estrous cycle in females in the 60 mg/kg/day group. Selexipag had no effect on the fertility of parental animals or on the development of fetuses. Based on the above, the applicant determined the NOAEL to be 6 mg/kg/day for general toxicity in parental animals and 60 mg/kg/day for fertility and embryos/fetuses.

**5.5.2 Study of embryo-fetal development in rats (CTD 4.2.3.5.2-2)**

Selexipag (0 [0.5% MC solution], 2, 6, 20 mg/kg/day) was administered orally to pregnant SD rats from Gestation Day 7 to Gestation Day 17 (n = 20/group). Findings observed in maternal animals were flushing of pinna in the ≥2 mg/kg/day groups, flushing of limbs in the ≥6 mg/kg/day groups, and hypotonia, decreased food consumption, and reduced body weight gain in the 20 mg/kg/day group. As the effect on fetuses, decreased mean body weight of surviving fetuses was observed in the 20 mg/kg/day group. Based on the above, the applicant determined the NOAEL to be 6 mg/kg/day both for the general toxicity and fertility of parental animals and for embryos/fetuses.

**5.5.3 Study of embryo-fetal development in rabbits (CTD 4.2.3.5.2-5)**

Selexipag (0 [0.5% MC solution], 3, 10, 30 mg/kg/day) was administered orally to pregnant New Zealand White rabbits from Gestation Day 6 to Gestation Day 18 (n = 21-22/group). One maternal animal in the 30 mg/kg/day group died on Gestation Day 7 (Day 2 of administration). Findings observed in the surviving maternal animals were flushing of pinna, eyelids, and lips in the ≥10 mg/kg/day groups, and increased respiratory rate, soiled perianal fur, inanimation, decreased food consumption, and decreased body weight in the 30 mg/kg/day group. Selexipag had no effect on fetuses. Based on the above, the applicant determined the NOAEL to be 10 mg/kg/day for the general toxicity in maternal animals and 30 mg/kg/day for fertility and embryo/fetal development.

**5.5.4 Study of effects on pre- and postnatal development, including maternal function in rats (CTD 4.2.3.5.3-1)**

Selexipag (0 [0.5% MC solution], 2, 6, 20 mg/kg/day) was administered orally to pregnant SD rats from Gestation Day 7 to Lactation Day 20 (n = 18-20/group). Effects observed in maternal animals were flushing of pinna in the ≥2 mg/kg/day groups, flushing of limbs in the ≥6 mg/kg/day groups, and hypotonia, decreased food consumption, and reduced body weight gain in the 20 mg/kg/day group. No abnormality was observed in fertility. Selexipag had no effect on the development of neonates. Based on the above, the applicant determined the NOAEL to be 6 mg/kg/day for the general toxicity in maternal animals and 20 mg/kg/day for fertility and for neonates.

**5.5.5 Thirty-nine-week repeated oral dose toxicity study in juvenile dogs (CTD 4.2.3.5.4-2)**

Male and female juvenile beagle dogs (27-32 days old) received oral selexipag (0 [0.5% MC solution], 1, 3, 6 mg/kg/day [6 mg/kg/day was decreased to 4 mg/kg/day from Week 7]) for 13 weeks, 26 weeks (only in the 0, 1, and 3 mg/kg/day groups), or 39 weeks (n = 8-14/sex; 4 each of them necropsied at Week 13, 4 each at Week 26, and 4-6 at Week 39). A male and a female in the 6 mg/kg/day group died or were euthanized because of intussusception associated with selexipag. Findings observed in surviving animals were reddening and depilation of skin, decreased body weight, increased bone formation, delayed closure of epiphyseal growth plate, and increased hematopoietic tissue in the ≥1 mg/kg/day groups; and delayed estrus, chronic dermatitis, decreased thymus, uterus, and ovary weight, increased adrenal weight, and lack of luteinization in the ≥3 mg/kg/day groups. Based on the above, the applicant determined the NOAEL to be <1 mg/kg/day.

**5.6 Local tolerance (CTD 4.2.3.6-1)**

Male and female New Zealand White rabbits received a single dose of selexipag (concentration; 0 [saline], 8, 40 μg/mL), administered intravenously (10 mL over 20 minutes) or perivenously (0.5 mL

over 25 seconds) (1 male and 2 females per group). Selexipag had no effect on these animals. Based on the result, the applicant determined that selexipag has no local irritant effect.

### 5.7 Other toxicity studies

#### 5.7.1 Effect on hepatic drug-metabolizing enzymes and on thyroid hormones (CTD 4.2.3.7.3-1)

In order to elucidate the mechanism of the increase in neoplastic changes in thyroid follicular cells observed in the carcinogenicity study in mice, selexipag (0 [0.5% MC solution], 62.5, 125, 250, 400 mg/kg/day) was administered orally to male and female B6C3F1 mice for 28 days (n = 10/sex/group). Findings observed were increased hepatic drug-metabolizing enzyme activities in the ≥62.5 mg/kg/day groups; increased CYP levels in the ≥125 mg/kg/day groups; and increases in thyroxine ($T_4$)-uridine diphosphate glucuronosyltransferase (UGT) activity, plasma triiodothyronine ($T_3$) and thyroid stimulating hormone (TSH) concentrations in the ≥250 mg/kg/day groups. The applicant considered that the increase in thyroid tumor observed in mice was specific to rodents, for the following reasons: (1) The increase in neoplastic change of thyroid follicular cells observed in the carcinogenicity study in mice was caused by the feedback mechanism whereby induction of $T_4$ UGT and other drug-metabolizing enzymes in the liver enhances the metabolism of thyroid hormones; and (2) rodents are highly sensitive to the variation of thyroid hormones, and rodents' thyroid tumor mediated by the induction of hepatic drug-metabolizing enzymes is unlikely to be relevant to humans (*Toxicol Sci.* 2011;120:S76-92).

#### 5.7.2 Toxicity of metabolites (CTD 4.2.3.7.5-1, 4.2.3.7.5-2)

The applicant considered that the general toxicity of the metabolite MRE-269 is evaluable from the toxicity studies of selexipag because sufficient exposure to MRE-269 was observed in these studies. MRE-269 was subjected to a bacterial reverse mutation test and a chromosomal aberration assay using cultured mammalian cells, and was shown to have no genotoxic potential in both studies. Based on the above, the applicant determined that the toxicity of MRE-269 has been evaluated.

#### 5.7.3 Toxicity of impurities (CTD 4.2.3.7.6-1 to 4.2.3.7.6-9, Reference data)

Bacterial reverse mutation tests were conducted on MRE-7300, MRE-7301, MRE-7307, MRE-9300, MRE-9301, MRE-9302, MRE-9304, MRE-9305, and MRE-9306 among impurities that may be contained in selexipag. Since these tests were all negative, the applicant determined that these impurities are unlikely to be genotoxic *in vivo*.

#### 5.7.4 Photosafety (CTD 4.2.3.7.7-1, 4.2.3.7.7-2)

*In vitro* phototoxicity studies of selexipag and MRE-269 were conducted using mouse fibroblasts (Balb/c 3T3). Based on the results of the studies, the applicant determined that both selexipag and MRE-269 are phototoxic.

### 5.R Outline of the review conducted by PMDA

#### 5.R.1 Decreased blood pressure

The applicant considered that the changes such as inanimation and hypotonia observed in repeat-dose toxicity studies in mice, rats, and dogs reflect decreased blood pressure. PMDA asked the applicant to explain the possibility of occurrence of clinically significant decrease in blood pressure in humans.

The applicant's explanation:
Table 9 shows the ratio of "exposure at the dose not causing changes possibly associated with decreased blood pressure (inanimation or hypotonia) in mice, rats, or dogs in repeat-dose toxicity studies" to "exposure at the maximum clinical dose (1.6 mg/dose twice daily)."

**Table 9. Ratio of exposure at the dose not causing inanimation or hypotonia in repeat-dose toxicity studies to exposure at the maximum clinical dose[a]**

| | Selexipag | | MRE-269 | |
|---|---|---|---|---|
| | $C_{max}$ | $AUC_{0\text{-}24h}$ | $C_{max}$ | $AUC_{0\text{-}24h}$ |
| Mice | 600-939 | 115-211 | 266-446 | 36.2-58.0 |
| | - | - | - | - |
| Rats | 0.989-186 | 0.101-31.9 | 17.0-442 | 3.44-166 |
| | 0.0341-6.42 | 0.00349-1.10 | 0.946-24.6 | 0.191-9.20 |
| Dogs | 99.4-733 | 74.3-402 | 218-591 | 184-728 |
| | 1.31-9.65 | 0.978-5.29 | 2.66-7.21 | 2.24-8.88 |

Upper box: Exposure ratio (min-max)
Lower box: Safety margin adjusted for species difference in the effect on IP receptors (cAMP formation)
-, Not calculated
[a] Clinical exposure values: Selexipag, 18.0 ng/mL ($C_{max}$) and 88.0 ng·h/mL ($AUC_{0\text{-}12h}$); MRE-269, 26.9 ng/mL ($C_{max}$) and 276 ng·h/mL ($AUC_{0\text{-}12h}$). These values were obtained by doubling $C_{max}$ and $AUC_{0\text{-}12h}$ of selexipag and MRE-269 following selexipag therapy at 1.6 mg twice daily.

There was no sufficient safety margin for decreased blood pressure. However, the clinical studies (Studies AC-065A201, NS-304/-02, AC-065A302, and AC-065A303) showed that there was no significant difference in the incidence of hypotension-related adverse events between the selexipag and placebo groups, and that dose increase or prolonged administration did not show any tendency of increase in the incidence of hypotension-related adverse events, nor had any significant effect on changes in laboratory values over time.

The following changes were associated with decreased blood pressure: increased heart weight in rats receiving ≥25 mg/kg/day in the 26-week repeat-dose toxicity study; and increased heart rate in dogs receiving ≥3 mg/kg/day in the safety pharmacology study. Both changes were caused by compensatory actions of the heart due to the vasodilating effect of selexipag and resulting decrease in blood pressure. No organic changes of the heart were observed in the carcinogenicity study in rats receiving higher doses for a long period. These results suggest that the effect of selexipag on the heart is limited.

Based on the above, the applicant considers that selexipag is unlikely to cause clinically significant hypotension. However, the package insert for selexipag will mention hypotension as an event warranting caution, as is the case with other drugs for PAH.

PMDA's view:
Decreased blood pressure was probably due to the vasodilating effect, the pharmacological action of selexipag. Since there were no organic changes in the heart or other organs in toxicity studies, PMDA considers that selexipag does not have decreased blood pressure-related effects on the heart or other organs. However, the toxicity studies showed no sufficient safety margin against decreased blood pressure, and decreased blood pressure is an adverse event common to vasodilating drugs and, depending on its severity, may have a serious outcome. Therefore the risk of hypotension in humans should be evaluated, and a necessary caution statement worked out, based on the incidences of related adverse events in clinical studies [see "7.R.4.1 Hypotension"].

### 5.R.2 Decreased platelet count

PMDA asked the applicant to explain the mechanism of the decrease in platelet count observed in the repeat-dose toxicity studies in rats and dogs, and to explain whether the finding is relevant to humans.

The applicant's explanation:
In the repeat-dose toxicity study in rats, a dose-dependent decrease in platelet count was observed in the selexipag ≥6 mg/kg/day groups. The exposure to selexipag and MRE-269 at a dose of 6 mg/kg/day in rats was 2.60 and 17.3 times, respectively, that at the maximum clinical dose in humans. In the repeat-dose toxicity study in dogs, decreased platelet count was observed in the selexipag ≥6 mg/kg/day groups and a particularly marked decrease was observed at a dose of 20 mg/kg/day after 2-week administration. The exposure to selexipag and MRE-269 at 6 mg/kg/day in dogs was 276 and 558 times, respectively, that at the maximum clinical dose in humans. Decrease in platelet count is generally caused by the following factors: suppressed platelet formation in the bone marrow; platelet destruction by immune mechanism such as anti-platelet antibody; enhanced consumption of platelets; and platelet capture by the spleen. In the 2-week repeated oral dose toxicity study in dogs, intussusception occurred at the same

dose (20 mg/kg/day) that caused a marked decrease in platelet count; this suggests that the decrease in platelet count was caused by enhanced platelet consumption due to haemorrhage, congestion, and/or inflammation at the site of intussusception. According to reports, beraprost, a $PGI_2$ preparation, suppresses the differentiation of bone marrow-derived cells into megakaryocytes (*Prostaglandins Other Lipid Mediat.* 2007;83:231-6), a platelet aggregation inhibitor induces platelet capture by the spleen in dogs (*Toxicol Pathol.* 2000;28:310-6), and $PGI_2$ administration into the splenic artery of anesthetized dogs increases blood flow in the splenic artery, accompanied by a significant decrease in blood cells including platelets in the splenic vein (*Clin Exp Pharmacol Physiol*. 2006;33:81-8). In contrast, the repeat-dose toxicity studies of selexipag in rats and dogs showed neither changes suggestive of suppression of differentiation into megakaryocytes or enhanced platelet capture by the spleen, nor changes suggestive of platelet consumption such as haemorrhage, except for intussusception. No changes suggestive of platelet destruction by immune mechanism were observed either. The mechanism of the selexipag-induced decrease in platelet count in rats and dogs is unclear, and whether this finding is relevant to humans is unknown. However, platelet count decrease is unlikely to pose any significant risk to long-term selexipag therapy in humans, because of the following observations: (1) the progression of symptoms did not correlate with the length of treatment; (2) there were no changes suggestive of platelet destruction by the immune mechanism such as anti-platelet antibodies; (3) the exposure to selexipag or MRE-269 was lower in humans than in animals; (4) clinical studies showed no effect of selexipag on platelet count.

PMDA's view:
The mechanism of decreased platelet count observed in the toxicity studies is unclear. In addition, the ratio of exposure at the dose not causing decrease in platelet count in rats to that at the maximum clinical dose in humans is <1. Given the possibility that decreased platelet count may aggravate haemorrhage to serious conditions, risks associated with decreased platelet count in humans should be evaluated carefully. Therefore, the details of cautions to be provided should be decided based on the incidences of related adverse events in clinical studies [see "7.R.4.2 Haemorrhage, thrombocytopenia, and coagulation disorder"].

### 5.R.3 Dilatation and tortuosity of retinal arterioles

The applicant's explanation on the dilatation and tortuosity of retinal arterioles observed in the long-term carcinogenicity study in rats:
The ratio of exposure at the dose not causing these findings to that at the clinical maximum dose in humans was 5.52 (0.190 when adjusted for the species difference in the effect on IP receptors) for selexipag and 34.5 (1.92 when adjusted for the species difference in the effect on IP receptors) for MRE-269, failing to provide a sufficient safety margin. However, these findings (changes) are due to the pharmacological action and not accompanied by related pathological disorders including those in the retina. This suggests that these changes per se do not immediately induce any disorder of visual function.

PMDA asked the applicant to explain the safety of selexipag in humans, by taking account of the information from published literature on other drugs that caused similar changes in non-clinical studies.

The applicant's explanation:
The dilatation of the retinal arterioles was probably caused by the vasodilating effect, the pharmacological action of selexipag, for the following reasons: (1) $PGI_2$ is involved in the regulation of the ocular blood flow in rats (*Eur J Pharmacol*. 2007;570:135-41, *J Pharmacol Sci.* 2007;103:103-12); and (2) the selexipag-induced dilatation of the retinal arterioles in rats disappeared on the next day of administration. The tortuosity of retinal arterioles is considered to be a secondary change caused by repeated dilation and contraction of the retinal arterioles over a lifetime, but was not accompanied by morphological change of the retina. Databases (Japan Medical Abstracts, JMEDPlus, JAPICDOC, MEDLINE, DDFU, EMBASE, PharmaPendium, etc.) were searched for drugs that caused changes similar to dilatation and tortuosity of the retinal arterioles in non-clinical studies. This search revealed that similar changes were observed in nonclinical studies of a combination drug containing acrivastine (which has antihistaminic activity) and pseudoephedrine hydrochloride (which has vasoconstrictive activity), cangrelor and heparin sodium (both of which have anticoagulant activity), and levcromakalim (which has vasodilating activity). However, there is no report of adverse events related to such changes

in humans treated with any of these drugs. The applicant therefore considers that the changes (dilatation and tortuosity of retinal arterioles) in rats given selexipag do not directly suggest any risk in humans. Fundoscopy in clinical studies did not detect any selexipag-related changes.

PMDA's view on the dilatation and tortuosity of retinal arterioles observed in the long-term carcinogenicity study in rats:
Although the safety margin for exposure at a clinical dose in humans is <2 times (value adjusted for the species difference of the effect on IP receptors), the findings in rats were not accompanied by morphological changes of the retina. Further, no clinically significant adverse events have been reported with other drugs that caused similar changes in nonclinical studies. Thus the findings in rats alone do not necessitate the issuance of alerts. However, the effect of selexipag on the eyes in humans and the necessity of providing a caution statement should be determined based on the incidences of related adverse events in clinical studies [see "7.R.4.4 Eye disorders including retinal disorder"].

### 5.R.4 Intussusception

The applicant's explanation on intussusception observed in single-dose and repeat-dose toxicity studies in dogs:
Other $PGI_2$ preparations also cause intussusception in dogs, suggesting that the intussusception in dogs given selexipag was an IP receptor-mediated effect. Since neither toxicity studies in other animal species nor clinical studies have reported the onset of intussusception following administration of other $PGI_2$ preparations, dogs are considered to be exceptionally sensitive to $PGI_2$ preparation-induced intussusception.

PMDA asked the applicant to explain the risk of intussusception in humans receiving selexipag, by clarifying (a) the safety margin for the dose of selexipag and other $PGI_2$ preparations against intussusception and (b) the species difference in IP receptor affinity between the preparations.

The applicant's explanation:
Table 10 shows the safety margin for selexipag, beraprost sodium, iloprost, and treprostinil against intussusception (intestinal volvulus for iloprost) observed in toxicity studies in dogs, and the adjusted safety margin (adjusted for the ratio of IP receptor-mediated effect). The adjusted safety margin was approximately 1 to 3 times for selexipag and MRE-269, approximately 4 to 7 times for iloprost, and approximately 0.08 times for treprostinil (calculated based on the plasma concentration because the efficacy ratio between humans and dogs is unknown). The safety margin of beraprost sodium was approximately 35 times; this value was calculated based on the dose per body weight because of the unavailability of the exposure data in toxicity studies, precluding the accurate comparison.

**Table 10. Ratio of exposure to selexipag, MRE-269, and other $PGI_2$ preparations at the dose not causing intussusception[a] to that at the maximum clinical dose**

| | Safety margin for plasma concentration[b] | Safety margin for $AUC_{0\text{-}24h}$ | Safety margin for dose per body weight |
|---|---|---|---|
| Selexipag | 99.4 [1.31][c] | 74.3 [0.978][c] | |
| MRE-269 | 218 [2.66][c] | 213 [2.60][c] | |
| Beraprost sodium | | | 34.7 |
| Iloprost | 4.90 [3.50][c] | 10.3 [7.34][c] | |
| Treprostinil | 0.0753[d] | | |

Minimum value [adjusted]
[a] Intestinal volvulus, instead of intussusception, occurred after iloprost administration.
[b] $C_{max}$ for selexipag and iloprost, plasma concentration at steady state for treprostinil
[c] Adjusted value calculated by dividing by the ratio of the effect using the IP receptor-mediated increase in cAMP formation as the index (selexipag, 76; MRE-269, 82; iloprost, 1.4)
[d] Since treprostinil was administered continuously both in humans and dogs, the safety margin for plasma concentration under steady state was assumed to be identical with the safety margin for $AUC_{0\text{-}24h}$.

The safety margin of each $PGI_2$ preparation against intussusception or intestinal volvulus in dogs varies widely, but the changes observed in toxicity studies were not noted in humans. Further, no caution statement against intussusception or intestinal volvulus is provided in the package insert for beraprost sodium, iloprost, or treprostinil. Based on the above, the applicant considers that intussusception

observed in the single-dose and repeat-dose toxicity studies of selexipag in dogs poses little, if any, risk in humans.

Based on the incidences of intussusception in dogs treated with $PGI_2$ preparation and on the reports in humans, PMDA concludes that the risk of selexipag-induced intussusception is unlikely to exceed that induced by $PGI_2$ preparations, and that, as is the case with other drugs, selexipag has only a low risk of inducing intussusception in humans.

## 6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

### 6.1 Summary of biopharmaceutic studies and associated analytical methods

The to-be-marketed formulations of selexipag are 0.2 and 0.4 mg tablets. The 0.2 mg tablets are the same formulation used in the clinical studies in patients with PAH: Japanese phase II study (Study AC-065A201), the foreign phase II study (Study NS-304/-02), and the foreign phase III study (Study AC-065A302). The 0.4 mg tablets, the other to-be-marketed formulation, have been shown to be biologically equivalent to 0.2 mg tablets by the dissolution test performed according to the BE Guideline for Different Contents.

Plasma concentrations of selexipag and its active metabolite MRE-269 were measured by liquid chromatography and tandem mass spectrometry (LC-MS/MS). The lower limit of quantitation was 0.01 ng/mL for both compounds.

Pharmacokinetic parameters are expressed in mean or mean ± SD unless specified otherwise.

#### 6.1.1 Absolute BA study (Study AC-065-110, CTD 5.3.1.1-1)

Sixteen non-Japanese healthy adults received a single dose of selexipag at 0.2 mg intravenously, or at 0.4 mg orally, by a two-treatment, two-period cross-over design (washout period, 7-10 days). As a result, the point estimate [90% confidence interval (CI)] of the absolute bioavailability (BA) (the geometric mean ratio of dose-adjusted $AUC_{0-\infty}$ [oral administration vs intravenous administration]) was 0.494 [0.426, 0.572]. Following a single intravenous dose of selexipag 0.2 mg, the geometric means [95% CI] of total clearance (CL) and volume of distribution at steady state ($V_{ss}$) of selexipag were 17.93 [14.95, 21.50] L/h and 11.73 [10.55, 13.04] L, respectively.

#### 6.1.2 Food effect

##### 6.1.2.1 Effect of standard meal (Study NS304/P1/01, CTD 5.3.3.1-1)

Four Japanese healthy adults received oral selexipag (two 0.2 mg tablets) as a single dose in the fasted state or after a standard meal (with lipid accounting for 33% of total calorie). The effect of food on the pharmacokinetics of selexipag and MRE-269 was investigated.

The geometric mean ratio [90% CI] (fed vs fasted) of $C_{max}$ and $AUC_{0-\infty}$ was 0.676 [0.557, 0.818] and 0.853 [0.721, 1.01], respectively, for selexipag, and 0.929 [0.818, 1.05] and 0.879 [0.766, 1.01], respectively, for MRE-269. $t_{max}$ of selexipag and MRE-269 delayed both by 0.8 hours in the fed state compared with the values in the fasted state.

##### 6.1.2.2 Effect of high fat meal (Study QGUY/2006/NS-304/-01, CTD 5.3.3.1-2)

A two-treatment, two-period, cross-over study (washout period, ≥7 days) was conducted in 12 non-Japanese healthy adults to investigate the effect of food on the pharmacokinetics of selexipag and MRE-269. Selexipag (one 0.4 mg tablet) was administered orally as a single dose in the fasted state or after a high fat meal (with lipid accounting for 55% of the total calorie).

The geometric mean ratio [90% CI] (fed vs fasted) of $C_{max}$ and $AUC_{0-\infty}$ was 0.65 [0.48, 0.88] and 1.10 [0.92, 1.30], respectively, for selexipag and 0.52 [0.41, 0.65] and 0.73 [0.65, 0.81], respectively, for MRE-269. $t_{max}$ of selexipag and MRE-269 delayed by 1.8 and 1.5 hours, respectively, in the fed state compared with the values in the fasted state.

## 6.2 Clinical pharmacology

### 6.2.1 *In vitro* studies using human biomaterials

#### 6.2.1.1 Plasma protein binding and distribution in blood cells (CTD 5.3.2.1-1, 5.3.2.1-2)

$^{14}$C-selexipag or $^{14}$C-MRE-269 (0.1 or 1 μg/mL [final concentration]) was added to human serum. The serum protein binding rate was 98.7% to 98.9% for selexipag and 98.3% to 98.7% for MRE-269, showing no concentration-dependent change for either compound. $^{14}$C-selexipag or $^{14}$C-MRE-269 (0.1 or 1 μg/mL [final concentration]) was added to 4% human serum albumin solution or 0.08% human $\alpha_1$-acid glycoprotein solution. The binding rate of selexipag or MRE-269 with human serum albumin or with human $\alpha_1$-acid glycoprotein solution did not show any concentration-dependent change. The binding rate with human serum albumin and with human $\alpha_1$-acid glycoprotein solution was 97.5% to 97.7% and 96.3% to 96.6%, respectively, for selexipag and 97.3% to 97.6% and 95.9% to 96.4%, respectively, for MRE-269.

$^{14}$C-selexipag or $^{14}$C-MRE-269 (0.1-50 μg/mL [final concentration]) was added to human plasma. The binding rate of selexipag or MRE-269 with plasma protein did not show any concentration-dependent change, being 99.7% to 99.8% for selexipag and 99.4% to 99.8% for MRE-269.

$^{14}$C-selexipag or $^{14}$C-MRE-269 (0.1 or 20 μg/mL [final concentration]) was added to human blood. The blood/plasma concentration ratio was 0.56 to 0.58 for selexipag and 0.58 to 0.59 for MRE-269.

#### 6.2.1.2 *In vitro* metabolism

##### 6.2.1.2.1 Metabolism of selexipag and MRE-269 (CTD 5.3.2.2-1)

Human liver microsomes and hepatocytes were incubated with $^{14}$C-selexipag (10 μmol/L [final concentration]) at 37°C for 60 minutes (liver microsomes) or 24 hours (hepatocytes). MRE-269 was the most abundant metabolite formed (percentage of the total radioactivity: 25.4% with liver microsomes, 57.2% to 71.9% with hepatocytes), followed by MRE-6300 (hydroxylated at phenyl group of MRE-269) (4.1% with liver microsomes, 5.5%-15.7% with hepatocytes).

Human liver microsomes and hepatocytes were incubated with $^{14}$C-MRE-269 (10 μmol/L [final concentration]) at 37°C for 60 minutes (liver microsomes) or 24 hours (hepatocytes). MRE-269 was metabolized more gradually compared with selexipag, but the resulting metabolites were similar to those obtained in the metabolic study using selexipag.

##### 6.2.1.2.2 Studies on enzymes involved in the metabolism of selexipag and MRE-269 (CTD 5.3.2.2-2 – 5.3.2.2-6, 5.3.2.2-8)

Human plasma, liver microsomes, and small intestinal microsomes were incubated with $^{14}$C-selexipag (10 μmol/L [final concentration]) at 37°C, and MRE-269 generated by the hydrolysis of selexipag was measured. Little or no MRE-269 was generated in plasma or small intestinal microsomes, whereas MRE-269 was generated in liver microsomes even in the absence of the NADPH-regenerating system.

Human liver microsomes were incubated with $^{14}$C-selexipag (10 μmol/L [final concentration]) at 37°C in the presence of hydrolase inhibitors, to investigate metabolic enzymes involved in the formation of MRE-269 generated by the hydrolysis of selexipag. The following hydrolase inhibitors were used at concentrations of 0.01 to 1 mmol/L: Bis(p-nitrophenyl) phosphate and phenylmethylsulfonyl fluoride (carboxylesterase [CES] inhibitors), ethylenediaminetetraacetic acid (paraoxonase inhibitor), and eserine (acetylcholinesterase inhibitor). Bis(p-nitrophenyl) phosphate and phenylmethylsulfonyl fluoride inhibited the formation of MRE-269 both at ≥0.01 mmol/L, with the inhibition being complete at 1 mmol/L. Eserine at 1 mmol/L inhibited the formation of MRE-269 by 31%, while ethylenediaminetetraacetic acid hardly inhibited the formation of MRE-269 even at the maximum concentration tested.

Based on the above, together with the report that CES1 is the CES specifically expressed in the liver (*Biochem Pharmacol.* 2009;77:238-47), the applicant considered that CES1 is mainly involved in the formation of MRE-269 in humans.

Human liver microsomes were incubated with selexipag (10 μmol/L [final concentration]) at 37°C in the presence of the inhibitors of CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4), to investigate CYP isoforms involved in the metabolism of selexipag. Montelukast (an inhibitor of CYP2C8, 3 μmol/L) inhibited the formation of P8 (hydroxylated at phenyl group of selexipag) and P39 (hydroxylated at isopropyl group of selexipag). Azamulin and ketoconazole (inhibitors of CYP3A, 5 and 1 μmol/L, respectively) inhibited the formation of P36 (hydroxylated at pyrazine ring of selexipag), P40 (*N*-dealkylated at aminopyrimidine group of selexipag), and P14 (*N*-dealkylated form of P41 [*N*-dealkylated selexipag]). The formation of P14 was also inhibited by furafylline (a CYP1A2 inhibitor, 20 μmol/L).

Microsomes expressing human CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) were incubated with selexipag (10 μmol/L [final concentration]) at 37°C. P8 and P39 were formed only in the presence of the CYP2C8-expressing system, and P14, P36, and P41 only in the CYP3A4-expressing system. The formation of P40 was observed in the presence of CYP2C9 and CYP3A4-expressing systems. The formation of P41 decreased in the presence of the CYP3A4 and CYP1A2-coexpression system compared with the system expressing CYP3A4 only, whereas the formation of P14 was increased by the CYP3A4 and CYP1A2 co-expression system. Selexipag was not metabolized in systems expressing other CYP isoforms.

Microsomes expressing human CYP isoforms (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4) were incubated with $^{14}$C-MRE-269 (10 μmol/L [final concentration]) at 37°C. MRE-6300, the main metabolite detected in the human feces, was formed only in the CYP2C8-expressing system. CYP3A4 and CYP2C8 were involved in the formation of other metabolites, whereas no MRE-269 metabolism occurred in other CYP-expressing systems. These results suggested that MRE-269 is metabolized most rapidly by the CYP2C8-expressing system, followed by the CYP3A4-expressing system, and that MRE-269 is metabolized mainly by CYP2C8, followed by CYP3A4.

Microsomes expressing human UGT isoforms (UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A7, UGT1A8, UGT1A9, UGT1A10, UGT2B4, UGT2B7, UGT2B15, and UGT2B17) were incubated with $^{14}$C-MRE-269 (10 μmol/L [final concentration]) at 37°C. MRE-6001 (acylglucuronide of MRE-269) was formed rapidly by the UGT1A3-expressing system, followed by UGT2B7- and UGT1A1-expressing systems in this order. MRE-6001 formation did not occur in other UGT isoform-expression systems.

#### 6.2.1.2.3 Enzyme inhibition (CTD 5.3.2.2-10 to 5.3.2.2-12)

Using human liver microsomes and the substrates for CYP isoforms (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A), the inhibitory effect of selexipag and MRE-269 (0.5-50 μmol/L [final concentration]) on the metabolism of the substrate of each isoform was investigated. Selexipag and MRE-269 exhibited the inhibitory effect against paclitaxel 6α-hydroxylating (CYP2C8) activity and diclofenac 4'-hyroxylating (CYP2C9) activity. $K_i$ of selexipag was 2.0 μmol/L (CYP2C8) and 3.5 μmol/L (CYP2C9), and $K_i$ of MRE-269 was 11μmol/L (CYP2C8) and 15 μmol/L (CYP2C9). Selexipag and MRE-269 had almost no inhibitory effect against other CYP isoforms. Selexipag and MRE-269 had no time-dependent inhibitory effect against CYP2C8, CYP2C9, CYP2D6, or CYP3A.

#### 6.2.1.2.4 Enzyme induction (CTD 5.3.2.2-13, 5.3.2.2-14)

CV-1 cells were incubated with selexipag or MRE-269 (0.01-100 or 0.01-50 μmol/L [final concentration]) for 24 hours at 37°C, and the human pregnane X receptor (PXR)-activating effect was investigated by reporter gene assay. Selexipag and MRE-269 activated human PXR with $EC_{50}$ of 1.9 to 3.3 and 2.3 to 3.8 μmol/L, respectively.

Human hepatocytes were incubated with selexipag (0.1-200 μmol/L [final concentration]) or with MRE-269 (0.1-100 μmol/L [final concentration]) for 68 hours at 37°C, to investigate CYP1A2-, CYP2B6-, CYP2C9-, and CYP3A4-inducing activities of selexipag and MRE-269. Expression of CYP2B6 messenger ribonucleic acid (mRNA) reached the maximum level in the presence of 30 to 60 μmol/L of

selexipag or MRE-269; the expression levels were 20% to 60% of that in the presence of the positive control (phenobarbital). Selexipag and MRE-269 both increased the expression levels of CYP2C9 and CYP3A4 mRNAs in a concentration-dependent manner. $EC_{50}$ for inducing these mRNAs were as follows: selexipag, 0.8μmol/L (CYP2C9) and 1.2 to 5.0 μmol/L (CYP3A4); MRE-269, 2.6 μmol/L (CYP2C9) and 3.1 to 12.7 μmol/L (CYP3A4). Neither selexipag nor MRE-269 did not induce CYP1A2 even at the maximum concentration tested.

Human hepatocytes were incubated with selexipag or MRE-269 (0.1-10 μmol/L [final concentration]) for 72 hours at 37°C, to investigate the CYP1A2 and CYP3A-inducing effect. Selexipag and MRE-269 both increased testosterone 6β-hydroxylating (CYP3A4) activity in a concentration-dependent manner. The rate of increase induced by selexipag and MRE-269 (10 μmol/L) was 37.8% and 26.1%, respectively, of that achieved by the positive control rifampicin. Neither selexipag nor MRE-269 showed the CYP1A2-inducing effect.

#### 6.2.1.2.5 Studies on transporters (CTD 5.3.2.3-1 to 5.3.2.3-3)

Selexipag (1-10 μmol/L [final concentration]) or MRE-269 (0.05-5 μmol/L [final concentration]) was added to MDCKII cells expressing multidrug resistance protein (MDR)1. The membrane permeability coefficient ratio was as follows: selexipag, 1.9 to 5.6 (without a P-glycoprotein [P-gp] inhibitor) and 1.0 to 2.0 (with a P-gp inhibitor); MRE-269, 0.7 to 4.3 (without a P-gp inhibitor) and 0.7 to 3.0 (with a P-gp inhibitor).

Selexipag (0.01-7.5 μmol/L [final concentration]) was added to membrane vesicles prepared from Sf9 cells expressing breast cancer resistance protein (BCRP). The ratio of selexipag uptake (with ATP/without ATP) was 0.8 to 1.4. MRE-269 (0.05-5 μmol/L [final concentration]) was added to MDCKII cells expressing BCRP; the membrane permeability coefficient ratio was 2.5 to 4.2 (without a BCRP inhibitor) and 0.8 to 1.0 (with a BCRP inhibitor).

MRE-269 (0.01-7.5 μmol/L [final concentration]) was added to membrane vehicles prepared from Sf9 cells expressing bile salt export pump (BSEP) or multidrug resistance-associated protein (MRP)2. The ratio of MRE-269 uptake (with ATP/without ATP) was 0.9 to 1.4 for BSEP-expressing cells and 0.5 to 1.0 for MRP2-expressing cells.

Selexipag (0.01-10 μmol/L [final concentration]) or MRE-269 (0.005-5 μmol/L [final concentration]) was added to CHO cells expressing organic anion transporting polypeptide (OATP)1B1 or OATP1B3. Selexipag uptake was higher both in OATP1B1-expressing cells and OATP1B3-expressing cells than in wild-type cells. MRE-269 uptake was higher in OATP1B3-expressing cells than in the wild-type cells. Michaelis-Menten constant ($K_m$) of selexipag for OATP1B1 and OATP1B3 was 2.0 and 2.3 μmol/L, respectively, and $K_m$ of MRE-269 for OATP1B3 was 2.5 μmol/L.

MRE-269 (0.01-0.1 μmol/L [final concentration]) was added to HEK293 cells expressing multidrug and toxin extrusion (MATE)1. The ratio of MRE-269 uptake (MATE1-expressing cells/wild-type cells) was 0.9 to 1.5.

The inhibitory effect of selexipag and MRE-269 (0.1-10 μmol/L [final concentration]) against P-gp-mediated transport of $^3$H-digoxin and rhodamine 123 was investigated using MDCKII cells expressing MDR1. Neither selexipag nor MRE-269 inhibited the transport of $^3$H-digoxin or rhodamine 123 even at the maximum concentration tested.

The inhibitory effect of selexipag and MRE-269 (0.003-1000 μmol/L [final concentration]) against the transport of substrates for transporters was investigated, using (1) membrane vesicles prepared from Sf9 cells expressing BCRP, MRP2, or BSEP, (2) CHO cells expressing OATP1B1, OATP1B3, or organic anion transporter (OAT)1, or (3) HEK293 cells expressing organic cation transporter (OCT)1, OCT2, OAT3, MATE1, or MATE2-K. The substrates are methotrexate 100 μmol/L for BCRP, estradiol-17-β-glucuronide 50 μmol/L for MRP2, taurocholic acid 5 μmol/L for BSEP and OATP1B3, atorvastatin calcium 0.5 μmol/L for OATP1B1, *p*-aminohippuric acid 1 μmol/L for OAT1, furosemide 5 μmol/L for OAT3, 1-methyl-4-phenylpyridinium iodide (MPP) 5 μmol/L for OCT1 and OCT2, metformin 50

μmol/L for MATE1, ASP 1 μmol/L for MATE2-K. Selexipag inhibited OATP1B1, OATP1B3, BCRP, OAT1, OAT3, MATE1, and BSEP with $IC_{50}$ of 2.4, 1.7, 1.9, 1.4, 1.7, 22, and 11 μmol/L, respectively. MRE-269 inhibited OATP1B1, OATP1B3, BCRP, OAT1, OAT3, MATE1, MRP2, and BSEP with $IC_{50}$ of 3.5, 4.1, 5.6, 25, 2.1, 30, 37, and 20 μmol/L, respectively.

### 6.2.2 Studies in healthy adults

#### 6.2.2.1 Single-dose and multiple-dose studies in Japanese healthy adults (Study NS304/P1/01, CTD 5.3.3.1-1)

Table 11 shows the pharmacokinetic parameters of selexipag and MRE-269 following a single oral administration of selexipag (0.2, 0.4, 0.6 mg) to 18 Japanese healthy adults in the fasted state. Urinary excretion of selexipag and its metabolites (MRE-269 and MRE-6001) within 48 hours after administration was extremely low in all groups; the urinary excretion rate of selexipag and its metabolites (percentage of the administered dose) was 0.22% to 0.27% in all dose groups up to 48 hours after administration.

**Table 11. Pharmacokinetic parameters of selexipag and MRE-269 following a single-dose administration of selexipag**

| Dose (mg) | n | $C_{max}$ (ng/mL) | $t_{max}$[a] (h) | $t_{1/2}$ (h) | $AUC_{0-\infty}$ (ng·h/mL) |
|---|---|---|---|---|---|
| Selexipag | | | | | |
| 0.2 | 6 | 7.14 ± 3.53 | 1 | 0.917 ± 0.156 | 15.5 ± 8.7 |
| 0.4 | 6 | 11.5 ± 3.1 | 1 | 1.52 ± 0.65 | 20.5 ± 5.5 |
| 0.6 | 6 | 17.3 ± 4.7 | 1 | 2.36 ± 0.99 | 38.9 ± 12.3 |
| MRE-269 | | | | | |
| 0.2 | 6 | 9.05 ± 5.23 | 3 | 8.68 ± 1.11 | 54.1 ± 27.7 |
| 0.4 | 6 | 11.2 ± 2.7 | 3.25 | 6.44 ± 1.48 | 70.6 ± 18.1 |
| 0.6 | 6 | 17.1 ± 3.8 | 3 | 6.18 ± 1.92 | 124 ± 50 |

[a] Median

Eighteen healthy adults received the following regimen of oral selexipag: (a) 0.2 or 0.4 mg once daily on Days 1 and 10, and twice daily from Day 3 to Day 9, all after a meal; or (b) 0.4 mg once daily on Day 1 and twice daily on Days 3 and 4, and 0.6 mg twice daily from Day 5 to Day 11 and once daily on Day 12, all after a meal. Table 12 shows the pharmacokinetic parameters of selexipag and MRE-269.

Urinary excretion of selexipag and MRE-269 was extremely low in all groups. In all dose groups, the urinary excretion rate (percentage of a single dose [=dose per administration]) of selexipag and the metabolite up to 48 hours after administration was 0.17% to 0.21% on Day 1 and 0.18% to 0.28% on the last day of multiple-dose administration.

**Table 12. Pharmacokinetic parameters of selexipag and MRE-269 in multiple-dose administration of selexipag**

| Dose per administration (mg) | n | Time point (Day) | $C_{max}$ (ng/mL) | $t_{max}$[a] (h) | $t_{1/2}$ (h) | AUC[b] (ng·h/mL) |
|---|---|---|---|---|---|---|
| Selexipag | | | | | | |
| 0.2 | 6 | 1 | 3.30 ± 0.81 | 1.75 | 0.849 ± 0.133 | 8.59 ± 2.64 |
| | 6 | 5 | 2.52 ± 0.75 | 1.5 | 0.852 ± 0.190 | 6.37 ± 2.19 |
| | 6 | 10 | 2.98 ± 0.85 | 1.5 | 0.855 ± 0.204 | 6.53 ± 2.36 |
| 0.4 | 6 | 1 | 8.55 ± 1.33 | 1.5 | 1.03 ± 0.26 | 18.8 ± 2.9 |
| | 6 | 5 | 6.05 ± 0.75 | 2 | 1.15 ± 0.21 | 17.8 ± 2.8 |
| | 6 | 10 | 8.71 ± 0.79 | 1.5 | 1.38 ± 0.62 | 17.5 ± 3.5 |
| 0.6[c] | 6 | 1 | 6.09 ± 2.13 | 1.5 | 0.815 ± 0.129 | 14.6 ± 3.1 |
| | 6 | 5 | 8.61 ± 1.39 | 2 | 1.34 ± 0.21 | 21.3 ± 2.9 |
| | 6 | 12 | 10.7 ± 3.0 | 1.5 | 1.89 ± 0.53 | 24.8 ± 3.7 |
| MRE-269 | | | | | | |
| 0.2 | 6 | 1 | 4.06 ± 0.94 | 4.5 | 10.5 ± 4.0 | 24.0 ± 5.5 |
| | 6 | 5 | 5.06 ± 1.23 | 3 | 4.96 ± 1.92 | 28.8 ± 6.7 |
| | 6 | 10 | 4.24 ± 0.81 | 3 | 10.7 ± 3.7 | 22.8 ± 5.8 |
| 0.4 | 6 | 1 | 7.40 ± 1.23 | 3.5 | 7.84 ± 2.43 | 45.7 ± 8.9 |
| | 6 | 5 | 9.66 ± 1.74 | 3.5 | 4.49 ± 0.76 | 60.7 ± 9.9 |
| | 6 | 10 | 10.2 ± 1.6 | 2.75 | 11.2 ± 4.0 | 60.5 ± 8.0 |
| 0.6 [c] | 6 | 1 | 6.97 ± 1.27 | 3 | 6.28 ± 2.15 | 39.4 ± 10.3 |
| | 6 | 5 | 9.61 ± 2.29 | 4.5 | 3.55 ± 0.70 | 57.4 ± 14.5 |
| | 6 | 12 | 12.4 ± 2.0 | 3 | 7.89 ± 2.36 | 69.7 ± 12.3 |

[a] Median
[b] $AUC_{0-\infty,}$ on Day 1, $AUC_{0-12h}$ on Days 5, 10, and 12
[c] 0.4 mg from Day 1 to Day 4

### 6.2.2.2 Single-dose and multiple-dose studies in non-Japanese healthy adults (Study QGUY/2006/NS-304/-01, CTD 5.3.3.1-2)

Table 13 shows pharmacokinetic parameters of selexipag and MRE-269 following a single oral administration of selexipag (0.1, 0.2, 0.4, 0.6, 0.8 mg) to 30 non-Japanese healthy adults in the fasted state.

Selexipag was not detected in urine up to 48 hours after administration in any of the groups. MRE-269 was detected in the ≥0.2 mg groups, but only at an extremely low level up to 48 hours after administration in any of those groups. The urinary excretion rate (percentage of the administered dose) of MRE-269 was 0.08% to 0.12%.

**Table 13. Pharmacokinetic parameters of selexipag and MRE-269 following a single-dose administration of selexipag**

| Dose (mg) | n | $C_{max}$ (ng/mL) | $t_{max}$[a] (h) | $t_{1/2}$ (h) | $AUC_{0-\infty}$ (ng·h/mL) |
|---|---|---|---|---|---|
| Selexipag | | | | | |
| 0.1 | 6 | 2.28 ± 0.70 | 1.26 | 0.71 ± 0.08 | 4.85 ± 1.83 |
| 0.2 | 6 | 3.79 ± 2.16 | 1 | 0.81 ± 0.11 | 7.40 ± 3.84 |
| 0.4 | 6 | 6.50 ± 2.99 | 1 | 1.06 ± 0.42 | 13.2 ± 5.5 |
| 0.6 | 6 | 11.6 ± 3.1 | 1 | 1.98 ± 0.67 | 23.5 ± 3.2 |
| 0.8 | 6 | 11.6 ± 1.8 | 1 | 2.48 ± 0.78 | 25.7 ± 6.6 |
| MRE-269 | | | | | |
| 0.1 | 6 | 2.02 ± 0.39 | 2.5 | 9.97 ± 1.75 | 12.8 ± 2.40 |
| 0.2 | 6 | 4.18 ± 0.86 | 2.75 | 12.7 ± 1.6 | 26.9 ± 5.9 |
| 0.4 | 6 | 8.89 ± 4.02 | 2.25 | 9.88 ± 1.23 | 60.8 ± 36.0 |
| 0.6 | 6 | 12.7 ± 2.5 | 2.5 | 9.40 ± 1.09 | 81.7 ± 24.6 |
| 0.8 | 6 | 14.6 ± 3.0 | 2.25 | 10.9 ± 2.4 | 96.6 ± 28.3 |

[a] Median

Eighteen non-Japanese healthy adults received the following regimen of oral selexipag: (a) 0.2 or 0.4 mg once daily on Days 1 and 8, and twice daily from Day 3 to Day 7, all after a meal; or (b) 0.4 mg once daily on Day 1 and twice daily on Days 3 and 4, and 0.6 mg twice daily from Day 5 to Day 7 and once daily on Day 8, all after a meal. Table 14 shows the pharmacokinetic parameters of selexipag and MRE-269.

Selexipag was not detected in urine in any groups. MRE-269 was excreted in urine mostly within 12 hours after administration. The urinary excretion rate (percentage of the administered dose) up to 12 hours after the last dose was 0.085% to 0.095%.

**Table 14. Pharmacokinetic parameters of selexipag and MRE-269 following multiple-dose administration of selexipag**

| Dose per administration (mg) | n | Time point (Day) | $C_{max}$ (ng/mL) | $t_{max}$[a] (h) | $t_{1/2}$ (h) | AUC[b] (ng·h/mL) |
|---|---|---|---|---|---|---|
| Selexipag | | | | | | |
| 0.2 | 6 | 1 | 2.58 ± 1.07 | 2 | 0.99 ± 0.27 | 6.21 ± 2.47 |
| | 6 | 8 | 1.99 ± 0.89 | 2.25 | 1.17 ± 0.27 | 5.63 ± 1.85 |
| 0.4 | 12 | 1 | 4.61 ± 1.54 | 2.5 | 1.32 ± 0.35 | 11.5 ± 3.11 |
| | 6 | 8 | 4.27 ± 1.19 | 2.26 | 1.43 ± 0.28 | 9.83 ± 1.75 |
| 0.6[c] | 6 | 8 | 5.47 ± 1.43 | 2 | 1.35 ± 0.64 | 14.0 ± 2.77 |
| MRE-269 | | | | | | |
| 0.2 | 6 | 1 | 3.51 ± 0.75 | 4 | 12.0 ± 0.74 | 25.5 ± 6.51 |
| | 6 | 8 | 3.45 ± 1.21 | 4 | 14.5 ± 3.31 | 23.6 ± 8.50 |
| 0.4 | 12 | 1 | 6.23 ± 2.06 | 4 | 10.6 ± 1.62 | 39.4 ± 12.1 |
| | 6 | 8 | 4.92 ± 1.87 | 4 | 13.8 ± 1.86 | 30.6 ± 10.8 |
| 0.6[c] | 6 | 8 | 8.83 ± 1.45 | 4 | 10.8 ± 2.88 | 47.6 ± 8.99 |

[a] Median
[b] $AUC_{0-\infty}$ on Day 1, $AUC_{\tau}$ on Day 8
[c] 0.4 mg from Day 1 to Day 4

### 6.2.2.3 Multiple-ascending-dose study in non-Japanese healthy adults (Study AC-065-101, CTD 5.3.3.1-3)

Twelve non-Japanese healthy adults received oral selexipag twice daily after a meal at the starting dose of 0.4 mg, which was increased by 0.2 mg increments every 3 days. Table 15 shows the pharmacokinetic parameters of selexipag and MRE-269 (after 3-day administration at each dose level).

**Table 15. Pharmacokinetic parameters of selexipag and MRE-269 in multiple-ascending-dose administration of selexipag**

| Dose per administration (mg) | n | $C_{max}$ (ng/mL) | $t_{max}$[a] (h) | $t_{1/2}$ (h) | $AUC_{\tau}$ (ng·h/mL) |
|---|---|---|---|---|---|
| Selexipag | | | | | |
| 0.4 | 12 | 2.94 ± 1.17 | 2 | - | 9.78 ± 4.60 |
| 0.6 | 11 | 3.57 ± 1.43 | 2 | - | 12.2 ± 6.72 |
| 0.8 | 10 | 6.92 ± 3.47 | 2 | - | 20.5 ± 10.7 |
| 1.0 | 9 | 8.76 ± 4.72 | 2 | - | 26.3 ± 14.9 |
| 1.2 | 9 | 10.4 ± 5.63 | 2 | - | 30.4 ± 15.1 |
| 1.4 | 9 | 11.2 ± 4.15 | 2 | - | 31.7 ± 12.2 |
| 1.6 | 9 | 11.0 ± 5.16 | 2 | - | 34.8 ± 14.9 |
| 1.8 | 8 | 13.8 ± 6.71 | 2 | 1.47 ± 0.29 | 44.6 ± 17.4 |
| MRE-269 | | | | | |
| 0.4 | 12 | 5.59 ± 2.20 | 4 | - | 41.4 ± 17.1 |
| 0.6 | 11 | 7.73 ± 2.81 | 4 | - | 54.7 ± 22.0 |
| 0.8 | 10 | 11.1 ± 5.14 | 4 | - | 74.1 ± 29.6 |
| 1.0 | 9 | 13.7 ± 5.79 | 4 | - | 98.8 ± 43.6 |
| 1.2 | 9 | 16.0 ± 7.55 | 4 | - | 111 ± 48.8 |
| 1.4 | 9 | 16.3 ± 6.23 | 4 | - | 117 ± 45.6 |
| 1.6 | 9 | 17.9 ± 8.17 | 4 | - | 137 ± 58.8 |
| 1.8 | 8 | 22.9 ± 9.55 | 4 | 8.74 ± 1.25 | 166 ± 77.1 |

-, Not calculated
[a] Median

### 6.2.2.4 Mass balance study (Study 186933, CTD 5.3.3.1-4)

$^{14}$C-selexipag (0.4 mg) was administered orally as a single dose to 6 non-Japanese healthy adult men after a meal. As a result, $t_{max}$ and $t_{1/2}$ of radioactivity were both similar in whole blood and plasma. The geometric means of $C_{max}$ and $AUC_{0-\infty}$ of radioactivity in plasma were 1.7 and 1.9 times, respectively, that in whole blood, suggesting that little or no radioactivity was distributed in blood cells.

The urinary and fecal excretion rates (percentage of the administered radioactivity) within 168 hours after administration were 11.9% and 92.7%, respectively, showing that the radioactivity was excreted mainly in feces. MRE-6300 and MRE-6302 (hydroxylated at isopropyl group of MRE-6300) were detected as the main metabolites in feces with the abundance rate (percentage of total radioactivity in feces) of 28.2% to 30.7% (MRE-6300) and 15.1% to 25.9% (MRE-6302).

### 6.2.3 Studies in patients

#### 6.2.3.1 Japanese phase II studies (Study AC-065A201, CTD 5.3.5.2-1)

Selexipag was administered to 37 Japanese patients with PAH at the starting dose of 0.2 mg per administration, which was up-titrated (not above 1.6 mg) to determine the maintenance dose for each patient before Week 12 (the maintenance dose period, Week 12-16). Table 16 shows the pharmacokinetic parameters of selexipag and MRE-269 following twice daily administration of oral selexipag at the maintenance dose after a meal.

**Table 16. Pharmacokinetic parameters of selexipag and MRE-269 in multiple-dose administration of selexipag at the maintenance dose**

| Time point | Dose per administration (mg) | n | $C_{max}$ (ng/mL) | $t_{max}$[a] (h) | $AUC_{0-t}$ (ng·h/mL) |
|---|---|---|---|---|---|
| Selexipag | | | | | |
| Day 1 | 0.2 | 37 | 2.52 ± 2.74 | 2.5 | 7.57 ± 7.98[b] |
| After administration at maintenance dose (Week 16) | 0.2 | 1 | 1.12 | 2.5 | 2.60 |
| | 0.4 | 2 | 3.33 | 2.5 | 7.91 |
| | 0.6 | 5 | 4.73 ± 6.28 | 2.5 | 16.0 ± 13.3[c] |
| | 0.8 | 6 | 8.84 ± 5.03 | 2.5 | 33.7 ± 24.6[d] |
| | 1.0 | 6 | 6.67 ± 3.44 | 3.25 | 27.3 ± 13.4 |
| | 1.2 | 3 | 12.5 ± 5.8 | 2.5 | 44.1[e] |
| | 1.4 | 2 | 10.3 | 4.0 | 37.7 |
| | 1.6 | 7 | 16.9 ± 6.8 | 2.5 | 54.0 ± 21.3 |
| MRE-269 | | | | | |
| Day 1 | 0.2 | 37 | 2.81 ± 1.29 | 2.5 | 11.6 ± 4.9[b] |
| After administration at maintenance dose (Week 16) | 0.2 | 1 | 3.17 | 4.0 | 14.3 |
| | 0.4 | 2 | 11.7 | 2.5 | 37.7 |
| | 0.6 | 5 | 8.15 ± 5.59 | 2.5 | 35.5 ± 22.5 |
| | 0.8 | 7 | 13.8 ± 9.0 | 2.5 | 59.3 ± 43.2[f] |
| | 1.0 | 6 | 12.7 ± 6.1 | 2.5 | 65.8 ± 40.7 |
| | 1.2 | 3 | 19.7 ± 10.6 | 4.0 | 86.8 ± 40.8 |
| | 1.4 | 2 | 21.7 | 4.0 | 111 |
| | 1.6 | 7 | 28.8 ± 14.8 | 2.5 | 136 ± 73 |

[a] Median, [b] n = 36, [c] n= 4, [d] n = 5, [e] n = 2, [f] n = 6

#### 6.2.3.2 Foreign phase II study (Study NS-304/-02, CTD 5.3.5.1-1)

Selexipag was administered to 33 non-Japanese patients with PAH at the starting dose of 0.2 mg per administration, which was up-titrated (not above 0.8 mg) to determine the maintenance dose for each patient before Day 35 (the maintenance dose administered from Week 13 to Week 17). Table 17 shows the pharmacokinetic parameters of selexipag and MRE-269 following twice daily administration of oral selexipag at the maintenance dose after a meal.

**Table 17. Pharmacokinetic parameters of selexipag and MRE-269 in multiple-dose administration of selexipag at the maintenance dose**

| Dose per administration (mg) | n | Time point (Week) | $C_{max}$ (ng/mL) | $t_{max}$[a] (h) | $AUC_{0\text{-}8h}$ (ng·h/mL) |
|---|---|---|---|---|---|
| Selexipag | | | | | |
| 0.2 | 2 | 5 | 0.74 | 2.5 | 2.4 |
| | 1 | 17 | 0.84 | 2.5 | 2.4 |
| 0.4 | 4 | 5 | 3.2 ± 1.0 | 2.5 | 8.8 ± 3.0 |
| | 4 | 17 | 4.4 ± 3.4 | 2.5 | 11.4 ± 9.0 |
| 0.6 | 7 | 5 | 12.5 ± 10.1 | 2.5 | 36.5 ± 27.4 |
| | 7 | 17 | 6.9 ± 7.5 | 2.5 | 17.9 ± 17.5 |
| 0.8 | 8 | 5 | 5.5 ± 4.0 | 2.5 | 14.2 ± 10.9 |
| | 7 | 17 | 7.9 ± 8.4 | 2.5 | 20.1 ± 21.2 |
| MRE-269 | | | | | |
| 0.2 | 2 | 5 | 3.5 | 3.2 | 18.3 |
| | 1 | 17 | 3.3 | 2.5 | 16.5 |
| 0.4 | 4 | 5 | 13.7 ± 9.6 | 2.5 | 71.7 ± 60.4 |
| | 4 | 17 | 16.7 ± 18.0 | 2.5 | 80.7 ± 89.8 |
| 0.6 | 7 | 5 | 17.0 ± 7.6 | 4 | 76.8 ± 34.7 |
| | 7 | 17 | 10.8 ± 5.4 | 2.5 | 50.1 ± 25.5 |
| 0.8 | 8 | 5 | 12.0 ± 3.8 | 2.5 | 50.4 ± 24.6 |
| | 7 | 17 | 13.9 ± 6.3 | 2.5 | 55.5 ± 27.4 |

[a] Median

### 6.2.4 PPK analysis (CTD 5.3.3.5-2)

The population pharmacokinetic (PPK) analysis was conducted using the plasma selexipag and MRE-269 concentration data obtained from 512 patients with PAH at 2398 time points in the foreign phase III study (Study AC-065A302). PK of selexipag was described by a 2-compartment model of selexipag that included absorption lag time, first-order absorption and elimination processes, and the rate constant of the primary metabolism to MRE-269 and by a 2-compartment model of MRE-269 with the first order elimination process.

Candidate covariates of pharmacokinetic parameters ($V_p/F$, $V_m/F$, CL/F, $k_{met}$, $k_m$, and $k_a$) were age, sex, body weight, race/ethnicity, creatinine clearance, hepatic function parameters (aspartate aminotransferase [AST], ALT, and total bilirubin), concomitant PAH drugs, NYHA/WHO functional class, concomitant digoxin, and concomitant CYP3A4 and CYP2C8 inhibitors. In the final PPK model, the following parameters were selected as the covariates with a significant effect: Body weight for $V_p$ and $V_m$, body weight and total bilirubin for CL, and sex and concomitant PAH drugs for $k_m$.

### 6.2.5 Studies of intrinsic factors

#### 6.2.5.1 Effect of age (Study NS304/P1/01, CTD 5.3.3.1-1)

Six Japanese healthy elderly subjects (65-74 years old) received oral selexipag (0.2 mg) as a single dose in the fasted state. Another 6 Japanese healthy elderly subjects (67-74 years old) received oral selexipag (0.4 mg) after a meal once daily on Days 1 and 10 and twice daily from Day 3 to Day 9. Table 18 shows the pharmacokinetic parameters of selexipag and MRE-269. The pharmacokinetic parameters of selexipag and MRE-269 in these healthy elderly subjects were similar to those in healthy younger adults receiving oral selexipag (0.4 mg) twice daily after a meal [see “6.2.2.1 Single-dose and multiple-dose studies in Japanese healthy adults”].

**Table 18. Pharmacokinetic parameters of selexipag and MRE-269 in single- and multiple-dose administration of selexipag to elderly subjects**

| | Dose per administration (mg) | Time point (Day) | n | $C_{max}$ (ng/mL) | $t_{max}$[a] (h) | $t_{1/2}$ (h) | AUC[b] (ng·h/mL) |
|---|---|---|---|---|---|---|---|
| Selexipag | | | | | | | |
| Single dose (fasted) | 0.2 | - | 6 | 5.71 ± 1.09 | 1 | 0.875 ± 0.117 | 11.5 ± 2.0 |
| Multiple dose (after a meal) | 0.4 | 1 | 6 | 7.75 ± 1.59 | 1.25 | 0.971 ± 0.271 | 20.5 ± 7.0 |
| | | 10 | 6 | 7.17 ± 3.21 | 1.75 | 1.01 ± 0.20 | 18.1 ± 7.4 |
| MRE-269 | | | | | | | |
| Single dose (fasted) | 0.2 | - | 6 | 5.44 ± 0.90 | 2.5 | 6.73 ± 2.06 | 32.1 ± 7.2 |
| Multiple dose (after a meal) | 0.4 | 1 | 6 | 7.79 ± 2.32 | 3.5 | 6.88 ± 1.24 | 44.0 ± 16.5 |
| | | 10 | 6 | 8.65 ± 1.61 | 4 | 12.3 ± 6.2 | 50.2 ± 13.4 |

[a] Median; [b] $AUC_{0-\infty}$ in single-dose administration, $AUC_{0-12h}$ in multiple-dose administration

### 6.2.5.2 Study on subjects with hepatic impairment (Study AC-065-104, CTD 5.3.3.3-1)

A single oral dose of selexipag was administered after a meal to non-Japanese subjects: 8 with normal hepatic function, 8 with mild hepatic impairment (Child-Pugh score: 5-6), and 8 with moderate hepatic impairment (Child-Pugh score: 7-9) received 0.4 mg; and 2 with severe hepatic impairment (Child-Pugh score: 10-15) received 0.2 mg. Table 19 shows the pharmacokinetic parameters of selexipag and MRE-269. One of the 2 subjects with severe hepatic impairment experienced Grade 3 hepatic encephalopathy on Day 2 of administration. A causal relationship to the study drug could not be ruled out for the event. Both subjects with severe hepatic impairment therefore discontinued treatment.

**Table 19. Pharmacokinetic parameters in subjects receiving selexipag who had normal hepatic function or hepatic impairment**

| | Dose (mg) | n | $C_{max}$ (ng/mL) | $t_{max}$[a] (h) | $t_{1/2}$ (h) | $AUC_{0-\infty}$ (ng·h/mL) | Cu/C (%) |
|---|---|---|---|---|---|---|---|
| Selexipag | | | | | | | |
| Normal hepatic function | 0.4 | 8 | 1.9 [1.5, 2.4] | 1 | 1.1 [0.8, 1.4] | 5.3 [4.5, 6.2] | 0.56 [0.43, 0.74] |
| Mild hepatic impairment | 0.4 | 8 | 3.9 [2.8, 5.3] | 1 | 1.6 [1.3, 2.1] | 10.9 [8.6, 13.8] | 0.55 [0.46, 0.65] |
| Moderate hepatic impairment | 0.4 | 8 | 5.4 [3.9, 7.3] | 2 | 2.2 [1.6, 3.0] | 23.5 [17.0, 32.4] | 0.73 [0.53, 1.02] |
| Severe hepatic impairment | 0.2 | 2 | 2.2 [NA] | 2 | 1.43[b] | 7.91[b] | 1.00 [NA] |
| MRE-269 | | | | | | | |
| Normal hepatic function | 0.4 | 8 | 3.8 [3.0, 5.0] | 4 | 12.6 [9.1, 17.5] | 25.3 [21.9, 29.3] | 0.64 [0.49, 0.84] |
| Mild hepatic impairment | 0.4 | 8 | 4.5 [3.1, 6.7] | 5 | 6.5 [4.9, 8.6] | 29.6 [20.6, 42.6] | 0.63 [0.54, 0.73] |
| Moderate hepatic impairment | 0.4 | 8 | 5.3 [4.6, 6.0] | 6 | 15.9 [10.1, 25.0] | 56.1 [42.8, 73.5] | 0.86 [0.63, 1.18] |
| Severe hepatic impairment | 0.2 | 2 | 2.3 [NA] | 5.5 | 7.3 [NA] | 36.9 [NA] | 1.30 [NA] |

Geometric mean [95% CI]; NA, Not assessable; [a] Median; [b] n = 1

### 6.2.5.3 Study on subjects with renal impairment (Study AC-065-105, CTD 5.3.3.3-2)

A single oral dose of selexipag (0.4 mg) was administered after a meal to 8 non-Japanese subjects with normal renal function (estimated glomerular filtration rate [eGFR] calculated by Modification of Diet in Renal Disease [MDRD], 90-141 mL/min/1.73 $m^3$) and to 8 non-Japanese subjects with severe renal impairment (eGFR, 15-29 mL/min/1.73 $m^3$). Table 20 shows the pharmacokinetic parameters of selexipag and MRE-269.

**Table 20. Pharmacokinetic parameters in subjects receiving selexipag who had normal renal function or severe renal impairment**

| | n | $C_{max}$ (ng/mL) | $t_{max}$[a] (h) | $t_{1/2}$ (h) | $AUC_{0-\infty}$ (ng·h/mL) | Cu/C (%) |
|---|---|---|---|---|---|---|
| Selexipag | | | | | | |
| Normal renal function | 8 | 3.1 [2.1, 4.5] | 1.5 | 1.4 [0.8, 2.2][b] | 9.9 [7.4, 13.2][b] | 0.17 [0.002, 13.9][c] |
| Severe renal impairment | 8 | 5.4 [3.9, 7.4] | 2 | 1.03 [0.71, 1.51][d] | 17.1 [13.4, 21.6][d] | 0.12 [0.04, 0.43][e] |
| MRE-269 | | | | | | |
| Normal renal function | 8 | 5.1 [3.2, 8.2] | 4.5 | 8.3 [7.0, 9.9][e] | 43.7 [14.6, 131][e] | 0.17 [0.12, 0.23][d] |
| Severe renal impairment | 8 | 7.3 [6.1, 8.7] | 4 | 13.4 [7.1, 25.4][f] | 70.6 [29.3, 170][f] | 0.17 [0.11, 0.29] |

Geometric mean [95% CI], [a] Median, [b] n = 6, [c] n = 2, [d] n = 7, [e] n = 5, [f] n = 4

### 6.2.6 Drug interaction studies

#### 6.2.6.1 Warfarin (Study QGUY/2006/NS-304/-01, CTD 5.3.3.1-2)

In a two-treatment, two-period, cross-over study (washout period, ≥7 days), selexipag (0.4 mg) or placebo was administered orally after a meal for 12 days (once daily on Day 1, twice daily from Day 2 to Day 12) to 19 non-Japanese healthy adults. A single oral dose of warfarin (20 mg) was administered concomitantly on Day 8.

The geometric mean ratio [90% CI] (selexipag + warfarin vs warfarin alone) for $C_{max}$ and $AUC_{0-\infty}$ of warfarin was 0.99 [0.95, 1.03] and 1.00 [0.96, 1.03], respectively, for R-warfarin and 1.01 [0.97, 1.06] and 1.02 [0.99, 1.05], respectively, for S-warfarin. The geometric mean ratio [90% CI] (selexipag + warfarin [Day 8] vs selexipag alone [Day 7]) for $C_{max}$ and $AUC_{\tau}$ was 0.94 [0.77, 1.16] and 0.93 [0.86, 1.01], respectively, for selexipag and 0.90 [0.83, 0.99] and 0.97 [0.92, 1.03], respectively, for MRE-269.

Pharmacodynamic parameters of international normalized ratio (INR), APTT, and prothrombin time (PT) showed no clear difference between warfarin monotherapy and combination therapy with warfarin and selexipag.

#### 6.2.6.2 Lopinavir/ritonavir combination tablets (Study AC-065-109, CTD 5.3.3.4-1)

In a two-treatment, two-period, cross-over study (washout period, 14-22 days), 20 non-Japanese healthy adults received (a) selexipag (0.4 mg) orally as a single dose, or (b) lopinavir/ritonavir combination tablets (400 mg/100 mg) orally twice daily for 12 days and a concomitant single oral dose of selexipag (0.4 mg) on Day 10 in the fasted state.

The geometric mean ratio [90% CI] (lopinavir/ritonavir + selexipag vs selexipag alone) for $C_{max}$ and $AUC_{0-\infty}$ was 2.07 [1.66, 2.58] and 2.23 [1.86, 2.69], respectively, for selexipag and 1.33 [1.12, 1.58] and 1.08 [0.91, 1.27], respectively, for MRE-269.

### 6.2.7 QT study (Study AC-065-106, CTD 5.3.4.1-2)

A total of 159 non-Japanese healthy adults received (1) selexipag orally twice daily after a meal at the starting dose of 0.4 mg, which was increased by 0.2 mg increments every 3 days to 1.6 mg, or (2) moxifloxacin (400 mg) or placebo orally after a meal as a single dose followed by multiple-dose administration of selexipag. The effect of these treatment on QT interval was investigated. The effect was evaluated after 3-day administration of selexipag (0.8, 1.6 mg) and after single-dose administration of moxifloxacin.

Table 21 shows the pharmacokinetic parameters of selexipag and MRE-269 on Day 3 of selexipag administration.

**Table 21. Pharmacokinetic parameters of selexipag and MRE-269 in multiple-dose administration of selexipag**

| Dose per administration (mg) | Analyte | n | $C_{max}$ (ng/mL) | $t_{max}$[a] (h) | $AUC_{\tau}$ (ng·h/mL) |
|---|---|---|---|---|---|
| 0.8 | Selexipag | 84 | 8.20 [7.45, 9.03] | 2 | 20.1 [18.3, 22.1] |
| | MRE-269 | 84 | 13.4 [12.3, 14.7] | 4 | 69.3 [63.3, 76.0] |
| 1.6 | Selexipag | 58 | 18.0 [16.0, 20.2] | 2 | 44.0 [39.7, 48.8] |
| | MRE-269 | 58 | 26.9 [24.3, 29.7] | 4 | 138 [124, 154] |

Geometric mean [95% CI], [a] Median

On Day 3 of selexipag (0.8, 1.6 mg) administration, ΔΔQTcI, (i.e., the mean difference from placebo in the change in QTcI [QT interval adjusted for each subject] from baseline) was 1.4 ms (0.8 mg) and -0.7 ms (1.6 mg) at the maximum; the upper limit of 90% CI of ΔΔQTcI interval did not exceed 10 ms at any time point. Similar results were obtained when QTc interval was adjusted by Fridericia correction formula (QTcF). No clear relationship was found between ΔΔQTcI interval and plasma selexipag or MRE-269 concentrations. The mean value [90% CI] of ΔΔQTcI interval after moxifloxacin administration was 7.5 [4.8, 10.2] ms at the maximum, with the lower limit of 90% CI not exceeding 5 ms. The applicant considered that these results were due to the lower-than-expected plasma concentration of moxifloxacin in the study, and thus investigated the relationship between plasma

moxifloxacin concentration and ΔΔQTcI interval. As a result, ΔΔQTcI interval was significantly prolonged with the increase in plasma moxifloxacin concentration. Taking account of this finding, the applicant considered that the study had sufficient analytical sensitivity.

### 6.2.8 Photosafety study (Study AC-065-102, CTD 5.3.4.1-1)

A parallel-group study was conducted to evaluate the photosafety in multiple-dose administration of selexipag. A total of 52 non-Japanese healthy adults (Fitzpatrick skin type II or III) received (a) oral selexipag twice daily after a meal at the starting dose of 0.4 mg, which was increased by 0.2 mg increments every 3 days to a maximum dose of 0.8 or 1.2 mg; or (b) oral placebo twice daily after a meal; or (c) oral ciprofloxacin (positive control) 500 mg once daily after a meal.

As a result, selexipag was judged to be mildly phototoxic when irradiated with UV-A and UV-B. However, the applicant explained that it is possible that this judgment was falsely made due to the presence of many subjects with low sensitivity to irradiation, and that selexipag is unlikely to have clinically significant phototoxicity.

## 6.R Outline of the review conducted by PMDA

### 6.R.1 Food effect

The proposed dosage and administration does not specify the timing of selexipag administration in relation to meals. However, PMDA considers that the dosage and administration should be modified to specify that selexipag should be administered after a meal, for the following reasons:
(a) In the studies on the food effect (Studies NS304/P1/01 and QGUY/2006/NS-304/-01), the exposures ($C_{max}$ and $AUC_{0-\infty}$) to selexipag and MRE-269 tended to be lower in the fed state than in the fasted state, demonstrating the effect of food on the pharmacokinetics of selexipag [see "6.1.2 Food effect"]. (b) Selexipag was shown to be effective and safe in the following studies, all of which required participating patients to receive the drug after a meal: the Japanese phase II study (Study AC-065A201), the foreign phase II study (Study NS-304/-02), and the foreign phase III study (Study AC-065A302), all of which involved patients with PAH.

### 6.R.2 Comparison of pharmacokinetics between Japanese and non-Japanese population

The applicant's explanation on the ethnic difference of the pharmacokinetics of selexipag:
The ethnic difference in the pharmacokinetics of selexipag was investigated based on the results of the Japanese phase I study (Study NS304/P1/01) and the foreign phase I study (Study QGUY/2006/NS-304/-01) in healthy adults. $C_{max}$ and AUC of selexipag were 1.49 to 2.04 times and 1.16 to 2.09 times, respectively, greater in Japanese healthy adults than in non-Japanese healthy adults. $C_{max}$ and AUC of MRE-269 were 1.23 to 2.17 times and 0.97 to 2.01 times, respectively, greater in Japanese healthy adults than in non-Japanese healthy adults. Thus, exposures to selexipag and MRE-269 tended to be higher in Japanese than in non-Japanese subjects (Table 22). Also, PPK analysis showed that body weight is a significant covariate for pharmacokinetic parameters of selexipag and MRE-269 [see "6.2.4 PPK analysis"], and the clinical study data (Studies NS304/P1/01 and QGUY/2006/NS-304/-01) used for the PPK analysis, showed a difference in body weight between Japanese and non-Japanese subjects. Therefore, $C_{max}$ and AUC of selexipag and MRE-269 were adjusted for dose per body weight. The body weight-adjusted $C_{max}$ and AUC of selexipag were 1.09 to 1.79 times and 0.84 to 1.63 times, respectively, greater in Japanese healthy adults than in non-Japanese healthy adults. The body weight-adjusted $C_{max}$ and AUC of MRE-269 were 0.93 to 1.77 times and 0.72 to 1.68 times, respectively, greater in Japanese healthy adults than in non-Japanese healthy adults. Thus, the difference in exposures to selexipag and MRE-269 between Japanese and non-Japanese subjects decreased after the adjustment for body weight. This suggests that, although the Japanese and non-Japanese subjects had different exposure levels due to the body weight difference, the difference in exposure is minor and unlikely to have any clinically significant effect. No parameter other than body weight was identified as a factor that caused the difference in exposures to selexipag and MRE-269 between the Japanese and non-Japanese subjects.

**Table 22. Pharmacokinetic parameters of selexipag and MRE-269 in single- or multiple-dose administration of selexipag**

| Dose per administration (mg) | | n | Japanese | | Non-Japanese | |
|---|---|---|---|---|---|---|
| | | | $C_{max}$ (ng/mL) | AUC[a] (ng·h/mL) | $C_{max}$ (ng/mL) | AUC[a] (ng·h/mL) |
| Selexipag | | | | | | |
| 0.2 | Single dose | 6 | 7.14 ± 3.53 | 15.5 ± 8.7 | 3.79 ± 2.16 | 7.40 ± 3.84 |
| | Multiple dose | 6 | 2.98 ± 0.85 | 6.53 ± 2.36 | 1.99 ± 0.89 | 5.63 ± 1.85 |
| 0.4 | Single dose | 6 | 11.5 ± 3.1 | 20.5 ± 5.5 | 6.50 ± 2.99 | 13.2 ± 5.5 |
| | Multiple dose | 6 | 8.71 ± 0.79 | 17.5 ± 3.5 | 4.27 ± 1.19 | 9.83 ± 1.75 |
| 0.6 | Single dose | 6 | 17.3 ± 4.7 | 38.9 ± 12.3 | 11.6 ± 3.1 | 23.4 ± 3.2 |
| | Multiple dose | 6 | 10.7 ± 3.0 | 24.8 ± 3.7 | 5.47 ± 1.43 | 14.0 ± 2.8 |
| MRE-269 | | | | | | |
| 0.2 | Single dose | 6 | 9.05 ± 5.23 | 54.1 ± 27.7 | 4.18 ± 0.86 | 26.9 ± 5.9 |
| | Multiple dose | 6 | 4.24 ± 0.81 | 22.8 ± 5.8 | 3.45 ± 1.21 | 23.6 ± 8.5 |
| 0.4 | Single dose | 6 | 11.2 ± 2.7 | 70.6 ± 18.1 | 8.89 ± 4.02 | 60.8 ± 36.0 |
| | Multiple dose | 6 | 10.2 ± 1.6 | 60.5 ± 8.0 | 4.92 ± 1.87 | 30.6 ± 10.8 |
| 0.6 | Single dose | 6 | 17.1 ± 3.8 | 124 ± 50 | 12.7 ± 2.5 | 81.7 ± 24.6 |
| | Multiple dose | 6 | 12.4 ± 2.0 | 69.7 ± 12.3 | 8.83 ± 1.45 | 47.6 ± 9.0 |

[a] $AUC_{0-\infty}$ in single-dose administration, $AUC_{0-12h}$ in multiple-dose administration

PMDA's view:
Results of Studies NS304/P1/01 and QGUY/2006/NS-304/-01 showed that the exposures to selexipag and MRE-269 tended to be higher in Japanese than in non-Japanese subjects, and that this tendency remained even after the data were adjusted for dose per body weight. Further, it remains unclear whether factors other than body weight may cause the difference in exposures to selexipag and MRE-269 between Japanese and non-Japanese subjects. Thus, the possibility that the pharmacokinetics of selexipag may differ between Japanese and non-Japanese subjects cannot be ruled out. Appropriateness of using foreign clinical study data to evaluate the efficacy and safety of selexipag in Japanese patients with PAH will be further discussed in "7.R.2 Use of the results of foreign clinical studies," based on the efficacy and safety results in the Japanese phase II study (Study AC-065A201) and the foreign phase II and III studies (Studies NS-304/-02 and AC-065A302, respectively).

### 6.R.3 Administration in patients with hepatic impairment

The applicant's explanation on the administration of selexipag in patients with hepatic impairment:
In the foreign phase I study (Study AC-065-104) in subjects with hepatic impairment, $C_{max}$ and $AUC_{0-\infty}$ of selexipag increased approximately 2-fold in subjects with mild hepatic impairment compared with subjects with normal hepatic function, whereas $C_{max}$ and $AUC_{0-\infty}$ of MRE-269 were similar in both subject groups. Since the agonist activity of selexipag for IP receptors is only approximately 1/37 times that of MRE-269, the pharmacological action of selexipag is exhibited mainly by MRE-269. This suggests that the increase in the exposure to selexipag alone does not pose any clinically significant problem in subjects with mild hepatic impairment. Also, the fractional rate of the unbound selexipag and MRE-269 in plasma in subjects with mild hepatic impairment was similar to that observed in subjects with normal hepatic function. Taking account of these findings, the applicant considers that there is no need to adjust the dose in administering selexipag to patients with mild hepatic impairment.

On the other hand, $C_{max}$ and $AUC_{0-\infty}$ of selexipag in subjects with moderate hepatic impairment were 2.8 and 4.5 times, respectively, higher than those in the subjects with normal hepatic function, and $C_{max}$ and $AUC_{0-\infty}$ of MRE-269 were 1.4 and 2.2 times, respectively, higher. Also, the fractional rate of unbound selexipag and MRE-269 in plasma was approximately 1.3 times higher in subjects with moderate hepatic impairment than in the subjects with normal hepatic function. In Study AC-065-104, the incidence of adverse events was 50.0% (4 of 8) of subjects with moderate hepatic impairment (myalgia in 3 subjects, diarrhoea, feeling cold, and pain in extremity in 1 subject each) and 25.0% (2 of 8) of subjects with normal hepatic function. The events observed in subjects with moderate hepatic impairment were consistent with the known safety profile of selexipag. All events were mild except for moderate diarrhoea observed in 1 subject. Based on the above results, appropriateness of once daily administration of selexipag in patients with moderate hepatic impairment was investigated. $C_{max}$ and AUC of selexipag and MRE-269 at steady state were predicted by simulation for the following 2 dosage regimens: (1) 5-day multiple-dose administration of selexipag (0.4 mg) twice daily in subjects with

normal hepatic function and (2) 5-day multiple-dose administration of selexipag (0.4 mg) once daily in subjects with moderate hepatic impairment. Results showed that $C_{max}$ and AUC of selexipag at steady state were approximately 3 and 2 times, respectively, greater in patients with moderate hepatic impairment than in subjects with normal hepatic function, whereas $C_{max}$ and AUC of MRE-269 were similar in both subject groups. Given that the pharmacological action of selexipag is exhibited mainly by MRE-269, the increase in the exposure to selexipag only in patients with moderate hepatic impairment is unlikely to pose any clinically significant problem. Therefore, the following dosage regimen was appropriate to treat patients with moderate hepatic impairment: The starting dose of selexipag is 0.2 mg administered orally once daily, which is increased by 0.2 mg increments at 7-day intervals to a level not above 1.6 mg once daily.

In Study AC-065-104, the dose of selexipag in subjects with severe hepatic impairment was half of that in the other subjects. This suggests that, in subjects with severe hepatic impairment, exposures to selexipag and MRE-269 will increase to the same extent as observed in subjects with moderate hepatic impairment. In subjects with severe hepatic impairment, the fractional rate of unbound selexipag and MRE-269 in plasma increased approximately 2-fold than those in subjects with normal hepatic function. In Study AC-065-104, Grade 3 hepatic encephalopathy for which a causal relationship to the study drug could not be ruled out was observed in 1 of 2 subjects with severe hepatic impairment on the day after administration. Urinary tract infection was considered to be a possible cause of the hepatic encephalopathy. This event resolved 8 days after administration without sequelae. No selexipag-related adverse event was observed in the other subject. Exposures to selexipag and MRE-269 are expected to increase in patients with severe hepatic impairment, as are the cases with patients with moderate hepatic impairment. Therefore, adjustment in selexipag dose is needed in patients with severe hepatic impairment in the same manner as that in patients with moderate hepatic impairment. The applicant considered it appropriate to provide a caution statement in the package insert that there is only limited use experience of selexipag in patients with severe hepatic impairment.

PMDA's view:
The applicant decided that no dose adjustment of selexipag is required in patients with mild hepatic impairment. This decision is acceptable given the results of Study AC-065-104 in subjects with hepatic impairment and the applicant's explanation. However, higher exposure to selexipag in patients with mild hepatic impairment compared with patients with normal hepatic function may possibly cause adverse events. Healthcare professionals should be advised to administer selexipag with care to patients with mild hepatic impairment.

The applicant explained that once daily administration of selexipag is appropriate for patients with moderate hepatic impairment (who are expected to be more highly exposed to selexipag and MRE-269 compared with patients with normal hepatic function), based on the results of the simulation of plasma selexipag and MRE-269 concentrations. However, no clinical study data are available on the pharmacokinetics, efficacy, or safety of selexipag administered once daily (i.e., the dose adjustment method proposed by the applicant) to patients with moderate hepatic impairment. PMDA cannot conclude that this dose adjustment method is appropriate because it is based solely on the simulation. Thus, the results of Study AC-065-104 should be provided appropriately to healthcare professionals using the package insert, etc., and the following caution statement should be provided: In administering selexipag to patients with moderate hepatic impairment, patient conditions should be closely monitored for possible occurrence of adverse events during the treatment with selexipag, and the dose increase, if deemed appropriate, should be performed carefully.

Study AC-065-104 showed that the total plasma concentration of MRE-269 was similar in subjects with severe hepatic impairment and in those with moderate hepatic impairment. In contrast, the fractional rate of unbound MRE-269 in plasma was higher in subjects with severe hepatic impairment than in subjects with moderate hepatic impairment. This suggests a higher plasma concentration of unbound selexipag in patients with severe hepatic impairment with higher associated risks. Also, enrollment of subjects with severe hepatic impairment was cancelled during Study AC-065-104 for safety reasons [see "6.2.5.2 Study on subjects with hepatic impairment"], and patients with severe hepatic impairment were excluded from Japanese and foreign clinical studies of selexipag; this precludes the safety evaluation in this patient population. Thus, selexipag should be contraindicated in patients with severe hepatic impairment. PMDA will draw a final conclusion regarding the appropriateness of administering

selexipag to patients with severe hepatic impairment, taking account of comments raised in the Expert Discussion.

### 6.R.4 Administration to patients with renal impairment

The foreign phase I study (Study AC-065-105) in subjects with renal impairment showed that exposures to selexipag and MRE-269 increased in subjects with severe renal impairment compared with subjects with normal renal function. PMDA asked the applicant to discuss (a) the necessity of decreasing the starting and maximum doses of selexipag in patients with severe renal impairment and (b) the necessity of providing a caution statement regarding selexipag administration in patients with mild or moderate renal impairment.

The applicant's explanation:
In Study AC-065-105, $C_{max}$ and AUC of selexipag were both approximately 1.7 times higher in subjects with severe renal impairment than in subjects with normal renal function, and $C_{max}$ and AUC of MRE-269 were approximately 1.4 and 1.6 times higher, respectively, in subjects with severe renal impairment than in subjects with normal renal function. The fractional rates of unbound selexipag and MRE-269 in plasma were similar in subjects with severe renal impairment and in subjects with normal renal function. Given that the pharmacological action of selexipag is exhibited mainly by MRE-269, the increased exposure to selexipag observed in subjects with severe renal impairment is unlikely to pose any clinically significant problem. The exposure to MRE-269 increased in subjects with severe renal impairment, but the increase is minor and manageable by confirming the tolerability in individual patients before dose adjustment. The incidence of adverse events in Study AC-065-105 was 62.5% (5 of 8 subjects) both in the subjects with severe renal impairment and subjects with normal renal function, and all events were mild or moderate. The incidence of headache (an adverse event characteristic to selexipag) was 50.0% (4 of 8 subjects) both in subjects with severe renal impairment and subjects with normal renal function. There were no adverse events unique to subjects with severe renal impairment. Thus, the safety profile in subjects with severe renal impairment was not clearly different from subjects with normal renal function, and was consistent with the known safety profile of selexipag.

These results suggest that severe renal impairment is unlikely to have a significant clinical effect on the pharmacokinetics or safety of selexipag. Therefore, the starting or maximum dose of selexipag need not be reduced in patients with severe renal impairment.

In patients with mild or moderate renal impairment, the impairment is unlikely to significantly affect the pharmacokinetics of selexipag, for the following reasons: (1) Renal excretion plays only a minor role in the elimination of selexipag [see "6.2.2.4 Mass balance study"], and (2) In PPK analysis, creatinine clearance was not identified as a significant covariate for the pharmacokinetics of selexipag or MRE-269 [see "6.2.4 PPK analysis"]. Furthermore, comparison was made for the incidences of adverse events between subjects with different severities of renal impairment in the selexipag group (276 subjects with normal renal function, 215 subjects with mild renal impairment, 81 subjects with moderate renal impairment) of the foreign phase III study (Study AC-065A302). The comparison showed no increasing tendency in the incidence of adverse events in patients with mild or moderate renal impairment compared with patients with normal renal function. Thus, it is unnecessary to add any particular caution statement for selexipag administration in patients with mild or moderate renal impairment.

PMDA's view:
The applicant decided that no specific caution statement is required for patients with mild or moderate renal impairment. This decision is appropriate given the results of Study AC-065-105 and the applicant's explanation. Also, PMDA considers it unnecessary to decrease the starting or maximum dose of selexipag in patients with severe renal impairment. However, healthcare professional should be advised, through the package insert etc., to administer selexipag with care to patients with severe renal impairment, for the following reasons: (1) patients with severe renal impairment may have higher exposure to selexipag and MRE-269 than patients with normal renal function, and therefore may experience adverse events; and (2) patients with severe renal impairment were excluded from the Japanese phase II study and the foreign phase III study (both studies involved patients with PAH).

### 6.R.5 Pharmacokinetic interactions

*In vitro* studies have shown that CYP2C8, UGT1A3, and UGT2B7 greatly contribute to the metabolism of selexipag and MRE-269 [see "6.2.1.2.2 Studies on enzymes involved in the metabolism of selexipag and MRE-269"].

The applicant's explanation on the combination of selexipag and the inhibitors or inducers of CYP2C8, UGT1A3, and UGT2B7:

The contribution of CYP2C8, UGT1A3, and UGT2B7 to the metabolic elimination of selexipag and MRE-269 was estimated based on the results of the studies on the metabolism of selexipag and MRE-269 using human liver microsomes. For UGT1A3 and UGT2B7, the combined contribution of the 2 molecular isoforms was estimated. As a result, the rate of contribution of CYP2C8 to the metabolic elimination of selexipag was estimated to be 28%, and the rate of contribution of CYP2C8 and UGT1A3 + UGT2B7 to the metabolic elimination of MRE-269 to be 46% and 42%, respectively. Based on the above estimates, the exposure to selexipag and MRE-269 under complete inhibition of CYP2C8 or UGT1A3 + UGT2B7-mediated metabolism of selexipag and MRE-269 was predicted. Results showed that, if CYP2C8 were inhibited, the exposure to selexipag and MRE-269 would increase 1.4- and 2.6-fold, respectively. If both UGT1A3 and UGT2B7 were inhibited, the exposure to selexipag would remain unchanged whereas the exposure to MRE-269 would increase 1.7-fold. In a similar manner, the applicant predicted the exposure to selexipag and MRE-269 under 5-fold increase in the hepatic intrinsic clearance of selexipag and MRE-269, caused by CYP2C8 or UGT1A3 + UGT2B7 induced by respective inducers. Results are as follows: (a) exposure to selexipag and MRE-269 with the CYP2C8 induction would be 0.47 and 0.17 times, respectively, that without the induction; (b) selexipag exposure would remain unchanged irrespective of the UGT1A3 + UGT2B7 induction, but MRE-269 exposure with the UGT1A3 + UGT2B7 induction would be 0.37 times that without the induction. These results suggest that concomitant use of inhibitors or inducers of CYP2C8, UGT1A3, and UGT2B7 may affect the exposure to selexipag. In the Japanese and foreign clinical studies, selexipag was used in combination with a CYP2C8 inhibitor teriflunomide (1 subject), a UGT inhibitor sodium valproate (7 subjects), or a CYP2C8/UGT inducer rifampicin (1 subject). Concomitant use of these drugs did not have any clear effect on the efficacy or safety in those subjects. However, since the clinical data provide only limited information on the concomitant use of these drugs, a caution statement should be provided regarding concomitant use of selexipag with inhibitors or inducers of CYP2C8, UGT1A3, and UGT2B7.

PMDA's view:

In light of the explanation of the applicant on the contribution of CYP2C8, UGT1A3, and UGT2B7 to the metabolic elimination of selexipag and MRE-269, concomitant use of inhibitors or inducers of these metabolic enzymes may affect the pharmacokinetics of selexipag. Taking account of the limited information available on the concomitant use with selexipag in clinical studies, the applicant's proposal to add a caution statement for concomitant use with inhibitors or inducers of CYP2C8, UGT1A3, and UGT2B7 is appropriate.

## 7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted evaluation data from 13 clinical studies (1 each of Japanese phase I and II studies, 9 foreign phase I studies, and 1 each of foreign phase II and phase III studies) [for pharmacokinetics, see "6. Biopharmaceutic studies and associated analytical methods, clinical pharmacology study data, and outline of the Review Conducted by PMDA"]. Main study results are described below.

### 7.1 Phase I studies

#### 7.1.1 Japanese phase I study (Study NS304/P1/01; CTD 5.3.3.1-1; study period, [redacted] 20[redacted] to [redacted] 20[redacted])

A randomized, double-blind study in Japanese healthy adults (36 in the selexipag group, 12 in the placebo group) and healthy elderly subjects (12 in the selexipag group, 4 in the placebo group) was conducted, to investigate the safety and pharmacokinetics of selexipag in single-dose and multiple-dose administration at a single study site in Japan. In the single-dose study, the study drug was administered orally as a single dose in the fasted state or after breakfast. In the multiple-dose administration study, the study drug was administered orally after breakfast on Day 1, after breakfast and after dinner on Day

3 to Day 9, and after breakfast on Day 10. In the 0.6 mg group of the multiple-dose study, the dose per administration was 0.4 mg from Day 1 to Day 4 and 0.6 mg from Day 5 to Day 12. All of 64 randomized subjects (48 in the selexipag group, 16 in the placebo group) received the study drug and were included in the safety analysis set.

The incidences of adverse events are shown in Table 23 (single-dose administration) and Table 24 (multiple-dose administration).

**Table 23. Main adverse events in single-dose administration of selexipag to Japanese healthy adult/elderly subjects (safety analysis set)**

| | Healthy adults | | | | | | Elderly subjects | |
|---|---|---|---|---|---|---|---|---|
| | Fasted | | | | Fed | | Fasted | |
| | Placebo | 0.2 mg | 0.4 mg | 0.6 mg | Placebo | 0.4 mg | Placebo | 0.2 mg |
| Number of subjects | 6 | 6 | 6 | 6 | 2 | 4 | 2 | 6 |
| Adverse events | 33.3 (2) | 50.0 (3) | 66.7 (4) | 83.3 (5) | 50.0 (1) | 50.0 (2) | 0 (0) | 50.0 (3) |
| Headache | 0 (0) | 16.7 (1) | 50.0 (3) | 66.7 (4) | 0 (0) | 25.0 (1) | 0 (0) | 16.7 (1) |
| Nausea | 0 (0) | 16.7 (1) | 16.7 (1) | 83.3 (5) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Vomiting | 0 (0) | 16.7 (1) | 16.7 (1) | 50.0 (3) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Diarrhoea | 0 (0) | 0 (0) | 0 (0) | 33.3 (2) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Adverse events for which a causal relationship to the study drug could not be ruled out | 0 (0) | 16.7 (1) | 50.0 (3) | 83.3 (5) | 0 (0) | 25.0 (1) | 0 (0) | 16.7 (1) |
| Headache | 0 (0) | 16.7 (1) | 50.0 (3) | 66.7 (4) | 0 (0) | 25.0 (1) | 0 (0) | 16.7 (1) |
| Nausea | 0 (0) | 0 (0) | 16.7 (1) | 83.3 (5) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Diarrhoea | 0 (0) | 0 (0) | 0 (0) | 33.3 (2) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Vomiting | 0 (0) | 0 (0) | 16.7 (1) | 50.0 (3) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |

Adverse events reported by ≥2 subjects in any group
% (n)

**Table 24. Main adverse events in multiple-dose administration of selexipag to Japanese healthy adult/ elderly subjects (safety analysis set)**

| | Healthy adults | | | | Elderly subjects | |
|---|---|---|---|---|---|---|
| | Placebo | 0.2 mg | 0.4 mg | 0.6 mg | Placebo | 0.4 mg |
| Number of subjects | 6 | 6 | 6 | 6 | 2 | 6 |
| Adverse events | 0 (0) | 33.3 (2) | 100 (6) | 66.7 (4) | 50.0 (1) | 83.3 (5) |
| Headache | 0 (0) | 0 (0) | 16.7 (1) | 50.0 (3) | 50.0 (1) | 66.7 (4) |
| Tension headache | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 33.3 (2) |
| Diarrhoea | 0 (0) | 0 (0) | 33.3 (2) | 33.3 (2) | 0 (0) | 50.0 (3) |
| Arthralgia | 0 (0) | 0 (0) | 100.0 (6) | 50.0 (3) | 0 (0) | 83.3 (5) |
| Myalgia | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 33.3 (2) |
| ALT increased | 0 (0) | 33.3 (2) | 0 (0) | 16.7 (1) | 0 (0) | 0 (0) |
| Adverse events for which a causal relationship to the study drug could not be ruled out | 0 (0) | 33.3 (2) | 100.0 (6) | 66.7 (4) | 50.0 (1) | 83.3 (5) |
| Headache | 0 (0) | 0 (0) | 16.7 (1) | 50.0 (3) | 50.0 (1) | 66.7 (4) |
| Diarrhoea | 0 (0) | 0 (0) | 33.3 (2) | 33.3 (2) | 0 (0) | 50.0 (3) |
| Arthralgia | 0 (0) | 0 (0) | 100.0 (6) | 50.0 (3) | 0 (0) | 83.3 (5) |
| Myalgia | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 33.3 (2) |

Adverse events reported by ≥2 subjects in any group
% (n)

Neither death nor serious adverse events were reported.

Adverse events leading to discontinuation were reported by 1 subject in the selexipag 0.4 mg group of the single-dose administration study (blood CK increased/blood lactate dehydrogenase [LDH] increased), but their causal relationship to the study drug was ruled out.

## 7.2 Phase II studies

### 7.2.1 Japanese phase II study (Study AC-065A201; CTD 5.3.5.2-1; study period, ongoing since[redacted] 20[redacted]; data cut-off, [redacted] [redacted], 20[redacted])

An open-label, uncontrolled study was conducted to investigate the efficacy, safety, and pharmacokinetics of selexipag in patients with PAH (target sample size, 30 subjects) at 26 study sites in Japan.

The treatment period consisted of a dose titration period from the start of administration to Week 12, a dose maintenance period from Week 12 to Week 16, and a long-term treatment period from Week 16 on. During all of these periods, selexipag was administered orally twice daily after a meal. During the dose titration period, the starting dose of selexipag was 0.2 mg and, if there was no tolerability problem after administration for ≥3 days at the same dose, the dose was increased by 0.2 mg increments. After the dose was increased to ≥0.8 mg, the same dose was administered for ≥7 days. If there was no tolerability problem, the dose was increased again by 0.2 mg increments to a maximum of 1.6 mg/dose whenever possible. In the long-term treatment period, selexipag therapy was continued at the dose used during the dose maintenance period (Week 12-16), and the dose could be adjusted at the discretion of the investigator (or subinvestigator) but not above 1.6 mg per administration.

The main inclusion criteria were ≥18-year-old patients with idiopathic pulmonary arterial hypertension (IPAH), heritable pulmonary arterial hypertension (HPAH), drug- or toxin-induced pulmonary hypertension, or PAH associated with connective tissue disease, congenital heart disease, or human immunodeficiency virus (HIV) infection who met the following criteria.

- WHO functional class I to IV
- Diagnosis of PAH meeting the following criteria by right heart catheterization
  - Mean pulmonary artery pressure (mPAP) ≥25 mmHg
  - Pulmonary capillary wedge pressure (PCWP) or left ventricular end-diastolic pressure <15 mmHg
- Baseline pulmonary vascular resistance (PVR) by right heart catheterization >400 dyn·sec·cm$^{-5}$

In patients using selexipag in combination with endothelin receptor antagonist (ERA), phosphodiesterase type 5 (PDE-5) inhibitors, or calcium blockers, the concomitant drugs were administered at a constant dose from ≥90 days before the start of study treatment and throughout the treatment period. Administration of $PGI_2$ preparation was prohibited from ≥4 weeks before the start of study treatment, and administration of beraprost sodium was prohibited from ≥1 week before the start of study treatment.

All of 37 subjects treated with the study drug were included in the safety analysis set, and 33 subjects (excluding 4 subjects without PVR data on Week 16) were included in per-protocol set (PPS) and in the primary efficacy analysis set. Four subjects discontinued the study at or before Week 16, for the following reasons: new administration of a restricted concomitant drug (1 subject), a serious adverse event (1 subject), administration of a prohibited concomitant drug (1 subject), and consent withdrawal (1 subject). Baseline WHO functional class of subjects in the safety analysis set was class I in 2 subjects, class II in 21 subjects, and class III in 14 subjects. No class IV subject was enrolled.

The mean daily dose of selexipag was 1.8 ± 0.89 mg/day (mean ± SD). The daily dose at the cut-off date (Week 136 at the maximum) was 2.1 ± 0.89 mg/day. The distribution of the maintenance dose (per administration) was 0.2 mg in 5.4% (2 of 37) of subjects, 0.4 mg in 5.4% (2 of 37) of subjects, 0.6 mg in 13.5% (5 of 37) of subjects, 0.8 mg in 18.9% (7 of 37) of subjects, 1.0 mg in 16.2% (6 of 37) of subjects, 1.2 mg in 8.1% (3 of 37) of subjects, 1.4 mg in 5.4% (2 of 37) of subjects, and 1.6 mg in 18.9% (7 of 37) of subjects.

(a) Efficacy evaluation period

Table 25 shows the change in PVR from baseline to Week 16 (the primary efficacy endpoint) and the change in pulmonary vascular resistance index (PVRI) from baseline to Week 16 (a secondary endpoint).

**Table 25. Changes in PVR and PVRI from baseline to Week 16 (PPS)**

| | PVR ($dyn \cdot sec \cdot cm^{-5}$) (n = 33) | PVRI ($dyn \cdot sec \cdot cm^{-5} \cdot m^2$) (n = 33) |
|---|---|---|
| Baseline | | |
| Mean ± SD | 683.2 ± 237.3 | 1076.7 ± 390.5 |
| Median | 671.8 | 1020.9 |
| Week 16 | | |
| Mean ± SD | 560.3 ± 238.7 | 881.9 ± 405.2 |
| Median | 491.4 | 825.3 |
| Change | | |
| Mean ± SD | -122.9 ± 115.2 | -194.9 ± 182.6 |
| Median | -120.9 | -185.2 |
| *P* value[a] | <0.0001 | - |

[a] Wilcoxon signed rank test

Six-minute walk distance (6MWD) (mean ± SD and median), a secondary endpoint, was as follows:
445.0 ± 102.2 m (mean) and 460.5 m (median) in 30 subjects at baseline;
459.1 ± 112.8 m (mean) and 468.0 m (median) in 30 subjects at Week 16.
6MWD increased by 14.1 ± 44.1 m (mean) and 19.5 m (median) from baseline to Week 16.

Adverse events were reported in 97.3% (36 of 37) of subjects during the efficacy evaluation period. Adverse events reported by ≥10 subjects were headache (24 subjects), diarrhoea (17 subjects), pain in jaw (16 subjects), and nausea (13 subjects).

Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 94.6% (35 of 37) of subjects. Adverse events reported by ≥10 subjects were headache (23 subjects), diarrhoea and pain in jaw (16 subjects each), and nausea (11 subjects).

No death occurred. Other serious adverse events were reported by 4 subjects (vomiting, pulmonary arterial hypertension, hypoxia, and blood pressure decreased in 1 subject each). A causal relationship to the study drug could not be ruled out for vomiting, hypoxia, and blood pressure decreased. The outcome of these events were "recovered/resolved."

An adverse event leading to treatment discontinuation (blood pressure decreased) was observed in 1 subject, and its causal relationship to the study drug could not be ruled out.

(b) Long term administration period
The change in 6MWD from baseline (mean ± SD and median) was as follows:
8.8 ± 46.2 m (mean) and 14.0 m (median) in 29 subjects at Week 24;
15.2 ± 33.4 m (mean) and 17.0 m (median) in 25 subjects at Week 48;
30.7 ± 51.0 m (mean) and 37.0 m (median) in 21 subjects at Week 72;
38.0 ± 49.1 m (mean) and 37.0 m (median) in 10 subjects at Week 96;
61.8 ± 85.8 m (mean) and 61.5 m (median) in 4 subjects at Week 120.

Adverse events were reported in 100% (37 of 37) of subjects, and adverse events reported by ≥10 subjects were headache (29 subjects), diarrhoea and nasopharyngitis (19 subjects each), pain in jaw (17 subjects), nausea (16 subjects), and flushing (12 subjects).

Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 100% (37 of 37) of subjects, and adverse events reported by ≥10 subjects were headache (27 subjects), diarrhoea and pain in jaw (17 subjects each), nausea (14 subjects), and flushing (12 subjects).

Death occurred in 2 subjects (both due to right ventricular failure), and a causal relationship to the study drug could not be ruled out for the death of one of them. Other serious adverse events were observed in 11 subjects (pulmonary arterial hypertension; right ventricular failure; thyroglossal cyst; colitis ulcerative; osteonecrosis; biliary colic/adenocarcinoma of colon/bile duct stone/varices oesophageal; dizziness/pulmonary arterial hypertension; dyspnoea/right ventricular failure; chest discomfort;

pneumonia influenza; and herpes zoster in 1 subject each). A causal relationship to the study drug could not be ruled out for dizziness and chest discomfort; the outcome of both events was "recovered/resolved."

Adverse events leading to treatment discontinuation were observed in 8 subjects (pulmonary arterial hypertension in 5 subjects, right ventricular failure in 2 subjects, systemic lupus erythematosus in 1 subject), but their causal relationship to the study drug was ruled out except for 1 subject of right ventricular failure.

### 7.2.2 Foreign phase II study (Study NS-304/-02; CTD 5.3.5.1-1; study period, April 2008 to June 2009)

An open-label, uncontrolled study (acute hemodynamic study) was conducted to investigate the pharmacodynamics, safety, and tolerability of a single-dose administration of selexipag in patients with PAH at 7 study sites overseas, and a subsequent randomized, double-blind, placebo-controlled, parallel-group study was conducted to investigate the efficacy, safety, and pharmacokinetics of multiple-dose administration of selexipag at the same 7 study sites (target sample size, 44 subjects [33 in the selexipag group, 11 in the placebo group]).

In the open-label, uncontrolled study, a single dose of selexipag (0.2 mg) was administered to the first 12 subjects, to evaluate the safety. Based on the safety evaluation in these 12 subjects, a single dose of selexipag (0.4 mg) was administered to the remaining subjects.

In the double-blind period (17 weeks starting from the day after the last day of the acute hemodynamic study), selexipag or placebo was administered orally twice daily after a meal. The starting dose of selexipag was 0.2 mg per administration, which was increased by 0.2 mg increments if the drug was well tolerated in the subject, to the final optimal dose by Day 35. The dose of 0.4 mg per administration was started on Day 3 or later, 0.6 mg on Day 7 or later, and 0.8 mg on Day 21 or later (the maximum dose, 0.8 mg per administration). The final optimal dose was maintained until the end of study. If there was a tolerability problem, the dose could be decreased at the discretion of the investigator (or subinvestigator), but the dose was not changed from Week 13 on.

The main inclusion criteria were ≥18-year-old patients with IPAH, familial PAH, or PAH associated with collagen-vascular disease, repaired congenital shunt disease, or use of anorectic agents who met the following criteria.

- WHO functional class I to III
- Symptomatic PAH despite treatment with anticoagulants, calcium blockers, diuretics, cardiotonics, oxygen inhalation, ERAs, and/or PDE-5 inhibitors
- Diagnosis of PAH meeting the following criteria by right heart catheterization.
  - mPAP >25 mmHg
  - PVR >240 dyn·sec·cm$^{-5}$
  - PCWP or left ventricular end-diastolic pressure <15 mmHg
- Baseline PVR by right heart catheterization >400 dyn·sec·cm$^{-5}$
- 6MWD at screening and at baseline was 150 to 500 m despite other PAH treatments, and the difference of the results at the 2 time points was ≤15%.

Patients were required to receive concomitant ERA and/or PDE-5 inhibitor. These drugs were administered at a constant dose from screening until the end of the double-blind period, except during a temporary withdrawal or dose reduction due to study drug-related adverse events (liver function test abnormal, retinopathy, and visual disturbance) during the baseline period. Administration of $PGI_2$ preparation was prohibited from ≥3 months before the screening.

All of 43 randomized subjects (33 in the selexipag group, 10 in the placebo group) received the study drug, and all of them were included in the safety analysis set and the all-treated DB set. Of the 43 subjects, 35 (29 in the selexipag group, 6 in the placebo group) were included in the per-protocol DB set and in the primary efficacy analysis set during the double-blind period. (The remaining 8 subjects were excluded because of inclusion criteria violation or lack of baseline PVR data [4 subjects each in

the selexipag group and the placebo group].) Of the 35 subjects, 33 (11 in the selexipag 0.2 mg group, 22 in the selexipag 0.4 mg group) were included in the per-protocol HD set and in the primary efficacy analysis set for acute hemodynamic study. (The remaining 2 subjects were excluded because of lack of PVR data at 4 hours after single-dose administration of selexipag [1 subject each in the selexipag 0.2 mg group and in the selexipag 0.4 mg group].) No subjects discontinued the study during the acute hemodynamic study. During the double-blind period, 3 subjects discontinued the study because of hospitalization due to aggravation of PAH (1 subject each in the selexipag group and in the placebo group) and an adverse event (1 subject in the selexipag group). Baseline WHO functional class of subjects in the safety analysis set was class II in 17 subjects (15 in the selexipag group, 2 in the placebo group), and class III in 26 subjects (18 in the selexipag group, 8 in the placebo group). No patients with class I or IV were enrolled.

(a) Acute hemodynamic study

Table 26 shows changes in PVR from baseline to 4 hours after a single-dose administration of selexipag, the primary efficacy endpoint.

**Table 26. Change from baseline in PVR (dyn·sec·cm$^{-5}$) at 4 hours after single-dose administration (per-protocol HD set)**

| | Selexipag 0.2 mg (n = 11) | Selexipag 0.4 mg (n = 22) |
|---|---|---|
| Baseline | | |
| Mean ± SD | 883.6 ± 369.4 | 895.8 ± 352.5 |
| Median | 751.0 | 836.5 |
| After 4 hours | | |
| Mean ± SD | 1025.0 ± 478.4 | 921.7 ± 350.0 |
| Median | 978.0 | 921.0 |
| Change | | |
| Mean ± SD | 141.4 ± 184.2 | 25.9 ± 163.2 |
| Median | 75.0 | 46.5 |

The incidence of adverse events was 66.7% (8 of 12) of subjects in the selexipag 0.2 mg group and 54.8% (17 of 31) of subjects in the 0.4 mg group. Adverse events reported by ≥20% of subjects in either group were headache (58.3%, 41.9%) and pain in extremity (25.0%, 0%).

Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 66.7% (8 of 12) of subjects in the selexipag 0.2 mg group and in 51.6% (16 of 31) of subjects in the 0.4 mg group. Adverse events reported by ≥20% of subjects in either group for which a causal relationship to the study drug could not be ruled out were headache (58.3%, 38.7%) and pain in extremity (25.0%, 0%).

Neither death nor other serious adverse events were observed. An adverse event leading to treatment discontinuation was observed in 1 subject in the selexipag 0.4 mg group (headache). A causal relationship to the study drug could not be ruled out for the headache. The outcome was "recovered/resolved."

(b) Double-blind period

The distribution of the maintenance dose (dose per administration from Week 13 to Week 17) in the selexipag group was 0.2 mg in 12.1% (4 of 33) of subjects, 0.4 mg in 18.2% (6 of 33) of subjects, 0.6 mg in 21.2% (7 of 33) of subjects, and 0.8 mg in 42.4% (14 of 33) of subjects.

Table 27 shows the change in PVR from baseline to Week 17, the primary efficacy endpoint.

**Table 27. Change from baseline in PVR (dyn·sec·cm$^{-5}$) at Week 17 (per-protocol DB set)**

| | Selexipag (n = 29) | Placebo (n = 6) |
|---|---|---|
| Baseline | | |
| Mean ± SD | 951.9 ± 434.5 | 826.8 ± 195.8 |
| Median | 832.0 | 844.0 |
| At Week 17 | | |
| Mean ± SD | 783.8 ± 393.2 | 964.0 ± 247.9 |
| Median | 692.0 | 985.0 |
| Change | | |
| Mean ± SD | -168.1 ± 241.6 | 137.2 ± 84.9 |
| Median | -166.0 | 124.0 |
| *P* value[a] | 0.0045 | - |

[a] Wilcoxon rank sum test
Last observation carry-forward (LOCF) (Missing value, if any, was imputed by the immediately preceding value.)

6MWD (mean ± SD and median), a secondary endpoint, was as follows:
394.7 ± 72.0 m (mean) and 409.5 m (median) in 32 subjects receiving selexipag at baseline;
350.3 ± 123.5 m (mean) and 390.5 m (median) in 10 subjects receiving placebo at baseline;
419.3 ± 106.3 m (mean) and 407.5 m (median) in 32 subjects receiving selexipag at Week 17;
350.7 ± 139.6 m (mean) and 378.5 m (median) in 10 subjects receiving placebo at Week 17.
6MWD increased by 24.7 ± 72.8 m (mean) and 25.0 m (median) in 32 subjects receiving selexipag, and by 0.4 ± 28.1 m (mean) and 6.0 m (median) in 10 subjects receiving placebo, from baseline to Week 17.

The incidence of adverse events was 93.9% (31 of 33) of subjects in the selexipag group and 100.0% (10 of 10) of subjects in the placebo group. Table 28 shows adverse events reported by ≥20% of subjects in either group.

**Table 28. Adverse events reported by ≥20% of subjects in either group (safety analysis set)**

| | Selexipag (N = 33) | Placebo (N = 10) |
|---|---|---|
| Headache | 66.7 (22) | 20.0 (2) |
| Pain in jaw | 36.4 (12) | 0 (0) |
| Pain in extremity | 30.3 (10) | 0 (0) |
| Nausea | 27.3 (9) | 0 (0) |
| Nasopharyngitis | 24.2 (8) | 20.0 (2) |
| Pulmonary arterial hypertension | 3.0 (1) | 20.0 (2) |
| Syncope | 0 (0) | 20.0 (2) |
| Musculoskeletal pain | 0 (0) | 20.0 (2) |

% (n)

Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 90.9% (30 of 33) of subjects in the selexipag group and in 30.0% (3 of 10) of subjects in the placebo group. Adverse events reported by ≥20% of subjects in either group for which a causal relationship to the study drug could not be ruled out were headache (66.7%, 20.0%), pain in jaw (36.4%, 0%), pain in extremity (30.3%, 0%), and nausea (24.2%, 0%).

No death occurred. Other serious adverse events were observed in 18.2% (6 of 33) of subjects and 40.0% (4 of 10) of subjects. The serious adverse event reported by ≥2 subjects in either group was headache (6.1%, 0%). Serious adverse events for which a causal relationship to the study drug could not be ruled out were headache (2 subjects, 0 subjects), nausea, vomiting, myalgia, dyspnoea, and chest pain (1 subject each, 0 subjects). Only headache (1 subject in the selexipag group) remained “not recovered/not resolved.”

Adverse events leading to treatment discontinuation were observed in 1 subject in the selexipag group (asthenia/myalgia) and in 2 subjects in the placebo group (pulmonary arterial hypertension/dyspnoea and pulmonary arterial hypertension in 1 subject each). A causal relationship to the study drug could not be ruled out for asthenia/myalgia, and only myalgia remained “not recovered/not resolved.”

## 7.3 Phase III studies

### 7.3.1 Foreign phase III studies (Study AC-065A302; CTD 5.3.5.1-2; study period, December 2009 to April 2014) and extension study (Study AC-065A303; CTD 5.3.5.1-2; study period, ongoing since [redacted] 20[redacted]; data cut-off, [redacted] [redacted], 20[redacted])

A randomized, placebo-controlled, double-blind, parallel-group study (Study AC-065A302) was conducted to investigate the efficacy, safety, and tolerability of selexipag in patients with PAH (target sample size, 1150 subjects [575 per group]) at 181 study sites overseas. In the original protocol, the primary efficacy endpoints were "the change in 6MWD from baseline to Week 16" and "the time to onset of the first morbidity/mortality event" [see Table 29 for the definition of morbidity/mortality events]. Subsequently, the importance of clinical outcome as a trial endpoint was emphasized at the Fourth World Symposium on Pulmonary Hypertension *(J Am Coll Cardiol*. 2009;54(1):S97-107). In response, the protocol was changed during the study period ([redacted] [redacted], 20[redacted]), to use "the time to onset of the first morbidity/mortality event" alone as the primary endpoint, and to change "the change in 6MWD from baseline to Week 16" from a primary to secondary endpoint. The original protocol specified the target event number of 203 in total and the target sample size of 544 in total. After the beginning of study, however, the applicant found that the distribution of subject characteristics was different from what had been expected: (a) the enrolled subjects were receiving 1 or 2 concomitant PAH drugs; and (b) the most of enrolled subjects had WHO functional class II or III. This suggested that selexipag would not reduce the incidence of events as much as expected. Therefore, the target event number was changed to 332 in total and the target sample size to 1150 in total, in a blinded manner. In order to exclude the possible effect of this change on the evaluation, morbidity/mortality events that had occurred before the change (August 16, 2011) (45 subjects in total [15, selexipag; 30, placebo]) were handled as cut-off cases, and an interim analysis was planned to promptly confirm the efficacy or futility of selexipag. Among subjects who had completed Study AC-065A302 or subjects who made the end of study (EOS) visit after a morbidity event, subjects who passed the inclusion/exclusion criteria were then enrolled in the open-label, uncontrolled study (Study AC-065A303), which was conducted at 171 study sites overseas to evaluate the safety and tolerability of long-term treatment with selexipag.

In Study AC-065A302, selexipag or placebo was administered orally twice daily after a meal. The starting dose of selexipag was 0.2 mg per administration. If there was no tolerability problem, the dose was increased by 0.2 mg increments at 7-day intervals to a level not above 1.6 mg per administration. If adverse events unique to IP receptor agonists (e.g., headache, diarrhoea, pain in jaw, myalgia, flushing, and nausea) occurred during dose titration, and if a tolerability problem was suspected by the investigator (or subinvestigator), the dose could be tapered by 0.2 mg without further dose escalation. The maximum tolerated dose was determined for each subject by Week 12, after which this dose was administered until Week 26. From Week 26, the dose could be increased by 0.2 mg increments up to 1.6 mg in subjects with the maximum tolerated dose of <1.6 mg, and the dose could be decreased in subjects with a tolerability problem, both at the discretion of the investigator (or subinvestigator). Subjects were required to make the EOS visit within 4 weeks after morbidity/mortality events (Table 29) occurred in a total of 331 subjects, and the time from the baseline visit to the EOS visit was defined as the study treatment period.

In Study AC-065A303, the starting dose of selexipag was 0.2 mg twice daily administered orally after a meal, regardless of the group in Study AC-065A302. If there was no tolerability problem, the dose was increased by 0.2 mg increments at 7-day intervals to a level not above 1.6 mg per administration. If a tolerability problem was suspected by the investigator (or subinvestigator), the dose could be tapered by 0.2 mg. The maximum tolerated dose was determined for each subject by Week 12, after which this dose was administered until Week 26. From Week 26, the dose could be increased or decreased (but not above 1.6 mg per administration).

**Table 29. Definition of morbidity/mortality events**

A morbidity/mortality is any of the following events that occurred during the period from randomization (the first day of study treatment) to 7 days after the last dose of study drug. All morbidity/mortality events were assessed for validity by the independent event assessment committee in a blinded manner.

(a) Death (all-cause)
(b) Hospitalization due to PAH aggravation (including signs and symptoms of right ventricular failure)
(c) PAH aggravation requiring lung transplantation or balloon atrial septostomy
(d) Initiation of parenteral prostanoid therapy or long-term oxygen therapy because of PAH aggravation
(e) Disease progression as defined below (patients with WHO functional class II to III at baseline)
- Decrease in 6MWD from baseline (≥15% decrease from baseline in two of 6MWD tests performed in the last 2 weeks)
- Aggravation of WHO functional class

(f) Disease progression as defined below (patients with WHO functional class III to IV at baseline)
- Decrease in 6MWD from baseline (≥15% decrease from baseline in two of 6MWD tests performed in the last 2 weeks)
- Addition of a PAH drug

The main inclusion criteria were ≥18- and ≤75-year-old patients with IPAH, HPAH, drug- or toxin-induced PAH, or PAH associated with connective tissue disease, repaired congenital shunt disease, or HIV infection who met the following criteria.

- WHO functional class I to IV
- mPAP ≥25 mmHg
- PCWP or left ventricular end-diastolic pressure ≤15 mmHg
- PVR ≥400 dyn·sec·cm$^{-5}$
- 6MWD ≥50 m and ≤450 m

In Study AC-065A302, ERA and PDE-5 inhibitor could be used if administered at a constant dose from ≥3 months before the start of study treatment to Week 26. $PGI_2$ preparation was prohibited from 1 month before the start of study treatment until the EOS visit, except for a single-dose administration during the right heart catheterization. In Study AC-065A303, concomitant ERA and PDE-5 inhibitors were permitted, while concomitant $PGI_2$ preparation was prohibited until the EOS visit in Study AC-065A303, except for a single-dose administration during the right heart catheterization.

(a) Study AC-065A302

A total of 1156 randomized subjects (574 in the selexipag group, 582 in the placebo group) were included in the full analysis set (FAS) and in the primary efficacy analysis set. Of these, 1152 subjects (575 in the selexipag group, 577 in the placebo group) were included in the safety analysis set. (The remaining 4 subjects were excluded because they did not receive the study drug.) Table 30 shows baseline WHO functional class of subjects in FAS.

The distribution of the maintenance dose (dose used for the longest period in each subject) per administration in the selexipag group was 0.2 mg in 11.8% (68 of 575) of subjects, 0.4 mg in 11.3% (65 of 575) of subjects, 0.6 mg in 10.8% (62 of 575) of subjects, 0.8 mg in 14.3% (82 of 575) of subjects, 1.0 mg in 6.1% (35 of 575) of subjects, 1.2 mg in 7.3% (42 of 575) of subjects, 1.4 mg in 7.1% (41 of 575) of subjects, and 1.6 mg in 28.3% (163 of 575) of subjects.

**Table 30. Baseline WHO functional class (FAS)**

| | Selexipag (N = 574) | Placebo (N = 582) |
|---|---|---|
| Class I | 0.7 (4) | 0.9 (5) |
| Class II | 47.7 (274) | 43.8 (255) |
| Class III | 51.0 (293) | 54.0 (314) |
| Class IV | 0.5 (3) | 1.4 (8) |

% (n)

An interim analysis was planned to be conducted at the time point when the independent event assessment committee confirmed morbidity/mortality events in the first 202 subjects, except for the first morbidity/mortality events (in 45 subjects) that occurred before the change of the target number of

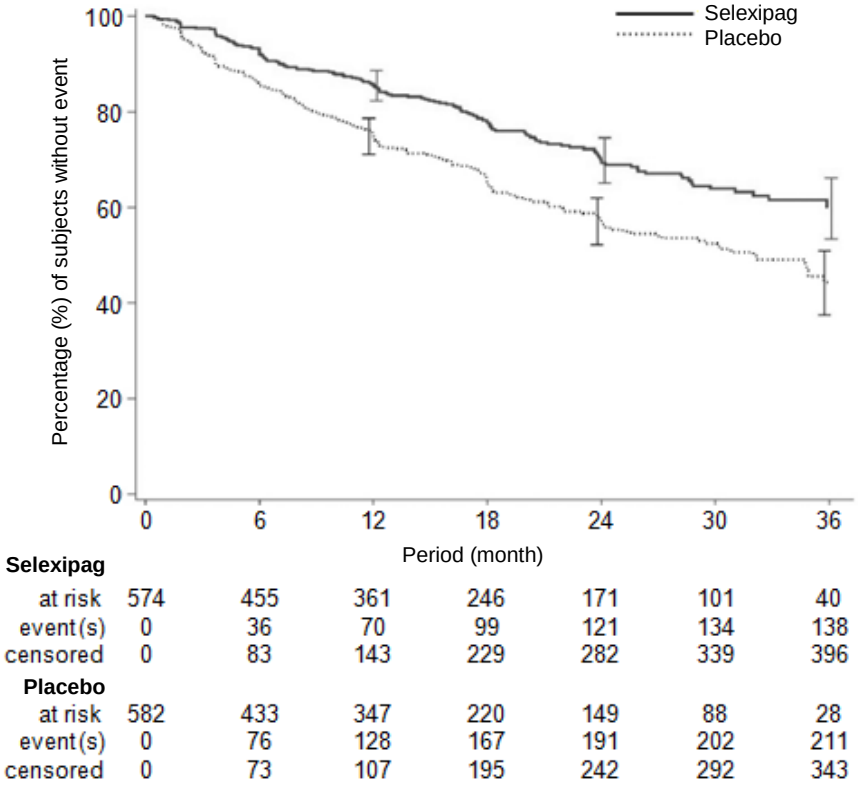
events. The Haybittle-Peto method was employed for correcting type 1 error associated with the interim analysis.

Table 31 and Figure 1 show the time to onset of the first morbidity/mortality event (the primary efficacy endpoint) in FAS. A significant difference was observed between the selexipag and placebo groups (one-sided log rank test, $P < 0.0001$; significance level of 0.005 [one-sided]). Similar results were obtained when the excluded events (in 45 subjects) were included.

**Table 31. Morbidity/mortality events (FAS)**

| | Selexipag | Placebo |
|---|---|---|
| Number of subjects | 574 | 582 |
| Number of subjects with morbidity/mortality events (%) | 140 (24.4) | 212 (36.4) |
| Hazard ratio[a] [99% CI] | 0.61 [0.46, 0.81] | |
| *P* value[b] | $P < 0.0001$ | |

[a] Proportional hazard model with treatment group as the factor
[b] One-sided log lank test, significance level of 0.005 (one-sided)




Bars indicate 95% CI.

**Figure 1: Kaplan-Meier curves of morbidity/mortality events (FAS)**

Table 32 shows the change in 6MWD from baseline to Week 26 (secondary endpoint).

**Table 32. Change in 6MWD (m) from baseline to Week 26 (FAS)**

| | Selexipag (n = 574) | Placebo (n = 582) |
|---|---|---|
| Baseline | | |
| Mean ± SD | 358.5 ± 76.3 | 348.0 ± 83.2 |
| Median | 376.0 | 369.0 |
| Week 26 | | |
| Mean ± SD | 306.5 ± 170.0 | 281.7 ± 173.8 |
| Median | 370.0 | 346.0 |
| Change | | |
| Mean ± SD | -52.00 ± 150.24 | -66.26 ± 148.23 |
| Median | 4.00 | -9.00 |

Adverse events were observed in 98.3% (565 of 575) of subjects in the selexipag group and in 96.9% (559 of 577) of subjects in the placebo group. Table 33 shows adverse events reported by ≥10% of subjects in either group.

**Table 33. Adverse events reported by ≥10% of subjects in either group (safety analysis set)**

| | Selexipag (N = 575) | Placebo (N = 577) |
|---|---|---|
| Headache | 65.2 (375) | 32.8 (189) |
| Diarrhoea | 42.4 (244) | 19.1 (110) |
| Nausea | 33.6 (193) | 18.5 (107) |
| Pain in jaw | 25.7 (148) | 6.2 (36) |
| Pulmonary arterial hypertension | 21.9 (126) | 35.7 (206) |
| Vomiting | 18.1 (104) | 8.5 (49) |
| Pain in extremity | 16.9 (97) | 8.0 (46) |
| Dyspnoea | 16.0 (92) | 21.0 (121) |
| Myalgia | 16.0 (92) | 5.9 (34) |
| Dizziness | 15.0 (86) | 14.7 (85) |
| Oedema peripheral | 13.9 (80) | 18.0 (104) |
| Upper respiratory tract infection | 13.0 (75) | 13.9 (80) |
| Nasopharyngitis | 13.0 (75) | 10.9 (63) |
| Flushing | 12.2 (70) | 5.0 (29) |
| Arthralgia | 10.8 (62) | 7.6 (44) |
| Cough | 9.7 (56) | 11.6 (67) |
| Fatigue | 8.0 (46) | 10.2 (59) |
| Right ventricular failure | 8.0 (46) | 10.1 (58) |

% (n)

Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 89.6% (515 of 575) of subjects in the selexipag group and in 56.7% (327 of 577) of subjects in the placebo group. Table 34 shows adverse events reported by ≥10% of subjects in either group for which a causal relationship to the study drug could not be ruled out.

**Table 34. Adverse events reported by ≥10% of subjects in either group for which a causal relationship to the study drug could not be ruled out (safety analysis set)**

| | Selexipag (N = 575) | Placebo (N = 577) |
|---|---|---|
| Headache | 61.4 (353) | 26.2 (151) |
| Diarrhoea | 36.0 (207) | 10.2 (59) |
| Nausea | 27.0 (155) | 11.4 (66) |
| Pain in jaw | 24.9 (143) | 5.0 (29) |
| Myalgia | 13.9 (80) | 3.8 (22) |
| Vomiting | 13.6 (78) | 3.3 (19) |
| Pain in extremity | 13.4 (7.7) | 4.0 (23) |
| Flushing | 11.7 (67) | 4.3 (25) |

% (n)

Death occurred in 8.5% (49 of 575) of subjects in the selexipag group and in 7.1% (41 of 577) of subjects in the placebo group. The causes of death common to ≥0.5% of subjects in either group were pulmonary arterial hypertension (3.3% in the selexipag group, 2.8% in the placebo group), right ventricular failure (1.2%, 1.0%), sudden death (0.9%, 0.7%), cardiopulmonary failure (0.5%, 0.2%), acute right ventricular

failure (0.3%, 0.5%), and acute renal failure (0.3%, 0.5%). A causal relationship to the study drug could not be ruled out for the death of 1 subject in the selexipag group (septic shock) and 2 subjects in the placebo group (pulmonary arterial hypertension/right ventricular failure, acute renal failure). Other serious adverse events were observed in 39.0% (224 of 575) of subjects in the selexipag group and in 43.7% (252 of 577) of subjects in the placebo group. Serious adverse events reported by ≥2% of subjects in either group were pulmonary arterial hypertension (11.3%, 19.4%), right ventricular failure (5.0%, 6.1%), dyspnoea (2.8%, 2.1%), pneumonia (2.6%, 4.0%), and syncope (1.7%, 3.5%). The serious adverse event reported by ≥3 subjects for which a causal relationship to the study drug could not be ruled out was syncope (4 subjects, 3 subjects). The outcome was "recovered/resolved" in all subjects except for 1 subject in the selexipag group (not resolved/not recovered).

Adverse events leading to treatment discontinuation were observed in 31.7% (182 of 575) of subjects in the selexipag group and in 37.1% (214 of 577) of subjects in the placebo group. Adverse events reported by ≥2% of subjects in either group were pulmonary arterial hypertension (13.6% in the selexipag group, 23.4% in the placebo group), headache (3.3%, 0.7%), right ventricular failure (2.4%, 4.0%), and diarrhoea (2.3%, 0%). A causal relationship to the study drug could not be ruled out for headache (19 subjects in the selexipag group, 3 subjects in the placebo group), diarrhoea (13 subjects, 0 subjects), right ventricular failure (1 subject, 1 subject), and pulmonary arterial hypertension (4 subjects, 8 subjects).

(b) Study AC-065A303
All of 218 subjects who proceeded to Study AC-065A303 were included in the safety analysis.

The distribution of the maintenance dose (per administration) was 0.2 mg in 9.2% (20 of 218) of subjects, 0.4 mg in 11.9% (26 of 218) of subjects, 0.6 mg in 10.6% (23 of 218) of subjects, 0.8 mg in 9.6% (21 of 218) of subjects, 1.0 mg in 9.6% (21 of 218) of subjects, 1.2 mg in 9.6% (21 of 218) of subjects, 1.4 mg in 10.6% (23 of 218) of subjects, and 1.6 mg in 26.6% (58 of 218) of subjects.

Adverse events were reported in 95.9% (209 of 218) of subjects. Adverse events reported by ≥10% of subjects were headache (54.6%), diarrhoea (35.8%), pulmonary arterial hypertension (25.7%), pain in jaw (21.1%), nausea (20.2%), right ventricular failure (16.5%), vomiting (14.2%), oedema peripheral (11.5%), pain in extremity (11.5%), and myalgia (10.1%).

Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 80.3% (175 of 218) of subjects, and those reported by ≥10% of subjects were headache (52.8%), diarrhoea (28.4%), pain in jaw (20.6%), and nausea (16.1%).

Death occurred in 25.2% (55 of 218) of subjects. The causes of death common to ≥2 subjects were pulmonary arterial hypertension (24 subjects), right ventricular failure (19 subjects), acute right ventricular failure (5 subjects), cardiopulmonary failure (4 subjects), cardiac arrest, pulmonary embolism, and sepsis (3 subjects each), cardiogenic shock and sudden death (2 subjects each). A causal relationship to the study drug could not be ruled out in 1 subject in the selexipag group (hypovolaemic shock/pulmonary arterial hypertension). Other serious adverse events were observed in 40.4% (88 of 218) of subjects. Serious adverse events reported by ≥5 subjects were pulmonary arterial hypertension (32 subjects), right ventricular failure (18 subjects), pneumonia (6 subjects), and syncope (5 subjects). The serious adverse event reported by ≥2 subjects for which a causal relationship to the study drug could not be ruled out was diarrhoea (3 subjects). The outcome was "recovered/resolved," "recovered/resolved with sequelae," and remained "not recovered/not resolved" in 1 subject each.

Adverse events leading to treatment discontinuation were observed in 23.9% (52 of 218) of subjects, and those reported by ≥5 subjects were pulmonary arterial hypertension (19 subjects) and right ventricular failure (10 subjects). Adverse events reported by ≥3 subjects for which a causal relationship to the study drug could not be ruled out were diarrhoea and headache (3 subjects each).

## 7.R Outline of the review conducted by PMDA

### 7.R.1 Clinical positioning

PMDA asked the applicant to explain the clinical positioning of selexipag in the treatment of PAH, including the comparison with drugs in the same class and choice between selexipag and other drugs.

The applicant's explanation:

The Japanese and foreign clinical studies have demonstrated the efficacy and acceptable safety of selexipag in patients with PAH regardless of the underlying disease of PAH or WHO functional class. Therefore, selexipag should be indicated for patients with PAH classified as Group 1 in the clinical classification of pulmonary arterial hypertension (Nice Classification), namely, IPAH, HPAH, drug/toxin-induced PAH, and PAH associated with various diseases, regardless of WHO functional class.

The Japanese and foreign clinical practice guidelines recommend that ERA, $PGI_2$ preparations, PDE-5 inhibitors, or soluble guanylate cyclase (sGC) stimulants be used as monotherapy for PAH of WHO functional class II and III, but do not recommend any specific drug as the first-line therapy. In medical practice, therapeutic agents most suited for each patient are selected based on the comprehensive judgment of the indication and the efficacy and safety profile of drugs, as well as the characteristics and symptoms of the patient; selexipag will serve as a first-line monotherapy for PAH among other drugs. Selexipag is the only drug acting on IP receptors recommended for PAH of WHO functional class II by the Guidelines for the diagnosis and treatment of pulmonary hypertension by the European Society of Cardiology and the European Respiratory Society (ESC/ERS Guidelines). Accordingly, selexipag will be selected, as the top priority among other drugs acting on IP receptors, by patients in class II who intend to use a drug acting on IP receptors as the first-line therapy. Further, selexipag is a highly recommended oral drug acting on IP receptors for PAH of WHO functional class III, and therefore will be selected, as the top priority among other drugs, by patients in class III who intend to use an oral drug acting on IP receptors as the first-line therapy.

As for the switching from a drug in the same class, since epoprostenol sodium and treprostinil are injections and may cause pain and infection due to the insertion and placement of the catheter, they may be switched to selexipag in order to avoid these problems. On the other hand, these injections are recommended for the treatment of PAH of WHO functional class IV by ESC/ERS Guidelines; this suggests that patients with severe PAH not sufficiently responsive to selexipag may switch from selexipag to the injections. Switching from the inhalant (iloprost) and the oral drug (beraprost) to selexipag is expected, while switching from selexipag to these drugs is unlikely given their clinical positioning and recommendation level in the clinical practice guidelines.

ESC/ERS Guidelines mention selexipag as one of the most highly recommended dual oral therapy (selexipag + ERA, selexipag + a PDE-5 inhibitor, macitentan + sildenafil, or riociguat + bosentan), and as the only highly recommended triple oral therapy. Selexipag is therefore expected to be preferentially used in combination therapies as well.

The Guidelines for Treatment of Pulmonary Hypertension (2012 edition) (2011 report of joint working group) were established in accordance with the clinical practice guidelines for pulmonary hypertension of the US and Europe, and are used in the treatment of PAH in Japan. This suggests that the treatment methods are basically similar in Japan and other countries. Thus, the applicant considers that the clinical positioning of selexipag in PAH treatment is similar in Japan and other countries, regardless of the approval status of other PAH drugs.

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PMDA's view:

In the treatment algorithm of pulmonary arterial hypertension updated as a result of the discussion at the Fifth World Symposium on Pulmonary Hypertension (*J Am Coll Cardiol*. 2013;62[25 Suppl D]:D60-72), the clinical positioning of $PGI_2$ preparations in PAH treatment is clearly defined. In ESC/ERS Guidelines, selexipag is rated as a drug of recommendation level I (Is recommended, Is indicated) and evidence level B (Data derived from a single randomized clinical trial or large non-randomized studies) for patients with WHO functional class II and III. In recent years, aggressive treatment from the early stage has been recommended for patients with class II (*J Am Coll Cardiol*. 2013;62:D60-72). For patients with class III or IV and patients with poor response to monotherapy, combination therapies

using multiple drugs with different action mechanism (selected from among $PGI_2$ preparations, ERA, PDE-5 inhibitors, and sGC stimulants) are proposed. Because the Japanese clinical practice guidelines have been prepared and revised in accordance with the most updated guidelines of the US and Europe, the positioning of selexipag in PAH treatment in Japan is expected to be similar to that in the foreign guidelines. Accurately comparing the efficacy and safety of selexipag and $PGI_2$ preparation is difficult, but the oral drug selexipag may improve the quality of life of some patients, for the following reasons: (1) Epoprostenol sodium and treprostinil are injections requiring continuous intravenous or subcutaneous administration, and patients have to carry a constant infusion pump, and these drugs may cause pain and infection at the insertion site; (2) the inhaler iloprost causes local irritation symptoms and, because of the frequent inhalations required every day, some patients may have difficulty maintaining compliance. Thus, if selexipag is made available in clinical practice in Japan, it will offer a new treatment option for PAH as a first-line monotherapy, in addition to ERA and PDE-5 inhibitors, or as combination therapy with ERA or PDE-5 inhibitors.

Only limited information is available on the switching from existing $PGI_2$ preparation and on the concomitant use of selexipag with other PAH drugs. Therefore, the applicant should appropriately collect information on the efficacy and safety of selexipag in Japanese patients with PAH under such situations after marketing, and provide the information to healthcare professionals.

### 7.R.2 Use of the results of foreign clinical studies

#### 7.R.2.1 Comparison of intrinsic and extrinsic ethnic factors in PAH treatment between Japanese and non-Japanese patients

PMDA asked the applicant to explain the difference in intrinsic and extrinsic ethnic factors between Japanese and non-Japanese patients, because the applicant used the results of foreign clinical studies to explain the efficacy and safety of selexipag in Japanese patients with PAH.

The applicant's explanation:
ESC/ERS Guidelines estimate that the morbidity of patients with PAH is at least 15 per 1 million adults. The results of the survey of PAH in Japan (*Research Project on Intractable Disease supported by Health and Labour Sciences Research Grants, Research on respiratory failure [Fiscal Year 2013], Fiscal Year 2013 General/Partial Research Report*. 2014:49-53) reported that the nationwide average of the morbidity in Japan was 15.6 per 1 million people, calculated based on the demographic statistics of 2011. These results suggest that there is no significant difference in the morbidity between Japan and the US or Europe. Also, the sex ratio or mean age of patients with PAH does not differ between Japan and the US or Europe, and IPAH and HPAH account for higher percentages of the underlying disease both in Japan and other countries. As for severity, patients with WHO functional class II or III accounted for a majority of patients both in Japan and other countries, and baseline PVR of patients was similar in Japan and other countries. In contrast, among the subjects enrolled in Studies AC-065A201, NS-304/-02, or AC-065A302, the baseline characteristics of age, body weight, and PVR differed between Japanese and non-Japanese subjects (Table 35). However, subgroup analysis stratified by patient characteristics suggested that the differences in these characteristics did not significantly affect the evaluation of efficacy or safety of selexipag. Based on the above, the applicant considers that there are no differences, between Japanese and non-Japanese patients with PAH, in intrinsic ethnic factors that would significantly affect the evaluation of efficacy or safety of selexipag.

**Table 35. Patient characteristics in Japanese and foreign clinical studies**

| | Study AC-065A201 | Study NS304/-02 | | Study AC-065A302 | |
|---|---|---|---|---|---|
| | Selexipag | Selexipag | Placebo | Selexipag | Placebo |
| Number of subjects | 37 | 33 | 10 | 574[a] | 582 |
| Age (years) | | | | | |
| Mean ± SD | 44.5 ± 13.3 | 54.8 ± 16.8 | 53.8 ± 16.3 | 48.2 ± 15.2 | 47.9 ± 15.6 |
| Median | 42.0 | 58.0 | 54.0 | 49.0 | 49.0 |
| Min, max | 23, 72 | 19, 80 | 25, 80 | 18, 78 | 18, 80 |
| Body weight (kg) | | | | | |
| Mean ± SD | 57.5 ± 15.2 | 68.7 ± 12.4 | 70.6 ± 13.9 | 71.6 ± 18.6 | 70.7 ± 17.7 |
| Median | 53.6 | 65.0 | 69.2 | 69.4 | 68.0 |
| Min, max | 34.3, 102.8 | 51.0, 100.0 | 51.6, 90.0 | 39.1, 150.0 | 38.9, 134.5 |
| PVR (dyn·sec·cm$^{-5}$) | | | | | |
| Mean ± SD | 725.3 ± 292.5 | 948.6 ± 428.0 | 867.2 ± 379.3 | 882.0 ± 437.4[b] | 939.4 ± 535.5[b] |
| Median | 680.9 | 829.0 | 771.5 | 777.0 | 800.0 |
| Min, max | 408, 1564 | 394, 2167 | 524, 1827 | 228, 2400 | 113, 3214 |

[a] n = 573 for body weight
[b] Value measured within 6 months before randomization (282 subjects in the selexipag group, 299 subjects in the placebo group)

In the US and Europe, PAH is treated according to the guidelines prepared based on the Fifth World Symposium on Pulmonary Hypertension in 2013 (*J Am Coll Cardiol*. 2013;62[25 Suppl D]:D60-72) and according to ESC/ERS Guidelines. In Japan, PAH is treated according to the treatment guidelines prepared based on these guidelines. Accordingly, there are no significant differences between Japan and other countries in the following extrinsic ethnic factors: diagnostic criteria of PAH, underlying disease, severity classification, and diagnostic algorithm. This suggests that diagnosis and treatment of PAH do not significantly differ between Japan and other countries.

The usage of PAH drugs in and outside Japan was compared based on the registry study in foreign countries (*Circulation.* 2010;122:164-72) and the FY2013 General/Partial Research Report in Japan. The results showed that the usage share of ERA was slightly higher and that of intravenous $PGI_2$ preparations was slightly lower in Japan, but the usage share of other drugs was similar in Japan and other countries. Thus, there is no significant difference in the usage of PAH drugs between Japan and other countries.

Thus, extrinsic ethnic factors, including the medical environment for PAH treatment, do not differ significantly between Japan and other countries.

PMDA's view:
As for the intrinsic ethnic factors, there appears to be no ethnic difference in the disease conditions of PAH between Japanese and non-Japanese patients, but baseline age, body weight, and PVR differed between Study AC-065A201 (Japanese subjects) and Studies NS-304/-02 and AC-065A302 (non-Japanese subjects). However, a comparison of the efficacy and safety in Japanese and non-Japanese subjects stratified by age or body weight revealed no significant difference in efficacy or safety between the 2 populations. PMDA therefore considers that differences in these patient characteristics (i.e., age and body weight) had no significant effect on the efficacy evaluation. The baseline PVR may have been affected by the following factors: (1) Usage of concomitant oral PAH drugs differed between Japanese and foreign clinical studies because these studies were conducted at different times in and outside Japan; (2) in recent years in Japan, patients with PAH receive active combination therapy from the early stage of PAH and increase their doses within a short period; this resulted in a higher percentage of subjects receiving both ERA and a PDE-5 inhibitor in combination with selexipag in Study AC-065A201 than in other studies. As a consequence, a certain extent of the treatment effect was achieved before the study, which may have affected on the baseline PVR. However, the rate of the change from baseline in each parameter observed after selexipag administration in clinical studies did not significantly differ between Japan and other countries; thus, baseline values were unlikely to have affected efficacy evaluation. As for pharmacokinetics, selexipag exposure may differ between Japanese and non-Japanese patients [see "6.R.2 Comparison of pharmacokinetics between Japanese and non-Japanese population]. Nevertheless, it is appropriate that Study AC-065A201 used the dosage similar to that used in Study AC-065A302, taking account of the profile of $PGI_2$ preparations and the results of the study on the extent of the difference in the exposure [see "7.R.6 Dosage and administration"].

As for the extrinsic ethnic factors, a comparison of Study AC-065A201 versus Studies NS-304/-02 and AC-065A302 showed regional difference in the percentage of the subjects using concomitant ERA and PDE-5 inhibitors. However, the protocols had stipulated that concomitant ERA and PDE-5 inhibitors should be administered without change in type or in daily dose at least for 90 days before the start of the study treatment. Therefore, the concomitant drugs would not have significantly affected the evaluation of the efficacy or safety of selexipag. Based on the above, PMDA has concluded that there are no differences in intrinsic or extrinsic ethnic factors that significantly affect the efficacy or safety of selexipag between Japanese and non-Japanese patients.

#### 7.R.2.2 Appropriateness of using foreign clinical study data

PMDA considers that the Japanese clinical study should have been conducted according to the same design of the foreign clinical studies, in order to compare the efficacy and safety of selexipag in Japanese and non-Japanese subjects. PMDA therefore asked the applicant to explain (a) the reason for the difference in the design of Studies AC-065A201, NS-304/-02, and AC-065A302, (b) the reason for considering that the Japanese study data could be compared with the foreign study data despite the difference in the study design, and (c) the appropriateness of using foreign clinical study data to evaluate the efficacy and safety of selexipag in Japanese patients with PAH.

The applicant's explanation:
The foreign clinical studies were placebo-controlled studies, whereas the Japanese clinical study was an open-label, uncontrolled study because of the limited number of patients, precluding conducting a large-scale study in only Japanese patients. Since PVR, the primary endpoint, is an objective index, it is considered appropriate to evaluate and compare the efficacy based on the change in PVR from baseline.

The design of Study AC-065A201 and Study NS-304/-02 are different from each other not only in that Study AC-065A201 is an open-label, uncontrolled study and Study NS-304/-02 is a placebo-controlled, double-blind study, but also in that the upper limit of the dose, inclusion/exclusion criteria, and rules for concomitant drugs were different from each other. However, there was no significant difference in the patient population studied, as judged from the following: (1) There was no major difference in the PAH treatment algorithm used based on the clinical practice guidelines available at the planning of each study; and (2) the protocols of both studies met the diagnostic criteria of PAH and used the same criteria for pulmonary hemodynamics. In addition, both studies used the same starting dose and the same dose adjustment method of increasing the dose according to the tolerability of the patient. In both studies, PVR decreased at the end of efficacy evaluation compared with the baseline level, and evaluation of the efficacy and safety at each maintenance dose did not detect the effect of dose.

The primary endpoint in Study AC-065A201 (PVR) was different from that in Study AC-065A302 (morbidity/mortality event). Given the report that PVR reflects the disease conditions of PAH and prognosis (*Eur Heart J.* 2007;9[Suppl H]:H68-74), PVR improvement is considered to have a strong correlation with the occurrence of morbidity/mortality event. In addition, the secondary endpoint 6MWD improved from baseline, WHO functional class improved, and N-terminal pro-brain natriuretic peptide (NT-proBNP) improved from baseline in both studies. These results suggest that it is appropriate to investigate the similarity of the results of both studies.

The patient population enrolled in each study was subjected to subgroup analysis stratified by patient characteristics. Results suggested that patient characteristics did not significantly affect the evaluation of efficacy or safety.

Based on the above, the applicant considers that it is appropriate to use the foreign clinical study data to evaluate the efficacy and safety in Japanese patients, and that it is appropriate to explain the efficacy and safety of selexipag in Japanese patients using the data of foreign clinical studies such as Study AC-065A302, based on the comparison of the data from Study AC-065A201 (a Japanese exploratory uncontrolled study) and the foreign placebo-controlled studies.

PMDA's view:
If the purpose of Study AC-065A201 was to compare the efficacy and safety of selexipag between Japanese and non-Japanese patients, Study AC-065A201 should have used the same design, as much as possible (including the primary efficacy endpoint and study duration), that used in the confirmatory

study AC-065A302. However, since PAH is a rare disease, the Japanese study could not be conducted on a scale large enough to use "the frequency of morbidity/mortality events" as the primary endpoint. PMDA understands this situation.

PVR was not used as an endpoint in Study AC-065A302, whereas in Study NS-304/-02, the change in PVR from baseline to 17 weeks after selexipag administration was used as the primary endpoint. A comparison of PVR measured at approximately same time points in Studies AC-065A201 and NS-304/-02 showed a similar improvement in PVR. In PAH treatment in Japan, hemodynamics is actively evaluated to assess the efficacy of PAH drugs. Given these circumstances, it is appropriate that hemodynamics was evaluated at 16 weeks after the start of administration in the Japanese clinical study based on the routine clinical practice. PMDA has concluded that it is appropriate to evaluate the efficacy and safety of selexipag in Japanese patients with PAH based also on the foreign clinical study data, for the following reasons: (a) only a limited number of Japanese patients with PAH were available for enrollment in the Japanese clinical study; (b) no difference was observed in intrinsic or extrinsic ethnic factors [see "7.R.2.1 Comparison of intrinsic and extrinsic ethnic factors in PAH treatment between Japanese and foreign patients"] or in the efficacy or safety between Japanese and non-Japanese patients [see "7.R.3 Efficacy" and "7.R.4 Safety"].

### 7.R.3 Efficacy

PMDA asked the applicant to provide the rationale for the composite endpoint in Study AC-065A302, to explain the relationship between "time to the first morbidity/mortality event" (the primary endpoint) and the true endpoint (improvement of life prognosis) in Study AC-065A302, and to discuss the appropriateness of the primary endpoint.

The applicant's explanation:
The true endpoint in PAH treatment is improvement in life prognosis. However, evaluation of life prognosis of patients with the rare disease PAH is impracticable because it requires many patients and a long study period. The Fourth World Symposium on Pulmonary Hypertension (*J Am Coll Cardiol*. 2009;54:S97-107) and the Guideline of the European Medicines Agency proposed the importance of clinical outcome as the endpoint, and the Fifth World Symposium on Pulmonary Hypertension recommends that phase III studies of PAH drugs be conducted as randomized studies using morbidity/mortality events as the endpoint (*J Am Coll Cardiol*. 2013;62:D82-91). Therefore, it is considered appropriate that Study AC-065A302 used "time to the first morbidity/mortality event" as the primary endpoint because it allows comprehensive evaluation of clinical outcome that is associated with life prognosis.
Among those defined as morbidity/mortality events, death (all-cause), hospitalization due to PAH aggravation, lung transplantation, and balloon atrial septostomy were used as objective events indicating PAH aggravation. Initiation of parenteral prostanoid therapy and long-term oxygen therapy both suggest the near-irreversibility or severity of the clinical symptoms, and were therefore used as the important events indicating PAH aggravation. "A decrease in 6MWD by ≥15% from baseline" accompanied by "increase in severity of WHO functional class" or "requirement of an additional PAH drug," indicate a clinically significant progression of PAH and were therefore handled as a morbidity indicating "disease progression." All these elements of the composite endpoint are consistent with the definition of morbidity/mortality events recommended at the Fourth World Symposium on Pulmonary Hypertension. All morbidity/mortality events were assessed by the independent event assessment committee to ensure the consistency and accuracy.

Based on the above, the applicant considers that the morbidity/mortality events defined as the primary endpoint in Study AC-065A302 accurately indicate the disease conditions and are of clinical significance. A landmark analysis performed to compare the overall survival time in subjects with and without a morbidity event at the landmark time points (Month 3, 6, 12, or 18) suggested a correlation between the occurrence of a morbidity event and a mortality risk. The applicant thus considers that "time to the first morbidity/mortality event" was an appropriate primary endpoint in this study with the true endpoint "improvement of life prognosis" in mind.

PMDA's view:
Although the true endpoint in PAH treatment is improvement of life prognosis, 6MWD has been used as the primary endpoint in a majority of clinical studies of PAH drugs approved in Japan and other countries. 6MWD was reported to be correlated with the severity of PAH and life prognosis (*Am J Respir Crit Care Med*. 2000;161:487-92), based on which American College of Cardiology (ACC) Guidelines revised in 2004 (*J Am Coll Cardiol.* 2004;43:48-55S) and in 2009 (*J Am Coll Cardiol*. 2009;54:S97-107) recommended 6MWD as the primary endpoint in clinical studies of PAH drugs. However, the Fourth World Symposium on Pulmonary Hypertension proposed the importance of clinical outcome as the endpoint, and recommended that the efficacy of PAH drugs be evaluated based on the time to clinical aggravation (*J Am Coll Cardiol.* 2009;54:S97-107). Furthermore, according to the Fifth World Symposium on Pulmonary Hypertension, phase III studies of PAH drugs should be conducted as randomized studies using morbidity/mortality event as the endpoint (*J Am Coll Cardiol.* 2013;62(25):D82-91).

Taking account of the above situations and the applicant's explanation, "time to the first morbidity/mortality event" was the appropriate primary endpoint in Study AC-065A302.

Changing the primary endpoint during the study should be avoided in general, but taking account of the discussions at the Fourth and Fifth World Symposium on Pulmonary Hypertension, it is understandable that the protocol of Study AC-065A302 was modified to use "time to the first morbidity/mortality event" as the only primary endpoint ("time to the first morbidity/mortality event" was one of 2 primary endpoints in the original protocol). 6MWD (the other primary endpoint in the original protocol) was evaluated as the secondary endpoint. The change (mean ± SD and median) in 6MWD from baseline to Week 26 was -52.00 ± 150.24 m and 4.0 m, respectively, in the selexipag group and -66.26 ± 148.23 m and -9.0 m, respectively, in the placebo group. During the course of the study, the target number of events was changed and subsequently, an interim analysis was planned. It is inappropriate that an unplanned change of the target number of events is made during the study. Thus, characteristics of subjects enrolled in the study should have been thoroughly investigated in advance. Also, the interim analysis should have been planned based on the investigation of the necessity in advance. However, planning the clinical study based on thorough prior survey and information was difficult because of the following factors: (1) the target disease of selexipag is PAH, (2) while the study was being conducted, the treatment algorithm for PAH was published based on the results of the Fourth World Symposium on Pulmonary Hypertension, and (3) a new therapeutic drug was introduced into the market. The protocol change was performed in a blinded manner and, in order to prevent any impact on efficacy evaluation, morbidity/mortality events occurring before the change of the target number of events (45 cases in total) were handled as cut-off cases. Furthermore, an additional analysis was performed as a sensitivity analysis in which the time to the first morbidity/mortality event, the primary endpoint, was evaluated including these 45 cases as those with morbidity/mortality events. Thus, evaluating the efficacy of selexipag from data of Study AC-065A302 is acceptable.

In Study AC-065A302, the hazard ratio [99% CI] for time to the first morbidity/mortality event (the primary endpoint) in the selexipag group versus the placebo group was 0.61 [0.46, 0.81], showing a significant difference in the primary endpoint between the selexipag and placebo groups. This demonstrates the efficacy of selexipag.

The change from baseline in PVR (an important and objective parameter) in the selexipag group was −168.1 ± 241.6 and −166.0 dyn·sec·cm$^{-5}$ (mean ± SD and median, respectively) at 17 weeks in Study NS-304/-02; and -122.9 ± 115.2 and -120.9 dyn·sec·cm$^{-5}$ (mean ± SD and median, respectively) at Week 16 in Study AC-065A201, showing an improving tendency to a similar extent. These results support the efficacy of selexipag in Japanese patients with PAH as in non-Japanese patients in foreign clinical studies.

**7.R.4 Safety**

**7.R.4.1 Hypotension**

PMDA asked the applicant to explain the incidences of hypotension-related adverse events in the Japanese and foreign clinical studies, and to explain the appropriateness of providing a caution statement in the package insert, based on the discussion of the relationship of these adverse events with dosing frequency, dose, as well as risk factors such as patient characteristics and concomitant drugs.

The applicant's explanation:
Table 36 shows the incidences of hypotension-related adverse events (adverse events corresponding to "blood pressure ambulatory decreased," "blood pressure decreased," "blood pressure diastolic decreased," "blood pressure orthostatic decreased," "blood pressure systolic decreased," "diastolic hypotension," "hypotension," "mean arterial pressure decreased," "orthostatic hypotension," or "procedural hypotension" in preferred terms of Medical Dictionary for Regulatory Activities [MedDRA]) in the Japanese and foreign clinical studies.

**Table 36. Incidence of hypotension-related adverse events (safety analysis set)**

| | Study AC-065A201 | Study NS-304/-02 | | Study AC-065A302 | |
|---|---|---|---|---|---|
| | Selexipag | Selexipag | Placebo | Selexipag | Placebo |
| Number of subjects | 37 | 33 | 10 | 575 | 577 |
| Hypotension-related adverse events | 16.2 (6) | 6.1 (2) | 0 (0) | 5.9 (34) | 3.8 (22) |
| Hypotension | 8.1 (3) | 3.0 (1) | 0 (0) | 5.0 (29) | 3.1 (18) |
| Blood pressure decreased | 10.8 (4) | 3.0 (1) | 0 (0) | 0 (0) | 0.2 (1) |
| Orthostatic hypotension | 0 (0) | 0 (0) | 0 (0) | 0.9 (5) | 0.5 (3) |

% (n)

The incidences of adverse events in long-term treatment were investigated based on the combined results of Study NS-304/-02 and Study NS-304/-03 (an open-label, uncontrolled, extension study in subjects who had completed Study NS-304/-02) and on the combined results of Study AC-065A302 and Study AC-065A303. Results showed that the incidence of hypotension-related adverse events was 17.1% (7 of 41) of subjects in Studies NS-304/-02 + NS-304/-03 and 6.0% (44 of 730) of subjects in Studies AC-065A302 + AC-065A303. The main event was hypotension. There was no increasing tendency in the incidence of adverse events after long-term treatment.

None of the studies showed tendency of dose-dependent increase in adverse events, either by dose at each evaluation time point during the dose titration period, or by maintenance dose during the dose maintenance period. No study drug-associated significant changes were noted in blood pressure over time in any study. Occurrences of hypotension were investigated in patient subgroups classified by characteristics (age, sex, body weight, WHO functional class, underlying disease of PAH), and by use or non-use of concomitant PAH drug. Results did not show any clear risk factors for hypotension.

These results suggest that selexipag has only a low risk of hypotension. However, there are concerns about fall, interference with driving, etc., associated with hypotension and orthostatic hypotension. The package insert for selexipag will therefore include a caution statement requiring healthcare professionals to administer the drug with care to hypotensive patients, as with the package inserts for other drugs in the same class.

PMDA's view:
Selexipag has a vasodilating effect, and is shown to cause hypotension-related adverse events in clinical studies, as is the case with other pulmonary vasodilators. Therefore, the risk of such events should be appropriately controlled. In the package insert, hypotensive drugs should be listed under "precautions for coadministration" and patients with hypotension under "careful administration," as proposed by the applicant. In addition, an additional caution should be issued to ensure that selexipag is administered with care to patients with specific underlying diseases that may be aggravated by the vasodilating effect of selexipag (e.g., decreased body fluid, severe left ventricle outflow tract obstruction, and autonomic disorder). PMDA considers that these precautions will allow a certain level of control. PMDA will draw a final conclusion regarding the content of caution statement against hypotension, taking account of comments raised in the Expert Discussion.

### 7.R.4.2 Haemorrhage, thrombocytopenia, and coagulation disorder

PMDA asked the applicant to explain the incidences of adverse events related to haemorrhage, thrombocytopenia, and coagulation disorder in Japanese and foreign clinical studies, and to explain the appropriateness of providing a caution statement in the package insert, based on the discussion of the relationship of these adverse events with dose, and risk factors such as patient characteristics and concomitant drugs.

The applicant's explanation:
The incidences of the following adverse events reported in Japanese and foreign clinical studies were investigated: Haemorrhage-related adverse events (adverse events corresponding to "Haemorrhage terms [excl laboratory terms]" and "Gastrointestinal haemorrhage" in MedDRA standardised MedDRA queries [SMQ]); thrombocytopenia-related adverse events (adverse events corresponding to "Haematopoietic thrombocytopenia" or "Haematopoietic cytopenias affecting more than 1 type of blood cell" in MedDRA SMQ, or to MedDRA preferred terms containing "Thrombocytop"); and coagulation disorder-related adverse events (adverse events corresponding to "Liver-related coagulation and bleeding disturbances" in MedDRA SMQ).

Table 37 shows the incidence of haemorrhage-related adverse events.

**Table 37. Incidence of main adverse events related to haemorrhage (safety analysis set)**

| | Study AC-065A201 | Study NS-304/-02 | | Study AC-065A302 | |
|---|---|---|---|---|---|
| | Selexipag | Selexipag | Placebo | Selexipag | Placebo |
| Number of subjects | 37 | 33 | 10 | 575 | 577 |
| Haemorrhage-related adverse events | 43.2 (16) | 6.1 (2) | 20.0 (2) | 15.5 (89) | 15.8 (91) |
| Epistaxis | 10.8 (4) | 3.0 (1) | 10.0 (1) | 5.2 (30) | 5.0 (29) |
| Haemoptysis | 2.7 (1) | 0 (0) | 10.0 (1) | 2.4 (14) | 3.1 (18) |
| Contusion | 10.8 (4) | 0 (0) | 0 (0) | 1.2 (7) | 1.2 (7) |
| Retinal haemorrhage | 10.8 (4) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |

% (n)

During the long-term treatment, haemorrhage-related adverse events were observed in 31.7% (13 of 41) of subjects in Studies NS-304/-02 + NS-304/-03 and in 15.8% (115 of 730) of subjects in Studies AC-065A302 + AC-065A303. The main events were epistaxis and haemoptysis.

Thrombocytopenia-related adverse events were observed in none of subjects in Study NS-304/-02, in 2.7% (1 of 37; thrombocytopenia) of subjects in the selexipag group of Study AC-065A201, in 1.7% (10 of 575; thrombocytopenia [6 subjects], platelet count decreased [2 subjects], pancytopenia and idiopathic thrombocytopenic purpura [1 subject each]) of subjects in the selexipag group, and in 1.9% (11 of 577; thrombocytopenia [9 subjects], platelet count decreased and pancytopenia [1 subject each]) of subjects in the placebo group of Study AC-065A302. During the long-term treatment, thrombocytopenia-related adverse events were observed in none of subjects in Studies NS-304/-02 + NS-304/-03 and in 2.2% (16 of 730) of subjects in Studies AC-065A302 + AC-065A303. The main events were thrombocytopenia.

Coagulation disorder-related adverse events were observed in none of the subjects in Studies AC-065A201 and NS-304/-02, and in 1.4% (8 of 575; INR increased [7 subjects], hypocoagulable state [1 subject]) of subjects in the selexipag group and in 1.4% (8 of 577; INR increased [7 subjects], PT increased [1 subject]) of subjects in the placebo group of Study AC-065A302. During the long-term treatment, coagulation disorder-related adverse events were observed in none of the subjects in Studies NS-304/-02 + NS-304/-03 and in 1.4% (10 of 730) of subjects in Studies AC-065A302 + AC-065A303. The main events were INR increased.

In any of the studies, there was no tendency of dose-dependent increase in adverse events, either by dose at each evaluation time point during the dose titration period or by maintenance dose during the dose maintenance period. No study drug-associated significant changes were noted in platelet count, INR, or APTT over time in any study.

The incidences of these adverse events were investigated in patient subgroups classified by characteristics (age, sex, body weight, WHO functional class, underlying disease of PAH) and by use or non-use of concomitant PAH drug or warfarin. Results did not show any clear risk factors. Also, the incidence of adverse events did not tend to increase after long-term treatment.

Thus, in the clinical studies, selexipag did not pose clinically significant risk of haemorrhage, thrombocytopenia, or coagulation disorder. However, because selexipag suppressed platelet aggregation in an *in vitro* study, the package insert for selexipag will include a caution statement requiring careful administration in patients with bleeding tendency or those predisposed to haemorrhage, as with the package inserts for other drugs in the same class.

PMDA's view:
Anticoagulants or antiplatelet drugs are expected to be used in combination with selexipag in patients with PAH. Selexipag may further increase the bleeding risk in patients taking these concomitant drugs. Combination of anticoagulants or antiplatelet drugs with selexipag, which has a platelet anti-aggregating effect, may enhance bleeding tendency, possibly resulting in serious adverse events. Caution statement against the risk of haemorrhage and countermeasures should be provided in the package insert, and patients should be alerted to the risk with detailed explanation.

### 7.R.4.3 Thyroid dysfunction

PMDA asked the applicant to explain the incidences of adverse events related to thyroid dysfunction in Japanese and foreign clinical studies, and to explain the appropriateness of providing a caution statement in the package insert, based on the discussion of the relationship of these adverse events with dose, and risk factors such as patient characteristics and concomitant drugs.

The applicant's explanation:
Table 38 shows the incidences of thyroid dysfunction-related adverse events (adverse events corresponding to "Hyperthyroidism" or "Hypothyroidism" in MedDRA SMQ) in Japanese and foreign clinical studies.

**Table 38. Incidence of main adverse events related to thyroid dysfunction (safety analysis set)**

| | Study AC-065A201 | Study NS-304/-02 | | Study AC-065A302 | |
|---|---|---|---|---|---|
| | Selexipag | Selexipag | Placebo | Selexipag | Placebo |
| Number of subjects | 37 | 33 | 10 | 575 | 577 |
| Adverse events related to thyroid dysfunction | 5.4 (2) | 3.0 (1) | 0 (0) | 4.0 (23) | 3.3 (19) |
| Hypothyroidism | 5.4 (2) | 3.0 (1) | 0 (0) | 1.4 (8) | 1.9 (11) |
| Hyperthyroidism | 0 (0) | 0 (0) | 0 (0) | 1.4 (8) | 0 (0) |
| Blood TSH increased | 0 (0) | 0 (0) | 0 (0) | 0.5 (3) | 0.9 (5) |
| Exophthalmos | 0 (0) | 0 (0) | 0 (0) | 0.2 (1) | 0.2 (1) |
| Autoimmune thyroiditis | 0 (0) | 0 (0) | 0 (0) | 0.3 (2) | 0 (0) |

% (n)

During the long-term treatment, the incidence of thyroid dysfunction-related adverse events was 7.3% (3 of 41) of subjects in Studies NS-304/-02 + NS-304/-03 and 3.8% (28 of 730) of subjects in Studies AC-065A302 + AC-065A303. The main event was hypothyroidism. The long-term treatment did not cause any increase in the incidence of thyroid dysfunction-related adverse events.

In any of the studies, there was no tendency of dose-dependent increase in adverse events, either by dose at each evaluation time point during the dose titration period or by maintenance dose during the dose maintenance period. No study drug-associated significant changes were observed in TSH, $T_3$, or $T_4$ level in the above studies. The incidences of thyroid dysfunction-related adverse events were investigated in patient subgroups classified by characteristics (age, sex, body weight, WHO functional class, underlying disease of PAH) and by use or non-use of concomitant PAH drug. Results did not show any clear risk factors.

Thus, in the clinical studies, selexipag did not pose risk of thyroid dysfunction. However, because PAH and thyroid dysfunction often occur concurrently (*Panminerva Med.* 2013;55:93-7), the package insert will include a caution statement (as with the package inserts for other drugs in the same class) to ensure that patients are closely monitored by thyroid function test, etc. during selexipag therapy. The applicant considers that these measures will allow appropriate control of thyroid dysfunction.

PMDA's view:
Patients treated with epoprostenol sodium, a drug in the same class, are alerted to hyperthyroidism as an adverse drug reaction. Thyroid disorder-related adverse events occurred also in the Japanese and foreign clinical studies of selexipag. These studies did not show any tendency of increase in the incidence of thyroid dysfunction with the increase in dose or in the administration period, and none of the patient characteristics nor concomitant drugs were identified as risk factors. Nevertheless, the risk of thyroid disorder should be appropriately controlled. PMDA has concluded that thyroid disorder will be controlled at a certain level by providing an appropriate caution statement in the package insert, as

proposed by the applicant. PMDA will draw a final conclusion regarding the appropriateness of the content of the caution statement, taking account of comments raised in the Expert Discussion.

### 7.R.4.4 Eye disorders including retinal disorder

In nonclinical studies, dilatation and tortuosity of retinal arterioles were observed [see "5.R.3 Dilatation and tortuosity of retinal arterioles"]. PMDA asked the applicant to explain the incidences of adverse events related to eye disorders (including retinal disorder) in the Japanese and foreign clinical studies, and to explain the necessity of providing a caution statement in the package insert, based on the discussion of the relationship of these adverse events with dose, and risk factors such as patient characteristics and concomitant drugs.

The applicant's explanation:
Tables 39 and 40 show the incidences of eye disorder (adverse events corresponding to "Eye disorders" in MedDRA system organ class [SOC]) and retinal disorder (adverse events corresponding to "Retinal disorders" in MedDRA SMQ), respectively.

**Table 39. Incidence of main adverse events related to eye disorder (safety analysis set)**

| | Study AC-065A201 | Study NS-304/-02 | | Study AC-065A302 | |
|---|---|---|---|---|---|
| | Selexipag | Selexipag | Placebo | Selexipag | Placebo |
| Number of subjects | 37 | 33 | 10 | 575 | 577 |
| Adverse events related to eye disorder | 24.3 (9) | 12.1 (4) | 0 (0) | 11.0 (63) | 7.8 (45) |
| Retinal haemorrhage | 10.8 (4) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Eye pain | 2.7 (1) | 0 (0) | 0 (0) | 1.6 (9) | 0.3 (2) |
| Cataract | 2.7 (1) | 0 (0) | 0 (0) | 1.4 (8) | 1.0 (6) |

% (n)

**Table 40. Incidence of main adverse events related to retinal disorder (safety analysis set)**

| | Study AC-065A201 | Study NS-304/-02 | | Study AC-065A302 | |
|---|---|---|---|---|---|
| | Selexipag | Selexipag | Placebo | Selexipag | Placebo |
| Number of subjects | 37 | 33 | 10 | 575 | 577 |
| Adverse events related to retinal disorder | 13.5 (5) | 3.0 (1) | 0 (0) | 3.5 (20) | 1.9 (11) |
| Retinal haemorrhage | 10.8 (4) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Vision blurred | 0 (0) | 3.0 (1) | 0 (0) | 0.9 (5) | 0.7 (4) |
| Visual acuity reduced | 0 (0) | 0 (0) | 0 (0) | 0.7 (4) | 0.7 (4) |
| Photophobia | 0 (0) | 0 (0) | 0 (0) | 0.7 (4) | 0.2 (1) |

% (n)

During the long-term treatment, the incidence of eye disorder-related adverse events was 14.6% (6 of 41) of subjects in Studies NS-304/-02 + NS-304/-03 and 9.7% (71 of 730) of subjects in Studies AC-065A302 + AC-065A303. The main events were eye pain and cataract. The incidence of retinal disorder-related adverse events was 2.4% (1 of 41) of subjects in Studies NS-304/-02 + NS-304/-03 and 3.3% (24 of 730) of subjects in Studies AC-065A302 + AC-065A303. The main event was vision blurred. The incidence did not increase with long-term treatment.

In any of the studies, there was no tendency of dose-dependent increase in adverse events, either by dose at each evaluation time point during the dose titration period or by maintenance dose during the dose maintenance period. The incidences of these adverse events were investigated in patient subgroups classified by characteristics (age, sex, body weight, WHO functional class, underlying disease of PAH) and by use or non-use of concomitant PAH drug. Results did not show any clear risk factors.

Based on the above, the applicant considers that selexipag has only a low risk of clinically significant eye disorder (including retinal disorder) and no particular caution statement is required.

PMDA's view:
In Japanese and foreign clinical studies, the incidence of eye disorder (including retinal disorder) showed no increasing tendency in a dose-proportional manner or after long-term treatment, and no patient characteristics or concomitant drugs were identified as risk factors. However, in Study AC-065A201, retinal haemorrhage occurred in 5.4% (2 of 37) of subjects as adverse events for which a causal relationship to the study drug could not be ruled out, and selexipag is a drug that may be used over a long-term period. Therefore, information on the risk of eye disorder including retinal disorder should be

provided in the adverse drug reactions section in the package insert. PMDA will draw a final conclusion regarding the necessity and details of a caution statement on selexipag-induced eye disorder, taking account of comments raised in the Expert Discussion.

#### 7.R.4.5 Other safety

PMDA's view on safety in terms of other events (i.e., other than haemorrhage, thrombocytopenia, coagulation disorder, hypotension, thyroid dysfunction, and eye disorder including retinal disorder):
Headache, flushing, dizziness, nausea, etc., occurred in patients receiving selexipag. These events are probably due to the pharmacological action of $PGI_2$ because they are known adverse events of existing $PGI_2$ preparations. Given the efficacy of selexipag [see "7.R.3 Efficacy"], the safety profile in terms of these systemic adverse drug reactions caused by selexipag is clinically acceptable. PMDA will draw a final conclusion on this matter (including the appropriateness of a caution statement), taking account of comments raised in the Expert Discussion.

### 7.R.5 Indication

#### 7.R.5.1 Underlying disease

PMDA asked the applicant to explain the appropriateness of indicating selexipag for "pulmonary arterial hypertension" regardless of the underlying disease(s) of PAH.

The applicant's explanation:
Tables 41 and 42 show the efficacy of selexipag in patients with PAH classified by the underlying disease, in the Japanese and foreign clinical studies. PAH tended to improve after selexipag administration regardless of the underlying disease.

**Table 41. Time to the first morbidity/mortality event in patients classified by the underlying disease of PAH**
**(Study AC-065A302; FAS)**

| | Selexipag | Placebo | Hazard ratio [99% CI] |
|---|---|---|---|
| IPAH or HPAH | 325 subjects | 350 subjects | 0.62 [0.43, 0.89] |
| CTD-associated PAH | 167 subjects | 167 subjects | 0.59 [0.36, 0.98] |
| Others<br>(PAH associated with congenital heart disease, drug/toxin-induced PAH, HIV-infection-associated PAH) | 82 subjects | 65 subjects | 0.74 [0.27, 1.99] |

**Table 42. Change in PVRI (dyn·sec·m$^2$·cm$^{-5}$) from baseline in patients classified by the underlying disease of PAH**
**(Studies AC-065A201 and NS-304/-02)**

| | | Study AC-065A201 (PPS) | Study NS-304/-02 (Per-protocol DB set) | |
|---|---|---|---|---|
| | | Selexipag | Selexipag | Placebo |
| IPAH or HPAH | Number of subjects | 29 | 22 | 5 |
| | Baseline | | | |
| | Mean ± SD | 1087.9 ± 382.1 | 1607.9 ± 734.4 | 1552.1 ± 97.8 |
| | Median | 1064.4 | 1368.0 | 1594.9 |
| | Change | | | |
| | Mean ± SD | -180.5 ± 178.6 | -321.4 ± 350.8 | 280.3 ± 142.2 |
| | Median | -166.6 | -301.1 | 312.2 |
| CTD-associated PAH | Number of subjects | 3 | 4 | 1 |
| | Baseline | | | |
| | Mean ± SD | 755.5 ± 189.3 | 1014.9 ± 372.9 | 781.7 |
| | Median | 719.7 | 954.1 | 781.7 |
| | Change | | | |
| | Mean ± SD | -259.8 ± 229.5 | -15.5 ± 254.1 | 50.7 |
| | Median | -335.9 | -90.1 | 50.7 |
| Others (PAH associated with congenital heart disease, drug/toxin-induced PAH, HIV-infection-associated PAH) | Number of subjects | 1 | 3 | 0 |
| | Baseline | | | |
| | Mean ± SD | 1715.7 | 2692.2 ± 174.9 | - |
| | Median | 1715.7 | 2765.3 | - |
| | Change | | | |
| | Mean ± SD | -417.9 | -374.3 ± 862.0 | - |
| | Median | -417.9 | -262.0 | - |

Some subgroups of patients with specific underlying disease showed no improvement in change in 6MWD from baseline to any evaluation time point. However, these subgroups had only a limited number of patients, and most patients showed consistent improvement. In Study AC-065A302, the percentage of subjects showing improvement in 6MWD within 26 weeks from baseline was higher in the selexipag group than in the placebo group regardless of the underlying disease.

As for safety, Table 43 shows the incidence of adverse events in subgroups classified by the underlying disease of PAH. No significant difference was observed in the tendency of incidences of adverse events among the subgroups classified by underlying diseases.

**Table 43. Incidence of main adverse events in subjects classified by underlying disease of PAH (safety analysis set)**

| | | Study AC-065A201 | Study NS-304/-02 | | Study AC-065A302 | |
|---|---|---|---|---|---|---|
| | | Selexipag | Selexipag | Placebo | Selexipag | Placebo |
| IPAH or HPAH | Number of subjects | 30 | 25 | 8 | 326 | 347 |
| | Adverse events | 100.0 (30) | 92.0 (23) | 100.0 (8) | 98.8 (322) | 96.8 (336) |
| | Hypotension[a] | 13.3 (4) | 4.0 (1) | 0 (0) | 4.6 (15) | 4.0 (14) |
| | Haemorrhage[b] | 46.7 (14) | 4.0 (1) | 12.5 (1) | 15.6 (51) | 17.3 (60) |
| | Thrombocytopenia[c] | 3.3 (1) | 0 (0) | 0 (0) | 0.9 (3) | 1.7 (6) |
| | Coagulation disorder[d] | 0 (0) | 0 (0) | 0 (0) | 1.5 (5) | 2.0 (7) |
| | Thyroid dysfunction[e] | 6.7 (2) | 0 (0) | 0 (0) | 4.0 (13) | 2.3 (8) |
| | Eye disorder[f] | 26.7 (8) | 8.0 (2) | 0 (0) | 8.9 (29) | 6.6 (23) |
| | Retinal disorder[g] | 13.3 (4) | 0 (0) | 0 (0) | 3.7 (12) | 2.3 (8) |
| CTD-associated PAH | Number of subjects | 6 | 4 | 2 | 167 | 165 |
| | Adverse events | 100.0 (6) | 100.0 (4) | 100.0 (2) | 98.2 (164) | 97.0 (160) |
| | Hypotension[a] | 33.3 (2) | 25.0 (1) | 0 (0) | 7.2 (12) | 4.8 (8) |
| | Haemorrhage[b] | 33.3 (2) | 0 (0) | 50.0 (1) | 13.8 (23) | 15.8 (26) |
| | Thrombocytopenia[c] | 0 (0) | 0 (0) | 0 (0) | 3.0 (5) | 1.8 (3) |
| | Coagulation disorder[d] | 0 (0) | 0 (0) | 0 (0) | 1.8 (3) | 0.6 (1) |
| | Thyroid dysfunction[e] | 0 (0) | 25.0 (1) | 0 (0) | 5.4 (9) | 4.2 (7) |
| | Eye disorder[f] | 16.7 (1) | 25.0 (1) | 0 (0) | 15.0 (25) | 9.1 (15) |
| | Retinal disorder[g] | 16.7 (1) | 0 (0) | 0 (0) | 3.0 (5) | 0.6 (1) |
| Others (PAH associated with congenital heart disease, drug/toxin-induced PAH, HIV-infection-associated PAH) | Number of subjects | 1 | 4 | 0 | 82 | 65 |
| | Adverse events | 100.0 (1) | 100.0 (4) | - | 96.3 (79) | 96.9 (63) |
| | Hypotension[a] | 0 (0) | 0 (0) | - | 8.5 (7) | 0 (0) |
| | Haemorrhage[b] | 0 (0) | 25.0 (1) | - | 18.3 (15) | 7.7 (5) |
| | Thrombocytopenia[c] | 0 (0) | 0 (0) | - | 2.4 (2) | 3.1 (2) |
| | Coagulation disorder[d] | 0 (0) | 0 (0) | - | 0 (0) | 0 (0) |
| | Thyroid dysfunction[e] | 0 (0) | 0 (0) | - | 1.2 (1) | 6.2 (4) |
| | Eye disorder[f] | 0 (0) | 25.0 (1) | - | 11.0 (9) | 10.8 (7) |
| | Retinal disorder[g] | 0 (0) | 25.0 (1) | - | 3.7 (3) | 3.1 (2) |

% (n)

[a] Adverse events corresponding to "blood pressure ambulatory decreased," "blood pressure decreased," "blood pressure diastolic decreased," "blood pressure orthostatic decreased," "blood pressure systolic decreased," "diastolic hypotension," "hypotension," "mean arterial pressure decreased," "orthostatic hypotension," or "procedural hypotension" in preferred terms of MedDRA

[b] Adverse events corresponding to "Haemorrhage terms (excl laboratory terms)" and "Gastrointestinal haemorrhage" in MedDRA SMQ

[c] Adverse events corresponding to "Haematopoietic thrombocytopenia" or "Haematopoietic cytopenias affecting more than 1 type of blood cell" in MedDRA SMQ, or to MedDRA preferred terms containing "thrombocytop"

[d] Adverse events corresponding to "Liver-related coagulation and bleeding disturbances" in MedDRA SMQ

[e] Adverse events corresponding to "Hyperthyroidism" or "Hypothyroidism" in MedDRA SMQ

[f] Adverse events corresponding to "Eye disorders" in MedDRA SOC

[g] Adverse events corresponding to "Retinal disorders" in MedDRA SMQ

In the US and European guidelines for the diagnosis and treatment of pulmonary hypertension, PAH is classified as Group 1 regardless of underlying disease, and the European guidelines recommend selexipag for the treatment of PAH. In view of this fact and the study results presented above, the proposed indication of selexipag ("pulmonary arterial hypertension" regardless of the underlying disease) is appropriate.

PMDA's view:

In Nice classification proposed at the Fifth World Symposium on Pulmonary Hypertension (*J Am Coll Cardiol*. 2013;62(25):D34-41), the underlying diseases of Group 1 pulmonary hypertension (PAH) vary widely. The results of Studies AC-065A201, NS-304/-02, and AC-065A302 do not mean that selexipag was shown to be effective and safe for PAH of all causes. However, PAH is a rare disease, and the number of patients with PAH with underlying diseases other than those evaluated in the clinical studies is even smaller. PMDA understands that conducting clinical studies in patients with these rare underlying diseases are practically impossible. Studies AC-065A201, NS-304/-02, and AC-065A302 suggested that the efficacy and safety of selexipag in patients with PAH are similar regardless of the type of PAH (i.e., IPAH or HPAH [main underlying diseases of PAH classified as Group 1], connective tissue disease-associated PAH, congenital heart disease-associated PAH, drug/toxin-associated PAH, or HIV-infection-associated PAH). In addition, Japanese and foreign guidelines including the most current treatment algorithm recommend the same treatment methods for all types of PAH in Group 1. This suggests that the recommendation is based on the concept that the same treatment effect is expected regardless of the

underlying disease. The existing $PGI_2$ preparations have been used for the treatment of PAH of all types regardless of the underlying disease, without clinically significant problems. In view of this fact, PMDA has concluded that selexipag should be indicated for the treatment of "pulmonary arterial hypertension" regardless of the underlying disease, including PAH caused by diseases that cannot be evaluated by clinical studies.

### 7.R.5.2 WHO functional class

PMDA asked the applicant to explain the appropriateness of indicating selexipag for all patients with PAH regardless of WHO functional class.

The applicant's explanation:
Tables 44 and 45 show the efficacy of selexipag in patients classified by WHO functional class in the Japanese and foreign clinical studies.

**Table 44. Time to the first morbidity/mortality event in patients classified by WHO functional class (Study AC-065A302, FAS)**

| | Selexipag | Placebo | Hazard ratio [99% CI] |
|---|---|---|---|
| Class I | 4 subjects | 5 subjects | - |
| Class II | 274 subjects | 255 subjects | 0.66 [0.41, 1.06] |
| Class III | 293 subjects | 314 subjects | 0.60 [0.42, 0.86] |
| Class IV | 3 subjects | 8 subjects | 0.50 [0.03, 9.02] |

**Table 45. Change in PVRI ($dyn \cdot sec \cdot m^2 \cdot cm^{-5}$) from baseline in patients classified by WHO functional class (Studies AC-065A201 and NS-304/-02)**

| | | Study AC-065A201 (PPS) | Study NS-304/-02 (Per-protocol DB set) | |
|---|---|---|---|---|
| | | Selexipag | Selexipag | Placebo |
| Class I | Number of subjects | 2 | 0 | 0 |
| | Baseline | | | |
| | Individual value | 617.8, 911.2 | - | - |
| | Median | 764.5 | - | - |
| | Change | | | |
| | Individual value | -408.1, -213.7 | - | - |
| | Median | -310.9 | - | - |
| Class II | Number of subjects | 20 | 12 | 2 |
| | Baseline | | | |
| | Mean ± SD | 1002.7 ± 355.4 | 1715.1 ± 971.9 | 1493.2 ± 159.1 |
| | Median | 1000.9 | 1307.1 | 1493.2 |
| | Change | | | |
| | Mean ± SD | -154.6 ± 160.8 | -345.5 ± 328.2 | 319.3 ± 10.1 |
| | Median | -130.0 | -271.2 | 319.3 |
| Class III | Number of subjects | 11 | 17 | 4 |
| | Baseline | | | |
| | Mean ± SD | 1268.1 ± 415.9 | 1584.0 ± 622.5 | 1388.9 ± 405.4 |
| | Median | 1286.1 | 1484.8 | 1579.2 |
| | Change | | | |
| | Mean ± SD | -246.9 ± 216.3 | -241.7 ± 457.4 | 203.4 ± 188.6 |
| | Median | -253.6 | -267.3 | 142.0 |

No subjects with WHO functional class IV were enrolled in these studies.

Subjects in WHO functional class II or III showed a decrease in the occurrence of morbidity/mortality events (the primary endpoint) in Study AC-065A302, and showed a tendency of improvement in PVRI in Studies AC-065A201 and NS-304/-02. The median 6MWD increased from baseline in subjects receiving selexipag in Studies AC-065A201 and NS-304/-02. In Study AC-065A302, the median 6MWD in the selexipag group did not increase from baseline but was not significantly shorter than that in the placebo group, and the percentage of subjects with improved 6MWD from baseline to Week 26 was higher in the selexipag group than in the placebo group.

There were only 6 subjects in class I and 3 subjects in class IV. These subjects showed consistent decrease in the occurrence of morbidity/mortality events and consistent improvement in PVRI and

6MWD as assessed by change from baseline. These subjects were treated with selexipag over a long-term period. In 2 of 3 subjects in class IV, WHO functional class improved to III.

Table 46 shows the incidences of adverse events in subjects classified by WHO functional class. No significant difference was observed in the incidences of adverse events between subjects in class II and III. No subjects in class I or IV experienced adverse events severely compromising the tolerability.

**Table 46. Incidence of main adverse events in patients classified by WHO functional class (safety analysis set)**

| | | Study AC-065A201 | Study NS-304/-02 | | Study AC-065A302 | |
|---|---|---|---|---|---|---|
| | | Selexipag | Selexipag | Placebo | Selexipag | Placebo |
| Class I | Number of subjects | 2 | 0 | 0 | 4 | 4 |
| | Adverse events | 100.0 (2) | - | - | 100.0 (4) | 100.0 (4) |
| | Hypotension[a] | 0 (0) | - | - | 0 (0) | 0 (0) |
| | Haemorrhage[b] | 50.0 (1) | - | - | 0 (0) | 50.0 (2) |
| | Thrombocytopenia[c] | 0 (0) | - | - | 0 (0) | 0 (0) |
| | Coagulation disorder[d] | 0 (0) | - | - | 0 (0) | 0 (0) |
| | Thyroid dysfunction[e] | 0 (0) | - | - | 25.0 (1) | 0 (0) |
| | Eye disorder[f] | 50.0 (1) | - | - | 0 (0) | 25.0 (1) |
| | Retinal disorder[g] | 50.0 (1) | - | - | 0 (0) | 0 (0) |
| Class II | Number of subjects | 21 | 15 | 2 | 274 | 252 |
| | Adverse events | 100.0 (21) | 93.3 (14) | 100.0 (2) | 97.8 (268) | 94.0 (237) |
| | Hypotension[a] | 19.0 (4) | 6.7 (1) | 0 (0) | 4.4 (12) | 2.4 (6) |
| | Haemorrhage[b] | 42.9 (9) | 6.7 (1) | 0 (0) | 11.3 (31) | 16.3 (41) |
| | Thrombocytopenia[c] | 0 (0) | 0 (0) | 0 (0) | 1.8 (5) | 2.0 (5) |
| | Coagulation disorder[d] | 0 (0) | 0 (0) | 0 (0) | 0.7 (2) | 0.8 (2) |
| | Thyroid dysfunction[e] | 4.8 (1) | 0 (0) | 0 (0) | 2.9 (8) | 4.0 (10) |
| | Eye disorder[f] | 14.3 (3) | 13.3 (2) | 0 (0) | 12.0 (33) | 8.7 (22) |
| | Retinal disorder[g] | 4.8 (1) | 6.7 (1) | 0 (0) | 4.0 (11) | 2.4 (6) |
| Class III | Number of subjects | 14 | 18 | 8 | 294 | 313 |
| | Adverse events | 100.0 (14) | 94.4 (17) | 100.0 (8) | 98.6 (290) | 99.0 (310) |
| | Hypotension[a] | 14.3 (2) | 5.6 (1) | 0 (0) | 7.5 (22) | 5.1 (16) |
| | Haemorrhage[b] | 42.9 (6) | 5.6 (1) | 25.0 (1) | 19.4 (57) | 14.4 (45) |
| | Thrombocytopenia[c] | 7.1 (1) | 0 (0) | 0 (0) | 1.7 (5) | 1.9 (6) |
| | Coagulation disorder[d] | 0 (0) | 0 (0) | 0 (0) | 2.0 (6) | 1.6 (5) |
| | Thyroid dysfunction[e] | 7.1 (1) | 5.6 (1) | 0 (0) | 4.8 (14) | 2.9 (9) |
| | Eye disorder[f] | 35.7 (5) | 11.1 (2) | 0 (0) | 10.2 (30) | 7.0 (22) |
| | Retinal disorder[g] | 21.4 (3) | 0 (0) | 0 (0) | 3.1 (9) | 1.6 (5) |
| Class IV | Number of subjects | 0 | 0 | 0 | 3 | 8 |
| | Adverse events | - | - | - | 100.0 (3) | 100.0 (8) |
| | Hypotension[a] | - | - | - | 0 (0) | 0 (0) |
| | Haemorrhage[b] | - | - | - | 33.3 (1) | 37.5 (3) |
| | Thrombocytopenia[c] | - | - | - | 0 (0) | 0 (0) |
| | Coagulation disorder[d] | - | - | - | 0 (0) | 12.5 (1) |
| | Thyroid dysfunction | - | - | - | 0 (0) | 0 (0) |
| | Eye disorder[f] | - | - | - | 0 (0) | 0 (0) |
| | Retinal disorder[g] | - | - | - | 0 (0) | 0 (0) |

% (n)

[a] Adverse events corresponding to "blood pressure ambulatory decreased," "blood pressure decreased," "blood pressure diastolic decreased," "blood pressure orthostatic decreased," "blood pressure systolic decreased," "diastolic hypotension," "hypotension," "mean arterial pressure decreased," "orthostatic hypotension," or "procedural hypotension" in preferred terms of MedDRA

[b] Adverse events corresponding to "Haemorrhage terms (excl laboratory terms)" and "Gastrointestinal haemorrhage" in MedDRA SMQ

[c] Adverse events corresponding to "Haematopoietic thrombocytopenia" or "Haematopoietic cytopenias affecting more than 1 type of blood cell" in MedDRA SMQ, or to MedDRA preferred terms containing "thrombocytop"

[d] Adverse events corresponding to "Liver-related coagulation and bleeding disturbances" in MedDRA SMQ

[e] Adverse events corresponding to "Hyperthyroidism" or "Hypothyroidism" in MedDRA SMQ

[f] Adverse events corresponding to "Eye disorders" in MedDRA SOC

[g] Adverse events corresponding to "Retinal disorders" in MedDRA SMQ

Based on the above, the applicant considers selexipag should be indicated for the treatment of "pulmonary arterial hypertension" regardless of WHO functional class.

PMDA's view:

In Study AC-065A201, 21 of 37 subjects treated with the study drug were in WHO functional class II, and 14 subjects in class III. In Study NS-304/-02, 17 subjects (2 receiving placebo, 15 receiving

selexipag) were in class II, and 26 subjects (8 receiving placebo, 18 receiving selexipag) in class III. In Study AC-065A302, 529 subjects (255 receiving placebo, 274 receiving selexipag) were in class II and 607 subjects (314 receiving placebo, 293 receiving selexipag) in class III. PMDA has concluded that the results of these studies demonstrated the efficacy and safety of selexipag in patients with WHO functional class II or III.

Two subjects in class I were enrolled in Study AC-065A201, and 9 subjects (5 in the placebo group, 4 in the selexipag group) in class I in Study AC-065A302. These studies enrolled only a small number of patients in class I although their inclusion criteria included "class I patients." PMDA understands this, because many patients in class I do not feel symptoms and therefore do not see a PAH specialist, and because making a definitive diagnosis of PAH is difficult for non-specialist physicians. In Study AC-065A302, no morbidity/mortality event occurred in any of 4 subjects in class I enrolled in the selexipag group. In Study AC-065A201, 2 subjects in class I showed improvement in PVRI from baseline to Week 16. All the subjects in class I at baseline remained in class I during the efficacy evaluation period, received the study drug over a long-term period (334-1098 days) without experiencing any morbidity/mortality event, and are continuing Study AC-065A201 or completed Study AC-065A302. These results, albeit obtained from a small number of subjects, suggest the efficacy of selexipag in patients in class I.

Eleven subjects (8 in the placebo group, 3 in the selexipag group) in class IV were enrolled in Study AC-065A302. The study enrolled only a small number of patients in class IV. PMDA understands this, because patients in class IV had already been treated for their severe conditions, and only a fraction of them met the inclusion criteria restricting concomitant use of other PAH drugs. In Study AC-065A302, the hazard ratio [99% CI] of morbidity/mortality events in the selexipag group relative to the placebo group was 0.50 [0.03, 9.02] among patients in class IV, showing a decrease in the risk of morbidity/mortality events in the selexipag group than in the placebo group. In 2 of 3 subjects in class IV at baseline in the selexipag group, WHO functional class improved to class III at Week 26. These results suggest the efficacy of selexipag in patients in class IV.

Selexipag should be offered as a treatment option to patients in class I (relatively mild conditions) and in class IV (severe conditions), because the efficacy of selexipag has been demonstrated in patients in class II and III, and for the following reasons: (1) PAH is a fatal progressive disease; (2) the Fifth World Symposium on Pulmonary Hypertension proposed that active treatment be initiated from an early stage of the disease, and that patients with severe conditions or with poor response to monotherapy receive combination therapy involving different mechanisms of action consisting of $PGI_2$ preparations, ERA, PDE-5 inhibitors, or sGC stimulants; and (3) WHO functional class alters depending on the treatment or change in disease conditions.

Based on the above, PMDA has concluded that selexipag should be indicated for the treatment of all patients with PAH, regardless of WHO functional class. PMDA will draw a final conclusion regarding (a) the indication of selexipag and (b) whether the efficacy in patients in class I and IV should be mentioned in the package insert, taking account of comments raised in the Expert Discussion.

### 7.R.6 Dosage and administration

The applicant's explanation on the dosage and administration of selexipag:

The efficacy of $PGI_2$ preparations for PAH treatment increases when the dose is aggressively increased to a maximum tolerated dose for each patient who can tolerate the treatment. Starting the treatment at a high dose may cause $PGI_2$-related adverse events such as hypotension, headache, diarrhoea, pain in jaw, myalgia, flushing, and nausea, leading to decreased or poor tolerability. In addition, sensitivity to $PGI_2$ preparations varies widely among patients. Therefore, in clinical practice, treatment with $PGI_2$ preparations is usually started at a low dose, which is then increased to a maximum tolerated level for each patient based on individual tolerability. In the Japanese and foreign clinical studies of selexipag as well, the dose was increased to a maximum tolerated level for each patient based on individual tolerability. In view of the pharmacokinetic profile of selexipag ($t_{1/2}$ after single-dose administration is approximately 0.7-2.5 hours for selexipag and approximately 6-13 hours for MRE-269), selexipag was administered twice daily in all studies. In the foreign phase I study, a single-dose administration of selexipag 0.1 to 0.8 mg showed a good tolerability up to 0.4 mg, but the incidence of adverse events increased at doses of ≥0.6 mg. Also, multiple-dose administration of selexipag at 0.2 or 0.4 mg/dose

twice daily showed a similar tolerability. Therefore, in Study NS-304/-02, selexipag was administered at 0.2 to 0.8 mg per dose. Study NS-304/-02 demonstrated the efficacy and safety of selexipag at a dose of 0.2 to 0.8 mg per administration but, 5 of 13 subjects receiving 0.8 mg still showed no decrease in PVR, which suggested that some patients required a dose exceeding 0.8 mg. Accordingly, in Studies AC-065A201 and AC-065A302, selexipag therapy was started at 0.2 mg twice daily, which was up-titrated by 0.2 mg increments to a maximum tolerated dose for each subject (not above 1.6 mg per administration). Results of the single- and multiple-dose Japanese and foreign phase I studies showed differences in pharmacokinetics (probably due to difference in body weight) between Japanese and non-Japanese healthy adults, but the differences were minor and suggested no clinically significant effect [see "6.R.2 Comparison of pharmacokinetics between Japanese and non-Japanese population"]. Therefore, Study AC-065A201 used the same dosage regimen used in Study AC-065A302.

Table 47 shows the efficacy (incidence of the first morbidity/mortality event) classified by maintenance dose in Study AC-065A302. The efficacy did not significantly vary depending on the maintenance dose. Also, PVRI improved from baseline in all subgroups of different maintenance doses in Studies AC-065A201 and NS-304/-02.

Thus, all maintenance doses showed a consistent efficacy of selexipag, suggesting that selexipag is effective at doses of 0.2 to 1.6 mg per administration. (This dose range was stipulated in the protocols of Studies AC-065A201 and AC-065A302.)

**Table 47. Incidences of the first morbidity/mortality event in patients classified by maintenance dose (Study AC-065A302, FAS)**

| | | Number of subjects | Occurrences of morbidity/mortality events[a] |
|---|---|---|---|
| Selexipag | | 574 | 140 (24.4) |
| Maintenance dose (mg/dose) | 0.2 | 68 | 12 (17.6) |
| | 0.4 | 65 | 14 (21.5) |
| | 0.6 | 62 | 12 (19.4) |
| | 0.8 | 82 | 21 (25.6) |
| | 1.0 | 35 | 8 (22.9) |
| | 1.2 | 42 | 9 (21.4) |
| | 1.4 | 41 | 7 (17.1) |
| | 1.6 | 163 | 55 (33.7) |
| Placebo | | 582 | 212 (36.4) |

[a] Number of patients who experienced morbidity/mortality event(s) (%)

Table 48 shows adverse events in patients classified by maintenance dose in Study AC-065A201. The safety profile did not differ between the different doses. Analysis of the incidence of adverse events, classified by the timing during the dose titration period, showed that the incidence of adverse events did not increase with dose escalation. In Study AC-065A302 as well, analysis of the incidence of adverse events classified by maintenance dose showed no difference in the safety profile between the different doses. These results suggest that the difference in the maintenance dose does not significantly affect the safety.

**Table 48. Incidence of adverse events in patients classified by maintenance dose (Study AC-065A201, safety analysis set)**

| Maintenance dose (per dose) | 0.2 mg | 0.4 mg | 0.6 mg | 0.8 mg | 1.0 mg | 1.2 mg | 1.4 mg | 1.6 mg |
|---|---|---|---|---|---|---|---|---|
| Number of subjects | 2 | 2 | 5 | 7 | 6 | 3 | 2 | 7 |
| Adverse events | 50.0 (1) | 100.0 (2) | 100.0 (5) | 100.0 (7) | 100.0 (6) | 100.0 (3) | 100.0 (2) | 85.7 (6) |
| Nasopharyngitis | - | - | 60.0 (3) | 85.7 (6) | 50.0 (3) | 66.7 (2) | 50.0 (1) | 42.9 (3) |
| Headache | - | 100.0 (2) | 20.0 (1) | 28.6 (2) | 33.3 (2) | 33.3 (1) | - | 57.1 (4) |
| Nausea | - | 50.0 (1) | 20.0 (1) | - | 33.3 (2) | 66.7 (2) | - | 14.3 (1) |
| Pulmonary arterial hypertension | - | 50.0 (1) | 20.0 (1) | 14.3 (1) | 16.7 (1) | 33.3 (1) | - | 28.6 (2) |
| Back pain | - | 50.0 (1) | - | 14.3 (1) | 16.7 (1) | 33.3 (1) | - | 14.3 (1) |
| Chest pain | - | - | 20.0 (1) | 28.6 (2) | 16.7 (1) | - | 50.0 (1) | - |
| Diarrhoea | 50.0 (1) | - | 40.0 (2) | - | 33.3 (2) | - | - | - |
| Epistaxis | - | 50.0 (1) | - | 28.6 (2) | - | 33.3 (1) | - | - |
| Retinal haemorrhage | - | - | - | - | 33.3 (2) | - | - | 28.6 (2) |
| Right ventricular failure | 50.0 (1) | - | - | 14.3 (1) | 33.3 (2) | - | - | - |
| Upper respiratory tract infection | - | - | - | - | 50.0 (3) | - | 50.0 (1) | - |

% (n)

Based on the above, the applicant considers that the starting dose of selexipag should be 0.2 mg per administration, which should be increased to a maximum tolerated dose in each patient (not above 1.6 mg per administration) based on individual tolerability.

PMDA's view:
PAH drugs are usually administered at a maximum effective dose within the approved dose range, based on tolerability, safety, and clinical symptoms of the patient. Study AC-065A201 used a dose adjustment method similar to that used in Study AC-065A302 based on the results of investigations on the intrinsic and extrinsic ethnic factors in Japanese and non-Japanese subjects, and demonstrated the efficacy of selexipag at each maintenance dose in Japanese patients with PAH as well. The safety in Japanese patients is within the range expected from the foreign clinical studies, and is acceptable given the seriousness of the disease and the safety of approved PAH drugs. PMDA thus concludes that selexipag therapy in Japanese adult patients with PAH should be started at 0.2 mg twice daily administered orally after a meal, which should be up-titrated, as much as possible, to a maximum tolerated dose for each patient based on individual tolerability, in the same manner as for the dosage for non-Japanese patients with PAH. As for the intervals of the dose increase, the proposed dosage and administration allowed dose increase at 3-day intervals, based on the results of Study AC-065A201, which allowed the dose increase at 3-day intervals to selexipag 1 mg. However, only a limited number of subjects were enrolled in Japanese clinical studies, and only 40.0% of patients underwent dose increase at <4-day intervals in Study AC-065A201 (14 of 35 subjects underwent dose increase at <4-day intervals at least once). Clinical data from a small number of Japanese subjects alone are insufficient to demonstrate the safety of up-titration at 3-day intervals. In Study AC-065A201, no subject underwent up-titration to >1 mg at 3-day intervals. Further, the protocol of Study AC-065A302 (which confirmed the efficacy of selexipag) stipulates that up-titrations should be performed at ≥7-day intervals for all dose levels. PMDA has therefore concluded that, also in Japan, selexipag doses should be increased at ≥7-day intervals and the proposed dosage and administration should be modified accordingly.

**7.R.7 Pediatric use**
PMDA asked the applicant to explain the development plan of selexipag for pediatric patients with PAH in Japan and other countries.

The applicant's explanation:
In foreign countries, [redacted]. Development of selexipag for pediatric patients with PAH in Japan is [redacted].

PMDA's view:
There are pediatric patients with PAH such as patients with IPAH, PAH associated with congenital heart disease, and PAH after open-heart surgery including Fontan surgery, indicating a high clinical need for increasing treatment options. Pediatric patients with IPAH, if left untreated, have a poorer prognosis than adult patients, but are more responsive to treatment than adult patients (*J Am Coll Cardiol*. 2009;53:1573-619, *Circulation.* 2009;119:2250-94). In addition, there are neonates and infants with PAH, requiring almost permanent treatment, for a longer period than in adult patients. Taking account of these situations, a clinical study in pediatric patients should be planned appropriately without delay to investigate the dosage regimen in this patient group.

**7.R.8 Post-marketing investigations**
The applicant's explanation on post-marketing investigations:
In order to evaluate the long-term safety and efficacy of selexipag in clinical use, a specified use-results survey (standard observation period; 1 year, 3 years at the maximum) will be conducted on all patients treated (target sample size, 1000 patients to be included in safety PK analysis). The survey will collect information on the incidences of hypotension, haemorrhage, etc., among others.

The target sample size was determined according to the following reasoning: According to the number of Intractable Disease Medical Treatment Recipient Certificates issued in Fiscal Year 2014, there are 2946 patients with PAH in Japan, and the number appears to be increasing by approximately 400 patients every year. The number of patients expected to use selexipag was predicted from the clinical positioning

of selexipag and, based on the prediction, it was decided to collect data from 1000 patients. If 1000 patients are included in safety analysis, important risks of selexipag such as hypotension can be detected (hypotension occurred with an incidence of 16.2% in Study AC-065A201).

PMDA's view:
Because of the extremely limited number of Japanese patients enrolled in clinical studies, the post-marketing surveillance should cover all patients treated with selexipag in order to actively and promptly collect the following information: The safety, efficacy, and incidences of hypotension, haemorrhage, etc., during long-term treatment in clinical use; the safety in populations with only limited data available from clinical studies (e.g., children, patients with hepatic impairment, patients with renal impairment); and the effect of concomitant drugs. Results obtained should be provided to healthcare professionals. In view of comments from the Expert Discussion, PMDA will draw a final conclusion regarding the details of the post-marketing surveillance (including appropriateness of safety specifications and risk classification as well as appropriateness of pharmacovigilance activities and risk minimization activities), according to "Risk Management Plan Guidance (PFSB/SD Notification No. 0411-1 and PFSB/ELD Notification No. 0411-2, dated April 11, 2012).

## 8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

### 8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The assessment is currently ongoing. Results and PMDA's conclusion will be reported in the Review Report (2).

### 8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The inspection is currently ongoing. Results and PMDA's conclusion will be reported in the Review Report (2).

## 9. Overall Evaluation during Preparation of the Review Report (1)

PMDA has concluded that the data submitted demonstrate the efficacy of selexipag in the treatment of patients with pulmonary arterial hypertension and acceptable safety in view of the benefits indicated by the data submitted. Selexipag is clinically meaningful because it offers a new treatment option for patients with pulmonary arterial hypertension. The indication, dosage and administration, caution statements in the package insert, and post-marketing investigations, should be discussed further.

PMDA has concluded that selexipag may be approved if selexipag is not considered to have any particular problems based on comments from the Expert Discussion.

**Review Report (2)**

August 15, 2016

**Product Submitted for Approval**

| | |
|---|---|
| **Brand Name** | Uptravi Tablets 0.2 mg,<br>Uptravi Tablets 0.4 mg |
| **Non-proprietary Name** | Selexipag |
| **Applicant** | Nippon Shinyaku Co., Ltd. |
| **Date of Application** | January 7, 2016 |

## 1. Content of the Review

Comments made during the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized in the following. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

### 1.1 Safety

#### 1.1.1 Hypotension

PMDA has concluded that hypotension-related risks are controllable at a certain level by providing a caution statement requiring careful administration in patients with specific underlying diseases that may be aggravated by the vasodilating effect of selexipag, in addition to the caution statement proposed by the applicant. This conclusion was supported by the expert advisors at the Expert Discussion.

Based on the above, PMDA instructed the applicant to provide a caution statement requiring careful administration in patients with specific underlying diseases that may be aggravated by the vasodilating effect of selexipag (e.g., decreased body fluid, severe left ventricle outflow tract obstruction, and autonomic disorder). The applicant responded appropriately.

#### 1.1.2 Thyroid dysfunction

PMDA has concluded that thyroid dysfunction-related risks are controllable at a certain level by providing a caution statement requiring detailed monitoring including a thyroid function test during the use of Uptravi Tablets (Uptravi), as proposed by the applicant. This conclusion was supported by the expert advisors at the Expert Discussion.

#### 1.1.3 Eye disorders including retinal disorder

PMDA has concluded that information on the risk of eye disorders including retinal disorder should be provided in the adverse drug reactions section in the package insert, as proposed by the applicant. This conclusion was supported by the expert advisors at the Expert Discussion.

#### 1.1.4 Other safety

PMDA has concluded that headache, flushing, dizziness, nausea, etc., are known adverse events of existing prostacyclin drugs as well, and that the safety profile of selexipag in terms of these systemic adverse drug reactions is clinically acceptable. This conclusion was supported by the expert advisors at the Expert Discussion. However, the following comment was raised from the expert advisors: The dose of selexipag should be increased carefully and gradually while closely monitoring the patient conditions, because headache and diarrhoea occurred frequently in the Japanese and foreign clinical studies, and because some patients in foreign clinical studies discontinued treatment due to adverse events or experienced serious adverse events for which a causal relationship to selexipag could not be ruled out.

Based on the above, PMDA instructed the applicant to provide a caution statement requiring careful and gradual dose increase while closely monitoring the patient conditions, because many adverse events (e.g., headache and diarrhoea) were reported to have occurred during the early phase of the treatment. The applicant responded appropriately.

### 1.2 Indication

PMDA has concluded the following indication of Uptravi is acceptable: The treatment of pulmonary arterial hypertension regardless of the underlying disease or WHO functional class. This conclusion was supported by the expert advisors at the Expert Discussion. Based on the above and on the results of the Japanese and foreign clinical studies, PMDA has concluded that the package insert need not include any specific caution statement regarding the efficacy of Uptravi in patients in WHO functional class I or IV who were enrolled in the clinical studies.

### 1.3 Dosage and administration

PMDA has concluded that the starting dose of selexipag should be 0.2 mg administered orally twice daily after a meal, which should be up-titrated at ≥7-days intervals to a maximum tolerated dose for each patient based on individual tolerability. This conclusion was supported by the expert advisors at the Expert Discussion.

Based on the above, PMDA has concluded that the following dosage and administration (see below) is appropriate, and instructed the applicant to modify the proposed dosage and administration accordingly. The applicant responded appropriately.

**Dosage and administration**

The usual starting dose for adults is 0.2 mg of Selexipag administered orally twice daily after a meal. Based on individual tolerability, the dose is increased by 0.2 mg increments at ≥7-day intervals to a maximum tolerated dose, to determine the maintenance dose. The maximum dose per administration is 1.6 mg. Selexipag is administered orally twice daily after a meal regardless of dose level.

### 1.4 Risk management plan (draft)

The conclusion by PMDA presented in the "7.R.8 Post-marketing investigations" section of the Review Report (1), was supported by the expert advisors at the Expert Discussion. The following comments were raised from some expert advisors: (1) It is important to promptly collect safety information in populations with scant clinical data such as children and patients with hepatic impairment, and to provide the obtained information to healthcare professionals; (2) the efficacy, safety, and appropriate dosage regimen should be investigated without delay, particularly in children.

Based on the above, PMDA has concluded that the risk management plan (draft) for Uptravi should include the safety and efficacy specifications presented in Table 49, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 50 as well as a specified use-results survey presented in Table 51. Additionally, PMDA instructed the applicant to promptly design and implement an appropriate clinical study in Japanese pediatric patients with pulmonary arterial hypertension (PAH) in order to investigate the efficacy, safety, and dosage regimen of Uptravi in Japanese pediatric patients with PAH. The applicant responded [redacted].

**Table 49. Safety and efficacy specifications in the risk management plan (draft)**

| Safety specification | | |
|---|---|---|
| Important identified risks | Important potential risks | Important missing information |
| • Hypotension<br>• Haemorrhage<br>• Patients with pulmonary veno-occlusive disease (PVOD)<br>• Thyroid dysfunction | • Eye disorders including retinal disorder | • Children<br>• Patients with hepatic impairment<br>• Patients with renal impairment<br>• Long-term safety |
| Efficacy specification | | |
| • Long-term efficacy in clinical use | | |

**Table 50. Summary of additional pharmacovigilance activities and risk minimization activities in the risk management plan (draft)**

| Additional pharmacovigilance activities | Additional risk minimization activities |
|---|---|
| • Early post-marketing phase vigilance<br>• Specified use-results survey (all-case survey)<br>• Post-marketing clinical study[a] | • Disseminate data gathered during early post-marketing phase vigilance |

[a] The ongoing Study AC-065A201 will be reclassified as a post-marketing clinical study after approval, and continued until Uptravi becomes widely available for use in medical institutions.

**Table 51. Outline of specified use-results survey (draft)**

| | |
|---|---|
| Objective | To investigate the long-term safety and efficacy of selexipag in clinical use |
| Survey method | All-case surveillance |
| Population | Patients with PAH |
| Observation period | 1 year (3 years at the maximum) |
| Planned sample size | 1000 patients included in safety analysis |
| Main survey items | Hypotension, haemorrhage, headache, etc. |

## 2. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

### 2.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. As a result, PMDA has concluded that there were no obstacles to conducting its review based on the application documents submitted.

### 2.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.2-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. As a result, PMDA has concluded that there were no obstacles to conducting its review based on the application documents submitted.

## 3. Overall Evaluation

As a result of its regulatory review, PMDA has concluded that the product may be approved for the indication and dosage and administration as shown below, with the following conditions. Since the product is an orphan drug, the re-examination period is 10 years. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug, and the drug product is not classified as a biological product or a specified biological product.

**Indication**

Pulmonary arterial hypertension

**Dosage and administration**

The usual starting dose for adults is 0.2 mg of Selexipag administered orally twice daily after a meal. Based on individual tolerability, the dose is increased by 0.2 mg increments at ≥7-day intervals to a maximum tolerated dose, to determine the maintenance dose. The maximum dose per administration is 1.6 mg. Selexipag is administered orally twice daily after a meal regardless of dose level.

**Conditions of Approval**

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Since only an extremely limited number of Japanese patients participated in clinical studies of the product, the applicant is required to conduct a use-results survey covering all Japanese patients treated with the product after the market launch until data from a certain number of patients have been gathered, in order to understand the characteristics of patients using the product, and to

promptly collect safety and efficacy data so that necessary measures are taken to ensure proper use of the product.