Efficacy and Safety of an Orally Administered Selective Prostacyclin Receptor Agonist, Selexipag, in Japanese Patients With Pulmonary Arterial Hypertension

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Background: Selexipag is an orally available prostacyclin receptor (IP receptor) agonist with a non-prostanoid structure. In this open-label Phase II trial, the efficacy and safety of selexipag in Japanese patients with pulmonary arterial hypertension (PAH) is examined.

Methods and Results: Selexipag was administered at 200 μg twice daily and titrated up to 1,600 μg by increments of 200 μg in 37 subjects to reach the individual maximum tolerated dose. At 16 weeks, in 33 patients comprising the per-protocol set, the pulmonary vascular resistance (PVR; primary endpoint) decreased from 683.2 ± 237.3 to 560.3 ± 238.7 dyn · s/cm² (P < 0.001). For the secondary endpoint, the 6-min walk distance (6MWD) increased from 445.0 ± 102.2 to 495.1 ± 112.8 m (P = 0.0324); World Health Organization functional class improved in 4 patients (12.1%), and was maintained in 29 patients (87.9%). A decrease in PVR was also shown in patients treated with selexipag, on top of a phosphodiesterase inhibitor and endothelin receptor antagonist. Most of the commonly reported adverse events were consistent with those reported for other PGI2 formulations. Thirty-four patients attained the individual maximum tolerated dose (maintenance dose).

Conclusions: The efficacy and tolerability of selexipag in Japanese PAH patients was confirmed by improvement in pulmonary hemodynamics, exercise capacity, symptoms. Selexipag is an efficacious treatment option for Japanese PAH patients. (Trial registration: JAPIC Clinical Trials Information [JapicCTI-111532].)

Key Words: Prostacyclin receptor agonist; Pulmonary arterial hypertension; Pulmonary hemodynamics; Safety; Selexipag

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In pulmonary arterial hypertension (PAH), pulmonary vascular resistance (PVR) increases due to pulmonary vasoconstriction and pulmonary vascular remodeling, which leads to increased pulmonary artery pressure (PAP). Ultimately, this causes right heart failure and leads to death.\(^1\) Since around 2000, effective new therapeutic drugs have become available for PAH treatment, such as prostacyclin and its derivatives, endothelin receptor antagonists (ERAs), and phosphodiesterase inhibitors. These drugs have significantly improved the prognosis of PAH patients.\(^4\) However, even with these treatments, PAH remains a progressive disease with a poor prognosis; development of a therapeutic drug that improves prognosis is therefore desired.\(^5,6\) In particular, PAH-specific medications that selectively target the PGI\(_2\) pathway are not available as convenient oral drugs\(^7\)–\(^10\) with strong evidence of long-term efficacy with respect to clinical outcome.

Selexipag is the first orally administered prostacyclin receptor (IP receptor) agonist with a non-prostanoid structure.\(^11\) An active metabolite of selexipag, MRE-269, shows high selectivity to the IP receptor, and its long half-life enables a twice-a-day oral dosing regimen.\(^12\)

Thirty-nine countries jointly participated in a double-blind, placebo-controlled Phase III study with selexipag, with 1,156 PAH patients (GRIPHON study).\(^13\) The primary endpoint was a composite of death from any cause or a complication related to PAH up to the end of the treatment period. The risk of the primary composite endpoint of death or a complication related to PAH was significantly lower with selexipag than with placebo. For the 1,000 \(\mu\)g dose or higher, the patient was required to stay in the hospital for at least 3 days and 2 nights from the time of titration.

Figure 1. Schema of the study design. The figure shows the fastest possible dose titration schedule. The study drug was initiated at 200 \(\mu\)g twice daily and titrated according to individual tolerance. Dose reduction and re-up-titration were both allowed. An 8-day interval was required for re-up-titration after dose reduction in order to confirm tolerability. For the 1,000 \(\mu\)g dose or higher, the patient was required to stay in the hospital for at least 3 days and 2 nights from the time of titration.

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Methods

Selection of Patients

Eligible subjects were Japanese patients aged 18 years or older who had idiopathic PAH (IPAH), hereditary PAH (HPAH), drug- or toxin-induced PAH, or PAH associated with connective tissue disease, congenital heart disease with a shunt repair surgery, or HIV infection and who were in WHO functional class I–IV. The diagnosis of PAH was confirmed within 30 days prior to the beginning of selexipag administration by measurement of pulmonary hemodynamics at rest under right heart catheterization. Hemodynamic eligibility criteria were as follows: mean PAP (mPAP) \(\geq 25\) mmHg; pulmonary capillary wedge pressure (PCWP) or left ventricular end-diastolic pressure \(\leq 15\) mmHg; and PVR at rest \(>400\) dyn \(\cdot\) s/cm\(^5\). Exclusion criteria were: pregnant women, patients with a total lung capacity (TLC) less than 70% of the predicted value, Child-Pugh class B or C patients, and patients with a serum creatinine value of 2.5 mg/dL (221 \(\mu\)mol/L) or higher. Furthermore, as the use of prostacyclin (PGI\(_2\)) or its derivatives was not permitted during the trial period, patients who had received PGI\(_2\) or its derivatives in the 4 weeks before the administration of the therapeutic drug were excluded; patients who received results in order to extrapolate the results of the international clinical trials to Japanese patients. In both the non-Japanese and Japanese Phase I trials, no notable differences in pharmacokinetics and tolerability between Japanese and non-Japanese patients were found.\(^14\) Therefore, we planned this open-label study in Japanese PAH patients to examine the efficacy of selexipag on the change in PVR from baseline to week 16 of administration (primary endpoint).
After 16 weeks, an increase or decrease of the dose was allowed with the upper limit of 1,600 μg twice daily. Pulmonary hemodynamics were measured in a supine position by using a Swan-Ganz catheter. To calculate the cardiac output (CO), either the Fick or thermodilution method was used. Throughout the trial, the same method was used consistently for each subject. The cardiac index (CI) was calculated by adjusting the CO relative to the body surface area (BSA): (CI=CO/BSA). PVR was calculated from the transpulmonary pressure difference and CO: PVR=80 (mPAP−PCWP)/CO.

In addition, change in 6MWD and N-terminal pro-brain natriuretic peptide (NT-pro-BNP) were evaluated from baseline to week 16. Subjects’ symptoms were evaluated using the Borg dyspnea index and World Health Organization (WHO) functional class. Pulmonary hemodynamics were measured at week 16. Hospitalization or death associated with PAH was observed until the cut-off at a maximum of 136 weeks. Safety and tolerability were evaluated at each visit from baseline to the cut-off (a maximum of 136 weeks) through side-effects, laboratory test values, vital signs, and electrocardiography.

**Statistical Analysis**

The primary endpoint PVR, secondary endpoints (other pulmonary hemodynamic measurements: mPAP, CI, mean right atrial pressure (mRAP), and mixed venous oxygen saturation (SvO2)); 6MWD; Borg dyspnea index; and NT-pro-BNP level) at week 16 were compared with the baseline in the per-protocol set (PPS) group using a Wilcoxon signed-rank test. Subjects for whom a week 16 PVR could not be obtained were excluded from the PPS analysis. A significant difference was defined as P<0.05 (a 2-tailed test). All analyses were performed with SAS (version 9.3).

**Results**

**Patients**

The study involved 37 subjects (11 males and 26 females), and comprised 25 patients with IPAH, 5 patients with HPAH, and 7 patients with PAH associated with other diseases (6 cases with connective-tissue disease, and 1 case of PAH repaired-congenital shunts) at 26 facilities since 2011. The age demographic of the patients at baseline is shown in Table 1. The mean age of subjects was (44.5±13.3) years (range: 23–72 years). The WHO functional classes at baseline were mainly class II (56.8%) and class III (37.8%). At baseline, (range: 23–72 years). The WHO functional classes at baseline were mainly class II (56.8%) and class III (37.8%). At baseline, (range: 23–72 years). The WHO functional classes at baseline were mainly class II (56.8%) and class III (37.8%). At baseline, (range: 23–72 years). The WHO functional classes at baseline were mainly class II (56.8%) and class III (37.8%). At baseline, (range: 23–72 years). The WHO functional classes at baseline were mainly class II (56.8%) and class III (37.8%). At baseline, (range: 23–72 years). The WHO functional classes at baseline were mainly class II (56.8%) and class III (37.8%). At baseline, (range: 23–72 years). The WHO functional classes at baseline were mainly class II (56.8%) and class III (37.8%). At baseline, (range: 23–72 years). The WHO functional classes at baseline were mainly class II (56.8%) and class III (37.8%). At baseline, (range: 23–72 years). The WHO functional classes at baseline were mainly class II (56.8%) and class III (37.8%).
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16 was $-120.9 \pm -184.5$ dyn · s/cm$^5$ (P<0.0001 Wilcoxon signed-rank test). In addition, improvements in other pulmonary hemodynamic variables were confirmed. Mean mPAP decreased from $41.8 \pm 9.2$ mmHg to $38.8 \pm 8.9$ mmHg (P=0.0091), while mean CI increased from $2.63 \pm 0.50$ L/min/m$^2$ to $2.96 \pm 0.74$ L/min/m$^2$ (P=0.0025). Of the 37 patients, CO was determined using the Fick method in 26 patients, and using the thermodilution method in 11 patients. Mean mRAP and mean SVO2 did not show significant differences between baseline and week 16. The mean (±SD) 6MWD increased from $445.0 \pm 102.2$ m at baseline to $459.1 \pm 112.8$ m at week16 (P=0.0324). The change in 6MWD continuously increased until the cut-off of 120 weeks (Figure 2). The Borg dyspnea index decreased slightly from $2.7 \pm 2.1$ to $2.5 \pm 2.0$ at week 16. Plasma NT-pro-BNP concentration slightly decreased from $111.1 \text{ pg/mL (95% CI: 71.4, 172.8)}$ to $105.7 \text{ pg/mL (95% CI: 66.4, 168.4)}$ (P=0.5634) at week 16. Moreover, regardless of concomitant use of both an ERA and a PDE-5 inhibitor at 16 weeks after selexipag administration, PVR (25 patients) decreased from $694.8 \pm 251.6$ dyn · s/cm$^5$ to $580.4 \pm 264.6$ dyn · s/cm$^5$, and 6MWD (23 patients) increased from $446.8 \pm 115.7$ m to $455.8 \pm 126.8$ m. The mean change in week 16 PVR (95% confidence interval) in patients receiving background therapy with ERA and PDE-5 inhibitor was $-114.4 \pm -320.0, -90.1$.

### Table 3. Pulmonary Hemodynamic Variables

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 16</th>
<th>Change from baseline to week 16</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVR (dyn · s/cm$^5$)</td>
<td>$683.2 \pm 237.3$ (408, 1,351)</td>
<td>$560.3 \pm 238.7$ (240, 1,103)</td>
<td>$-122.9 \pm 115.2$ (−402, 90)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>mPAP (mmHg)</td>
<td>$41.8 \pm 9.2$ (26, 59)</td>
<td>$38.8 \pm 8.9$ (21, 56)</td>
<td>$-3.1 \pm 6.0$ (−16, 8)</td>
<td>0.0091</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>$4.137 \pm 0.870$ (2.31, 6.13)</td>
<td>$4.639 \pm 1.285$ (2.52, 8.67)</td>
<td>$0.502 \pm 0.936$ (−1.05, 2.97)</td>
<td>0.0034</td>
</tr>
<tr>
<td>CI (L/min/m$^2$)</td>
<td>$2.63 \pm 0.50$ (1.5, 3.5)</td>
<td>$2.96 \pm 0.74$ (1.5, 4.5)</td>
<td>$0.33 \pm 0.57$ (−0.6, 1.7)</td>
<td>0.0025</td>
</tr>
<tr>
<td>mRAP (mmHg)</td>
<td>$4.5 \pm 2.5$ (0, 10)</td>
<td>$4.7 \pm 2.7$ (0, 10)</td>
<td>$0.2 \pm 3.7$ (−8, 6)</td>
<td>0.7010</td>
</tr>
<tr>
<td>SVO2 (%)</td>
<td>$70.46 \pm 6.96$ (50.5, 82.8)</td>
<td>$70.00 \pm 8.35$ (39.0, 82.9)</td>
<td>$-0.41 \pm 5.38$ (−16.4, 13.7)</td>
<td>0.9771</td>
</tr>
</tbody>
</table>

n=33. Data are shown as the mean ± SD (min, max). *P-value determined using a Wilcoxon signed-rank test. CI, cardiac index; CO, cardiac output; mPAP, mean pulmonary artery pressure; mRAP, mean right atrial pressure; PVR, pulmonary vascular resistance; SVO2, mixed venous oxygen saturation.

selexipag without PAH background therapies. The distribution of a maintenance dose is shown in Table 2. Seven patients (18.9%) were treated with the maximum final maintenance dose of 3,200 μg/day. Three patients did not attain their final maintenance dose due to premature discontinuation from the study drug. The mean (±SD) daily dose at the cut-off (or final) was $2,130.4 \pm 893.6$ μg/day.

All 37 patients were included in the safety set (SS). Thirty-three patients were analyzed in the PPS group. Three patients in WHO functional class III, and 1 in class II, were excluded from statistical analysis (the PPS group) because of missing pulmonary hemodynamics at week 16 due to “incidence of serious adverse events”, “use of prohibited concomitant drugs or implementation of prohibited concomitant therapy”, “withdrawal of consent”, and “new administration of ERAs, phosphodiesterase-5 inhibitor, or calcium antagonists” respectively. Therefore, the participation of these 4 patients in the study was discontinued.

**Efficacy**

Pulmonary hemodynamic variables at baseline and at week 16 are shown in Table 3. At 16 weeks after selexipag administration, PVR decreased from $683.2 \pm 237.3$ dyn · s/cm$^5$ (mean ±SD) to $560.3 \pm 238.7$ dyn · s/cm$^5$ (P<0.0001). The median (95% confidence interval, CI) change in PVR at week 16 was $-120.9 \pm -184.5$ to $-59.5$ dyn · s/cm$^5$ (P<0.0001 Wilcoxon signed-rank test). In addition, improvements in other pulmonary hemodynamic variables were confirmed. Mean mPAP decreased from $41.8 \pm 9.2$ mmHg to $38.8 \pm 8.9$ mmHg (P=0.0091), while mean CI increased from $2.63 \pm 0.50$ L/min/m$^2$ to $2.96 \pm 0.74$ L/min/m$^2$ (P=0.0025). Of the 37 patients, CO was determined using the Fick method in 26 patients, and using the thermodilution method in 11 patients. Mean mRAP and mean SVO2 did not show significant differences between baseline and week 16. The mean (±SD) 6MWD increased from $445.0 \pm 102.2$ m at baseline to $459.1 \pm 112.8$ m at week16 (P=0.0324). The change in 6MWD continuously increased until the cut-off of 120 weeks (Figure 2). The Borg dyspnea index decreased slightly from $2.7 \pm 2.1$ to $2.5 \pm 2.0$ at week 16. Plasma NT-pro-BNP concentration slightly decreased from $111.1 \text{ pg/mL (95% CI: 71.4, 172.8)}$ to $105.7 \text{ pg/mL (95% CI: 66.4, 168.4)}$ (P=0.5634) at week 16. Moreover, regardless of concomitant use of both an ERA and a PDE-5 inhibitor at 16 weeks after selexipag administration, PVR (25 patients) decreased from $694.8 \pm 251.6$ dyn · s/cm$^5$ to $580.4 \pm 264.6$ dyn · s/cm$^5$, and 6MWD (23 patients) increased from $446.8 \pm 115.7$ m to $455.8 \pm 126.8$ m. The mean change in week 16 PVR (95% confidence interval) in patients receiving background therapy with ERA and PDE-5 inhibitor was $-114.4 \pm -320.0, -90.1$.
most commonly reported adverse events in all headache (73.0%), diarrhoea (45.9%), jaw pain (45.9%), nausea (37.8%), and flushing (32.4%). Six patients experienced adverse events related to low blood pressure (low blood pressure: 8.1% [3 patients]; decrease in blood pressure: 10.8% [4 patients]). Of these 6 events of hypotension, 1 patient (2.7%) was reported as serious, and consequently the patient discontinued selexipag. These adverse events were consistent with those observed with other PGI 2 analogue or agonists use. Adverse events reported in the efficacy evaluation and long-term treatment phases are listed in Table 5. Adverse events occurred more frequently in the efficacy evaluation phase, which is during dose-adjustment phase.

Overall, for 15 patients, a serious adverse event was reported. Two of these patients died due to right ventricular failure. A total of 9 patients discontinued selexipag due to following adverse events: PAH 13.5% (5 patients), right ventricular failure 5.4% (2 patients), blood pressure decreased and systemic lupus erythematosus 2.7% (1 patient each). There were no clinical abnormalities found in the clinical tests, pulse measurements, and electrocardiograms conducted during the trial period.

### Safety
Selexipag administered in Japanese patients with PAH twice-daily at the maximum dose of 1600 μg was well tolerated, even if selexipag was administered on top of other PAH medications (ERA and/or PDE5i).

At the cut-off date for this analysis (a maximum duration of selexipag treatment of 136 weeks), all 37 patients (100.0%) patients enrolled in this study received selexipag and reported at least 1 adverse event in this study. The most commonly reported adverse events in all headache (73.0%), diarrhoea (45.9%), jaw pain (45.9%), nausea (37.8%), and flushing (32.4%). Six patients experienced adverse events related to low blood pressure (low blood pressure: 8.1% [3 patients]; decrease in blood pressure: 10.8% [4 patients]). Of these 6 events of hypotension, 1 patient (2.7%) was reported as serious, and consequently the patient discontinued selexipag. These adverse events were consistent with those observed with other PGI1 analogue or agonists use. Adverse events reported in the efficacy evaluation and long-term treatment phases are listed in Table 5. Adverse events occurred more frequently in the efficacy evaluation phase, which is during dose-adjustment phase.

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There were no clinical abnormalities found in the clinical tests, pulse measurements, and electrocardiograms conducted during the trial period.

### Discussion
The targeting of the PGI1 pathway has been proven to be efficacious in PAH treatment by epoprostenol, and this is supported by clinical trials that evaluated a PGI1 deriv
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Table 6. PVR and World Health Organization Functional Class (Japanese PII, Non-Japanese PII18)

<table>
<thead>
<tr>
<th>Evaluation period</th>
<th>Japanese Phase II trial</th>
<th>Non-Japanese Phase II trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVR (dyn·s/cm²)</td>
<td>Selexipag</td>
<td>Selexipag</td>
</tr>
<tr>
<td></td>
<td>Week 16</td>
<td>Week 17</td>
</tr>
<tr>
<td>Baseline Mean±SD</td>
<td>683.2±237.3</td>
<td>951.9±434.5</td>
</tr>
<tr>
<td>Change Mean±SD</td>
<td>−122.9±115.2</td>
<td>−168.1±241.6</td>
</tr>
<tr>
<td>Percent ratio</td>
<td></td>
<td>79.7 (74.0–86.0)</td>
</tr>
<tr>
<td>WHO functional class</td>
<td>n=33采集</td>
<td>n=29采集</td>
</tr>
<tr>
<td>No. of improved patients (%)</td>
<td>4 (12.1%)</td>
<td>5 (15.6%)</td>
</tr>
<tr>
<td>95% CI</td>
<td>3.4–28.2</td>
<td>683.2±237.3</td>
</tr>
</tbody>
</table>

PVR, pulmonary vascular resistance. *Per protocol set; †all-treated set.

Table 6. PVR and World Health Organization Functional Class (Japanese PII, Non-Japanese PII18)

...tive with a prostanoid structure (treprostinil, beraprost, and iloprost). However, as these drugs have short half-lives, medications using continuous infusion, subcutaneous injection, or frequent inhalation are necessary. Therefore, an orally available PGI2 receptor agonist with a long half-life was developed.11 Selexipag is rapidly absorbed after oral administration, and hydrolyzed to the active metabolite, MRE-269, by carboxylesterase (CES). The high binding affinity of the active metabolite, MRE-269, to the IP receptor and the long elimination half-life contribute to the efficacy of selexipag. In the Phase I single dose trial, the maximum blood concentration of selexipag was reached after 1 h, and was eliminated with a half-life of 0.917–2.36 h. The maximum blood concentration of MRE-269 was reached 3 h after administration, with a half-life of 6.18–8.68 h. These characteristics enabled oral administration twice daily.

In the recently published Phase III randomized, placebo-controlled, double-blind trial of selexipag (the GRIPHON trial),13 a composite of death from any cause or a complication related to PAH up to the end of the treatment period was chosen as the primary endpoint, because it was considered that this composite endpoint would represent clinically highly relevant outcomes for patients with a progressive disease such as PAH. Although ~80% of the patients were receiving one or more PAH therapeutic drug(s), and ~30% were treated with double combination therapy (i.e., an ERA and a PDE-5 inhibitor), the risk of morbidity/mortality events decreased by 40% in the selexipag group as compared with that in the placebo group. The therapeutic effect of selexipag in the GRIPHON trial was consistently confirmed in all pre-specified subgroups such as combined use with other PAH therapeutic drugs, NYHA/WHO functional class, age, and PAH disease etiology. In addition, at all maintenance doses, uniform efficacy was confirmed. In all analyses, the effect of selexipag was observed at an early stage and was maintained during the trial period (median of 1.4 years and maximum of 4.2 years).

As Japanese patients were not included in the GRIPHON trial, and in order to extrapolate the GRIPHON results to Japanese patients, the pharmacokinetics, efficacy, and safety of this drug must be discussed. When pharmacokinetic parameters were compared after single and repeated administration of selexipag in Japanese and non-Japanese healthy adults, the values of Cmax and AUC for Japanese adults were 1.23–2.17 and 0.97–2.09-fold higher, respectively, for both selexipag and MRE-269. This was attributed to differences in weight; however, the differences were not significant, confirming that there was little difference in pharmacokinetics and tolerability in healthy Japanese and non-Japanese adults.14 In addition, there were no reports of the effect of gene polymorphism on the main metabolizing enzyme of selexipag, CES1, and because there are no important gene polymorphisms in the CYP molecular species associated with the metabolism of selexipag and MRE-269, it is unlikely that gene polymorphism has a clinically serious impact on the exposure to selexipag and MRE-269. These findings provide a strong base to extrapolate the international clinical trial results to Japanese patients.

In this trial with Japanese PAH patients, effects on pulmonary hemodynamics (decreased PVR and PVR1) were shown with twice-daily oral administration of 200–1,600 μg selexipag, which was gradually increased based on individual patient tolerance. In a Phase II placebo-controlled, double-blind comparison trial18 conducted in 7 European countries, selexipag was orally administered twice a day at 200–800 μg for 17 weeks, and the primary endpoint, PVR, was significantly decreased compared to the placebo (P=0.0045). The geometric mean percent ratio of PVR at week 16 of this trial and week 17 of the Phase II non-Japanese trial from each baseline was similar: 79.7% (95% confidence interval: 74.0–86.0%) and 80.7% (95% confidence interval: 72.8–89.6%), respectively (Table 6). PVR is an objective variable that reflects the right ventricular load. In a clinical trial of a 3-month continuous infusion of epoprostenol, a correlation between the improvement in PVR and prognosis of PAH was reported, and this was used to evaluate the efficacy of PAH therapeutic drugs.19–21

In this trial, the improvement of 6MWD in patients treated with selexipag was confirmed. From baseline to week 16, the median of 6MWD increased by 19.5 m (95% confidence interval: 0.0–37.0 m). This effect continued up to week 120 (data cut-off). In addition, there was an improvement in the WHO functional class, as with the Phase II non-Japanese trial (Table 6). These results were similar to the therapeutic effects observed in 6MWD and WHO functional class in the GRIPHON trial.13 The improvements of PVR and 6MWD with selexipag were observed despite patients receiving background therapy with 2-agent combination therapy with an ERA and a PDE-5 inhibitor. On the basis of these...
results, selexipag can be a useful drug for add-on therapy, as well as non-Japanese reports. The efficacy of add-on or combination therapy with drugs of different modalities, such as an ERA and a PDE-5 inhibitor, has been evaluated and is recommended in current treatment guidelines.22

In previously discussed non-Japanese and Japanese Phase I trials, in this trial, the non-Japanese Phase II trial, and the GRIPHON trial, the pharmacokinetics and efficacy of selexipag were shown to be similar in Japanese and non-Japanese patients; therefore, the reduction in risk for the occurrence of morbidity/mortality events can be extrapolated to Japanese PAH patients.

With regard to safety, adverse events associated with the mode of action of selexipag have been observed frequently, in particular during the phase of selexipag dose titration. Most of these adverse events were not serious and none were reported as having a fatal outcome. In this study, one of the 2 patients who died due to lethal right ventricular failure (death on day 223) was initially diagnosed by the physician to have suffered from deterioration of the underlying disease; however, since death occurred during the trial of a therapeutic drug, a causal relationship with selexipag could not be excluded. The other patient (death on day 339) was determined to have died of deterioration of the underlying disease, and a causal relationship with selexipag was excluded. Except for these 2 patients, the remaining 13 patients were hospitalized due to non-fatal adverse events, which were mostly associated with prostacyclin treatment. And 9 patients discontinued treatment owing to safety issues. Almost all the adverse events leading to discontinuation of study treatment were associated with prostacyclin treatment, or PAH and concomitant disease. There was little difference in the safety profile between Japanese PAH patients and non-Japanese PAH patients. It is not expected that selexipag and MRE-269 affect the PK of other drugs through CYP enzymes or drug transporters, and they both showed no impact on the pharmacokinetics or pharmacodynamics of warfarin.23 There were no clinically relevant issues in patients treated with the combined use of selexipag with an ERA and a PDE-5 inhibitor. In our study, tolerance of selexipag was similar among Japanese patients who received any dose within the selexipag regimen.

Given that efficacy of selexipag was confirmed in adult PAH patients in a multicenter randomized clinical trial (GRIPHON) abroad, this medication is recommended to be administered as monotherapy or as combination therapy with an ERA and/or a PDE-5 inhibitor by the current PAH treatment guidelines.16

Study Limitations
One limitation of this study was that as an open-label trial, both patients and physicians were aware of the dose and the name of the drug; therefore, subjective variables such as WHO functional class and 6MWD may be biased, compared to an objective variable such as plasma NT-pro-BNP concentration. To some degree, measured pulmonary hemodynamic values may also be biased. This trial had a limited number of patients, and the duration of the trial was short. In addition, efficacy and safety were not compared with a placebo group or a control group. However, pulmonary hemodynamics, exercise capacity, and tolerability in this study were similar to non-Japanese clinical trials, and pharmacokinetics do not differ greatly; therefore, it was considered that results of the GRIPHON trial could be extrapolated to Japanese patients.

Conclusions
This trial investigated the administration of selexipag to Japanese PAH patients for the first time. In this trial, selexipag was well tolerated and showed an acceptable safety profile in addition to significant improvement in pulmonary hemodynamics, exercise tolerance, and symptoms. Selexipag could be a useful treatment option for Japanese PAH patients.

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References
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