Selexipag for the treatment of chronic thromboembolic pulmonary hypertension

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Selexipag significantly improved pulmonary vascular resistance and other haemodynamics in patients with chronic thromboembolic pulmonary hypertension, although exercise capacity remained unchanged https://bit.ly/3HfPA9s

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Abstract

Background Treatment options for inoperable chronic thromboembolic pulmonary hypertension (CTEPH) remain limited. Selexipag, an oral selective IP prostacyclin receptor agonist approved for pulmonary arterial hypertension, is a potential treatment option for CTEPH.

Methods In this multicentre, randomised, double-blind, placebo-controlled study, 78 Japanese patients with inoperable CTEPH or persistent/recurrent pulmonary hypertension after pulmonary endarterectomy and/or balloon pulmonary angioplasty were randomly assigned to receive placebo or selexipag. The primary end-point was the change in pulmonary vascular resistance (PVR) from baseline to week 20. Secondary end-points were changes in other haemodynamic parameters: 6-min walk distance (6MWD), Borg dyspnoea scale score, World Health Organization (WHO) functional class, EuroQol five-dimension five-level tool and N-terminal pro-brain natriuretic peptide.

Results The change in PVR was −98.2±111.3 dyn·s·cm^{-5} and −4.6±163.6 dyn·s·cm^{-5} in the selexipag and placebo groups, respectively (mean difference −93.5 dyn·s·cm^{-5}; 95% CI −156.8 to −30.3; p=0.006). The changes in cardiac index (p<0.001) and Borg dyspnoea scale score (p=0.036) were also significantly improved over placebo. 6MWD and WHO functional class were not significantly improved. The common adverse events in the selexipag group corresponded to those generally observed following administration of a prostacyclin analogue.

Conclusion Selexipag significantly improved PVR and other haemodynamic variables in patients with CTEPH, although exercise capacity remained unchanged. Further large-scale investigation is necessary to prove the role of selexipag in CTEPH.

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a life-threatening disease characterised by pulmonary artery obstruction due to unresolved organised thrombus, leading to worsening of pulmonary hypertension (PH), right heart failure and death if left untreated [1].

Pulmonary endarterectomy (PEA) is the first-line and only curative treatment for CTEPH [1–4]. However, patients with comorbidities, or those who refuse treatment, are not eligible for PEA [5–8]. Even if PEA is performed successfully, patients may have residual or recurrent PH [2, 4]. Meanwhile, balloon pulmonary angioplasty (BPA) is an emerging treatment for patients who are ineligible for PEA [4]. However, some CTEPH patients are ineligible for BPA. Furthermore, a portion of patients have symptomatic residual PH following BPA [9]. Thus, a need exists for the implementation of new effective therapeutics for inoperable CTEPH or residual PH after PEA/BPA.

CTEPH histopathological studies have revealed small-vessel vasculopathy similar to that observed in pulmonary arterial hypertension (PAH) [2]. Hence, a pulmonary vasodilator targeting small-vessel vasculopathy is a treatment option for inoperable CTEPH or residual PH following PEA and BPA. For instance, results of the CHEST-1 study revealed that riociguat, a soluble guanylate cyclase stimulator, improved both the 6-min walk distance (6MWD) by 39±79 m and pulmonary vascular resistance (PVR) by −226±248 dyn·s·cm^{-5} from baseline values in inoperable CTEPH or residual PH [10].

Selexipag is an orally selective prostacyclin receptor (IP receptor) agonist with a nonprostanoid structure. Its metabolite, MRE-269, has a high selectivity for the IP receptor [11, 12]. Selexipag increases cAMP, leading to relaxation of vascular smooth muscle [12]. One previous study in PAH patients demonstrated the beneficial effects of selexipag on the risk of morbidity/mortality events in a placebo-controlled double-blind international phase 3 study [13], leading to its approval for the treatment of PAH in many countries, including the United States, the European Union and Japan.

In the context of CTEPH, a previous proof-of-concept clinical trial of selexipag in Japanese patients suggested a possible signal for improved haemodynamics with selexipag [14]. Here, we report the results of a placebo-controlled, double-blind study to examine the efficacy and safety of selexipag (NS304C-P3-1) in Japanese patients with inoperable CTEPH or persistent/recurrent PH after PEA and/or BPA.

Methods

Study subjects

We selected patients with CTEPH (age 20–85 years) as confirmed by a pulmonary ventilation/perfusion scan, pulmonary angiography and a chest computed tomography scan, two or more of which revealed areas of deficient pulmonary blood flow. Pulmonary haemodynamic variables at rest, as determined by right heart catheterisation, were set as the baseline. The mean pulmonary arterial pressure (mPAP) was set at ⩾25 mmHg; the pulmonary artery wedge pressure (PAWP) was set at ⩽15 mmHg; and PVR was set at >360 dyn·s·cm^{-5}. The population consisted of patients who could not undergo PEA due to the presence of organised peripheral thrombus. This study also included patients who could not undergo PEA due to their high risk (*e.g.* comorbidities or old age), or for other reasons (*e.g.* refusal to undergo surgery). These disease classifications were assessed by each investigator at their own institution. The population also consisted of some patients who had persistent or recurrent PH after PEA or BPA.

Those who had received prostacyclin and/or its derivatives were excluded. Concomitant use of riociguat, an endothelin receptor antagonist (ERA), a phosphodiesterase-5 inhibitor or a calcium antagonist was allowed if the doses administered had been stable for ⩾90 days before the baseline right heart catheterisation and it was maintained until the end of this double-blind study. While patients who had undergone PEA and/or BPA were included, PEA and BPA were not allowed during the study. Details of the inclusion and exclusion criteria are provided in the supplementary material.

This study was conducted in accordance with the ethical principles set out by the institutional human ethics committees of the participating facilities or regions and the Declaration of Helsinki. The study design was approved by the institutional review board at each study site, including the National Cerebral and Cardiovascular Centre (reference number #924). All subjects provided written informed consent to participate in the study.

Study design

This study was a phase 3, multicentre, double-blind, placebo-controlled parallel-group comparison study of NS304C-P3-1 conducted at 42 sites in Japan. The full list of investigators is provided in the supplementary

material. Treatment was initiated with selexipag (200 µg) twice daily, with up to 1600 µg twice daily when tolerability was acceptable. Thereafter, the dose was titrated in increments of 200 µg with a minimum interval of 3 days (a total of six doses). The duration of treatment was 20 weeks. The maximum tolerated dose was determined for each subject over 12 weeks and was subsequently maintained for 8 weeks (figure 1).

Assessment of outcome

The primary end-point was the change in resting PVR from baseline to week 20. The secondary end-points were changes in the PVR index (PVRI), mPAP, cardiac index, mean right atrial pressure (mRAP), total pulmonary resistance (TPR), mixed venous oxygen saturation (S_{vO_2}) and EuroQol five-dimension five-level (EQ-5D-5L) after 20 weeks of treatment; changes in 6MWD, Borg dyspnoea scale score and N-terminal pro-brain natriuretic peptide (NT-proBNP) at each visit; and shifts in World Health Organization (WHO) functional class over time at each visit. The exploratory efficacy end-point was time from randomisation to first clinical worsening event (*e.g.* death, hospitalisation due to worsening or complication of PH or use of any additional interventions to treat the worsening of CTEPH, and fulfilling the following two requirements: worsening of New York Heart Association/WHO functional class and a >15% reduction in 6MWD) up to 20 weeks. Pulmonary haemodynamics were evaluated using the Swan–Ganz catheter method while the patient was recumbent. The thermodilution method or the indirect Fick method was used to calculate cardiac output.

The safety end-points were adverse drug reactions (ADRs), laboratory test values, vital signs and electrocardiogram at each visit.

Statistical analysis

The target sample size was set at 72 subjects, who were randomised to receive either selexipag or placebo in a 1:1 ratio by minimisation. A placebo-controlled, double-blind, phase 2 study of selexipag in Japanese CTEPH patients [14] found a change (mean±SD) in PVR in the selexipag group of −104±191 dyn·s·cm^{-5} and a change in PVR in the placebo group of 26±180 dyn·s·cm^{-5}. Using these results and assuming a power of 80% and a two-sided significance level of 5%, the sample size required to detect a significant difference by the Wilcoxon rank sum test was calculated to be 34 subjects per group, or 68 in total. It was assumed that ∼5% would be excluded from the full analysis set. The randomisation method is provided in the supplementary material.

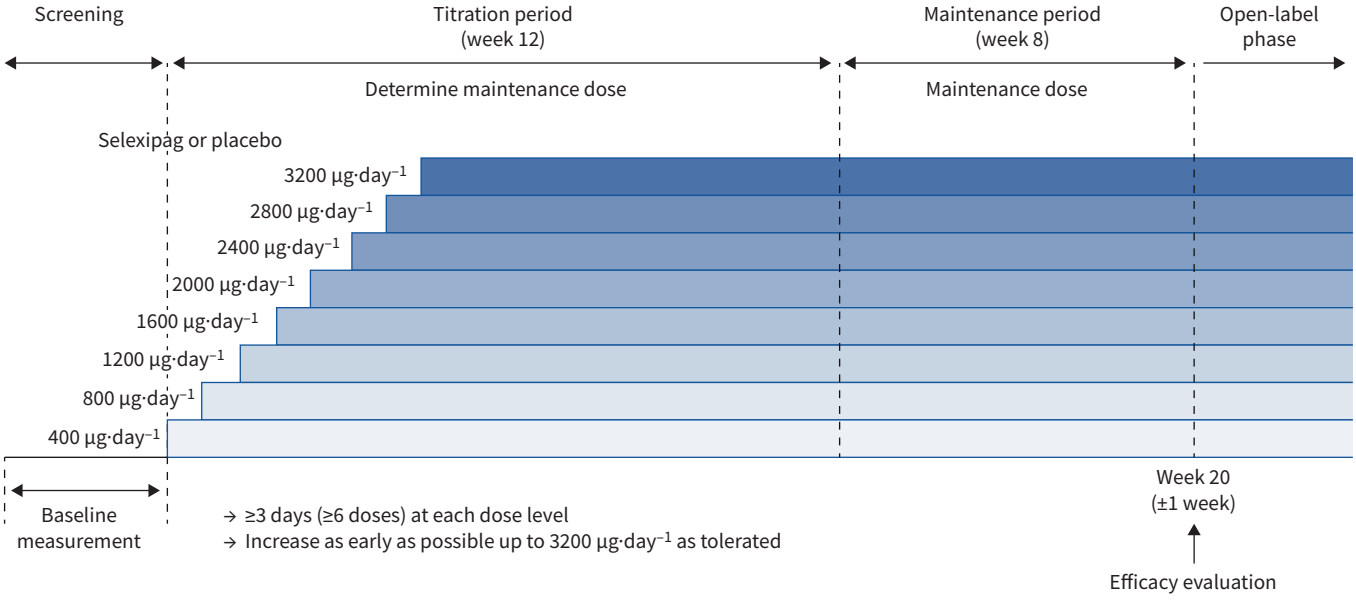

FIGURE 1 Schematic of study design. 200 µg of the study drug was administered twice daily and titrated according to individual tolerance. Dose reduction and re-uptitration were allowed during the titration period.

Data are presented as mean±SD, median (range) or percentage. The primary analysis of the efficacy end-points was performed for the full analysis set. Changes in PVR, PVRI, S_{vO_2}, Borg dyspnoea scale score and NT-proBNP levels were compared between the selexipag and placebo groups using the Wilcoxon rank sum test. mPAP, cardiac index, mRAP, TPR, 6MWD and EQ-5D-5L were compared using the unpaired t-test. Subgroup analysis was performed for PVR by sex, age, disease classification, presence/absence of prior PEA/BPA and presence/absence of concomitant riociguat or ERA and baseline PVR, and the difference in means and 95% confidence intervals are shown in figure 4. All subgroups were pre-specified in the statistical analysis plan. Shifts in WHO functional class over time at each visit were compared using Fisher's exact test. If data at 20 weeks of treatment were missing, which occurred primarily with patients who had been prematurely withdrawn from the study, the missing data were imputed by baseline observation carried forward, last observation carried forward or worst value (in the case of PH worsening) and data including the imputed values served as the data at the end of the study. For the time to first clinical worsening, the survival curve was compared between the groups using the log-rank test. A sensitivity analysis was performed for the primary efficacy variable PVR (supplementary material). The safety evaluation variables were analysed in the safety analysis set. A significant difference was defined as $p<0.05$ (two-tailed test). No statistical adjustment for multiplicity was performed. All analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC, USA).

The primary end-point in phase 3 studies involving CTEPH patients is 6MWD. However, since this study was conducted exclusively in Japan and CTEPH is a rare disease, the number of cases was limited. Thus, after discussing with the Pharmaceuticals and Medical Devices Agency in Japan, PVR was set as the primary end-point for this phase 3 study. However, in terms of current clinical trials for PH, this study may be considered a phase 2 study.

Results

Patients

Between 2016 and 2019, 78 subjects were enrolled from 42 institutions. A full analysis set of 78 subjects (39 subjects were assigned to selexipag and 39 to placebo) was used for the main analysis. Patient demographic characteristics at baseline are presented in table 1. Patients who could not undergo PEA because of distal organised thrombus were observed to predominate in this entire cohort. In the group of patients who could not undergo PEA due to high risk or for other reasons, patients with a proximal distribution of chronic fibrotic clots were enrolled. Approximately 60% of patients were receiving riociguat. The distribution of the maintenance doses is shown in table 2. The maintenance dose in 33.3% (13 out of 39) of patients was 1600 μg, which was the maximum allowable dose in this study. Comparison of the baseline data from this study with the other randomised controlled trials on the use of medical therapies in CTEPH patients is shown in supplementary table S1.

Of the 39 patients in the selexipag group, five discontinued the study (three developed adverse events, and two withdrew their consent), while of the 39 patients in the placebo group, four discontinued the study (because of adverse events) (figure 2). For the rules of the imputation of missing data, see the statistical analysis section.

Efficacy

The changes in PVR from baseline to week 20 are shown in figure 3, and the outline of changes in pulmonary haemodynamic variables and other efficacy end-points are presented in table 3. The change in PVR from baseline to week 20 in the selexipag group was −98.2±111.3 dyn·s·cm^{-5}, whereas that in the placebo group was −4.6±163.6 dyn·s·cm^{-5}. The mean difference (95% CI) in PVR between the groups after 20 weeks of treatment was −93.5 (−156.8 to −30.3) dyn·s·cm^{-5}, indicating a significant decrease in PVR in the selexipag group compared with the placebo group ($p=0.006$). This result was confirmed in the sensitivity analysis (supplementary table S2). All subgroup analyses indicated a consistent beneficial effect of selexipag on PVR (figure 4). In patients who could not undergo PEA because of distal organised thrombus, the mean difference (95% CI) in PVR between the groups after 20 weeks of treatment was −135.2 (−221.8 to −48.6) dyn·s·cm^{-5}, indicating a significant decrease in PVR in these patients compared with patients with persistent or recurrent PH after PEA, or who had a high risk (*e.g.* comorbidities or old age), or who did not undergo PEA for other reasons (*e.g.* refusal of surgery). In patients who had undergone BPA, the mean difference (95% CI) in PVR between the groups after 20 weeks of treatment was −83.1 (−141.5 to −24.6) dyn·s·cm^{-5}. In the selexipag group that did not concomitantly receive a pulmonary vasodilator (n=13), the therapeutic effect (mean difference (95% CI)) after 20 weeks of treatment was −140.1 (−264.7 to −15.4) dyn·s·cm^{-5}. PVR showed a larger decrease in patients on selexipag alone than in patients on selexipag taken concomitantly with pulmonary vasodilators. An

TABLE 1 Patient baseline characteristics (full analysis set)

	Placebo	Selexipag
Patients	39	39
Sex		
Male	10 (25.6)	10 (25.6)
Female	29 (74.4)	29 (74.4)
Age (years)		
Mean±SD	68.3±9.6	66.3±11.1
Median (range)	71.0 (44–84)	69.0 (36–82)
6MWD (m)		
Mean±SD	384.0±87.0	407.9±90.9
Median (range)	390.0 (183–534)	405.0 (195–628)
WHO functional class		
I/II/III/IV	2/26/11/0	1/23/15/0
Disease classification		
PEA not indicated		
Distal organised thrombus	25 (64.1)	24 (61.5)
High risk for PEA or PEA could not be performed for other reasons	9 (23.1)	10 (25.6)
Persistent or recurrent pulmonary hypertension after PEA	5 (12.8)	5 (12.8)
History of BPA		
Persistent or recurrent pulmonary hypertension after BPA	22 (56.4)	19 (48.7)
No history of BPA	17 (43.6)	20 (51.3)
Concomitant use of pulmonary vasodilator		
Present	26 (66.7)	26 (66.7)
Riociguat	24 (61.5)	24 (61.5)
PDE5 inhibitor	1 (2.6)	2 (5.1)
ERA	7 (17.9)	6 (15.4)
None	13 (33.3)	13 (33.3)
Time since diagnosis (years)	4.45±5.24	2.72±3.24

Data are presented as n, n (%), mean±SD or median (range). 6MWD: 6-min walk distance; WHO: World Health Organization; PEA: pulmonary endarterectomy; BPA: balloon pulmonary angioplasty; PDE5: phosphodiesterase type 5; ERA: endothelin receptor antagonist.

analysis of the maintenance dose of selexipag indicated that a higher maintenance dose was associated with a greater decrease in PVR (supplementary figure S1).

As for PVRI, cardiac index, TPR, S_{vO_2} and the Borg dyspnoea scale score, the mean differences (95% CI) between the groups after 20 weeks of treatment were −154.4 (−255.3 to −53.4) dyn·s·m^{2}·cm^{-5} (p=0.004), 0.487 (0.262 to 0.711) L·min^{-1}·m^{-2} (p<0.001), −116.8 (−189.3 to −44.2) dyn·s·cm^{-5} (p=0.002), 2.58% (0.30% to 4.87%) (p=0.029) and −0.85 (−1.58 to −0.11) (p=0.036), respectively, indicating a significant

TABLE 2 Dose distribution (full analysis set)

	Placebo	Selexipag
Patients	39	39
Final maintenance dose[#] µg·day^{-1}		
400	0	1
800	2	3
1200	0	6
1600	2	3
2000	2	2
2400	1	4
2800	0	2
3200	28	13
Unknown[¶]	4	5

Data are presented as n. [#]: dose prescribed at the start of the dose maintenance period; [¶]: subjects withdrawn by the start of the dose maintenance period.

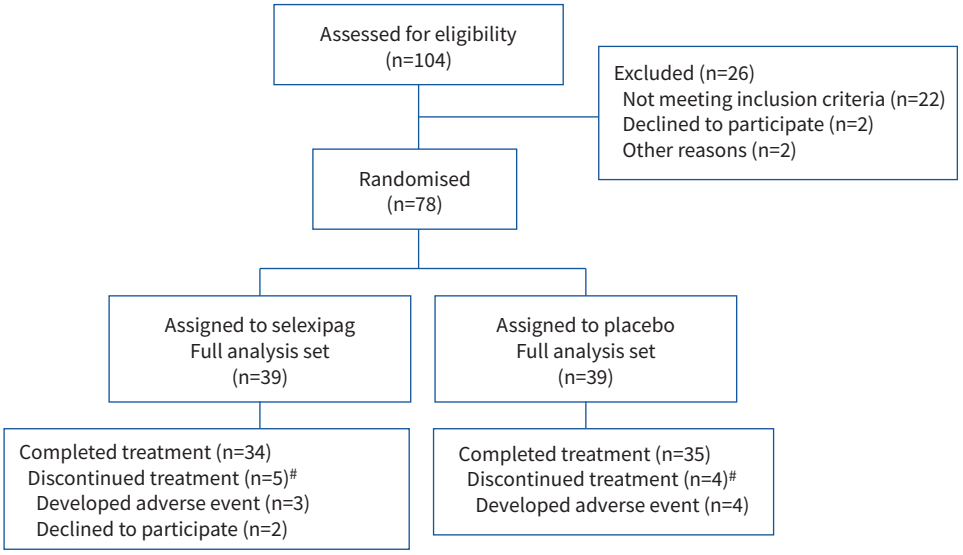

FIGURE 2 Patient disposition. #: if data at 20 weeks of treatment were missing, the missing data were imputed by baseline observation carried forward, last observation carried forward, or worst value (in the case of pulmonary hypertension worsening) and the data that included the imputed data served as the data at the end of the study.

improvement in the selexipag group compared with the placebo group. In contrast, no significant differences between the groups were observed regarding changes in mPAP, mRAP, 6MWD, NT-proBNP or EQ-5D-5L from baseline to week 20. In most patients, the WHO functional class remained unchanged throughout the full 20 weeks of treatment. For reference, PAWP did not change significantly from baseline to week 20 in either the selexipag group or the placebo group. Clinical worsening was observed in one patient in the selexipag group and in one patient in the placebo group.

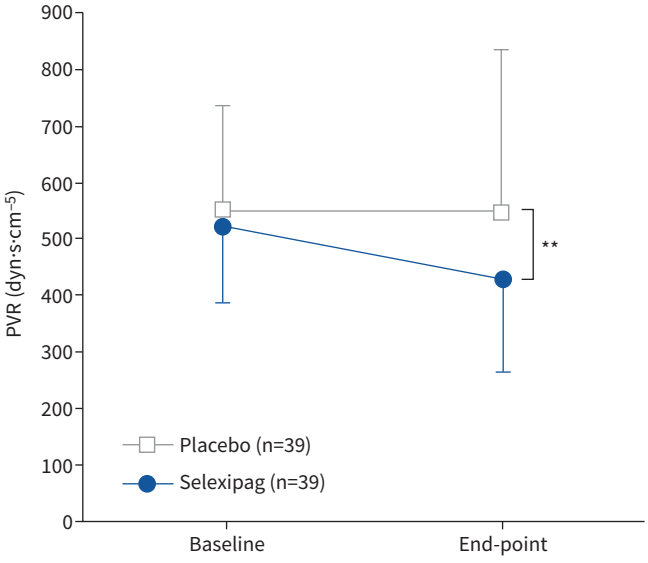

FIGURE 3 Change in pulmonary vascular resistance (PVR) from baseline to week 20. Data are presented as mean±SD. The mean change from baseline to 20 weeks of treatment was −98.2 dyn·s·cm^{-5} (95% CI −134.2 to −62.1 dyn·s·cm^{-5}) in the selexipag group and −4.6 dyn·s·cm^{-5} (95% CI −57.7 to 48.4 dyn·s·cm^{-5}) in the placebo group. A significant treatment effect for selexipag *versus* placebo groups was observed (treatment effect −93.5, 95% CI −156.8 to −30.3; p=0.006 with the use of the Wilcoxon rank sum test). **: p<0.01.

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TABLE 3 Changes in pulmonary haemodynamic variables, 6-min walk distance (6MWD), Borg dyspnoea scale score, N-terminal pro-brain natriuretic peptide (NT-proBNP), EuroQol five-dimension five-level tool (EQ-5D-5L) and World Health Organization (WHO) functional class (full analysis set)

	Placebo				Selexipag				Treatment effect	p-value
	Patients	Baseline	End-point	Change	Patients	Baseline	End-point	Change		
PVR (dyn·s·cm^{-5})	39	553.1±184.0 (387 to 1146)	548.5±288.4 (235 to 1429)	−4.6±163.6 (−220 to 695)	39	523.4±132.8 (362 to 918)	425.3±158.6 (176 to 927)	−98.2±111.3 (−359 to 186)	−93.5	0.006[#]
PVRI (dyn·s·m^2·cm^{-5})	39	850.7±299.4 (497 to 1818)	850.8±463.1 (362 to 2278)	0.0±263.3 (−321 to 1155)	39	810.8±214.9 (540 to 1662)	656.5±257.6 (303 to 1481)	−154.3±174.4 (−599 to 293)	−154.4	0.004[#]
mPAP (mmHg)	39	35.5±8.3 (26 to 55)	33.7±10.2 (22 to 66)	−1.7±4.6 (−11 to 11)	39	35.2±5.4 (25 to 47)	33.1±6.6 (22 to 44)	−2.2±3.8 (−11 to 4)	−0.4	0.650[¶]
Cardiac index (L·min^{-1}·m^{-2})	39	2.587±0.414 (1.97 to 4.04)	2.463±0.475 (1.54 to 3.76)	−0.124±0.409 (−1.38 to 0.83)	39	2.693±0.601 (1.54 to 4.71)	3.056±0.788 (1.77 to 5.89)	0.363±0.572 (−0.89 to 2.19)	0.487	<0.001[¶]
TPR (dyn·s·cm^{-5})	39	731.7±203.5 (509 to 1401)	738.2±304.2 (388 to 1683)	6.5±173.0 (−250 to 699)	39	704.5±184.4 (437 to 1262)	594.3±191.3 (295 to 1086)	−110.2±147.5 (−477 to 261)	−116.8	0.002[¶]
mRAP (mmHg)	39	5.4±4.0 (1 to 24)	5.8±5.2 (1 to 32)	0.5±2.7 (−6 to 8)	39	5.5±3.2 (0 to 13)	5.5±3.7 (−2 to 21)	0.0±3.0 (−7 to 8)	−0.5	0.451[¶]
S_{vO_2} (%)	38[+]	66.24±7.43 (45.3 to 77.6)	64.63±8.05 (34.4 to 78.8)	−1.61±5.13 (−12.1 to 9.8)	38[+]	67.17±5.65 (48.6 to 77.8)	68.14±6.59 (48.6 to 82.8)	0.97±4.87 (−9.7 to 13.9)	2.58	0.029[#]
6MWD (m)	39	384.0±87.0 (183 to 534)	390.9±111.6 (0 to 575)	6.9±56.2 (−228 to 111)	39	407.9±90.9 (195 to 628)	417.0±96.1 (211 to 657)	9.1±32.9 (−72 to 108)	2.2	0.835[¶]
Borg dyspnoea scale score	39	2.90±1.99 (0.0 to 9.0)	3.54±2.36 (0.5 to 10.0)	0.64±1.98 (−3.0 to 9.0)	39	3.26±1.75 (0.5 to 8.0)	3.05±1.39 (0.5 to 6.0)	−0.21±1.16 (−3.0 to 2.0)	−0.85	0.036[#]
NT-proBNP (pg·mL^{-1})	39	512.02±709.60 (14.4 to 2920.0)	664.39±1210.41 (12.7 to 6820.0)	152.38±961.26 (−2313.0 to 4400.0)	39	591.98±928.20 (7.0 to 3220.0)	531.28±855.26 (8.1 to 3400.0)	−60.70±604.48 (−1906.0 to 1700.0)	−213.08	0.964[#]
EQ-5D-5L utility score	39	0.8502±0.1413 (0.542 to 1.000)	0.8339±0.1865 (−0.025 to 1.000)	−0.0164±0.1647 (−0.765 to 0.229)	39	0.8256±0.1414 (0.524 to 1.000)	0.8237±0.1202 (0.567 to 1.000)	−0.0020±0.1299 (−0.409 to 0.256)	0.0144	0.669[¶]
EQ-5D-5L VAS	39	71.5±16.4 (35 to 100)	75.4±19.3 (0 to 100)	3.9±19.6 (−60 to 45)	39	71.4±17.5 (30 to 90)	76.6±15.1 (45 to 100)	5.3±15.5 (−25 to 45)	1.4	0.736[¶]
WHO functional class	39	I: 2 II: 26 III: 11 IV: 0	I: 3 II: 25 III: 10 IV: 1	Improved: 3 (7.7%) 95% CI 2.7 to 20.3 Deteriorated: 1 (2.6%) 95% CI 0.5 to 13.2	39	I: 1 II: 23 III: 15 IV: 0	I: 2 II: 25 III: 12 IV: 0	Improved: 4 (10.3%) 95% CI 4.1 to 23.6 Deteriorated: 0 (0.0%)	Improved: 2.6% 95% CI −11.5% to 16.8% Deteriorated: −2.6% 95% CI −13.2% to 6.6%	Improved: >0.999[§] Deteriorated: >0.999[§]

Data are presented as n or mean±SD (range), unless otherwise stated. PVR: pulmonary vascular resistance; PVRI: pulmonary vascular resistance index; mPAP: mean pulmonary artery pressure; TPR: total pulmonary resistance; mRAP: mean right atrial pressure; S_{vO_2}: mixed venous oxygen saturation; VAS: visual analogue scale. [#]: Wilcoxon rank sum test; [¶]: unpaired t-test; [+]: one patient was excluded from the full analysis set analysis because of a missing baseline value; [§]: Fisher's exact test.

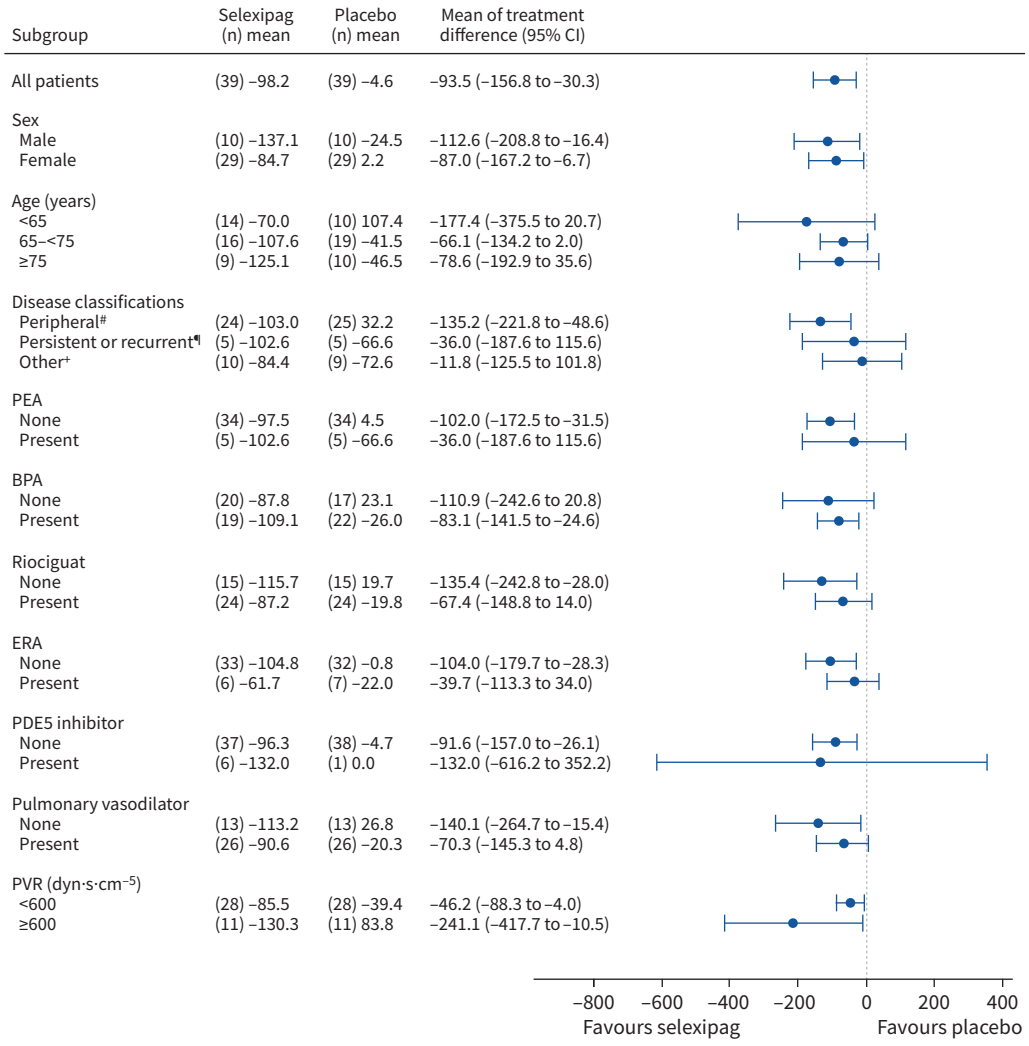

FIGURE 4 Change from baseline in pulmonary vascular resistance (PVR) in baseline characteristics subgroup. #: pulmonary endarterectomy (PEA) not indicated because of distal organised thrombus; ¶: persistent or recurrent pulmonary hypertension after PEA; +: high-risk case (*e.g.* comorbidities and old age) or PEA could not be performed for other reasons. BPA: balloon pulmonary angioplasty; ERA: endothelin receptor antagonist; PDE5: phosphodiesterase type 5.

Safety

The ADRs (excluding those not related to selexipag) that occurred at a rate of ⩾10% in the selexipag and placebo groups are shown in table 4. ADRs occurred in 35 (89.7%) out of 39 patients in the selexipag group. The ADRs that occurred at a rate of ⩾10% in the selexipag group were headache (53.8%), diarrhoea (41.0%), nausea (33.3%), malaise (23.1%), pain in the jaw and decreased appetite (both 20.5%), myalgia and vomiting (both 15.4%) and arthralgia (10.3%). These reactions are the same as those generally observed when a prostacyclin analogue is administered. Most ADRs occurred in the early phase of treatment and at low doses. Most patients improved or recovered with symptomatic treatment without discontinuation of the study drug.

Of the 39 patients in the selexipag group, three discontinued the study due to adverse events (diarrhoea, nausea and vertigo n=1, nausea n=1, headache n=1), while of the 39 patients in the placebo group, four discontinued the study due to adverse events (abdominal discomfort n=1, decreased white blood cell count n=1, headache n=1, cardiorespiratory arrest n=1).

Serious adverse events in the study included atrial tachycardia and right ventricular failure, each in one (2.6%) patient in the selexipag group, and cardiorespiratory arrest, colon cancer and haemoptysis, each in

TABLE 4 Adverse events related to selexipag usage (safety analysis)

	Placebo	Selexipag
Patients	39	39
Total patients with ⩾1 adverse event	20 (51.3)	35 (89.7)
Adverse events		
Headache	10 (25.6)	21 (53.8)
Diarrhoea	2 (5.1)	16 (41.0)
Nausea	3 (7.7)	13 (33.3)
Malaise	1 (2.6)	9 (23.1)
Pain in jaw	5 (12.8)	8 (20.5)
Decreased appetite	0 (0.0)	8 (20.5)
Myalgia	0 (0.0)	6 (15.4)
Vomiting	1 (2.6)	6 (15.4)
Arthralgia	3 (7.7)	4 (10.3)

Data are presented as n or n (%). Adverse events (related to selexipag) with a frequency of ⩾10.0% were extracted.

one (2.6%) patient in the placebo group. The atrial tachycardia that occurred in the selexipag group, for which a causal relationship could not be ruled out, was moderate. The right ventricular failure was also moderate, and a causal relationship was ruled out.

In both groups, blood pressure or pulse rate did not change (supplementary table S3) and no abnormal laboratory test values or electrocardiography results that could be considered a clinical problem occurred throughout the study period.

Discussion

Selexipag improved haemodynamics in Japanese patients with inoperable CTEPH or persistent/recurrent PH after PEA and/or BPA compared with placebo, but did not improve exercise capacity. It was well tolerated and safe.

Compared with placebo, selexipag improved PVR, the primary end-point in this study. PVR reflects the fundamental haemodynamic condition of PH and is associated with long-term prognosis in PAH [15]. Reduced PVR was associated with improved prognosis after PEA in CTEPH patients [16]. Therefore, PVR is clinically relevant and has been used as a measure of the treatment effect in PH [17]. The improvement in PVR observed in the present study was consistent with that in previous studies of pulmonary vasodilators in CTEPH [10, 18–20]. Moreover, a previous proof-of-concept clinical trial in Japanese CTEPH patients suggested a possible signal for improved haemodynamics with selexipag [14]. PVR improvement was paralleled by an improvement in other haemodynamic characteristics (*e.g.* PVRI, cardiac index, TPR, S_{vO_2}).

The degree of change in PVR induced by selexipag in the present study was relatively modest (−98 dyn·s·cm^{-5}) compared to that in previous studies (−116– −239 dyn·s·cm^{-5}) [10, 18–20]. This may be due to the relatively lower baseline PVR in our study (523.4±132.8 dyn·s·cm^{-5}) than in the previous international studies (778–984 dyn·s·cm^{-5}) (supplementary table S1) [10, 21, 22] and the previous Japanese CTEPH study (700–756 dyn·s·cm^{-5}) [14]. Our study included CTEPH patients receiving a relatively high proportion of background treatment with riociguat (61.5%) and BPA (52.6%). Post-market surveillance of riociguat in a Japanese CTEPH population showed that riociguat with BPA reduced PVR by 280 dyn·s·cm^{-5} [23]. Therefore, the background treatment in the present study may have reduced the baseline PVR, consequently attenuating the treatment effect of selexipag. This hypothesis may be supported by the subgroup analysis, showing a larger PVR decrease in patients on selexipag alone than in patients on selexipag receiving background pulmonary vasodilators. Although the PVR reduction observed in this study was modest compared to that in previous studies, the geometric mean PVR at 20 weeks decreased to 78.7% and 94.1% of baseline in the selexipag and placebo groups, respectively. The selexipag:placebo ratio of geometric means (95% CI), which was used as the primary end-point in the MERIT-1 study, was 83.6% (74.9–93.3%), which is similar to the ratios obtained in other clinical studies [10, 21, 22].

BPA has gained widespread popularity for the clinical treatment of inoperable CTEPH patients [4]. The benefit of selexipag treatment for residual PH following BPA is not clear. In the subgroup analysis with

post-BPA patients, PVR significantly decreased in the selexipag group compared with the placebo group (p=0.009), suggesting a role of selexipag in the treatment of residual PH following BPA. Considering the small sample applied to the subgroup analysis, these results should be regarded as exploratory.

However, in the present study, two of the secondary end-points, 6MWD and WHO functional class, were not significantly improved in the selexipag group compared with the placebo group. One potential reason for the discrepancy between the results of haemodynamic and exercise capacity is the sample size. We had set the sample size to enable observation of a significant difference in PVR, not in other parameters, such as 6MWD and WHO functional class. Further large-scale investigation is necessary to prove the efficacy of selexipag in exercise capacity. Another hypothesis is that the baseline haemodynamic and other parameters, including 6MWD, were closer to normal than in previous studies (supplementary table S1) [10, 21, 22], possibly due to the presence of background therapy such as BPA and PH drugs. The dominant baseline WHO functional class was also lower in the present study than the CHEST-1 study (class II (59%) and class III (67%), respectively) [10]. Mild haemodynamic impairment and relatively well-preserved exercise tolerance at baseline might have attenuated the treatment effect on 6MWD and WHO functional class, as well as other haemodynamic parameters (mPAP and mRAP) and clinical parameters (NT-proBNP and EQ-5D-5L). Furthermore, a ceiling effect of 6MWD might mask efficacy in mild symptomatic PH patients who have high baseline 6MWD [24]. However, in the present study, the Borg dyspnoea scale score after 6MWD showed a significant decrease.

With selexipag, the incidence of adverse events characteristic of prostacyclin drugs is high, and the safety profile seen in this study is similar to those seen in other selexipag studies in PAH [13, 25, 26]. Serious adverse events were limited, and most of the adverse events were mild or moderate. The incidence of adverse events was highest with doses ranging between 400 and 800 $\mu g \cdot day^{-1}$, and most occurred during the dose titration period. None of the adverse events showed an increase in incidence in association with dose increases. The incidence of hypotension-related adverse events was 7.7% in the selexipag group; however, the events were mild and resolved without any change in selexipag treatment. No adverse events related to thyroid dysfunction were observed. These findings show that selexipag up to 1600 µg per dose twice daily was safe and well tolerated by patients with CTEPH.

There are several limitations to this study. The study had a shorter treatment period than those usually reported in clinical settings and had a small sample size. Furthermore, the study was conducted only in Japan. Therefore, the results of the efficacy end-points other than pulmonary haemodynamics need to be further investigated with a larger number of patients worldwide. We excluded patients with severe obstructive pulmonary disease, restrictive pulmonary disease, moderate or severe renal or hepatic disorders and pregnancy or conditions that may interfere with the 6MWD test, such as those with complications such as angina pectoris or intermittent claudication.

The results of this study suggest that selexipag is well tolerated and safe, and that it improves pulmonary haemodynamics in CTEPH patients who cannot undergo PEA or those with persistent or recurrent PH after PEA and/or BPA. No improvement was observed in exercise capacity. Further large-scale investigation is necessary to prove the role of selexipag in CTEPH.

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