Early View

Original research article

Selexipag for the treatment of chronic thromboembolic pulmonary hypertension

Takeshi Ogo, Hiroto Shimokawahara, Hideyuki Kinoshita, Seiichiro Sakao, Kohtaro Abe, Satoaki Matoba, Hirohiko Motoki, Noriaki Takama, Junya Ako, Yasuhiro Ikeda, Shuji Joho, Hisataka Maki, Takahiro Saeki, Teruyasu Sugano, Ichizo Tsujino, Koichiro Yoshioka, Naoki Shiota, Shinichi Tanaka, Chieko Yamamoto, Nobuhiro Tanabe, Koichiro Tatsumi,

Please cite this article as: Ogo T, Shimokawahara H, Kinoshita H, *et al.* Selexipag for the treatment of chronic thromboembolic pulmonary hypertension. *Eur Respir J* 2021; in press (<https://doi.org/10.1183/13993003.01694-2021>).

This manuscript has recently been accepted for publication in the *European Respiratory Journal*. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJ online.

Selexipag for the treatment of chronic thromboembolic pulmonary hypertension

Takeshi Ogo, MD, PhD¹; Hiroto Shimokawahara, MD, PhD²; Hideyuki Kinoshita, PhD³;
Seiichiro Sakao, MD, PhD⁴; Kohtaro Abe, MD, PhD⁵; Satoaki Matoba, MD, PhD⁶; Hirohiko
Motoki, MD, PhD⁷; Noriaki Takama, MD, PhD⁸; Junya Ako, MD, PhD⁹; Yasuhiro Ikeda MD,
PhD¹⁰; Shuji Joho, MD, PhD¹¹; Hisataka Maki, MD, PhD¹²; Takahiro Saeki, MD, PhD¹³;
Teruyasu Sugano, MD¹⁴; Ichizo Tsujino, MD, PhD¹⁵; Koichiro Yoshioka, MD, PhD¹⁶; Naoki
Shiota¹⁷; Shinichi Tanaka¹⁸; Chieko Yamamoto¹⁷; Nobuhiro Tanabe, MD, PhD^{4, 19}; Koichiro
Tatsumi, MD, PhD⁴; for the Study Group²⁰

Affiliations: ¹ Division of Advanced Medical Research in Pulmonary Hypertension, Division
of Pulmonary Circulation, Department of Cardiovascular Medicine, National Cerebral and
Cardiovascular Centre, Suita, Osaka, Japan, ² Department of Cardiology, National Hospital
Organization Okayama Medical Centre, Okayama, Okayama, Japan, ³ Department of
Community Medicine Supporting System, Kyoto University Graduate School of Medicine,
Kyoto, Kyoto, Japan, ⁴ Department of Respiriology, Graduate School of Medicine, Chiba
University, Chiba, Chiba, Japan, ⁵ Departments of Cardiovascular Medicine, Kyushu
University Graduate School of Medical Sciences, Fukuoka, Fukuoka, Japan, ⁶ Department of
Cardiovascular Medicine, Graduate School of Medical Science, Kyoto Prefectural University

of Medicine, Kyoto, Kyoto, Japan,⁷ Department of Cardiology, Shinshu University School of Medicine, Matsumoto, Nagano, Japan,⁸ Department of Cardiovascular Medicine, Gunma University Graduate School of Medicine, Maebashi, Gunma, Japan,⁹ Department of Cardiovascular Medicine, Kitasato University, Sagamihara, Kanagawa, Japan,¹⁰ Department of Cardiology, Yamaguchi Prefectural Grand Medical Centre, Hofu, Yamaguchi, Japan,¹¹ Second Department of Internal Medicine, University of Toyama, Toyama, Toyama, Japan,¹² Department of Cardiology, The University of Tokyo Hospital, Tokyo, Tokyo, Japan,¹³ Cardiovascular Medicine, National Hospital Organization Kanazawa Medical Centre, Kanazawa, Ishikawa, Japan,¹⁴ Department of Medical Science and Cardiorenal Medicine, Yokohama City University Graduate School of Medicine, Yokohama, Kanagawa, Japan,¹⁵ Internal Medicine I, Hokkaido University Hospital, Sapporo, Hokkaido, Japan,¹⁶ Department of Cardiology, Tokai University School of Medicine, Isehara, Kanagawa, Japan,¹⁷ Clinical Development Dept., Nippon Shinyaku Co., Ltd., Kyoto, Kyoto, Japan,¹⁸ Data Science Dept., Nippon Shinyaku Co., Ltd., Kyoto, Kyoto, Japan,¹⁹ Chibaken Saiseikai Narashino Hospital, Narashino, Chiba, Japan,²⁰ See Supplementary Material.

Correspondence:

Takeshi Ogo, MD, PhD

Division of Advanced Medical Research in Pulmonary Hypertension, Division of Pulmonary Circulation, Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, 6-1 Kishibe-Shimmachi, Suita, Osaka, 564-8565, Japan.

Tel: +81-6-6170-1070

FAX: +81-6-6170-1348

E-mail: tak@ncvc.go.jp

Take home message:

Selexipag significantly improved pulmonary vascular resistance and other haemodynamics in patients with chronic thromboembolic pulmonary hypertension, although exercise capacity remained unchanged.

Abstract

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.

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 endpoint was the change in pulmonary vascular resistance (PVR) from baseline to week 20. The secondary endpoints were changes in other haemodynamic parameters, 6-min walk distance (6WMD), Borg Dyspnoea Scale score, World Health Organisation (WHO) functional class, EuroQol 5 dimensions 5-level and N-terminal pro-brain natriuretic peptide.

The change in PVR was $-98.2 \pm 111.3 \text{ dyn}\cdot\text{s}/\text{cm}^5$ and $-4.6 \pm 163.6 \text{ dyn}\cdot\text{s}/\text{cm}^5$ in the selexipag and placebo groups, respectively (mean difference, $-93.5 \text{ dyn}\cdot\text{s}/\text{cm}^5$; 95% confidence interval, $-156.8, -30.3$; $p = 0.006$). The changes in cardiac index ($p < 0.001$) and Borg Dyspnoea Scale score ($p = 0.036$) were also significantly improved over placebo. 6WMD and WHO functional class were not significantly improved. The common adverse events in the selexipag group were corresponded to those generally observed following a prostacyclin analogue is administered.

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.

Trial registration: JAPIC Clinical Trials Information (JapicCTI-163279).

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 co-morbidities, or those that refuse treatment, are not eligible for PEA [5–8]. Even if PEA is successfully performed, 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. Also, 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 histopathologic 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 PVR by -226 ± 248 dyn·s/cm⁵ from baseline values in inoperable CTEPH or residual PH [10].

Selexipag is an orally selective prostacyclin receptor (IP receptor) agonist with a non-prostanoid structure. Its metabolite, MRE-269, has a high selectivity for the IP receptor [11, 12]. Selexipag increases cyclic adenosine monophosphate, 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 (CT) 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 PAP (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/cm⁵. 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., co-morbidities 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 (PDE5) inhibitor, or a calcium antagonist was allowed if the doses administered had been stable for at least 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 Helsinki Declaration. The study design was approved by the Institutional Review Board at each study site, including the National Cerebral and Cardiovascular Centre (reference no. #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 1,600 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 endpoint was the change in resting PVR from baseline to week 20. The secondary endpoints were changes in the PVR index (PVRI), mPAP, cardiac index, mean right atrial pressure (mRAP), total pulmonary resistance (TPR), mixed venous oxygen saturation

(SvO₂), and EuroQol 5 dimensions 5-level (EQ-5D-5L) after 20 weeks of treatment, changes in 6MWD, Borg Dyspnoea Scale score, and NT-proBNP at each visit, and shifts in World Health Organisation (WHO) functional class over time at each visit. The exploratory efficacy endpoint was time from randomisation to first clinical worsening event (e.g., death, hospitalisation due to worsening or complication of PH, use of any additional interventions to treat the worsening of CTEPH, and fulfilling the following two requirements: worsening of NYHA/WHO functional class and a more than 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 (CO).

The safety endpoints 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 $\pm$ standard deviation) in PVR in the selexipag group of -104 ± 191 dyn·s/cm⁵ and a change in PVR in the placebo group of 26 ± 180 dyn·s/cm⁵. 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 approximately 5% would be excluded from the Full Analysis Set (FAS). The randomisation method is provided in the Supplementary Material.

Data are presented as mean $\pm$ standard deviation, median (min, max), or percentage. The primary analysis of the efficacy endpoints was performed for the FAS. Changes in PVR, PVRI, SvO₂, 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, presence/absence of concomitant riociguat or ERA and baseline PVR, and the difference in means and 95% confidence intervals (CIs) are shown in Figure 4. All subgroups were prespecified 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 $P < 0.05$ (2-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 endpoint 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 PMDA (Pharmaceuticals and Medical Devices Agency) in Japan, PVR was set as the primary endpoint 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 FAS 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% (13/39) of patients was 1,600 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 Statistical Analysis.

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 endpoints 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/cm⁵, whereas that in the placebo group was -4.6 ± 163.6 dyn·s/cm⁵. The mean difference (95% CI) in PVR between the groups after 20 weeks of treatment was -93.5 (-156.8 , -30.3) dyn·s/cm⁵, 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 , -48.6) dyn·s/cm⁵, 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., co-

morbidities 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, -24.6) dyn·s/cm⁵. 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, -15.4) dyn·s/cm⁵. PVR showed a larger decrease in patients on selexipag alone than in patients on selexipag taken concomitantly with pulmonary vasodilators. An 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, SvO₂, and the Borg Dyspnoea Scale score, the mean differences (95% CI) between the groups after 20 weeks of treatment were -154.4 (-255.3, -53.4) dyn·s·m²/cm⁵ (p = 0.004), 0.487 (0.262, 0.711) L/min/m² (p < 0.001), -116.8 (-189.3, -44.2) dyn·s/cm⁵ (p = 0.002), 2.58% (0.30%, 4.87%) (p = 0.029), and -0.85 (-1.58, -0.11) (p = 0.036), respectively, indicating a significant 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.

Safety

The ADRs (excluding those not related to selexipag) that occurred at a rate of $\geq 10\%$ in the selexipag and placebo groups are shown in Table 4. ADRs occurred in 35 of 39 patients (89.7%) in the selexipag group. The ADRs that occurred at a rate of $\geq 10\%$ in the selexipag group were headache (53.8%), diarrhoea (41.0%), nausea (33.3%), malaise (23.1%), pain in the jaw and decreased appetite (20.5%), myalgia and vomiting (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 in one patient and nausea and headache in one patient each), while of the 39 patients in the placebo group, four discontinued the study due to adverse events (abdominal discomfort, decreased white blood cell count, headache, and cardiorespiratory arrest in one patient each).

Serious adverse events in the study included atrial tachycardia and right ventricular failure in one patient (2.6%) each in the selexipag group, and cardiorespiratory arrest, colon cancer, and haemoptysis in one patient (2.6%) each 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 endpoint 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, SvO₂).

The degree of change in PVR induced by selexipag in the present study was relatively modest ($-98 \text{ dyn}\cdot\text{s}/\text{cm}^5$) compared to that in previous studies (-116 to $-239 \text{ dyn}\cdot\text{s}/\text{cm}^5$) [10, 18-20]. This may be due to the relatively lower baseline PVR in our study ($523.4 \pm 132.8 \text{ dyn}\cdot\text{s}/\text{cm}^5$) than in the previous international studies (778 to $984 \text{ dyn}\cdot\text{s}/\text{cm}^5$) (supplementary Table S1) [10, 21, 22] and the previous Japanese CTEPH study (700 to $756 \text{ dyn}\cdot\text{s}/\text{cm}^5$) [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 $280 \text{ dyn}\cdot\text{s}/\text{cm}^5$ [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 endpoint 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 endpoints, 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, WHO functional class, as well as other hemodynamic 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]. In the present study, however, 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 µg/day, 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 1,600 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 endpoints other than pulmonary haemodynamics need to be further investigated with a larger number of patients

worldwide. We excluded patients with severe obstructive pulmonary disease and restrictive pulmonary disease, and those with complications such as angina pectoris, intermittent claudication, or conditions that may interfere with the 6MWD test, such as moderate or severe renal or hepatic disorders and pregnancy.

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.

Acknowledgements

This study was sponsored by Nippon Shinyaku Co., Ltd, and Janssen Pharmaceutical K.K. The sponsors of the study were involved in the study design, data collection, statistical analysis, data interpretation, and medical writing. The authors wish to thank the study group, subinvestigators, study staff, and patients.

Data availability

The de-identified participant data and study protocol will not be shared.

Funding

This study was funded by Nippon Shinyaku Co., Ltd, and Janssen Pharmaceutical K.K.

Investigational products were provided by Nippon Shinyaku Co., Ltd.

Conflict of interest

NIPPON SHINYAKU CO., LTD. provided grants for this study group. TO reports personal fees from NIPPON SHINYAKU CO., LTD. during the conduct of the study; personal fees from Janssen Pharmaceutical K.K., Bayer Yakuhin, Ltd., NIPPON SHINYAKU CO., LTD. GlaxoSmithKline K.K., Pfizer Japan Inc., and MOCHIDA PHARMACEUTICAL CO., LTD., outside the submitted work. HS reports grants from KANEKA CORPORATION, Bayer Taiwan Co., Ltd., Bayer Yakuhin, Ltd., DAIICHI SANKYO COMPANY, LIMITED., Japan Lifeline Co., Ltd., Actelion Pharmaceuticals Ltd., Pfizer Inc., and MOCHIDA PHARMACEUTICAL CO., LTD., outside the submitted work. HK reports grants and personal fees from NIPPON SHINYAKU CO., LTD., during the conduct of the study; personal fees from Janssen Pharmaceutical K.K., NIPPON SHINYAKU CO., LTD. and Bayer Yakuhin, Ltd., outside the submitted work. SS reports personal fees from Actelion Pharmaceuticals Ltd., Bayer Yakuhin, Ltd., DAIICHI SANKYO COMPANY, LIMITED., and Pfizer Japan Inc., grants from the Ministry of Health, Labour, and Welfare of Japan (No. 27280401), and Grant-in-Aid for Scientific Research B from the Japan Society for the Promotion of Science (JSPS) (No. JP18H03664), outside the submitted work. KA reports grants from MOCHIDA PHARMACEUTICAL CO., LTD., and DAIICHI SANKYO HEALTHCARE CO., LTD., outside the submitted work. H Maki reports grants from Bayer Yakuhin, Ltd, and MOCHIDA PHARMACEUTICAL CO., LTD., outside the submitted work.

T Sugano reports personal fees from Janssen Pharmaceutical K.K., Bayer Holding Ltd., MOCHIDA PHARMACEUTICAL CO., LTD., DAIICHI SANKYO COMPANY, LIMITED., Takeda Pharmaceutical Company Limited., Amgen Inc., Otsuka Pharmaceutical Co., Ltd., Novartis Pharma K.K., and NIPPON SHINYAKU CO., LTD., outside the submitted work. IT reports grants from Actelion Pharmaceuticals Japan Ltd., MOCHIDA PHARMACEUTICAL CO., LTD., and Nippon Boehringer Ingelheim Co., Ltd., personal fees from Bayer Yakuhin, Ltd., Janssen Pharmaceutical K.K., Pfizer Japan Inc., and NIPPON SHINYAKU CO., LTD., outside the submitted work. N Tanabe reports personal fees from NIPPON SHINYAKU CO., LTD., during the conduct of the study; personal fees from NIPPON SHINYAKU CO., LTD., Bayer AG, and Janssen Pharmaceutical K.K., outside the submitted work. KT reports personal fees from NIPPON SHINYAKU CO., LTD., Janssen Pharmaceutical K.K., and Actelion Pharmaceuticals Ltd., during the conduct of the study. SM, H Motoki, N Takama, JA, YI, SJ, T Saeki, KY, have no conflicts of interest outside the submitted work. NS, ST, and CY are employees of Nippon Shinyaku Co., Ltd.

Author contributions

KT, N Tanabe, NS, ST, and CY participated in the study design, data collection, data analysis and interpretation. TO, HS, HK, SS, KA, SM, H Motoki, N Takama, JA, YI, SJ, H Maki, T Saeki, T Sugano, IT, and KY participated in the data collection. All authors participated in the development of the manuscript, gave final approval of the manuscript for submission, and agree to be accountable for the integrity of the work.

References

1. Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J* 2015; 46: 903–975.
2. Kim NH, Delcroix M, Jaïs X, et al. Chronic thromboembolic pulmonary hypertension. *Eur Respir J* 2019; 53: 1801915.
3. Delcroix M, Lang I, Pepke-Zaba J, et al. Long-term outcome of patients with chronic thromboembolic pulmonary hypertension: Results from an international prospective registry. *Circulation* 2016; 133: 859–871.
4. Madani M, Ogo T, Simonneau G, The changing landscape of chronic thromboembolic pulmonary hypertension management, *Eur Respir Rev* 2017; 26: 170105.
5. Miwa H, Tanabe N, Jujo T, et al. Long-term outcome of chronic thromboembolic pulmonary hypertension at a single Japanese pulmonary endarterectomy center. *Circ J* 2018; 82: 1428–1436.
6. Pepke-Zaba J, Delcroix M, Lang I, et al. Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. *Circulation* 2011; 124: 1973–1981.
7. Quadery SR, Swift AJ, Billings CG, et al. The impact of patient choice on survival in chronic thromboembolic pulmonary hypertension. *Eur Respir J* 2018; 52: 1800589.

8. Rahnavardi M, Yan TD, Cao C, et al. Pulmonary thromboendarterectomy for chronic thromboembolic pulmonary hypertension: a systematic review. *Ann Thorac Cardiovasc Surg* 2011; 17:435–445.
9. Brenot P, Jaïs X, Taniguchi Y, et al. French experience of balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension. *Eur Respir J* 2019; 53: 1802095.
10. Ghofrani HA, D'Armini AM, Grimminger F, et al. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. *New Engl J Med* 2013; 369: 319–329.
11. Kuwano K, Hashino A, Asaki T, et al. 2-[4-[(5,6-Diphenylpyrazin-2-yl)(isopropyl)amino]butoxy]-N-(methylsulfonyl)acetamide (NS-304), an orally available and long-acting prostacyclin receptor agonist prodrug. *J Pharmacol Exp Ther* 2007; 322: 1181–1188.
12. Asaki T, Kuwano K, Morrison K, et al. An oral and selective IP prostacyclin receptor agonist for the treatment of pulmonary arterial hypertension. *J Med Chem* 2015; 58: 7128–7137.
13. Sitbon O, Channick R, Chin KM, et al. Selexipag for the treatment of pulmonary arterial hypertension. *New Engl J Med* 2015; 373: 2522–2533.
14. Tanabe N, Fukuda K, Matsubara H, et al. Selexipag for chronic thromboembolic pulmonary hypertension in Japanese patients - A double-blind, randomized, placebo-controlled, multicenter phase II study. *Circ J* 2020; 84: 1866–1874.

15. Sitbon O, Humbert M, Nunes H, et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. *J Am Coll Cardiol* 2002; 40: 780–788.
16. Bonderman D, Skoro-Sajer N, Jakowitsch J, et al. Predictors of outcome in chronic thromboembolic pulmonary hypertension. *Circulation* 2007; 115: 2153-2158.
17. Galiè N, Rubin L, Hoeper MM, et al. Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial. *Lancet* 2008; 371: 2093-2100.
18. Skoro-Sajer N, Bonderman D, Wiesbauer F, et al. Treprostinil for severe inoperable chronic thromboembolic pulmonary hypertension. *J Thromb Haemost* 2007; 5: 483–489.
19. Olschewski H, Simonneau G, Galiè N, et al. Inhaled iloprost for severe pulmonary hypertension. *New Engl J Med* 2002; 347: 322–329.
20. Hoeper MM. Pharmacological therapy for patients with chronic thromboembolic pulmonary hypertension. *Eur Respir Rev* 2015; 24: 272–282.
21. Ghofrani HA, Simonneau G, D'Armini AM, et al. Macitentan for the treatment of inoperable chronic thromboembolic pulmonary hypertension (MERIT-1): results from the multicentre, phase 2, randomised, double-blind, placebo-controlled study. *Lancet Respir Med* 2017; 5: 785–794.

22. Jaïs X, D'Armini AM, Jansa P, et al. Bosentan for treatment of inoperable chronic thromboembolic pulmonary hypertension: BENEFiT (Bosentan Effects in iNopErable Forms of chronIc Thromboembolic pulmonary hypertension), a randomized, placebo-controlled trial. *J Am Coll Cardiol* 2008; 52: 2127–2134.
23. Tanabe N, Ogo T, Hatano M, et al. Safety and effectiveness of riociguat for chronic thromboembolic pulmonary hypertension in real-world clinical practice: interim data from post-marketing surveillance in Japan. *Pulm Circ* 2020; 10: 2045894020938986.
24. Lee WT, Brown A, Peacock AJ, et al. Use of non-invasive haemodynamic measurements to detect treatment response in precapillary pulmonary hypertension. *Thorax* 2011; 66: 810–814.
25. Tanabe N, Ikeda S, Tahara N, et al. Efficacy and safety of an orally administered selective prostacyclin receptor agonist, selexipag, in Japanese patients with pulmonary arterial hypertension. *Circ J* 2017; 81: 1360–1367.
26. Simonneau G, Torbicki A, Hoeper MM, et al. Selexipag: An oral, selective prostacyclin receptor agonist for the treatment of pulmonary arterial hypertension. *Eur Respir J* 2012; 40: 874–880.

Figure Legends

Figure 1: Schematic of study design. A total of 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.

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.

Figure 3. Change in pulmonary vascular resistance from baseline to week 20. Data are presented as mean $\pm$ standard deviation. The mean change from baseline to 20 weeks of treatment was $-98.2 \text{ dyn}\cdot\text{s}/\text{cm}^5$ (95% confidence interval: $-134.2, -62.1 \text{ dyn}\cdot\text{s}/\text{cm}^5$) in the selexipag group and $-4.6 \text{ dyn}\cdot\text{s}/\text{cm}^5$ (95% confidence interval: $-57.7, 48.4 \text{ dyn}\cdot\text{s}/\text{cm}^5$) in the placebo group. A significant treatment effect for selexipag versus placebo groups was observed (treatment effect, -93.5 ; 95% confidence interval: $-156.8, -30.3$; $P = 0.006$ with the use of the Wilcoxon rank sum test).

Figure 4. Change from baseline in pulmonary vascular resistance in baseline

characteristics subgroup.

* PEA not indicated because of distal organised thrombus

† Persistent or recurrent pulmonary hypertension after PEA

‡ High-risk case (e.g., co-morbidities and old age) or PEA could not be performed for other reasons

Tables

Table 1. Patient Baseline Characteristics (FAS)

Variables	Placebo n = 39	Selexipag n = 39
Sex [n (%)]		
Male	10 (25.6%)	10 (25.6%)
Female	29 (74.4%)	29 (74.4%)
Age (years)		
Mean $\pm$ SD	68.3 $\pm$ 9.6	66.3 $\pm$ 11.1
Median (min, max)	71.0 (44, 84)	69.0 (36, 82)
6MWD (m)		
Mean $\pm$ SD	384.0 $\pm$ 87.0	407.9 $\pm$ 90.9
Median (min, max)	390.0 (183, 534)	405.0 (195, 628)
WHO functional class (n)		
I/II/III/IV	2/26/11/0	1/23/15/0
Disease classification [n (%)]		
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 [n (%)]		
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, mean $\pm$ SD)	4.45 $\pm$ 5.24	2.72 $\pm$ 3.24
SD, standard deviation; 6MWD, 6-min walk distance; WHO, World Health Organisation; PEA, pulmonary endarterectomy; BPA, balloon pulmonary angioplasty; PDE5, phosphodiesterase type 5; ERA, endothelin receptor antagonist.		

Table 2. Dose Distribution (FAS)

Final maintenance dose (µg/day) *	Placebo n = 39	Selexipag n = 39
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
* Dose prescribed at the start of the dose maintenance period. † Subjects withdrawn by the start of the dose maintenance period.		

Table 3. Changes in Pulmonary Haemodynamic Variables, 6MWD, Borg Dyspnoea Scale score, NT-proBNP, EQ-5D-5L and WHO

Functional Class (FAS)

Variable	Placebo				Selexipag				Treatment effect	P-value
	n	Baseline	Endpoint	Change	n	Baseline	Endpoint	Change		
PVR (dyn•s/cm ⁵)	39	553.1 ± 184.0 (387, 1146)	548.5 ± 288.4 (235, 1429)	-4.6 ± 163.6 (-220, 695)	39	523.4 ± 132.8 (362, 918)	425.3 ± 158.6 (176, 927)	-98.2 ± 111.3 (-359, 186)	-93.5	0.006*
PVRI (dyn•s•m ² / cm ⁵)	39	850.7 ± 299.4 (497, 1818)	850.8 ± 463.1 (362, 2278)	0.0 ± 263.3 (-321, 1155)	39	810.8 ± 214.9 (540, 1662)	656.5 ± 257.6 (303, 1481)	-154.3 ± 174.4 (-599, 293)	-154.4	0.004*
mPAP (mmHg)	39	35.5 ± 8.3 (26, 55)	33.7 ± 10.2 (22, 66)	-1.7 ± 4.6 (-11, 11)	39	35.2 ± 5.4 (25, 47)	33.1 ± 6.6 (22, 44)	-2.2 ± 3.8 (-11, 4)	-0.4	0.650 [†]
Cardiac index (L/min/m ²)	39	2.587 ± 0.414 (1.97, 4.04)	2.463 ± 0.475 (1.54, 3.76)	-0.124 ± 0.409 (-1.38, 0.83)	39	2.693 ± 0.601 (1.54, 4.71)	3.056 ± 0.788 (1.77, 5.89)	0.363 ± 0.572 (-0.89, 2.19)	0.487	<0.001**
TPR (dyn•s/cm ⁵)	39	731.7 ± 203.5 (509, 1401)	738.2 ± 304.2 (388, 1683)	6.5 ± 173.0 (-250, 699)	39	704.5 ± 184.4 (437, 1262)	594.3 ± 191.3 (295, 1086)	-110.2 ± 147.5 (-477, 261)	-116.8	0.002 [†]
mRAP (mmHg)	39	5.4 ± 4.0 (1, 24)	5.8 ± 5.2 (1, 32)	0.5 ± 2.7 (-6, 8)	39	5.5 ± 3.2 (0, 13)	5.5 ± 3.7 (-2, 21)	0.0 ± 3.0 (-7, 8)	-0.5	0.451 [†]
SvO ₂ (%)	38 [‡]	66.24 ± 7.43 (45.3, 77.6)	64.63 ± 8.05 (34.4, 78.8)	-1.61 ± 5.13 (-12.1, 9.8)	38 [‡]	67.17 ± 5.65 (48.6, 77.8)	68.14 ± 6.59 (48.6, 82.8)	0.97 ± 4.87 (-9.7, 13.9)	2.58	0.029*
6MWD (m)	39	384.0 ± 87.0 (183, 534)	390.9 ± 111.6 (0, 575)	6.9 ± 56.2 (-228, 111)	39	407.9 ± 90.9 (195, 628)	417.0 ± 96.1 (211, 657)	9.1 ± 32.9 (-72, 108)	2.2	0.835 [†]

Table 4. Adverse Events Related to Selexipag Usage (SAF)

Patients (n, %)	Placebo (n = 39)	Selexipag (n = 39)
Total patients with ≥ 1 AE	20 (51.3)	35 (89.7)
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)
Adverse events (related to selexipag) with a frequency of at least 10.0% were extracted. AE, Adverse Event.		

SUPPLEMENTARY MATERIAL

Contents

Study group	2
Inclusion and exclusion criteria.....	4
Blinding	7
Sensitivity analysis under alternative assumptions about the missing data.....	7
Figure S1. Change in PVR from baseline by final maintenance dose.....	8
Table S1. Randomised controlled trial data on the use of medical therapies in patients with chronic thromboembolic pulmonary hypertension.	9
Table S2. Sensitivity analysis of PVR.....	10
Table S3. Changes from baseline in SBP, DBP, and PR.	11

Study group

Takeshi Ogo, Division of Advanced Medical Research in Pulmonary Hypertension, Division of Pulmonary Circulation, Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Centre

Hiroto Shimokawahara, Department of Cardiology, National Hospital Organization Okayama Medical Centre

Hideyuki Kinoshita, Department of Community Medicine Supporting System, Kyoto University Graduate School of Medicine

Seiichiro Sakao, Department of Respiriology, Graduate School of Medicine, Chiba University

Kohtaro Abe, Departments of Cardiovascular Medicine, Kyushu University Graduate School of Medical Sciences

Satoaki Matoba, Department of Cardiovascular Medicine, Graduate School of Medical Science, Kyoto Prefectural University of Medicine

Hirohiko Motoki, Department of Cardiology, Shinshu University School of Medicine

Noriaki Takama, Department of Cardiovascular Medicine, Gunma University Graduate School of Medicine

Junya Ako, Department of Cardiovascular Medicine, Kitasato University

Yasuhiro Ikeda, Department of Cardiology, Yamaguchi Prefectural Grand Medical Center

Shuji Joho, Second Department of Internal Medicine, University of Toyama

Hisataka Maki, Department of Cardiology, The University of Tokyo Hospital

Takahiro Saeki, Cardiovascular Medicine, National Hospital Organization Kanazawa Medical Centre

Teruyasu Sugano, Department of Medical Science and Cardiorenal Medicine, Yokohama City University Graduate School of Medicine

Ichizo Tsujino, Internal Medicine I, Hokkaido University Hospital

Koichiro Yoshioka, Department of Cardiology, Tokai University School of Medicine

Nobuhiro Tanabe, Chibaken Saiseikai Narashino Hospital, and Department of Respiriology, Graduate School of Medicine, Chiba University

Koichiro Tatsumi, Department of Respiriology, Graduated School of Medicine, Chiba University

Toshikazu Hashizume, Department of Cardiology, National Hospital Organization Minami Wakayama Medical Centre

Akiyoshi Hashimoto, Division of Health Care Administration and Management,
Sapporo Medical University School of Medicine

Nobutaka Ikeda, Department of Cardiology, Toho University Medical Centre Ohashi
Hospital

Takanori Ikeda, Department of Cardiovascular, Toho University Medical Centre Omori
Hospital

Hidekazu Ikemiyagi, Department of Cardiovascular Medicine, Nephrology and
Neurology, Graduate School of Medicine, University of the Ryukyus

Yasushi Imai, Department of Pharmacology, Jichi Medical University

Kouji Kajinami, Department of Cardiology, Kanazawa Medical University

Masa-aki Kawashiri, Department of Cardiovascular Medicine, Kanazawa University
Graduate School of Medical Sciences

Yasuki Kihara, Hiroshima University, and Kobe City Medical Centre General Hospital

Hakuoh Konishi, Department of Cardiovascular Biology and Medicine, Juntendo
University Graduate School of Medicine

Kayoko Kubota, Department of Cardiovascular Medicine and Hypertension, Graduate
School of Medical and Dental Sciences, Kagoshima University

Toyoaki Murohara, Department of Cardiology, Nagoya University Graduate School of
Medicine

Yoshito Ogihara, Department of Cardiology and Nephrology, Mie University Graduate
of Medicine

Osamu Okazaki, Department of Cardiology, National Centre for Global Health and
Medicine

Masataka Sata, Department of Cardiovascular Medicine, Tokushima University
Graduate School of Biomedical Sciences

Toru Satoh, Department of Cardiovascular Medicine, Kyorin University

Toshiro Shinke, Division of Cardiology, Department of Medicine, Showa University
School of Medicine

Kengo Suzuki, Division of Cardiology, Department of Internal Medicine, St. Marianna
University School of Medicine

Nobuhiro Tahara, Division of Cardiovascular Medicine, Department of Medicine,
Kurume University School of Medicine

Toru Takase, Division of Cardiology, Kindai University Faculty of Medicine

Yasuchika Takeishi, Department of Cardiovascular Medicine, Fukushima Medical
University

Yuichi Tamura, Department of Cardiology, International University of Health and

Welfare School of Medicine

Yu Taniguchi, Department of Cardiology, Kobe University Graduate School of Medicine

Hiroshi Watanabe, Hamamatsu University School of Medicine

Eiichiro Yamamoto, Department of Cardiovascular Medicine, Kumamoto University Hospital

Jun Yamashita, Department of Cardiology, Tokyo Medical University Hospital

These affiliations are relevant to the time during which this study was conducted.

Inclusion and exclusion criteria

[Inclusion criteria]

Patients with chronic thromboembolic pulmonary hypertension (CTEPH) who provided written informed consent and met all of the following criteria:

- (1) Diagnosed with CTEPH and judged to meet any of a) to c) below by the investigator/subinvestigator based on at least two of the following tests: pulmonary ventilation/perfusion scan, pulmonary angiography, and chest contrast computed tomography (CT)
 - a) Unable to undergo pulmonary endarterectomy (PEA) due to organised thrombus localised in the peripheral region
 - b) Persistent or recurrent pulmonary hypertension (PH) after PEA without any sign of recurrent acute thromboembolism and reoperation not applicable
 - c) Unable to undergo PEA owing to high risks (e.g., concomitant disease and advanced age) or other reasons
- (2) PH of World Health Organisation functional class I–IV
- (3) Definitive diagnosis of PH based on right cardiac catheterisation according to criteria a) and b) below:
 - a) Mean resting pulmonary arterial pressure (mPAP) ≥ 25 mmHg
 - b) Pulmonary capillary wedge pressure or left ventricular end diastolic pressure ≤ 15 mmHg
- (4) Baseline pulmonary vascular resistance (PVR) higher than $360 \text{ dyn} \cdot \text{sec}/\text{cm}^5$ from right cardiac catheterisation in the period fulfilling all conditions a) to e) below:
 - a) Within 30 days before the start of the study treatment
 - b) At least 90 days after the end of the study treatment if any of the following drugs were administered:

- Prostacyclin (PGI₂) or any of its derivatives
(However, acute treatment during catheterisation to examine the vascular reactivity of the study drug and temporary treatment within 3 days at least 7 days before right cardiac catheterisation were excluded. Beraprost sodium should be administered at least 7 days after the end of the study treatment.)
 - Drugs for the treatment of CTEPH other than endothelin receptor antagonists (ERAs), soluble guanylate cyclase (sGC) stimulators, and phosphodiesterase (PDE) 5 inhibitors
(excluding background medications such as anticoagulants, diuretics, and calcium antagonists)
 - Other investigational drugs
- c) In patients receiving an ERA, sGC stimulator, PDE5 inhibitor, or calcium antagonist, at least 90 days had passed since the start of treatment at a fixed dose on consecutive days and after any short-term effect on the haemodynamics of these drugs had disappeared (See Annex 3 Procedures for right cardiac catheterisation to Attachment 16.1.1).
- d) At least 180 days after PEA if the patient had a history of PEA
- e) At least 90 days after balloon pulmonary angioplasty (BPA) in patients who underwent BPA
- (5) Anticoagulants administered at the effective dose specified in the package insert from at least 90 days before the date of right cardiac catheterisation (the date of baseline measurement) meeting criterion (4) above until the date of starting the study treatment.
- (6) Six-minute walk distance was ≥ 150 m on the date of providing informed consent
- (7) Aged ≥ 20 years and ≤ 85 years at the time of providing informed consent
- (8) Sex: Male or female
However, patients had to consent to contraception and use reliable contraceptive methods during the study period. Women of childbearing potential had to have a negative pregnancy test prior to the study treatment. Women without childbearing potential included postmenopausal women (amenorrhoea for at least 1 year), sterile women, or women who had undergone sterilisation.
- (9) Japanese (Asian) ethnicity

[Exclusion criteria]

Patients who met any of the following criteria:

- (1) Severe obstructive pulmonary disease (forced expiratory volume in 1 second [FEV₁]/forced vital capacity [FVC] <0.6)
- (2) Severe restrictive pulmonary disease (total lung capacity [TLC] <60% of the predicted value)
- (3) Acute or chronic disorders (excluding dyspnoea) that may interfere with study requirements (especially the 6-minute walk test), such as angina pectoris and intermittent claudication
- (4) Developed acute symptomatic pulmonary embolism within 180 days before the study treatment
- (5) Consent could not be obtained owing to a mental disorder, dependency, dementia, or other diseases, or did not meet the requirements of the study
- (6) Human immunodeficiency virus with an opportunistic infection
- (7) Disease with life expectancy <180 days
- (8) Moderate or severe liver disorder (Child-Pugh classification [See Annex 7 Child-Pugh classification to Attachment 16.1.1] class B or C [except a condition caused by treatment with anticoagulants])
- (9) Moderate or severe renal disorder (serum creatinine $\geq$ 2.5 mg/dL ([221 μ mol/L])
- (10) Pregnant or lactating
- (11) Systolic blood pressure <85 mmHg before the study treatment
- (12) Met criteria a) to f) below in the period between the date of baseline measurement and the date of starting the study treatment
 - a) Received treatment with PGI₂ or any of its derivatives
 - b) History of treatment with drugs for CTEPH other than ERAs, sGC stimulators, and PDE5 inhibitors (excluding background medications such as anticoagulants, diuretics, and calcium antagonists)
 - c) Newly started treatment with an ERA, sGC stimulator, PDE5 inhibitor, or calcium antagonist, or not continued at a fixed dose on consecutive days.
 - d) Underwent PEA or BPA
 - e) Received clopidogrel
 - f) Received another investigational drug
- (13) History of hypersensitivity to any of the excipients of the product
- (14) Previous treatment with selexipag
- (15) Judged inappropriate for the study by the investigator (subinvestigator)

Blinding

The assignment was performed in a 1:1 ratio by minimisation, taking into account the presence or absence of the concomitant use of riociguat, disease classification, and PVR at baseline. It followed a procedure manual of dynamic allocation managed by an assignment manager. Treatment assignment was blinded. All participants, investigators, study staff, sponsors, and monitors remained blinded to the study treatment until the end of the study.

Sensitivity analysis under alternative assumptions about the missing data

For the primary efficacy variable PVR, the following two types of sensitivity analysis were performed as a post-hoc analysis.

- Multiple imputation assumed that the data are missing at random (MAR)
- Control-based imputation assumed that the data are missing not at random (MNAR)

In both cases, a regression method was used as the imputation method. The explanatory variables in the imputation model were treatment, presence/absence of concomitant riociguat, disease classification, and PVR at baseline. The number of imputations was 100. An ANCOVA analysis was performed, and the analysis model was the same as that used in the imputation model.

Figure S1. Change in PVR from baseline by final maintenance dose.

Data are presented as mean $\pm$ standard deviation. The mean change from baseline was -4.6 ± 163.6 dyn·s/cm⁵ in the placebo group, -4.2 ± 9.4 dyn·s/cm⁵ in the group withdrawn by the start of the dose maintenance period, -39.5 ± 75.6 dyn·s/cm⁵ in the 400–800 µg/day group, -104.7 ± 108.7 dyn·s/cm⁵ in the 1,200–2,000 µg/day group, and -131.4 ± 119.2 dyn·s/cm⁵ in the 2,400–3,200 µg/day group. * Dose prescribed at the start of the dose maintenance period. ** Subjects withdrawn by the start of the dose maintenance period. PVR, pulmonary vascular resistance

Table S1. Randomised controlled trial data on the use of medical therapies in patients with chronic thromboembolic pulmonary hypertension.

Clinical Trial	Medical Therapies	n	Baseline of PVR (dyn·s/cm ⁵)	Baseline of mPAP (mmHg)	Baseline of 6MWD (m)
NS304C-P3-1 (this study)	Placebo	39	553.1 ± 184.0	35.5 ± 8.3	384.0 ± 87.0
	Selexipag	39	523.4 ± 132.8	35.2 ± 5.4	407.9 ± 90.9
CHEST-1	Placebo	82	779 ± 401	-	-
	Riociguat	151	791 ± 432	-	-
	Placebo	84	-	44 ± 10	-
	Riociguat	156	-	45 ± 13	-
	Placebo	88	-	-	356 ± 75
	Riociguat	173	-	-	342 ± 82
MERIT-1	Placebo	40	984 ± 487.1	51.7 ± 14.13	351.2 ± 73.79
	Macitentan	40	929 ± 379.7	49.9 ± 11.73	353.0 ± 87.90
BENEFiT	Placebo	80	787 ± 333	47.4 ± 12.5	344.5 ± 82.6
	Bosentan	77	778 ± 323	44.2 ± 10.4	340.0 ± 85.3

Data are presented as mean ± standard deviation.

PVR, pulmonary vascular resistance; 6MWD, 6-min walk distance; mPAP, mean pulmonary artery pressure

Table S2. Sensitivity analysis of PVR.

Method	Estimate	SE	95% CI
Multiple imputation	-84.3	28.6	-140.4, -28.2
Control-based imputation	-77.7	28.3	-133.1, -22.2

Estimates of the difference between the selexipag and placebo for the change from baseline to week 20 in PVR.

PVR, pulmonary vascular resistance; SE, standard error; CI, confidence interval

Table S3. Changes from baseline in SBP, DBP, and PR.

End Point	Placebo			Selexipag		
	Baseline (n = 39)	Week 20 (n = 35)	Change	Baseline (n = 39)	Week 20 (n = 34)	Change
SBP (mmHg)	116.1 ± 16.4 (89, 158)	110.8 ± 14.0 (84, 138)	-4.8 ± 13.8 (-34, 34)	112.5 ± 15.9 (92, 163)	107.2 ± 13.5 (86, 140)	-4.9 ± 11.9 (-33, 15)
DBP (mmHg)	66.1 ± 12.5 (43, 96)	66.5 ± 12.3 (47, 92)	0.7 ± 9.8 (-20, 28)	66.5 ± 12.4 (46, 103)	60.7 ± 11.1 (40, 88)	-5.6 ± 8.0 (-19, 10)
PR (beats/min)	75.2 ± 11.1 (53, 104)	74.9 ± 13.1 (40, 103)	0.4 ± 11.4 (-36, 25)	82.3 ± 14.3 (49, 107)	79.4 ± 12.0 (57, 109)	-3.8 ± 17.3 (-46, 26)

Data are presented as mean ± standard deviation (min, max).

SBP, Systolic blood pressure; DBP, diastolic blood pressure; PR, pulse rate