

SUPPLEMENTARY MATERIAL

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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 $360 \text{ dyn} \cdot \text{s} \cdot \text{cm}^{-5}$ 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 (PGI_2) 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.
- 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 class B or C [except a condition caused by treatment with anticoagulants])
- (9) Moderate or severe renal disorder (serum creatinine ≥ 2.5 mg/dL ([221 $\mu\text{mol/L}$])
- (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.

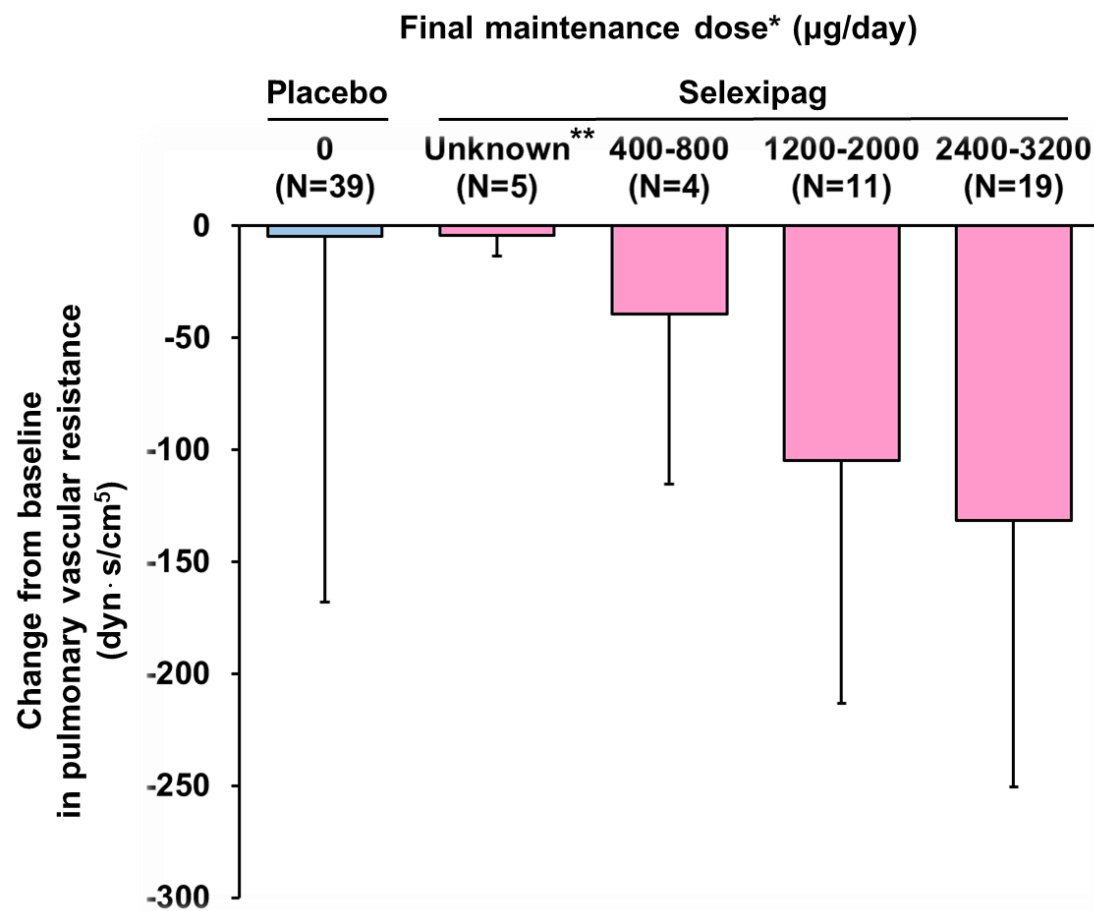


Figure S1. Change in PVR from baseline by final maintenance dose.

Data are presented as mean \pm standard deviation. The mean change from baseline was -4.6 ± 163.6 dyn·s·cm⁻⁵ in the placebo group, -4.2 ± 9.4 dyn·s·cm⁻⁵ in the group withdrawn by the start of the dose maintenance period, -39.5 ± 75.6 dyn·s·cm⁻⁵ in the 400–800 µg/day group, -104.7 ± 108.7 dyn·s·cm⁻⁵ in the 1,200–2,000 µg/day group, and -131.4 ± 119.2 dyn·s·cm⁻⁵ 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 ± SD.

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 ± SD (range).

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