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RESEARCH ARTICLE

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SATISFY-JP, a phase II multicenter open-label study on Satralizumab, an anti-IL-6 receptor antibody, use for the treatment of pulmonary arterial hypertension in patients with an immune-responsive-phenotype: Study protocol

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Abstract

Pulmonary arterial hypertension (PAH), an intractable disease with a poor prognosis, is commonly treated using pulmonary vasodilators modulating the endothelin, cGMP, and prostacyclin pathway. Since the 2010s, drugs for treating pulmonary hypertension based on mechanisms other than pulmonary vasodilation have been actively developed. However, precision medicine is based on tailoring disease treatment to particular phenotypes by molecular-targeted drugs. Since interleukin-6 (IL-6) is involved in the development of PAH in animal models, and some patients with PAH have elevated IL-6 levels, the cytokine is expected to obtain potentials for therapeutic targeting. Accordingly, we identified a phenotype with elevated cytokine activity of

the IL-6 family in the PAH population by combining case data extracted from the Japan Pulmonary Hypertension Registry with a comprehensive analysis of 48 cytokines using artificial intelligence clustering techniques. Including an IL-6 threshold ≥2.73 pg/mL as inclusion criteria for reducing the risk of insufficient efficacy, an investigator-initiated clinical study using satralizumab, a recycling anti-IL6 receptor monoclonal antibody, for patients with an immune-responsive phenotype is underway. This study is intended to test whether use of patient biomarker profile can identify a phenotype responsive to anti-IL6 therapy.

KEYWORDS
antibody, artificial intelligence clustering, IL6R-blocking therapy, precision medicine, pulmonary artery hypertension

Nonclinical studies demonstrated the involvement of interleukin-6 (IL-6) in pulmonary arterial hypertension (PAH). Particularly, in rodents, IL-6 can cause pulmonary vascular remodeling and pulmonary hypertension (PH) or exaggerate the pulmonary hypertensive response to chronic hypoxia.[1,2] Similarly, mice overexpressing IL-6 develop PH and pulmonary vascular remodeling, similar to the obstructive vascular remodeling observed in humans. Conversely, IL-6 knockout mice show resistance to hypoxia-induced PH.[3,4] In a mouse model of hypoxia-induced PH, IL-21, a downstream signal of IL-6, polarizes macrophages in the lung into M2 macrophages, resulting in the increased proliferation of pulmonary artery smooth muscle cells and induction of vascular remodeling characteristic of PH.[5] Based on the above, rodent models have demonstrated the effectiveness of blocking the IL-6 receptor for treating PH.[6] In humans, Soon et al.[7] reported that IL-6 is a prognostic and predictive cytokine in PAH patients.[8] Subsequently, a phase II clinical trial (TRANSFORM-UK Study)[9] of tocilizumab, an anti-IL-6 receptor antibody, treatment showed overall negative regarding improvement in pulmonary vascular resistance (PVR). Four out of 6 patients with connective tissue disease (CTD) showed improvement in PVR, suggesting that CTD patients may be more likely to respond than other PAH patients. The higher prevalence rate of PAH in CTDs, such as systemic lupus erythematosus and mixed tissue connectivity, suggests that inhibition of the IL-6 pathway can be a target for PAH therapy.[10,11] Additionally, Zamanian et al.[12] conducted a placebo-controlled trial of rituximab in systemic sclerosis-associated PAH patients, utilizing machine learning to analyze treatment response. Despite failing to achieve the primary endpoint of enhanced 6-min walking distance, a machine learning-based post-hoc analysis identified a biomarker-based subgroup that benefited the most from rituximab. These findings suggest that validating efficacy using machine learning could be advantageous for developing drugs with novel mechanisms of action. Recently, the importance of precision medicine, that is, "medicine that provides an optimal treatment for each patient," has been widely accepted. We established a method for identifying a clinical phenotype of PAH developing the induction of the IL-6 family and related cytokines by using artificial intelligence clustering techniques based on a comprehensive analysis of 48 cytokines and registry-based case data analyses.

Therefore, we designed a clinical trial (SATISFY-JP, NCT05679570) to confirm the efficacy of the anti-IL-6 receptor antibody satralizumab[13] using the PVR as an improvement index in PAH patients who present with an immune-responsive phenotype and are under inadequate control with existing drugs.

METHODS

Clinical trial study design

The multicenter, single-arm, open-label SATISFY-JP trial aims to assess the efficacy and safety of 24-week satralizumab administration to PAH patients with an immune-responsive phenotype.

Sample size

The mean percent change from baseline in PVR at week 12 in a Japanese phase III study of iloprost for PH was −21.68% (standard deviation 20.12%). Thus, in this study, the mean percent change in PVR was set as −20%

(standard deviation 20) based on the assumption that the study drug has similar efficacy and that at week 24 it has similar or greater effectiveness than at week 12. To achieve 90% power, a sample size of 21 patients using a *t*-test with a threshold of 5% and a two-sided 5% level of significance would be needed. Thus, assuming a 10% dropout rate we defined a sample size of 24. The study will be conducted in the following six Japanese institutions: the International University of Health and Welfare Mita Hospital in Tokyo, the Nippon Medical School Hospital in Tokyo, the Kyushu University Hospital in Fukuoka, the Chiba University Hospital, the Kobe University Hospital, and the Nagoya University Hospital between January 2022 and September 2024 (cases will be registered between January 2022 and June 2023).

Eligibility

The inclusion and exclusion criteria are shown in Table 1. Eligible participants should have a confirmed diagnosis of Group 1 PAH (Nice Classification, 2018) classification as WHO Functional Class as I, II, or III, an immune-responsive phenotype (IL-6 ≥ 2.73 pg/mL), and treatment with 1–3 PAH drugs on a stable dose for ≥90 days before enrollment. In addition, in the 30 days preceding inclusion, participants must have hemodynamic parameters with a mean pulmonary arterial pressure ≥25 mmHg and a PVR > 5 Wood units at rest.

Patients showing >15 mmHg in pulmonary artery wedge pressure measured by the right heart catheterization while screening, treated with epoprostenol or treprostinil and unable to withdraw from these drugs, and those taking steroids ≥10 mg/day prednisone equivalent will be excluded from this study.

Identification of the immune-responsive phenotype

Before this study, sera samples were extracted from 143 patients enrolled in the Japanese PH Patient Registry (JAPHR)[14,15] from the six participating institutions, then, patients were classified using comprehensive cytokine analysis and artificial intelligence clustering. The Human Magnetic Luminex Assay kit (R&D Systems, Inc.) was used to evaluate the presence of 48 cytokines in each of the 143 samples (Table S1). After excluding two cytokines with low assay sensitivity, the measured data on all cytokines other than IL-6 were arranged to construct vectors for 143 samples or 143 dimensions. The vector thus obtained was considered to represent the characteristics of each cytokine. We then calculated the cosine similarity for IL-6 and all other cytokines (45 species) using the following formula:

TABLE 1 Eligibility criteria.

Inclusion criteria	Exclusion criteria
1. Age: 20–79 years 2. The current diagnosis of group 1 PAH with following subtypes: – Idiopathic or Heritable PAH – PAH associated CTD – Drug/toxin-induced PAH – PAH associated with congenital heart disease (only after repair surgery) 3. WHO function classes I, II, or III. 4. Patients with an immune-responsive-phenotype (serum IL-6 level: ≥2.73 pg/mL) 5. 6-min walk distance; 150–600 m at screening. 6. Hemodynamic values within 30 days before enrollment at rest – mPAP ≥ 25 mmHg – PVR > 4 Wood units 7. Use of up to three PAH drugs in stable doses for at least 90 days before enrollment on an unchanged PAH therapeutic regimen	1. A history of severe allergy to any of the study drug's components 2. Infectious diseases such as pneumonia or tuberculosis, during the screening period. 3. PAWP: >15 mmHg in the last RHC performed during the screening period. 4. Continuous use of epoprostenol (intravenous) or treprostinil (intravenous or subcutaneous). 5. Active or recurrent bacterial, viral, fungal, or mycobacterial infections, or with other infectious diseases 6. Hospitalization within 4 weeks before the baseline visit, or have an infection that necessitates intravenous administration of antibiotics or an infection that necessitates oral administration of antibiotics within 2 weeks before the baseline visit. 7. Currently being treated with steroids at a dose higher than 10 mg/day of prednisone (PSL) equivalent.

Note: If the subject uses continuous oxygen therapy, it must be under the same conditions for ≥30 days before enrollment.

Abbreviations: mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PAH-CTD, PAH associated with connective tissue disease; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RHC, right heart catheterization; WHO, World Health Organization.

$$\frac{\vec{x}\cdot\vec{y}}{|\vec{x}||\vec{y}|}=\frac{x_1y_1+x_2y_2+\cdots+x_ny_n}{\sqrt{x_1^2+x_2^2+\cdots+x_n^2}\sqrt{y_1^2+y_2^2+\cdots+y_n^2}},$$

where x is the content of IL-6, y is other cytokines, and n represents the number of data ($n = 143$).

Cosine similarity corresponds to cosθ, where θ is the angle between the x and y vectors; the closer the cosine similarity w to 1, the closer the x vector (vector of IL-6 content) and the y vector (vector of other cytokines) are in the same direction. In other words, vector similarity indicates the similarity between the behavior of IL-6 and that of each other cytokine (Table S2).

Regarding the cosine similarity between IL-6 and the other cytokines, we classified the cytokines into three groups: close to IL-6 with a cosine similarity >0.6 ("Close"), distant to IL-6 with cosine similarity 0.5–0.6 ("Distant"), and independent of IL-6 with a cosine similarity <0.5 ("Independent"; Table S2).

The IL-6-close cytokine group included IL-1α/IL-1F1, IL-1β/IL-1F2, IL-4, IL-18/IL-1F4, IL-1RA/IL-1F3, TNF-α, IFN-γ, GDF-15, CCL3/MIP-1α, CCL4/MIP-1β, G-CSF, CXCL9/MIG, CXCL10/IP-10/CRG-2, CCL27/CTACK, SCF/c-kit Ligand, SCGF/CLEC11a, CD25/IL-2Rα, HGF, and CCL11/Eotaxin. The network graphs created for each cytokine in the IL-6-close group are shown in Figure 1.

Based on the cytokine contents in the IL-6 and the IL-6-close group, the 143 samples were clustered into three groups using the k-medoids method. Each of these clusters can be considered as a collection of open and close IL-6 cytokine dispositions. After clustering, the specimens were classified into cluster 0 (not altered IL-6 and the IL-6-close cytokine levels, 54.5%), cluster 1 (elevated IL-6 and the IL-6-close cytokine levels, 39.3%), and cluster 2 (significantly elevated IL-6 and the IL-6-close cytokine levels, 6.2%). In addition, attending at the distribution of IL-6 and IL-6-close cytokines in each cluster, we can determine if the clustering was effective (Figure S1).

The sensitivity and specificity for each cytokine were calculated based on the clustering groups. To determine which cytokines can identify the groups, the area under the curve was calculated by drawing the receiver operating characteristic curves using the sensitivity and specificity for each cytokine in the IL-6 itself and IL-6-close group (Table S3).

In addition to IL-6, several cytokines (CXCL9/MIG, CCL4/MIP-1β, CCL27/CTACK, IL-1β/IL-1F2, GDF-15, IL-4, G-CSF, CXCL10/IP-10/CRG-2, and IL-1α/IL-1F1) were appropriate markers for the cluster of elevated IL-6 and IL-6-close cytokines. Because of their use as screening tools in clinical trials, IL-6 and IL1β were considered as final candidates for screening based on the readiness and commercial availability of the corresponding assays. Moreover, as there was no discernible difference between IL-6 and IL-1′s area under the curve performance, we decided to use IL-6 as a biomarker for the prediction of IL-6 and IL-6-close cytokine activation. Onwards, patients with activated IL-6 and IL-6 close cytokines will be referred to as patients with an "immune-responsive phenotype." This phenotype could be predicted with a sensitivity of 0.81 and specificity of 0.76 in patients with IL-6 levels ≥2.73 pg/mL.

In summary, this study aims to follow a precision medicine approach by administering the study drug only to patients with the immune-responsive phenotype. Therefore, IL-6 ≥2.73 pg/mL is an important inclusion criterion.

Study procedure

This study consists of three main periods (Figure 2): the screening period (≤30 days), the efficacy evaluation period (24 weeks), and the continuous dosing period (28 weeks). The timeline of efficacy and safety assessments in this study is provided in Table S4. Chugai Pharmaceutical will provide the research product, of which 120 mg will be administered subcutaneously at weeks 0, 2, 4 and administered every 4 weeks thereafter.

SCREENING PERIOD

Following informed consent from PAH patients with an immune-responsive phenotype and inadequate response to existing drugs, screening tests within 30 days after receiving the consent determine eligibility for the study. Baseline tests will be conducted before the initiation of the study drug administration.

EFFICACY EVALUATION PERIOD

The study drug will be administered at a dose of 120 mg subcutaneously at week-0, 2-week, 4-week, and at 4-week intervals thereafter. Efficacy will be assessed after 24 weeks of the initial study drug administration.

CONTINUED DOSING PERIOD

Participants demonstrating efficacy during the efficacy evaluation period and wishing to continue the treatment will receive satralizumab at 120 mg subcutaneously once every 4 weeks.

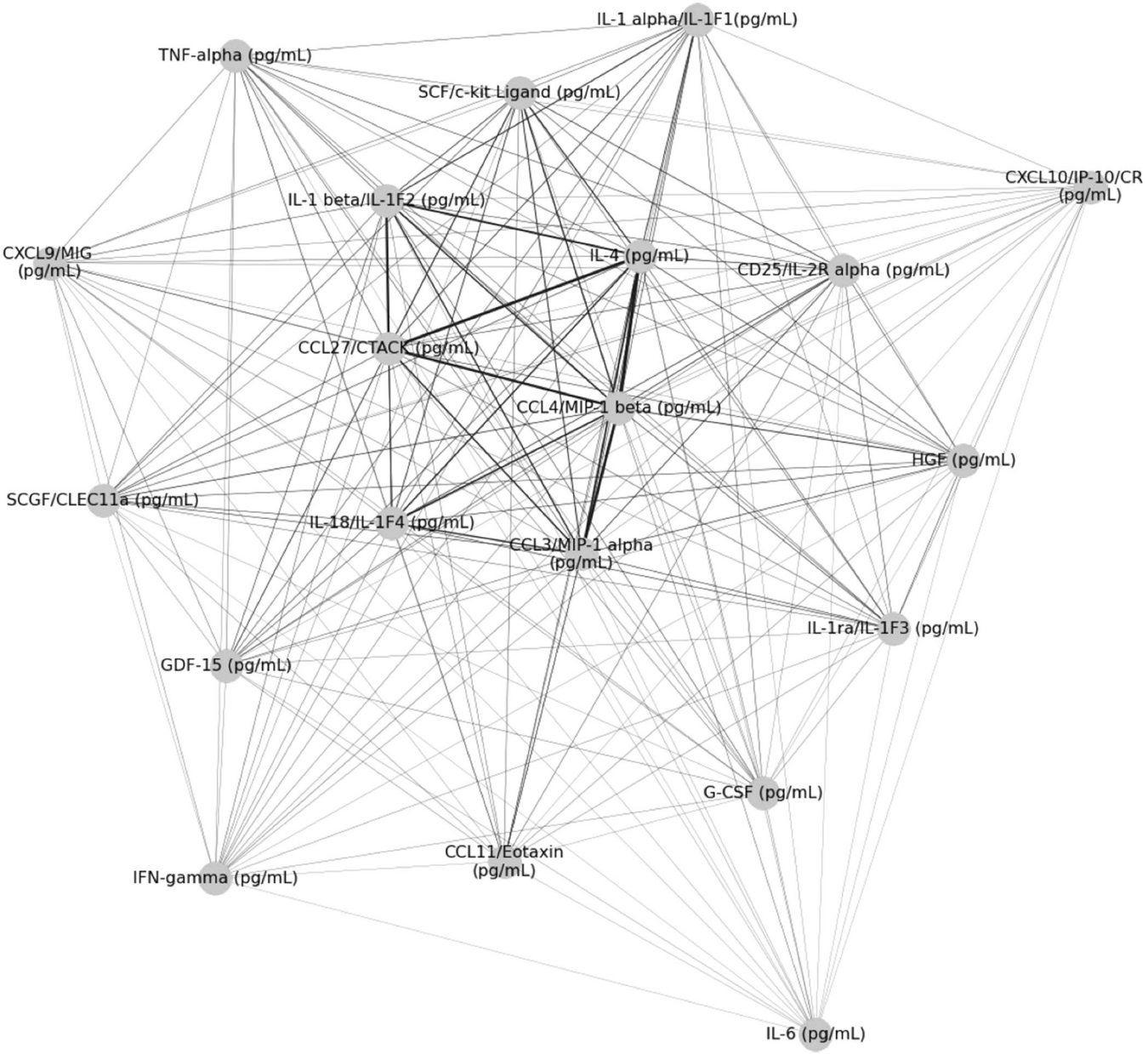

FIGURE 1 Network graphs of IL-6 and other cytokines in the IL-6-close group. The edge thickness in the graph corresponds to the size of the cosine similarity. IL-6, interleukin-6.

Outcome measures

Primary, secondary, and exploratory endpoints are shown in Table 2. The primary endpoint is defined as the percent change in PVR from baseline to 24 weeks. The difference between walking distance at baseline and at 24-week is one secondary endpoint. The percent change in PVR from baseline to 24 weeks will also be compared between the satralizumab-treated group and an external control group, which will comprise patients not included in the study but those having an immune-responsive phenotype (IL-6 ≥ 2.73 pg/mL) among the PAH patients registered in the JAPHR. A change in echocardiography findings (TAPSE/PASP) will be an exploratory endpoint. Clinical assessments will be performed according to the 2022 ESC/ERS Guidelines.[16]

Safety consideration

IL-6 induces an acute-phase immune response (e.g., fever, increased C-reactive protein). However, the study drug administration may inhibit these responses and suppress the typical symptoms associated with infections,

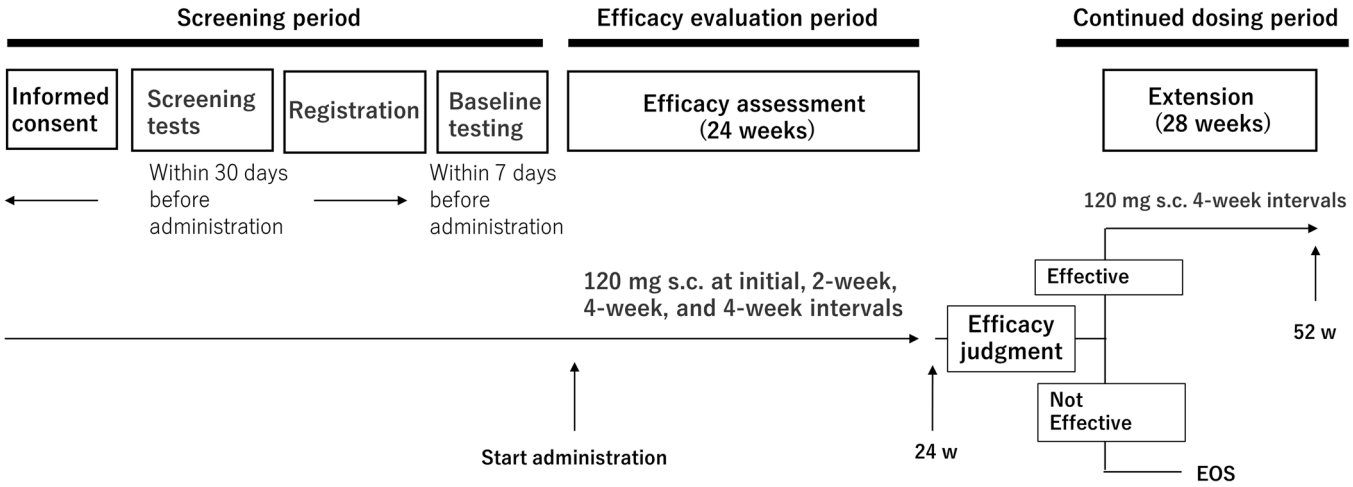

FIGURE 2 Schematic indicating the study plan.

TABLE 2 Endpoints for the SATISFY-JP trial.

Primary	Percent change in pulmonary vascular resistance (PVR) from baseline to 24 weeks
Secondary	(1) Change in 6-min walking distance from baseline to 24 weeks. (2) Comparison of percent change in PVR from baseline to 24 weeks between the satralizumab and the external control group (selected from patients registered in JAPHR who presented serum IL-6 level: ≥2.73 pg/mL). (3) Safety (adverse events, general laboratory tests, blood coagulation system tests, 12-lead ECG, chest X-ray, vital signs, respiratory function tests, and arterial blood gas analysis) during the efficacy assessment period. The 52-week safety in subjects judged as "effective" in the efficacy evaluation period. (4) PK parameters and anti-drug antibody
Exploratory	(1) Change in the hemodynamic parameters mRAP, mPAP, RVedp, CI, SvO_2 (2) Change in WHO-FC (3) Changes in clinical variables 6-min walk distance, RAP, WHO-FC, NT-proBNP (4) Time to clinical worsening PVR, 6-min walk distance, RAP, WHO-FC, NT-proBNP (5) Biomarkers changes CCL11/Eotaxin, CD25/IL-2R alpha, G-CSF, GDF-15, HGF, IFN-gamma, IL-6, IL-1 beta/IL-1F2, IL-18/IL-1F4, TNF-alpha, and hsCRP (6) QOL changes emPHasis-10, EQ-5D (7) ECHO changesTAPSE/PASP ratio

Abbreviations: CI, Cardiac Index; ECHO, echocardiography; EQ-5D, Euro Qol 5-Dimension; G-CSF, granulocyte colony-stimulating factor; GDF15, growth differentiation factor 15; HGF, hepatocyte growth factor; hsCRP, high sensitive C-reactive protein; INF-gamma, interferon gamma (IFNγ); JAPHR, Japan Pulmonary Hypertension Registry; mPAP, modified pulmonary artery pressure; mRAP, modified right atrial pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAP, pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PK, pharmacokinetics; QOL, quality of Life; RVedp, right ventricular end-diastolic pressure; SvO2, mixed venous oxygen saturation; TAPSE/PASP, tricuspid annular plane systolic excursion/pulmonary artery systolic pressure; TNF-alpha, tumor necrosis factor-alpha; WHO-FC, WHO functional class.

which could delay detection of infectious diseases and severe conditions. Therefore, the participants will be carefully monitored and interviewed about their needs during the study period.

DISCUSSION

We have devised a clinical trial to test a drug in patients for which there is promising efficacy (PAH patients with an immune-responsive phenotype). Thus, this clinical trial is considered an ethically and scientifically valid study to more sensitively detect the effectiveness of satralizumab for PAH by excluding the patient population who may be less likely to benefit from IL-6 suppressive therapy.

Before initiating this trial, we analyzed date from participants registered in JAPHR to identify useful indicators to predict responders to immunosuppressive therapy with satralizumab. To that end, 143 patients with PAH from 6 PH expert centers that participated in JAPHR were enrolled. Through the analysis of

biomarkers in sera and artificial intelligence clustering techniques, we identified three phenotype clusters based on IL-6 and IL-6-close family cytokine levels among those patients: those with highly increased levels, those with moderately increased levels, and those with little or no increased levels. Based on the assumption that the two former clusters respond to immunosuppressive therapy, we could demonstrate that the clinical characteristics associated with IL-6 family activation may be detected with a sensitivity of 0.81 and specificity of 0.76 at a threshold of IL-6 ≥ 2.73 pg/mL. Thus, we defined IL-6 ≥ 2.73 pg/mL as threshold to select the patients with an immune-responsive phenotype for this and the previous study. Moreover, IL-6 > 1.6 pg/mL is associated with a worse prognosis in PAH patients.[17] Meanwhile, a phase II trial (TRANSFORM-UK Study) of tocilizumab (an IL-6 receptor antagonist) in PAH patients reported that patients with CTD-associated PAH showed an improved response to immunosuppressive therapy by blocking IL-6.[9] Therefore, we hypothesize that the IL-6 family is activated in response to immunosuppressive therapy. Moreover, IL-6 has been substantially associated with progression, suggesting its role as a (negative) prognostic factor.[7,8,18–20] Accordingly, this trial aimed to use a responder-specific therapeutic intervention based on a precision medicine approach that targeted only the PAH patients expected to respond to IL-6 signal block.

This study will include patients with an inadequate response to treatment with existing drugs as well as those who would add the study drug to their current regimen to lower the risk of symptom deterioration. In addition, as the study drug is assumed to be used in patients with no or moderately progressing symptoms, we will include patients who fall in WHO-FC-I, II, or III to evaluate the efficacy in those with similar disease progression status and those who are assumed to receive the therapy. However, due to the lack of information regarding the risk of infection associated with IL-6 blockade in PAH patients, patients on parenteral prostanoid agents will be excluded from this trial for safety reasons.

In light of the innovative mechanisms and inclusion criteria employed in this clinical trial, we devised an exploratory single-arm, open-label study to administer the study drug to all participants. In addition, the efficacy evaluation after the first 24 weeks of treatment was set to determine whether further treatment continuation is acceptable. This allows responders to continue receiving the treatment while preventing nonresponders from receiving the study drug indiscriminately.

Currently, there are approximately 4000 PAH patients in Japan.[21] Approximately 60% are assumed to be resistant to conventional drugs (including combination therapy with up to three drugs)[15] and approximately 40% of those were estimated to be potential responders to IL-6 suppressive therapy. Therefore, we selected patients with an immune-responsive phenotype from JAPHR and used them as external control, i.e., a nonintervention group relative to the treatment group, to compare efficacy (secondary endpoints). The background factors are to be adjusted between the treatment group and the external control group, such as sex, primary diseases (idiopathic or hereditary PAH, and others), and NYHA classification.

In this study, to measure the improvement in right ventricular function in response to the intervention, we will assess the TAPSE/PASP ratio in the echocardiography as exploratory endpoint. PAH prognosis is affected by the severity of right-sided heart failure, and right ventricular-pulmonary arterial coupling failure is often observed in PAH patients. The end-systolic elastance/vascular elastance ratio (Ees/Ea), derived from invasively measured ventricular pressure-volume relationship, has traditionally been used to measure RV-PA coupling. A low Ees/Ea ratio has been regarded as an indicator of a decrease in cardiac energy efficiency, or hemodynamic deterioration. However, Tello et al. recently demonstrated that the right ventricular-arterial uncoupling (Ees/Ea 0.805) may be distinguished by a TAPSE/PASP cutoff of 0.31 mm/mmHg with a sensitivity of 87.5% and specificity of 75.9%, and concluded that the TAPSE/PASP ratio is a simple substitute for Ees/Ea.[22] As a result, we chose the TAPSE/PASP ratio as a measure of the clinical progression of PAH.

In the TRANSFORM-UK Study that assessed the efficacy of the IL-6 receptor antagonist, decreased PVR was observed in four of the six subjects with CTD-associated PAH.[9] However, they did not clarify a relationship between IL-6 levels and the effectiveness of IL-6 receptor antagonists. This study will be able to develop a suitable therapy with IL-6 receptor antagonist in the appropriately stratified PAH patients.

AUTHOR CONTRIBUTIONS

Yuichi Tamura: developed the study concept, and is the guarantor. Rika Takeyasu and Tomohiro Takata performed artificial intelligence clustering. All authors contributed to the study design.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

ETHICS STATEMENT

This study will be conducted in accordance with the Declaration of Helsinki-based ethical standards, legislation on quality, efficacy, and safety of drugs and medical devices, ordinances for Good Clinical Practice (Ministerial GCP), and other regulatory requirements. The conduct of this study is subject to ethical, scientific, and medical/pharmaceutical assessment by the Institutional Review Board.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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