Notice: This is a translation of a notice in Japanese and is made solely for the convenience of foreign shareholders. In the case of any discrepancy between the translation and the Japanese original, the latter shall prevail.

(Translation)

October 19, 2023

To Shareholders,

Company Name Renascience Inc.
Representative: Koji Naito, President and CEO
(Code: 4889 TSE Growth)
For inquiries, please contact Administration Dept.

Announcement of Initiation of Phase II study for the treatment of interstitial lung disease associated with systemic scleroderma begins.

The Company is pleased to announce the initiation of a phase II investigator-initiated clinical trial of the PAI-1 inhibitor RS5614 for interstitial lung disease (ILD)[*1] associated with systemic scleroderma (SSc)[*2].

An exploratory phase II investigator-initiated clinical trial to investigate the efficacy and safety of RS5614 for SSc-ILD during treatment with immunosuppressive drugs is being conducted in collaboration with Tohoku University Hospital and 11 other medical institutions in Japan.

SSc is a systemic autoimmune disease characterized by vasculopathy and fibrosis of the skin and various internal organs, and is designated as an intractable disease. SSc has three main pathological conditions, "immune abnormalities ", "vasculopathy", and "fibrosis", and the clinical symptoms due to organ fibrosis include Raynaud's symptoms[*3] , skin sclerosis, interstitial lung disease (ILD), scleroderma renal crisis[*4] , cardiac involvement, and pulmonary arterial hypertension[*5] , resulting in a variety of multi-organ damage and it has limited response to steroids and immunosuppressive drugs compared to other autoimmune diseases. Seventy (70)% of deaths in SSc are related to this disease, especially ILD, which accounts for 35% of deaths, and even when ILD is not the direct cause of deaths, ILD severely impairs respiratory function leads to a significant decline in quality of life (QOL) and activities of daily living (ADL). Steroids and immunosuppressive drugs are the first-line treatment for ILD, but their efficacy is limited. Nintedanib, an antifibrotic[*6] drug, has been approved for the treatment of ILD, but its efficacy is limited to inhibiting the progression of ILD and has not been shown to improve it.

The PAI-1 inhibitor RS5614 reduces inflammation, vascular damage, thrombosis, and fibrosis

(including pulmonary fibrosis) in nonclinical studies. When RS5614 was administered orally daily to an animal model of SSc-ILD, RS5614 reduced lung fibrosis in a dose-dependent manner and the efficacy was superior to nintedanib. This investigator-initiated clinical trial will confirm the efficacy and safety of RS5614 in patients with SSc-ILD.

This investigator-initiated clinical trial is supported by the "Practical Research Project for Intractable Diseases" of the Japan Agency for Medical Research and Development (AMED) (Tohoku University is the representative research organization and the Company is the sharing research organization). In the phase II investigator-initiated clinical trial to investigate the efficacy and safety of RS5614 for SSc-ILD, the first patient was enrolled on October 6, 2023.

There is currently no material impact of this matter on our business performance.

End

*1 Interstitial lung disease (ILD)

Interstitial lung disease is a general term for diseases that cause inflammation mainly in the area of the lungs called the interstitium. The lungs are a collection of small pouches called alveoli. Air inhaled through the mouth or nose is carried through the airways to the alveoli, where oxygen is taken in through the alveolar walls. The alveoli are largely divided into parenchyma and interstitium. The inside of the alveoli is called parenchyma, and the walls of the alveoli and surrounding tissues are called interstitium. In interstitial lung disease, the alveolar walls gradually become thicker and stiffer (fibrosis) due to inflammation. When this happens, the lungs do not expand properly, causing suffocation and coughing. In advanced stages, respiratory failure may occur.

*2 Systemic scleroderma (SSc)

Systemic scleroderma (SSc) is a chronic, progressive autoimmune disease characterized by changes in the skin and internal organs that harden (called sclerosis). It is designated as an intractable disease, and more than 20,000 patients have been identified in Japan.

*3 Raynaud's symptom

The fingers turn pale to purple when touched by cold objects, a symptom that is most common in winter and is the most common initial symptom of SSc.

*4 Scleroderma renal crisis

It is a disorder of the blood vessels of the kidneys, resulting in hypertension. Headache and nausea occur along with a sudden rise in blood pressure.

*5 Pulmonary arterial hypertension

Humans need to breathe and take in oxygen from the atmosphere into the lungs, but breathing in the lungs alone does not take oxygen into the body. The oxygen taken into the lungs must be returned once to the heart and then sent to the rest of the body.

The blood vessels that carry blood from the heart to the lungs are called pulmonary arteries. Pulmonary arterial hypertension is an abnormal increase in the blood pressure in these pulmonary arteries. The reason for the increased pressure in the pulmonary arteries is that the small blood vessels in the lungs become abnormally narrow and stiff, resulting in poor blood flow. In order to send necessary oxygen to the body, the volume of blood leaving the heart must be kept above a certain level. Blood pressure in the pulmonary arteries rises as the heart strives to force blood to flow through the narrow, thin blood vessels. Pulmonary arterial hypertension is designated as an intractable disease.

*6 Antifibrotic agents

As the name suggests, it is a drug that suppresses fibrosis of tissues. They may be prescribed to patients who are considered to have fibrosis or who are expected to develop fibrosis in the future. There are two types of antifibrotic drugs: pirfenidone and nintedanib.

[Reference: QA regarding this timely disclosure]

- **How is interstitial lung disease (ILD) associated with systemic scleroderma (SSc) treated?**

Steroids, immunosuppressive drugs, and the antifibrotic drug nintedanib are used to treat SSc-ILD. However, their effects are limited to inhibition of lung disease progression and they do not improve the disease. Thus, there are several treatment options for SSc-ILD, but their efficacy is limited, and there is a strong need to develop new drugs that can improve SSc-ILD as a single agent or in combination with existing drugs.

- **How does RS5614 change the treatment of systemic scleroderma?**

The PAI-1 inhibitor RS5614 ameliorates various lung injuries (fibrosis and inflammation) and protects epithelial cells in various animal models. In an animal model of systemic scleroderma, RS5614 also showed efficacy against lung fibrosis that exceeded that of nintedanib, an antifibrotic drug used as a control.

Furthermore, we have completed the early phase II investigator-initiated clinical trial (open-label study) and the late phase II investigator-initiated clinical trial (multicenter placebo-controlled double-blind study) to evaluate the efficacy and safety of RS5614 for the treatment of lung injury (fibrosis and inflammation) associated with novel coronavirus (COVID-19) infection, The results suggest that RS5614 is effective against COVID-19-associated lung injury.

If the efficacy of RS5614 against SSc-ILD can be demonstrated in this clinical trial, a new treatment for this difficult disease can be proposed.

- **Is RS5614 effective for lung diseases other than systemic scleroderma?**

As a result of numerous collaborative studies, the PAI-1 inhibitor shows improvement of various lung injuries (fibrosis and inflammation) and epithelial cell protection, such as reducing lung fibrosis, improving lung inflammation, and providing lung epithelial cell protection. In fact, RS5614 has completed the phase II investigator-initiated clinical trial (open-label study) and the phase II investigator-initiated clinical trial (multicenter placebo-controlled double-blind study) in patients with pneumonia (fibrosis and inflammation) associated with novel coronavirus (COVID-19) infection, with results suggesting its efficacy. The safety of the drug in patients with lung injury was also confirmed.

The PAI-1 inhibitor RS5614 inhibits lung fibrosis, pulmonary inflammation, and thrombus formation, and is expected to be effective in a variety of lung diseases regardless of their cause.

RS5614 Prevents and treats pulmonary inflammation and pulmonary fibrosis caused by various causes