December 26, 2024

To Shareholders,

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(Code: 4889 TSE Growth)
For inquiries, please contact Administration Dept.

Announcement of completion to enroll the planned sample size in the investigator-initiated Phase II clinical trial with a PAI-1 inhibitor RS5614 in systemic sclerosis (scleroderma)-associated interstitial lung disease (SSc-ILD)

We would like to inform you that we have completed to enroll the planned sample size (50 cases) in the investigator-initiated Phase II clinical trial with a PAI-1 inhibitor RS5614 in systemic sclerosis (scleroderma, SSc, designated as refractory disease 51) [*1]-associated interstitial lung disease (SSc-ILD), which we are conducting at a total of 12 sites including Tohoku University, the University of Tokyo and Osaka University. We plan to compile the results of the evaluation and data analysis of this trial into a clinical trial report after the 48-week treatment period.

This project was selected in 2023 by the Japan Agency for Medical Research and Development (AMED) for its " Practical Research Project for Intractable Diseases" (Tohoku University is the representative research organization and Renacsience is the sharing research organization) and, in September 2023, we will conduct a placebo-controlled, double-blind study [*2] to confirm the safety and efficacy of PAI-1 inhibitor RS5614 in patients with SSc-ILD as an investigator-initiated clinical trial.

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 the Raynaud's symptom[*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. Especially, ILD 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 very 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. Therefore, there is strong need to develop new treatments that can improve SSc-ILD.

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, so it is expected to be a new treatment. In addition, RS5614 has shown efficacy and safety in an investigator-initiated Phase II clinical trial for the treatment of the new coronavirus (SARS-CoV-2) .

There will be no changes to the earnings forecast for the fiscal year ending March 2025 due to this matter.

*1 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.

*2 Double-blind

A clinical trial method in which patients are randomly divided into a group that receives the investigational drug (RS5614 in this case) and a group that receives a control drug (an ineffective placebo in this case), and both groups are administered drugs at the same time under the condition that neither the doctor nor the patient knows which drug will be administered. This is a test method to reduce the opportunity for doctors to administer the investigational drug to patients who are expected to respond to the drug, and to avoid the possibility that preconceived notions that the drug should be effective will be reflected in the evaluation, or that even if the patient knows, it will affect the response to the treatment or the evaluation.

*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.