(Translation)

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To Shareholders,

Company Name Renascience Inc.
Representative: Koji Naito, President & CEO
(Code: 4889 TSE Growth)
Inquiries: Department of Administration

# Results of Placebo-Controlled, Double-Blind, Phase II Investigator-Initiated Clinical Trial of RS5614, a PAI-1 Inhibitor, for Novel Coronavirus (SARS-CoV-2) Pneumonia.

The Company have been collaborating on a placebo-controlled, double-blind, investigator-initiated clinical trial (the "Clinical Trial") of PAI-1 inhibitor RS5614 against SARS-CoV-2 pneumonia with 20 medical institutions and universities in Japan since June 2021 as a sharing research organization in the "Research Program for Emerging and Re-emerging Infectious Diseases" of Japan Agency for Medical Research and Development (AMED) (Tohoku University is the representative research organization).

The Company is pleased to announce that the result of the Clinical Trial is reported.

Summary

- ☐ This placebo-controlled Phase II trial was eventually conducted in 75 hospitalized patients (39 in the RS5614 group and 36 in the placebo group) since the number of hospitalized pneumonia patients eligible for the Clinical Trial decreased, due to the impact of the timing of the epidemic of the new coronavirus (SARS-CoV-2) and the viral mutation.
- ☐ The primary efficacy endpoint, "Sum of Oxygenation Scale (*1)" , showed no statistically significant difference between the two groups, but there was a reduction in worsening in the RS5614 group versus the placebo group, suggesting the efficacy of RS5614 in the pneumonia, particularly in patients of moderate-I (*2). Furthermore, the proportion of patients requiring oxygen therapy was lower in the RS5614 group during the first 3 to 5 days after hospitalization, suggesting the efficacy of RS5614 in early treatment. The incidence of adverse events was similar in the RS5614 and placebo groups, confirming the safety of this investigational drug (RS5614) in patients with novel coronavirus pneumonia.
- ☐ RS5614 has a completely different mechanism of action from antivirals and is a therapeutic for pneumonia. At present, the medicines for novel coronavirus lung injury other than antivirals are the expensive injectables. RS5614 can be a convenient medicine since it is a safe, small molecule that can be administered orally.
- ☐ Although the new coronavirus infection has currently settled down, the Company is preparing to conduct the next phase clinical trial (for patients with mild to moderate I pneumonia) as soon as possible in the event of an outbreak of a variant causing pneumonia.

*1 The oxygenation status of the subjects was compared by summing up a score from no oxygen (0 points) to

wearing a ventilator or an ECMO (5 points) (e.g., “Point 2” for oxygen administration of 2L or more, but less than 5L) daily for a total of 14 days.

*2 (Clinical Management of Patients with COVID-19: A guide for front-line healthcare workers, Version 9.0)

- Moderate I: Novel coronavirus infection, with blood oxygen levels between 93% and 96%, dyspnea and initial findings of pneumonia, but no respiratory failure and no oxygen administration therapy.
- Moderate II: Stage in which the blood oxygen level is less than 93%, respiratory failure is present, and oxygen administration therapy is required.
- Severe: Stage requiring intensive care or ventilator management

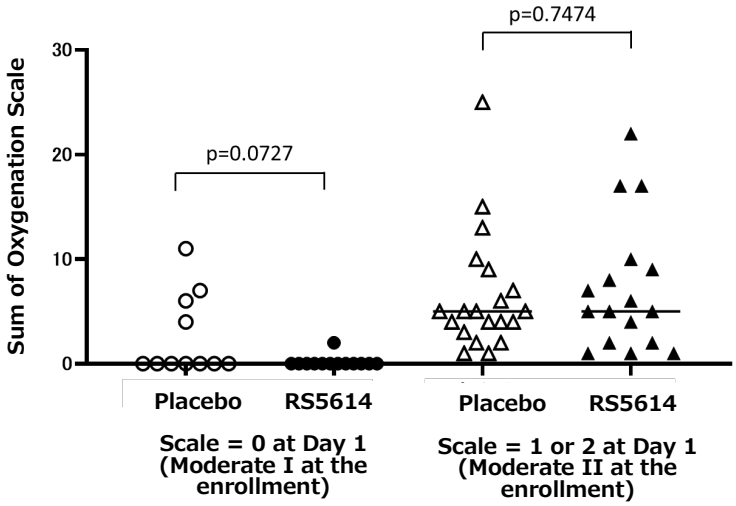
This clinical trial was conducted to investigate the efficacy and safety of RS5614 by orally administering RS5614 or placebo once daily for 14 days in hospitalized patients with novel coronavirus pneumonia. Initially, the study was initiated with a target of 100 subjects, but due to a decrease in the number of eligible patients with novel coronavirus pneumonia (moderate, hospitalized patients) due to mutations to the Omicron variants, the study was eventually terminated at the end of October 2022 with the enrollment of 75 subjects. The primary efficacy endpoint in this clinical trial, "Sum of Oxygenation Scale," is the sum of scores that assess oxygenation that requires oxygen therapy or ventilator management up to 14 days after the start of the drug administration and was set based on scientific and medical adequacy after thorough discussions with pulmonologists and Pharmaceuticals and Medical Device Agency (PMDA).

The results of this study showed that for the primary endpoint (Sum of Oxygenation Scale) and the secondary endpoint (Number of days of oxygenation required after the initiation of the administration), both endpoints improved in patients treated with RS5614 compared to the placebo group, but the differences did not reach statistical significance due to the small number of patients in the study. Median values for the primary and secondary endpoints for patients in the RS5614 and placebo groups are shown below.

The primary endpoint (Sum of Oxygenation Scale)

| | |
|---|---|
| RS5614 group | 1.5 |
| Placebo group | 4.0 |

The subgroup analysis suggested that RS5614 administration reduces oxygen administration in moderate I patients (see figure below).

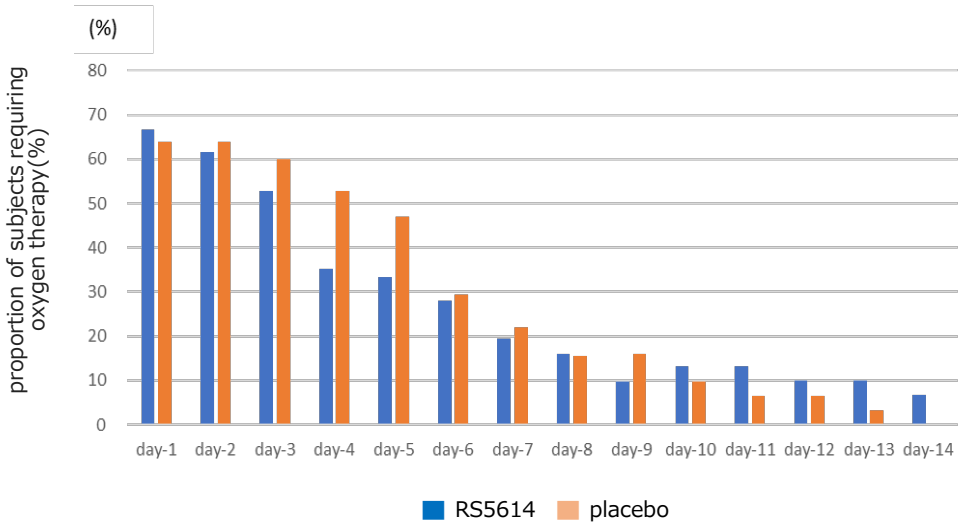


Secondary endpoint (Number of days of oxygen required after the initiation of the administration)

RS5614 group 2.0 days

Placebo group 3.5 days

In addition, the proportion of subjects requiring oxygen therapy was also lower in the RS5614 group in the first 3-5 days after hospitalization.




There were no differences in safety between the RS5614 and placebo groups, and no significant adverse events were observed in the RS5614 group.

The results of this clinical trial will be presented in future academic papers and conferences.

RS5614 is a small molecule drug that can be orally taken easily and safely at home. If the classification of novel coronavirus infection under the Infectious Diseases Law is lowered from "Class 2" to "Class 5," the number of patients receiving treatment at home is likely to increase further, making the development of this oral medicine significant. As a result of this clinical trial, an outline of the next phase of the clinical trial, including the target patients and the study endpoints, has been clarified. Currently, the number of pneumonia patients eligible for this therapeutic agent is small, but the Company is preparing for the prompt start of the next phase of the clinical trial in case the number of eligible pneumonia patients increases in the future due to mutant strains causing pneumonia. PMDA consultation was already conducted on April 11, 2023.

The impact on the business results for the fiscal year ending March 31, 2024, is expected to be marginal, but the Company will disclose the information in a timely manner if any matters arise that should be disclosed in the future.

The Company has executed an agreement with Daiichi Sankyo Company, Limited ("Daiichi Sankyo") on December 25, 2020, for a preferential negotiating right with option rights to license the development and commercialization of RS5614 for the treatment of pulmonary diseases such as novel coronavirus pneumonia and other lung injuries. There is no change in the agreement.

Reference: Q&A regarding this disclosure

**How will be the future development of RS5614?**

This clinical trial was designed to investigate the efficacy and safety of RS5614 by administering RS5614 or placebo once daily for 14 days in hospitalized patients with novel coronavirus pneumonia. Although the number of patients was too small to find statistically significant differences, total scores on the primary efficacy endpoint (Sum of Oxygenation Scale) and the secondary endpoint (Number of days of oxygenation required after the initiation of the administration) improved in patients receiving RS5614 compared to those receiving placebo. Given that the number of patients with novel coronavirus infection has settled down and the number of patients with lung injury eligible for this treatment is small, it is unlikely that this drug will be subject to emergency approval, and a pivotal study is further required. As a result of this clinical trial, the outline of the next phase of the clinical trial, including the target patients and the study endpoints, has been clarified, and the next phase of the clinical trial will be started as soon as the number of patients with lung injury increases due to mutant strains causing pneumonia.

**There are many therapeutic agents for novel coronavirus infection. What is the significance of developing RS5614?**

The medicines for novel coronavirus infection are basically vaccines for healthy people and antiviral agents for infected people (which inhibit the growth of the virus), but even so, some patients still develop pneumonia. RS5614, unlike vaccines and antiviral drugs, inhibits the lung injury of pneumonia itself. Antibody therapeutics have similar efficacy against lung injury, but they can only be administered in hospitals because they are not oral drugs, and they are expensive. On the other hand, RS5614 is a small molecule medicine that can be orally taken easily and safely at home and can be manufactured at a low cost. If the classification of novel coronavirus infection under the Infectious Diseases Law is lowered from "Class 2" to "Class 5," the number of patients receiving treatment at home is likely to increase further, making the development of this oral medicine highly significant. Currently, the number of patients with pneumonia eligible for this therapeutic agent is small, but if the number of patients with lung injury eligible for this agent increases due to mutant strains causing pneumonia, or if lung injury becomes a problem due to a different type of infection, RS5614 will be a useful therapeutic. Therefore the Company actively continues the clinical development.

**When will the next phase of the clinical trial begin?**

Currently, due to the small number of lung injury patients eligible for this treatment, we cannot immediately start the next phase of the clinical trial. However, the Company is preparing to start the next phase of the clinical trial as soon as the number of target patients with lung injury increases due to mutant strains, etc. We have already finished manufacturing the investigational drug necessary for the next study, and based on the results of this clinical trial, we already conducted a consultation with PMDA on April 11, 2023, regarding the next phase of the clinical trial.

**Will RS5614 be developed as a treatment for lung diseases other than novel coronavirus pneumonia?**

RS5614 may be effective not only against lung injury by viruses, but also against lung injuries caused by a variety of causes, including anticancer agents, autoimmune diseases, and unknown (idiopathic) causes. In addition to novel coronavirus pneumonia, the Company investigates the efficacy of RS5614 against lung injury by other

causes in clinical trials. As part of this effort, the Company has initiated a collaboration with the Department of Respiratory Medicine, Kyoto University Hospital, with a view to conducting clinical trials for acute exacerbations of idiopathic interstitial pneumonia. Acute exacerbation of idiopathic interstitial pneumonia is a poor prognosis condition that accounts for approximately 40% of deaths from idiopathic interstitial pneumonia. We have also extended our agreement with Daiichi Sankyo with a view to conducting clinical trials to confirm the efficacy of RS5614 in interstitial pneumonia arising from anticancer drug therapy and other treatments. Furthermore, a placebo-controlled, double-blind, Phase II investigator-initiated clinical trial to evaluate the efficacy and safety of RS5614 for interstitial pneumonia associated with systemic scleroderma is conducted at Tohoku University Hospital, the University of Tokyo Hospital and other medical institutions in Japan (adopted by Japan Agency for Medical Research and Development under “Practical Research Program for Intractable Diseases”).

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