July 16, 2025

To Shareholders,

Company Name: Renascience Inc.
Representative: Toshio Miyata, Chairman and CEO
(Code: 4889 TSE Growth)
For inquiries, please contact Administration Dept.

Notice of selection for the National Institute of Biomedical Innovation, Health and Nutrition's Orphan Disease Drug Research and Development Promotion Program

The malignant melanoma[1)] treatment drug RS5614 (PAI-1 inhibitor) developed by our company has been designated as an orphan disease drug[2)] by the Ministry of Health, Labor and Welfare on August 28, 2024. We applied for the National Institute of Biomedical Innovation, Health and Nutrition's "Orphan Disease Drug Research and Development Promotion Program for FY2025," a grant program that only drug development designated as an orphan disease drug can apply for, for our Phase III investigator-initiated clinical trial for malignant melanoma (a randomized placebo-controlled double-blind investigator-initiated clinical trial verifying the efficacy and safety of the combination of RS5614 with nivolumab[3)]), and we are pleased to announce that it has been selected.

1. About the grant

Project name: FY2025 "Orphan Disease Drug Research and Development Promotion Program"
Drug: RS5614 (PAI-1 inhibitor) for the treatment of malignant melanoma
Subsidy period: Three fiscal years between April 2025 and March 2026 (up to three fiscal years in principle).
However, grant applications must be submitted for each fiscal year.

Subsidy recipient: Testing and research necessary for the application for manufacturing and sales approval of an orphan disease drug designated by the Minister of Health, Labor and Welfare (development costs for the preparation of attached documents related to manufacturing and sales approval applications).

Subsidy amount: The subsidy amount will be determined for each fiscal year within the FY2025 "Orphan Disease Drug Research and Development Promotion Program" budget, with a maximum of half of the eligible expenses.

The incidence rate of malignant melanoma patients is 1.5 to 2.0 *per* 100,000 in Japan, with a total of approximately 5,000 patients, but in the United States, it is an intractable skin cancer with 21.0 *per* 100,000 patients and 1.4 million patients. With the advent of the anti-PD-1 antibody nivolumab, an immune checkpoint inhibitor[4], the treatment of advanced malignant melanoma has improved significantly. In addition, the anti-CTLA-4 antibody ipilimumab[5] has been developed, and combination therapy is being carried out to increase the response rate (about 20 %) of anti-PD-1 antibodies alone. However, due to the severe side effects of autoimmune diseases, the incidence of discontinuation is four times higher than with monotherapy, and there is also the issue of high medical costs, so the development of a drug that has little side effects and increases the response rate is eagerly awaited.

Our PAI-1 inhibitor RS5614 is a small molecule drug that is extremely safe and can be taken orally at home. In a phase II investigator-initiated clinical trial aimed at confirming efficacy and safety, we obtained the proof-of-concept[6] in humans, and it was designated as an orphan disease drug by the Ministry of Health, Labor and Welfare on August 28, 2024. Currently, a phase III investigator-initiated clinical trial is being conducted in a multi-center collaboration of 18 facilities in Japan, including Tohoku University Hospital. This Phase III trial is a verification test to obtain pharmaceutical approval for RS5614 against malignant melanoma, and we applied for this grant because it is eligible. As mentioned above, April 2025 to March 2026 (up to a maximum of three fiscal years in principle) , the Company will submit a subsidy application for each fiscal year, and will be able to receive subsidies for each fiscal year within the scope of the National Institutes of Biomedical Innovation, Health and Nutrition's business budget, up to a maximum of half of the expenses incurred for melanoma-related research in that fiscal year.

2. Future outlook

The subsidy has been estimated in as 20% of related expenses in the full-year financial forecast for the fiscal year ending March 2026, which was announced on May 14, 2025. There is currently no impact on the financial results for the fiscal year ending March 2026, but if any matters requiring disclosure arise in the future, we will make a timely disclosure.

[1] Malignant melanoma

Malignant melanoma is a type of skin cancer that occurs when skin cells called melanocytes, which produce melanin pigment related to skin color, become malignant. It has a high metastasis rate and is considered to be extremely malignant among skin cancers. The incidence rate of malignant melanoma patients in Japan is low at 1.5 to 2 per 100,000, but in the United States it is 21.0.Malignant melanoma is a highly malignant cancer (the 5-year survival rate is about 50 %

if the size of the cancer exceeds 4 mm, about 40 % if there is regional lymph node metastasis, and several percent if there is distant metastasis). Furthermore, it has been reported that the progression of malignant melanoma in Japan is about three times higher than in the United States. This is thought to be because melanoma in Japan is genetically different from that in Europe and the United States, making it difficult for treatment drugs to be effective.

[2)] Orphan disease drug

These are mainly drugs for diseases that are considered intractable, such as those with a small number of patients and no established treatment. There are designation criteria such as the number of target patients being less than 50,000, targeting serious diseases such as intractable diseases, high medical need, lack of suitable alternative drugs or treatments, expected to be significantly more effective or safe than existing drugs, and high possibility of development. If a drug is designated as a rare disease drug, it will be subject to priority review by the PMDA (shortening the review period), a marketability premium in drug price calculation, and an extension of the reexamination period after approval, resulting in a longer monopoly period for this treatment drug business. In addition, support measures such as subsidies through the National Institutes of Biomedical Innovation, Health and Nutrition will be available.

[3)] Nivolumab

An antibody drug (human anti-human PD-1 monoclonal antibody) that targets the immune checkpoint molecule called programmed cell death 1 (PD-1), a drug that aims to have an anti-cancer effect by releasing the inhibition of the immune system. It is a typical immune checkpoint inhibitor. In Japan, the response rate of nivolumab for malignant melanoma is 22.2%, and the development of new combination therapies is desired.

[4)] Immune checkpoint inhibitors

Drugs that inhibit the action of immune checkpoint molecules. All drugs currently used as treatments are antibody drugs that directly bind to and inhibit immune checkpoint molecules.

[5)] Ipilimumab

Ipilimumab is an antibody drug (human anti-human CTLA-4 monoclonal antibody) that targets the immune checkpoint molecule cytotoxic T-lymphocyte antigen-4 (CTLA-4), and is an immune checkpoint inhibitor with a different target than nivolumab. For cases where nivolumab is ineffective, it has been approved for insurance coverage as a combination drug of nivolumab and ipilimumab, and its response rate is thought to be 21 % overseas and 13.5 % in Japan. However, nivolumab-ipilimumab combination therapy causes severe side effects in more than

half of patients, and the incidence of severe immune-related side effects that lead to discontinuation of treatment is four times higher than with monotherapy, which poses the problem of requiring hospitalization for several months or interruption of cancer treatment. In addition, there is the issue of high medical costs, and there is a need for a combination drug that is different from antibodies in modalities, can be administered orally, has few side effects, increases the response rate, and is inexpensive.

[6] Proof-of-Concept (POC)

This refers to confirming the effectiveness of a new drug candidate substance through non-clinical and clinical trials. If the expected results are obtained, POC is said to have been obtained.