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(Translation)

October 26, 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 Cutaneous Angiosarcoma

The Company is pleased to announce that a phase II investigator-initiated clinical trial of the PAI-1 inhibitor RS5614 for cutaneous angiosarcoma*¹ has started.

The phase II investigator-initiated clinical trial to investigate the efficacy and safety of RS5614 in combination with the anticancer drug paclitaxel*² in patients with cutaneous angiosarcoma who have failed paclitaxel as the first-line treatment will be conducted in collaboration with medical institutions including Tohoku University, Jichi Medical University, Kyushu University, Nagoya City University, National Cancer Center Hospital, and Ehime University.

Cutaneous angiosarcoma is an extremely rare tumor resulting from cancerous transformation of vascular endothelial cells*³. Although the anticancer drug paclitaxel is the first-line treatment for angiosarcoma, long-term shrinkage or disappearance of the tumor is difficult to achieve in the majority of cases, even when paclitaxel is combined with radiation therapy. Therefore, the development of effective and safe second-line treatments and medications is eagerly desired.

PAI-1 is expressed on vascular endothelial cells, and is also strongly expressed in angiosarcoma. It has been reported that paclitaxel is ineffective in patients with high PAI-1 expression. Although paclitaxel induces apoptosis*⁴ in angiosarcoma, the cancer cells that strongly express PAI-1 are less likely to undergo apoptosis. These findings strongly suggest that the combination of paclitaxel and the PAI-1 inhibitor RS5614 may enhance the therapeutic effect of paclitaxel on angiosarcoma.

This is the phase II investigator-initiated clinical trial to evaluate the efficacy and safety of RS5614 in combination with paclitaxel in 16 patients with recurrent or unresectable cutaneous angiosarcoma who have been previously treated with paclitaxel and are still receiving paclitaxel even after paclitaxel failure (second-line treatment). The clinical trial protocol notice was submitted on August 17, 2023,

and the first patient was enrolled on October 25, 2023. If the efficacy of RS5614 can be verified in this study, the new treatment can be proposed for cutaneous angiosarcoma with no effective treatment.

There is no impact of this matter on our business performance at this time.

End

*1 Cutaneous angiosarcoma

Angiosarcoma is a type of skin cancer. The angiosarcoma of the scalp is particularly rare (about 2.5 cases per million), but it is extremely malignant, progresses rapidly, and the disease-free survival rate at 5 years is reported to be less than 20%. No standard treatment has been established, and multiple possible treatments are immediately implemented at each medical facility.

*2 Paclitaxel

It is a chemotherapeutic agent (anticancer drug) discovered to have anticancer activity in the bark of the Pacific yew (*Taxus brevifolia*), and is now chemically synthesized. It is considered to bind to "microtubules" involved in cell division, thereby stopping the division of cancer cells and causing the cell death.

*3 Vascular endothelial cells

These cells line the lumen of blood vessels. Vascular endothelial cells not only build blood vessels, but also play roles for exchange of substances such as oxygen and nutrients between blood and tissues. They also produce various physiologically active substances to maintain tissue and organ functions.

*4 Apoptosis

This is a cell death phenomenon in which the cell itself commits suicide by activating its own program. Apoptosis eliminates the cells no longer needed.

[Reference: QA regarding this timely disclosure]

- **How is cutaneous angiosarcoma treated?**

Based on the results of overseas clinical trials, the taxane anticancer drug paclitaxel was covered by the National Health Insurance through the public knowledge-based application in 2011, and is now the first-line treatment for angiosarcoma. However, a subsequent multicenter retrospective study showed that it is difficult to achieve long-term remission in angiosarcoma even after radiochemotherapy with the taxane anticancer agents. Currently, the second-line treatments include the anticancer agents pazopanib, eribulin, and trabectedin, but their efficacy is not high and there are also concerns about their safety, and therefore useful treatments and medications are eagerly desired.

- **How will RS5614 change cutaneous angiosarcoma treatment?**

Paclitaxel, the apoptosis inducer, is used as the first-line drug in the treatment of cutaneous angiosarcoma, and the development of an effective second-line treatment for patients who become resistant to it has been eagerly anticipated. Since PAI-1 expression is extremely high in angiosarcoma, and the cancer cells with high expression of PAI-1 are resistant to apoptosis, the PAI-1 inhibitor may enhance the therapeutic effect of paclitaxel in angiosarcoma. If the efficacy of RS5614 is proven in this clinical trial, it may become a breakthrough therapy that can induce long-term survival in patients with cutaneous angiosarcoma after failure of first-line therapy.