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In the case of any discrepancy between the translation and the Japanese original, the latter shall prevail.

(Translation)

June 21, 2024

To Shareholders,

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

Results of Phase II Investigator-Initiated Clinical Trial of Pyridoxamine RS8001 for Premenstrual Syndrome with Psychiatric Symptoms /Premenstrual Dysphoric Disorder

The Company, in collaboration with Kinki University, Tohoku University, Tokyo Medical and Dental University, Tokyo Women's Medical University and several other private medical institutions, has conducted a phase II investigator-initiated clinical trial (placebo lead-in design[*1], placebo controlled, double-blind, three-arm comparative study) of RS8001 (pyridoxamine) for premenstrual syndrome with psychiatric symptoms (PMS)/premenstrual dysphoric mood disorder (PMDD) [*2].

On June 21, 2024, the results after full data analysis of the study were summarized. The primary endpoint did not reach statistical significance. The secondary endpoints showed a trend toward a decrease in the active drug group, but the difference was not statistically significant. A summary of the results is as follows:

[Result]

The efficacy, safety and dosage of pyridoxamine for PMS/PMDD were investigated in a randomized, double-blind, placebo-controlled, three-arm, comparative study.

Efficacy

(The primary endpoint)

- The primary endpoint was the change in the sum of DRSP negative mood score [*3] at the late luteal phase, from the third menstrual cycle (v3) to the last evaluation time point (v7 below). No statistically significant differences were observed between the low-dose, high-dose, and placebo groups

(The secondary endpoints)

- The mean change (absolute value) of the DRSP negative mood score and the sum of DRSP

from Visit 3 to Visit 7 was greater in the low-dose group and high-dose group, in that order, than in the placebo group, but there was no significant difference.

- There was no significant difference in the change in the total anxiety scale of the luteal phase HADS score from Visit 3 to Visit 7, although there was a trend toward a decrease in the active drug group.

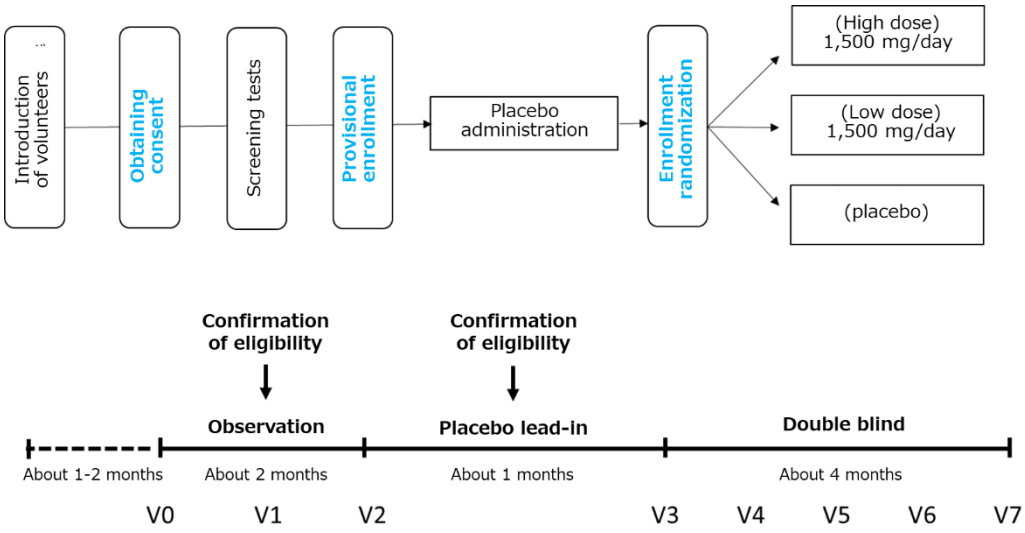
Safety

- None of the adverse events or side effects occurred particularly frequently in the low-dose group or the high-dose group of the study drug, and therefore there were no safety issues.

The details of this clinical trial are described below.

As society becomes more complex, many people live under stress, but compared to physical illnesses, medical treatment for mental illnesses is still insufficient. The Company is therefore engaged in the research and development of a therapeutic to treat PMS/PMDD that makes it difficult for women to lead a social life. PMS is a disorder unique to women in which mental and physical symptoms last for 3-10 days before menstruation, and then lighten or disappear with the onset of menstruation. More severe mental symptoms are classified as PMDD, but it is now common to consider them as a continuum of illnesses. While 70-80% of women of reproductive age have some premenstrual symptoms, the subjects are eligible for medical treatment, in case that the symptoms affect their daily and social life. Studies in Japan have reported that the frequency of PMS with social difficulties is 5.4% and that of PMDD is 1.2%. As medical treatment, antidepressants (SSRIs)[*4] and low-dose pills[*5] are used in off-label prescriptions, but they are not sufficiently widespread due to the side effects and resistance to the use. The Company has conducted a phase II investigator-initiated clinical trial of RS8001 for PMS/PMDD in collaboration with several universities and medical institutions (placebo lead-in design, placebo-controlled, double-blind, three-arm comparative study with a target number of 105 patients).

(Schematic diagram of the clinical trial design)



The project was adopted by the Japan Agency for Medical Research and Development (AMED) for the Cyclic Innovation for Clinical Empowerment (CiCLE) project in FY2019, and the clinical trial began in November 2020. Since there were challenges to secure the enrolled cases due to a significant decrease in the number of patient visits by the spread of the novel coronavirus infection, the countermeasures have been taken, such as adding private medical institutions; creating in-hospital posters and educational booklets; conducting webinars for pharmacists by the clinical trial investigators; and utilizing volunteer panels. As a result, by the end of October 2023, the full enrollment of 120 cases exceeded the target number of cases, and the clinical trial was completed in February 2024.

As with drug development in psychiatry, the biggest challenge in this trial was the impact of the placebo effect. Therefore, a placebo lead-in design was adopted to eliminate the placebo effect, but there was still a large degree of variability and no statistically significant difference was observed. The reasons for the variability may include the fact that the efficacy evaluation was based on a subjective interview form rather than an objective numerical value such as test values, and that the PMS/PMDD disorder may include a wide range of target patients, which may have caused the heterogeneity of the patient population.

[Plans]

Further development policy has been discussed with the Japan Agency for Medical Research and Development (AMED).

[Impact on business performance]

There is no impact on the business results for the fiscal year ending March 31, 2025, at this time, but the Company will disclose such information in a timely manner if any matters that should be disclosed arise in the future.

*1 Placebo lead-in design

A placebo does not contain active ingredients, but it may improve disease symptoms due to psychological effects (placebo effect). Therefore, the phase II study was conducted with a study design in which the subjects were asked to take a placebo for a certain period of time prior to administration of the active drug, and the trial was conducted after excluding the subjects with a large placebo effect (placebo lead-in).

*2 Premenstrual syndrome (PMS) with psychiatric symptoms/premenstrual dysphoric disorder (PMDD)

PMS is a mental and/or physical symptom that lasts for 3 to 10 days before menstruation and improves or disappears with the onset of menstruation. In women who have a rhythm of ovulation, follicular and luteal hormones are secreted in large quantities during the period between ovulation and menstruation (luteal phase). It is believed that the cause of PMS is a sudden drop in these hormones during the latter half of the luteal phase, causing abnormalities in the hormones and neurotransmitters in the brain. Psychoneurotic symptoms include emotional instability, irritability, depression, anxiety, drowsiness, difficulty in concentration, and sleep disturbances; autonomic disorders (including hot flash, anorexia and overeating, dizziness, and fatigue); and physical symptoms (including abdominal pain, headache, back pain, swollenness, bloated stomach, and breast tenderness). PMDD is the severe case in which psychiatric symptoms, such as depression, agitation, anxiety, compulsion, and loss of identity, are apparent and become a serious obstacle to social life.

*3 DRSP negative mood score

DRSP stands for Daily Records of Severity of Problems. Since there are no abnormalities in blood tests or imaging tests, the only way to diagnose PMS or PMDD is to observe the relationship between symptoms and the menstrual cycle. The DRSP was developed as a tool to record symptoms for diagnosis and is recommended internationally, including by Royal College of Obstetricians and Gynaecologists.

The DRSP is also the most widely used PMS severity scale in clinical trials. It consists of 24 items, 21 of which are PMS symptoms and 3 of which are interference with daily life, each of which is rated on a 6-point scale from 1 (not at all) to 6 (very severe).

DRSP negative mood score is the sum of the core symptoms of DRSP: depression, anxiety, lability, and anger/irritability.

(DRSP negative mood score)

1a	Low mood, sadness, depression	3a	Mood instability (sudden sadness, tearfulness)
1b	Sense of hopelessness	3b	Hypersensitivity to rejection and easily hurt feelings
1c	Feeling of self-worthlessness/guilt	4a	Feeling angry or easily angered
2	Anxiety, nervousness, excitement	4b	Interpersonal friction

*4 Antidepressants (SSRIs)

SSRI stands for selective serotonin reuptake inhibitor. They inhibit the reuptake of serotonin, a neurotransmitter, in the brain, thereby increasing the serotonin concentration in the brain and facilitating neurotransmission, which is thought to exert antidepressant and anxiolytic effects.

*5 Low-dose pills

The pill is a hormonal drug that contains female hormones (follicular and luteal hormones) that control the menstrual and ovulatory cycles. A low-dose pill is one in which the amounts of hormones are kept as low as possible to minimize the side effects. Although the purpose of the pill is to suppress ovulation and provide contraception, it also has several positive effects such as improving PMS as well as making the menstrual cycle more regular.

End