May 14, 2026

To Shareholders

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

Preliminary Results of the XPRIZE Healthspan Semi-Final Clinical Trial

We are pleased to announce the completion of the semi-final clinical trial for XPRIZE Healthspan[1)], conducted in collaboration with Tohoku University, Hiroshima University, and Tokai University (disclosed in August 18, 2025 as the "Notice of Commencement of XPRIZE Healthspan Semi-Final Clinical Trial"). The trial has now concluded and preliminary results are available.

For an overview of the test results, please also refer to the following explanatory video:

https://www.renascience.co.jp/wp-content/uploads/2026/05/xprize_en.mp4

[Background]

In Japan and other developed nations, rapid population aging presents an urgent challenge. A gap of approximately 10 years exists between average life expectancy and healthy life expectancy - the period during which a person can live independently, free from conditions such as being bedridden or developing dementia. Reducing the burden of age-related diseases, including cancer, arteriosclerosis, chronic obstructive pulmonary disease (COPD), diabetes, chronic kidney disease (CKD), cerebrovascular disease, dementia, sarcopenia, and osteoporosis, is widely regarded as the key to extending healthy life expectancy.

Like cancer cells, senescent cells are known to evade immune clearance by overexpressing plasminogen activator inhibitor-1 (PAI-1). The efficacy of our PAI-1 inhibitor, RS5614, against cancer is currently being evaluated across multiple clinical trials targeting chronic myeloid leukemia (Phase III), malignant melanoma (Phase III), angiosarcoma (Phase III), non-small cell lung cancer (Phase II), and pancreatic cancer (Phase II). To investigate the anti-aging potential of RS5614, we applied for the XPRIZE Healthspan, an international competition for longevity, under the concept of a "senolytic drug", a novel oral medicine that eliminates senescent cells and suppresses a variety of age-related diseases. We were selected as a semi-finalist (TOP 40) in May 2025 and have been conducting the semi-final clinical trial since August 2025.

[Semi-Final Clinical Trial]

According to the XPRIZE Healthspan guidelines, semi-finalists (TOP 40) are required to conduct a short-term (4 to 8 weeks), small-scale (5 to 20 subjects) clinical trial to support the feasibility of the final four-year clinical trial.

Accordingly, we conducted an open-label trial as the semi-final clinical trial, administering RS5614 for 16 weeks to 20 subjects aged 50 to 75 with stable age-related conditions (hypertension, type 2 diabetes, chronic kidney disease, and/or hyperlipidemia).

Although RS5614 has been administered to many cancer patients, it had never previously been given to relatively healthy older adults, making safety confirmation essential. Given the limited administration period, direct evaluation of anti-aging effects on individual organs was considered challenging; we therefore assessed changes in biomarkers[2)] across multiple aging-related functions, including epigenomics (gene modifications), gene expression, proteins, and cellular markers associated with aging, immunity, metabolism, bone and muscle, cognitive and neurophysiological function, antioxidation, hematopoietic stem cells, and so on.

The trial was conducted at Tohoku University Hospital, with Hiroshima University and Tokai University participating as collaborating institutions for laboratory testing. Of the 20 subjects who received RS5614, 19 (mean age 60.4 ± 5.6 years; 13 males, 6 females) who completed both pre- and post-administration assessments were included in the efficacy analysis (FAS); all 20 were included in the safety analysis (SAS).

Safety

A causal relationship with RS5614 could not be ruled out in one adverse event (mild liver function abnormality); however, no other serious adverse events, including bleeding events, were observed.

Efficacy

Despite the relatively short administration period of four months, a 2–3-year decrease in estimated epigenetic age was observed. A proteome analysis of plasma proteins revealed similar changes in many of the 19 subjects. RS5614 affects levels of proteins related to functions of immune, cognitive, and muscle systems. In addition, the improvement in the number of immune and hematopoietic stem cells at the cellular level, and in the levels of oxidative stressin the serum were observed. RS5614 thus induces various genetic, epigenetic and molecular changes related to systemic rejuvenation.

(1) Epigenetic and Gene-Level Improvements

1) Rejuvenation of Biological Age (Epigenetic Clock[3)])

DNA methylation analysis of leukocytes was used to estimate biological age (Epigenetic clock) using both the Horvath method and the PC-Horvath method[4)]. At baseline, estimated biological ages were 61.7 years and 58.0 years, respectively, both close to the subjects' mean chronological age of 60.4 years. Following four months of administration, significant rejuvenation was observed: to 58.3 years by the Horvath method ($p < 0.001$; decreased in 15 of 19 subjects) and

to 56.1 years by the PC-Horvath method ($p < 0.001$; decreased in 18 of 19 subjects), corresponding to reductions in biological age of 3.4 years and 1.9 years, respectively (Figure 1).

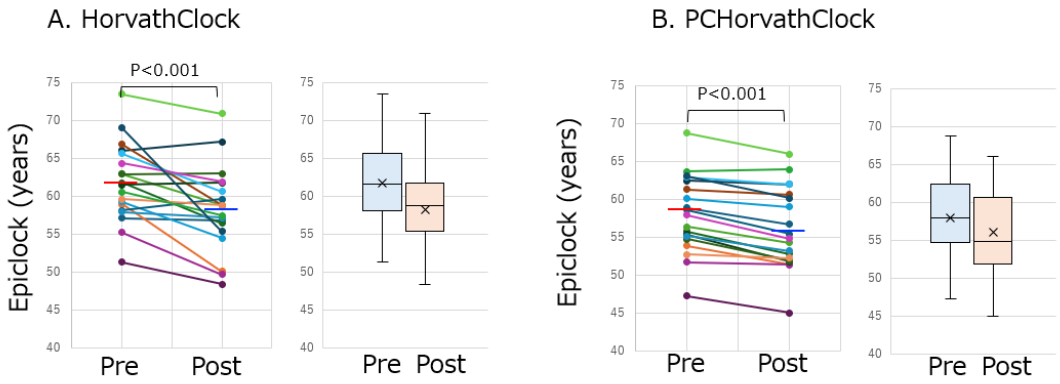

Figure 1. Rejuvenation of the epigenetic clock

DNA methylation was analyzed in leukocytes of subjects before and after the treatment of TM5614 and the epigenetic clock was estimated *via* HorvathClock (A) and principal component-based HorvathClock (B) algorithm. Epigenetic clock was decreased by 2-3 years.

2) Reduction of Senescence-Associated microRNA (SA-miRNA[5])

MicroRNA (miRNA) is an approximately 20-nucleotide RNA molecule that regulates gene expression. Analysis of senescence-associated (SA)-miRNA in serum revealed that all measured SA-miRNAs (miR-22-3p, miR-18a-5p, miR-28-5p, miR-17-3p, miR-195-5p, and miR-205-5p) decreased significantly, suggesting an attenuation of pro-aging gene expression control (Figure 2).

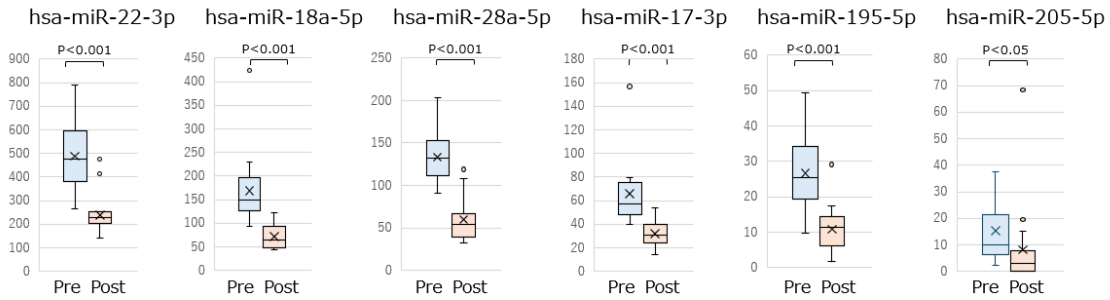

Figure 2 . Decrease in senescence-associate microRNA (SA-miRNA) levels in the serum

Six SA-miRNAs were detected, and levels of all of them were significantly decreased.

(2) Protein-Level Improvements

Comprehensive analysis of 7,596 plasma proteins using the SomaScan assay[6] with aptamers identified 356 significantly increased proteins (4.7%) and 199 significantly decreased proteins (2.6%). Consistent directional changes were observed across most of the 19 subjects, and

changes in multiple proteins associated with anti-aging effects were identified (Figure 3), suggesting improvements in the following anti-aging functions:

- Anti-inflammatory effects
- Improvement of macrophage functions
- Improvement of bone and muscle tissue formation
- Improvement of cognitive and neurophysiological functions
- Enhancement of the fibrinolytic system
- Antithrombotic effects
- Improvement of lipid metabolisms
- Reduction of endoplasmic reticulum (ER) stress
- Reduction of oxidative stress and advanced glycation end products (AGEs)[7)]

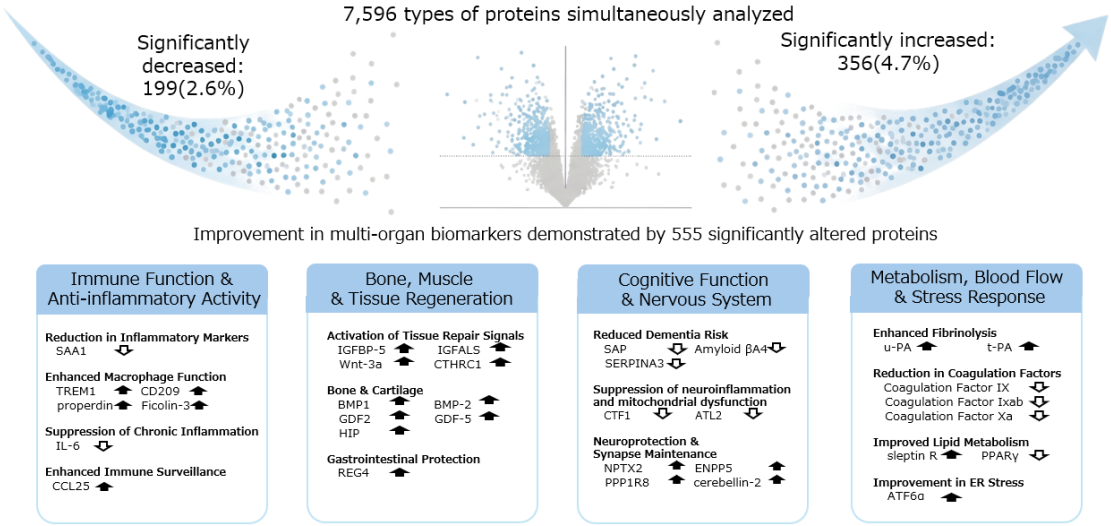

Figure 3. Improvement in Plasma Protein Levels

(3) Cellular-Level Improvements

1) Activation of the Immune System

Fractionation of peripheral blood immune cells by surface markers revealed a significant decrease in natural killer (NK) cell[8)] counts ($p < 0.05$; decreased in 14 of 19 subjects). NK cells are the principal lymphocytes of innate immunity responsible for eliminating cancer cells and senescent cells; their function declines with age, and compensatory expansion of NK cell numbers is a well-recognized feature of immune-senescence. In addition, a significant increase in dendritic cell[9)] counts ($p < 0.05$; increased in 12 of 19 subjects) was confirmed, suggesting enhanced immune surveillance against senescent cells and other aberrant cells.

2) Functional Recovery of Hematopoietic Stem Cells

The number of hematopoietic stem and progenitor cells (HSPCs)[10)] in peripheral blood declines with age, reflecting a reduction in hematopoietic capacity. Analysis of peripheral blood mononuclear cells revealed a significant increase in HSPCs ($p < 0.05$; increased in 15 of 19

subjects), with a particularly notable increase in multi-lymphoid progenitor (MLP) cells ($p < 0.05$; increased in 15 of 19 subjects), a cell type implicated in age-related decline of lymphocyte production. Comprehensive RNA-seq analysis[11] of gene expression in HSPCs revealed significant changes in gene sets defining their differentiation stages, suggesting an overall rejuvenation of the HSPC transcriptional program.

(4) Improvement in Oxidative Stress Markers

Oxidative stress is closely linked to aging. A downward trend was observed in serum levels of oxidative stress marker 8-OHdG[12] ($p = 0.118$; decreased in 14 of 19 subjects). Furthermore, a significant reduction was confirmed in CML (carboxymethyl lysine)[13], an advanced glycation end product (AGE) and recognized indicator of aging ($p < 0.01$; decreased in 16 of 19 subjects) (Figure 4).

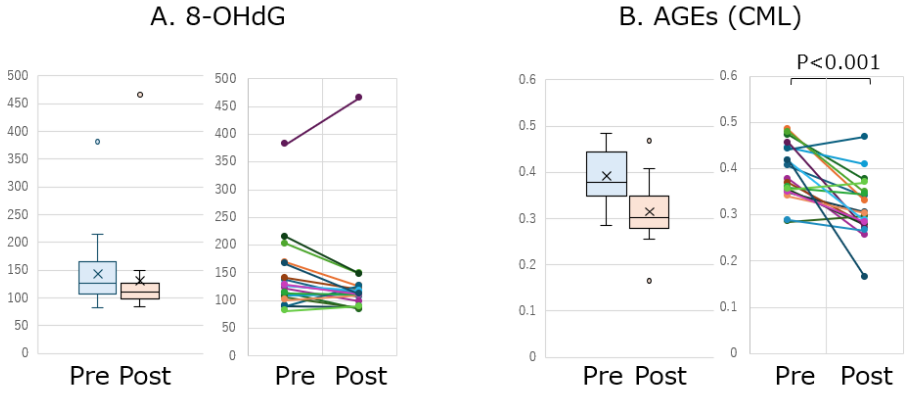

Figure 4. Reduction of oxidative stress

Oxidative stress markers, 8-OHdG (A) and advanced glycation end products (CML) (B), in the serum.

Conclusion

Four months of administration of the PAI-1 inhibitor RS5614 produced improvements at gene expression and epigenetic (gene modification) levels. Most notably, biological age (epigenetic clock) was rejuvenated by 2 to 3 years. At the protein level, improvements were observed in multiple proteins involved in anti-aging effects, encompassing immune, bone and muscle, metabolic, and cognitive function. At the cellular level, functional recovery and rejuvenation of immune cells and hematopoietic stem cells were demonstrated, along with a reduction in systemic oxidative stress. RS5614 was suggested to be safe for oral administration in relatively healthy older adults and, despite the short four-month administration period, anti-aging effects were definitely suggested across multiple organ systems, including immunity, metabolism, bone and muscle, cognitive and neurophysiological function, antioxidation, and hematopoietic stem cells (Fig. 5). Whether these molecular-level changes will translate into measurable anti-aging effects in individual organs and ultimately contribute to the extension of healthy life expectancy remains a question of great scientific interest.

In this semi-final clinical trial, we used the epigenome-based Horvath Clock, developed by Dr. Steve Horvath, to confirm that biological age decreased by 2 to 3 years following RS5614 administration. Dr. Horvath subsequently developed GrimAge[14], which incorporates smoking

history and plasma protein levels; notably, PAI-1 is one of its key components. Our trial results with the specific PAI-1 inhibitor RS5614 therefore provide the first direct pharmacological evidence bearing on whether inhibition of PAI-1 activity has a causal relationship with biological age.

These semi-final trial results and the final trial protocol had been compiled and submitted to the XPRIZE Healthspan Evaluation Committee (April 2026). If selected as a finalist (TOP 10) in August 2026, the final trial will be conducted as an international multi-site clinical trial involving Japan, the United States, Saudi Arabia, and Taiwan, evaluating effects of a novel, oral senolytic drug candidate RS5614 on immune, muscle, and cognitive functions in a placebo-controlled, blinded trial of approximately 150 older adults. Multi-omics analysis of RS5614-induced changes in gene expression (transcriptome[15)]), epigenome and proteins (proteome[16)]) is also planned, with the goal of identifying aging biomarkers and developing more precise methods for biological age assessment.

Traditional drug development is based on the premise of "single disease," "single target," and "clear endpoints." On the other hand, "senescence" is an extension of the aging process and is not considered as a "disease." Furthermore, because aging is continuous and varies greatly from person to person, developing a drug for "senescence" as a single indication is difficult. Therefore, there are various challenges in commercialization, including regulations, clinical trial design, insurance reimbursement systems, and business models. However, in recent years, novel gerotherapeutics based on novel mechanisms such as epigenetic reprogramming (cell rejuvenation)[17)] and senolytics (removal of senescent cells)[18)] have been proposed, differing from previous classical gerotherapeutics (dietary therapy, exercise therapy, sleep therapy, supplements, etc.), and clinical trials are beginning in some cases.

The PAI-1 inhibitor RS5614 is an oral medication for senolytics and senomorphics. Senescence is a state in which the homeostasis of the body, including epigenetic information, metabolism, inflammation, and stem cell function, is deteriorated. Therefore, intervening in senescence requires integrated intervention across multiple systems. We believe it is important to adopt a perspective that focuses not on "improving a specific pathological condition," but rather on "broadly improving the senescent environment and reconstructing the overall balance of the body." When senescent cells are not removed by the immune system and accumulate, they continuously release inflammatory cytokines and chemokines called senescence-associated secretory phenotype, causing chronic inflammation in surrounding healthy cells and tissues. RS5614 is a drug candidate that can intervene comprehensively across multiple systems and reconstruct the disrupted homeostasis of the entire body. We consider it to be a potential gerotherapeutics that can improve the senescent environment (senomorphics), remove senescent cells (senolytic), reverse biological age, and prevent and treat various age-related diseases.

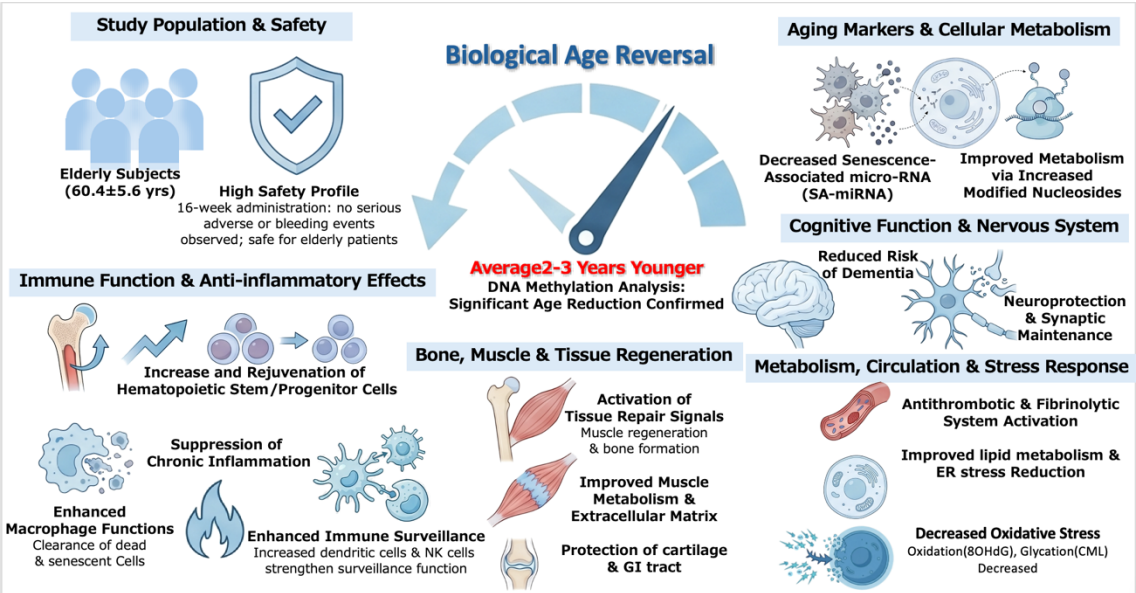

Figure 5. Multi-Faceted Effects of a PAI-1 Inhibitor RS5614 on Rejuvenation

[Impact on Financial Performance]

There is no material impact on financial performance for the fiscal year ending March 2027 from this matter.

[1] XPRIZE Healthspan: A global competition with a total prize of USD 100 million, awarded to the research team best able to extend healthy life expectancy. Hosted by the XPRIZE Foundation, it aims to revolutionize therapeutic approaches to human aging and longevity, with the ambitious goal of extending healthy life expectancy by 10 or more years. (https://www.xprize.org/prizes/healthspan)

[2] Biomarker: A measurable biological substance that objectively indicates a condition within the body or the state of a disease.

[3] Biological age (Epigenetic clock): An estimate of the body's physiological age based on the condition of its cells and tissues, distinct from chronological age.

[4] Horvath method and PC-Horvath method: First-generation methods for estimating biological age from DNA methylation patterns.

[5] microRNA (miRNA): An approximately 20-nucleotide RNA molecule that fine-tunes gene expression by binding to specific mRNA targets, inducing their degradation or suppressing their translation into protein.

[6] SomaScan assay with aptamers: A high-throughput platform for comprehensive protein profiling using nucleic acid aptamers engineered to bind specific proteins.

[7] Advanced glycation end products (AGEs): Substances formed when proteins and sugars combine. This process is known as "glycation" and is drawing significant attention as one of the

major factors that accelerate aging.

[8] NK cells (Natural Killer cells): Lymphocytes that continuously patrol the body and eliminate cancer cells, virus-infected cells, and other aberrant cells. They play a central role in innate immunity.

[9] Dendritic cells: Macrophage-like cells distributed in the blood and throughout the body. They identify and eliminate foreign and abnormal cells, and initiate adaptive immune responses.

[10] Hematopoietic stem and progenitor cells (HSPCs): Cells present in bone marrow and blood that give rise to red blood cells, white blood cells, and platelets, as well as their developmental intermediates.

[11] RNA-seq analysis: A technology used to comprehensively investigate which genes are active and to what extent within a cell at any given moment. If DNA is considered the body's blueprint, then RNA serves as the work orders sent to the site.

[12] 8-OHdG (8-hydroxy-2'-deoxyguanosine): A DNA oxidative damage marker in which the C-8 position of the DNA base deoxyguanosine (dG) is oxidized by reactive oxygen species.

[13] CML (Carboxymethyl lysine): An advanced glycation end product (AGE) formed through protein glycation reactions and recognized as an indicator of aging.

[14] GrimAge: A second-generation biological age and mortality-risk prediction method that combines DNA methylation data with smoking history and multiple plasma proteins. PAI-1 is one of the key plasma proteins incorporated into the model; pharmacological inhibition of PAI-1 by RS5614 therefore provides important scientific evidence for the possibility of biological age rejuvenation.

[15] Transcriptome: The complete set of RNA transcripts present in a cell at a given time. In contrast to the relatively invariant genomic DNA, the transcriptome is dynamic, changing in response to tissue type, environment, and cellular state. It provides a real-time, comprehensive picture of which genes are active and to what degree under specific disease or environmental conditions.

[16] Proteome: The complete complement of proteins expressed in a specific cell or tissue. Unlike genomic DNA, the proteome changes dynamically with time, environment, and disease state. Because a single gene can give rise to multiple protein variants, the protein diversity far exceeds the number of genes. As a direct reflection of the current state of biological processes, the proteome is increasingly recognized as a critical resource for disease diagnosis and drug discovery.

[17] Epigenetic Reprogramming: This technology resets cell fate by rewriting gene modifications such as methylation without altering the DNA sequence. Using Yamanaka factors (OCT4, SOX2, KLF4), it is attracting attention as a technology to revert differentiated somatic cells back into pluripotent stem cells like iPS cells, or to rejuvenate them.

[18] Senolytics: This is a pharmaceutical that removes "senescent cells (zombie cells)" that accumulate in the body and cause chronic inflammation and disease. It approaches the root cause of aging and is expected to extend healthy lifespan and be a treatment for age-related diseases (such as cancer).