COMPANY RESEARCH AND ANALYSIS REPORT

HEALIOS K.K.

4593

TSE Growth Market

10-Dec.-2024

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Summary

Decision taken to apply for conditional and time-limited approval for ARDS treatment in Japan

Guided by its mission, "To foster a 'Life Explosion' that enriches the lives of people around the world," HEALIOS K.K. <4593> ("Healios" or "the Company") is a biotech venture company researching, developing, and manufacturing cell therapies and regenerative medicine products for the main causes of death in developed countries and for therapeutic fields where new treatments are needed (acute respiratory distress syndrome [ARDS*], ischemic strokes, and intractable solid tumors).

> * ARDS: A general term for the symptoms of acute respiratory failure arising from a number of conditions, including pneumonia. No drug currently exists that can directly improve the patient's vital prognosis, with artificial respiration being the current method of treatment. However, after onset, the mortality rate is as high as 30-58%, requiring the development of an effective treatment. The number of patients worldwide affected by the condition is estimated to be more than 1.1 million annually.

1. ARDS treatment development strategy

On October 2, 2024, Healios published its development strategy for its ARDS treatment (somatic stem cell regenerative medicine HLCM051*). Based on the positive results of Phase 2 studies in Japan, the U.S., and the UK, and on the assumption that a Phase 3 study will be conducted in the U.S. from 2025 as a confirmatory study, the Company has decided to submit an application in Japan for conditional and time-limited approval for HLCM051. As such, the product could be launched in Japan as early as 2025. The Company aims to complete clinical studies in the U.S. in around 2-3 years, and estimates sales could peak at US$3-5bn if a successful global launch is achieved, including in the U.S.

> * Development code for MultiStem® ("MultiStem"), licensed from U.S. company Athersys, Inc. Athersys experienced financial difficulties and filed for bankruptcy in January 2024. Healios acquired MultiStem and other related assets from Athersys in April 2024.

2. Growth strategy

The Company's growth strategy is focused on the development of HLCM051, mainly for the treatment of ARDS, cancer immunotherapies using eNK® cells ("eNK cells"; discussed in more detail below), and licensing activities in Asia and Europe. In addition, it is employing a hybrid strategy to achieve profitability by expanding the medical materials business, which has the potential to generate profits at an early stage. The Company's medical materials are primarily made from supernatant produced during cell cultivation. It aims to sell these materials to beauty clinics and cosmetics manufacturers. In April 2024, Healios signed a joint research agreement with AND medical group, one of Japan's leading beauty clinic companies. It plans to begin supplying the materials to the company in FY12/25 and estimates sales of several billion yen by FY12/26. Also, in the future, Healios plans to raise funds for R&D for pipeline drugs from investment funds and other sources through its subsidiaries. For now, the Company intends to prioritize the development of its ARDS treatment. If successful, the drug is expected to help reduce Japan's trade deficit in pharmaceuticals. This alone means future developments are likely to be watched closely.

3. Development strategy for other pipeline drugs

The Company is also developing HLCM051 as a treatment for the acute phase of cerebral infarction. It is currently conducting integrated data analysis of a Phase 2/3 study conducted in Japan and a Phase 3 study conducted by Athersys in the U.S. It plans to analyze data from over 400 patients in total (around 200 each in Japan and US) to determine its development policy. It also continues to conduct a Phase 2 study of HLCM051 in the U.S. for the indication of trauma. The study is being funded by the U.S. Department of Defense and is scheduled to complete at the end of 2025. If study results are positive, the drug is expected to move to Phase 3, potentially to be funded again by the U.S. Department of Defense, and a successful ultimate outcome could lead to large-volume use by the U.S. military. Healios also plans to begin a clinical study in 2025 for a next-generation cancer immunotherapy using engineered natural killer cells (eNK cells) for the treatment of solid tumors, with an eye on the U.S. market.

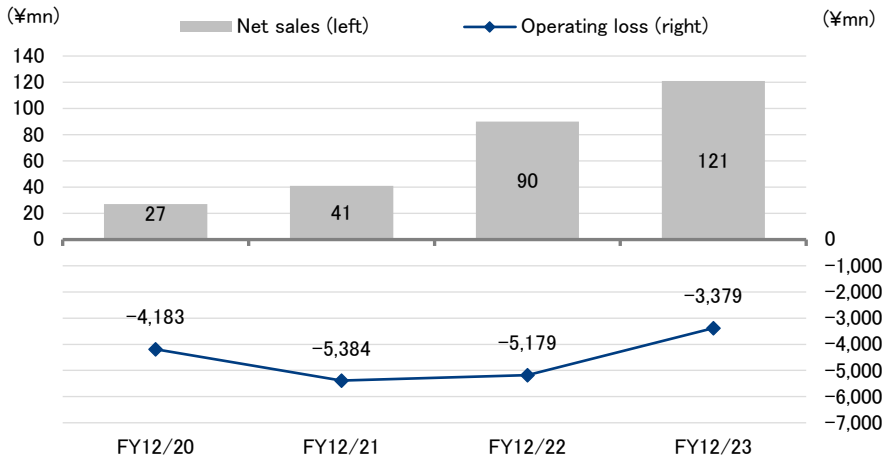
4. Results trends

For 1H FY12/24 (Jan-Jun 2024), the Company reported consolidated revenue of ¥508mn (up ¥401mn or 372.4% YoY) and an operating loss of ¥1,331mn (versus a loss of ¥1,555mn in 1H FY12/23). Net sales growth was mainly driven by an upfront licensing payment (US$3mn) from a subsidiary of Astellas Pharma Inc. <4503> related to a production method for iPS cell-derived retinal pigment epithelial (RPE) cells. The Company has not disclosed full-year forecasts, citing many uncertainties.

Key Points

- Plans to conduct Phase 3 study of ARDS treatment in the U.S., apply for conditional and time-limited approval in Japan
- Forecasts sales of medical materials using cultured supernatant will grow to several billion yen by FY12/26
- 1H FY12/24 net sales rose sharply due to recognition of one-time contract payment

Results trends



Source: Prepared by FISCO from the Company's financial results

Company profile

Bioventure researching, developing, and manufacturing cell therapies and regenerative medicine products

1. Company history

Guided by its mission, "To foster a 'Life Explosion' that enriches the lives of people around the world," Healios is a biotech venture company researching, developing, and manufacturing cell therapies and regenerative medicine products for the main causes of death in developed countries and for therapeutic fields where new treatments are needed (ARDS: respiratory field; cerebral infarction: cerebral nervous system field; solid tumors: oncology field). Healios was founded in 2011 by current Chairman and CEO Tadahisa Kagimoto, who is also a former clinical ophthalmologist.

In 2013, the Company signed a patent license agreement with iPS Academia Japan, Inc. and independent administrative institution RIKEN (now a national research and development institute), and began developing a therapy using iPS cell-derived RPE cell products for age-related macular degeneration, for which no cure is currently available. In December 2013, the Company signed a domestic joint development agreement and in 2014 established an equal joint venture, Sighregen Co., Ltd., with Sumitomo Dainippon Pharma Co., Ltd. (now Sumitomo Pharma Co., Ltd. <4506>). In 2013, the ophthalmic viscoelastic preparation (BBG250) business developed by Aqumen Biopharmaceuticals K.K., a company that Mr. Kagimoto founded in 2005, was transferred to Healios. The business was subsequently transferred to D. Western Therapeutics Institute, Inc. <4576> in 2017.

In 2016, the Company turned its attention to somatic stem cell product* MultiStem, which Athersys was developing in the U.S. for the indication of the acute phase of cerebral infarction. It signed a license agreement with Athersys to develop and market the product in Japan and began Phase 2/3 studies (development code: HLCM051). In the same year, Healios signed a joint development agreement with U.S. biotechnology company Universal Cells, Inc. for a pluripotent cell product that uses gene editing technology to suppress immune rejection.

* Stem cells exist in the body and are important for the long-term health of tissues and organs by differentiating into multiple cell types and reducing excessive inflammation.

In 2019, the Company revised its joint development framework in Japan with Sumitomo Pharma in order to focus management resources on the development of HLCM051. Specifically, the development lead was changed from Healios to Sumitomo Pharma and clinical studies were moved to Sumitomo Pharma, reducing development costs for Healios. Due to the change in development policy, the total amount of milestone payments to be paid by Sumitomo Pharma in line with development progress was changed to ¥1.0bn from ¥1.6bn (of which ¥0.7bn has been received).

In 2021, the Company established fund subsidiaries in the field of regenerative medicine, including Saisei Ventures LLC in the U.S. In 2023, it set up subsidiary ProcellCure, Inc, which is leading the development of HLCM051, and subsidiary eNK Therapeutics, Inc., which is conducting research and development into cancer immunotherapies using eNK cells derived from gene-edited allogeneic iPS cells.

Company profile

After the bankruptcy of Athersys in January 2024, Healios announced the acquisition of MultiStem and related assets from Athersys the following April. Also this year, the Company has been pushing ahead with its alliance strategy. In April, the Company signed a joint research agreement with AND medical group, a general medical group, to use the Company's technology and cultured supernatant, and in June 2024, the Company and Alfresa Corporation signed a basic business alliance agreement related to the distribution and sale of products handled by Healios and concluded a bond purchase agreement* for ¥1.6bn in corporate straight bonds issued by Healios.

* Two tranches of straight bonds (¥0.8bn each, 2% interest rate), issued in June 2024. Redemption dates are June 28, 2027 and June 28, 2030.

Company history

Date	Key events
February 2011	Retina Institute Japan, K.K. (now HEALIOS K.K. <4593>; headquarters: Tokyo) established in Fukuoka City, Fukuoka Prefecture
February 2013	Concluded patent license agreement (non-exclusive) with iPS Academia Japan, Inc. regarding basic technology for iPS cell establishment
March 2013	Concluded exclusive patent license agreement with RIKEN (now a national research and development institute) for regenerative medical products using iPS cell-derived RPE cells
July 2013	Signed business alliance agreement in preclinical field with Shin Nippon Biomedical Laboratories, Ltd.
December 2013	Concluded agreement with Sumitomo Dainippon Pharma Co., Ltd. (now Sumitomo Pharma Co., Ltd. <4506>) on joint development in Japan of iPS cell-derived RPE cells for treatment of age-related macular degeneration, as well as patent license agreement and joint venture contract Acquired ophthalmic viscoelastic preparation business from Aqumen Biopharmaceuticals K.K.
February 2014	Established joint venture Sighregen Co., Ltd. with Sumitomo Dainippon Pharma Co., Ltd.
October 2014	Started collaborative research with Yokohama City University on 3D organs (liver) using iPS and other cells
June 2015	Listed on Tokyo Stock Exchange (TSE) Mothers market
January 2016	Concluded license agreement with Athersys, Inc. for regenerative medicine products using somatic stem cell product MultiStem in Japan
February 2017	Signed business and capital alliance agreement with Nikon Corporation <7731> in field of regenerative medicine
April 2017	Ophthalmic viscoelastic preparation (BBG250) business transferred to D. Western Therapeutics Institute, Inc. <4576>
February 2018	Subsidiary Healios NA, Inc. established in the U.S.
March 2018	Strategic investment in Athersys
June 2018	Expanded exclusive MultiStem license agreement with Athersys
June 2019	Revised joint development framework with Sumitomo Dainippon Pharma Co., Ltd. in Japan for treatments using iPS cell-derived RPE cells
July 2019	Expanded business and capital alliance with Nikon in field of regenerative medicine
January 2021	Established fund subsidiaries in field of regenerative medicine, including Saisei Ventures LLC in the U.S.
August 2021	Signed agreement with Athersys to expand overall scope of collaboration for commercialization
April 2022	Listing moved to TSE Growth Market due to market restructuring
July 2023	Established subsidiary ProcellCure, Inc.
August 2023	Established subsidiary eNK Therapeutics, Inc.
October 2023	Obtained global license from Athersys for MultiStem for treatment of acute respiratory distress syndrome (ARDS)
April 2024	Acquired substantially all MultiStem and related assets following bankruptcy of Athersys Concluded joint research agreement with AND medical group for use of cultured supernatant
June 2024	Signed basic business alliance agreement and bond purchase agreement with Alfresa Corporation Signed non-exclusive license agreement with Astellas Pharma Inc. <4503> subsidiary, Astellas Institute for Regenerative Medicine (AIRM), for patents for RPE cell production and purification in all countries except Japan

Source: Prepared by FISCO from the Company's website, securities report, and prospectuses for new share issue and secondary share offering

Company's strength is proprietary control over all processes and manufacturing facilities needed for cell therapy research and development

2. Business structure and group companies

The Company currently has three businesses organized by field: 1) the development of cell therapies using HLCM051, a bone marrow-derived somatic stem cell product acquired from Athersys, for the treatment of ARDS, the acute phase of cerebral infarction and trauma, 2) the development of new cancer immunotherapies using iPS cell-derived eNK cells, and 3) medical materials, which includes the manufacture and sale of supernatant created in the HLCM051 culture process, universal donor cells (UDC*1) and iPS cell lines, and the licensing and sale of a secure integrated freezer unit (SIFU*2), an automated freezing and thawing inventory management system for cell therapies acquired from Athersys.

*1 Allogenic iPS cells in which the induction of immune rejection (human leukocyte antigen [HLA] mismatch) has been suppressed through gene editing, allowing them to be transplanted into any patient irrespective of HLA type. Healios has significantly improved the safety of UDCs derived from allogenic iPS cells through the deletion of multiple HLA genes responsible for inducing immune rejection and the introduction of immunosuppression-related molecules and suicide genes (capable of eliminating cells that cause abnormalities by inducing cell death). Healios aims to use these UDCs for applications in next-generation immuno-oncology therapy, ophthalmology, and organ buds, engaging in both in-house development and collaboration with academia.

*2 Cell therapies need to be cryopreserved using liquid nitrogen in temperatures below -130°C and thawed when used. However, liquid nitrogen is designated as a hazardous material with the risk of explosion, creating costs associated with ensuring safety during transportation and storage. SIFU is a special cryogenic storage system with a temperature range of -150 to -180°C. The system, which was developed by Athersys, is manufactured on an outsourcing basis. While the system requires an external power source, it simplifies the handling of cell therapies during transportation and storage. In addition, the Company operates the Kobe Research Institute, which is staffed by multiple PhD-qualified researchers and has cell culture facilities. This allows it to conduct all necessary R&D processes in-house, from exploratory research into cell therapies to genetic recombination experiments, animal experiments, process development research, and analytical work. In April 2024, Healios also acquired from Athersys a 3D cell culture technology that can produce cell therapies in large volumes with stable quality. The technology has been introduced at the institute. If cell therapy development progresses smoothly, the Company plans to invest in expanding cell culture facility capacity, aiming to grow its business through in-house manufacturing.

As of June 30, 2024, the Healios group consisted of the Company, seven consolidated subsidiaries, and one jointly controlled equity-method affiliate, with 59 employees on a consolidated basis. The number of employees has been reduced to half of the peak of 116 at the end of December 2021 following a review of the development pipeline. The Company aims to maintain headcount at the current level while targeting a move into profit. Saisei Bioventures, L.P. ("Saisei Fund"), which was established in 2021, is backed by several major Japanese financial institutions, including SMBC Nikko Securities Inc., Mizuho Capital Co., Ltd. and Japan Investment Corporation. The fund has invested in several biotech ventures engaged in R&D for next-generation therapies and basic technologies in the field of regenerative medicine.

Consolidated subsidiaries

Company	Date of establishment	Business	Investment stake
Healios NA, Inc.	February 2018	Overseas drug development	100.0%
Saisei Ventures LLC	January 2021	Fund management in the field of regenerative medicine	49.0%
Saisei Capital Ltd.	January 2021	Fund management in the field of regenerative medicine	49.0%
Saisei Bioventures, L.P.	January 2021	Investment in regenerative medicine-related fields	8.3%
ProcellCure, Inc.	July 2023	Promotion of ARDS development	100.0%
eNK Therapeutics, Inc.	August 2023	Promotion of eNK® cell R&D	100.0%
Other			

Jointly controlled equity-method affiliate

Company	Date of establishment	Business	Investment stake
Sighregen Co., Ltd.	February 2024	Manufacture of iPSC regenerative medicine products	50.0%

Source: Prepared by FISCO from the Company's securities report, business plan, and materials on growth potential

Acquired substantially all assets from Athersys

3. Acquisition of substantially all Athersys assets

Following the bankruptcy* of Athersys in January 2024, the Company acquired MultiStem and related assets, including intellectual property, in April of the same year. With this acquisition, the Company's obligation to pay milestone and sales royalties to Athersys related to MultiStem (HLCM051) was eliminated, significantly reducing the future payment burden. It also acquired Athersys intellectual property, including over 400 patents, allowing for global development. The value of these assets would likely significantly increase if the development of HLCM051 is successful.

> * Triggered by an interim analysis of a Phase 3 study of HLCM051 for cerebral infarction in the U.S. and Europe, which found it had not reached a sufficient sample size to achieve the primary endpoint, making it difficult to raise funds. Problems with the company's management system are also believed to have contributed to the company's failure.

The main assets acquired include all clinical data* for the three MultiStem pipelines (cerebral infarction, ARDS, trauma) that were under development by Athersys, as well as several hundred MultiStem investigational agent doses, 3D bioreactors and manufacturing know-how, a license agreement in the veterinary field (US market), and SIFU technology for the safe transport and storage of cell therapies. Healios plans to utilize these assets in the future development and commercialization phases for HLCM051.

> * Healios obtained clinical data up to Phase 3 for cerebral infarction, Phase 2/3 for ARDS and Phase 2 for trauma, which can be used in future development.

Development pipeline

Targeting management resources on HLCM051 ARDS indication to achieve early launch

The Company's pipeline currently includes the development of HLCM051 for treatment in the inflammation field of ARDS, the acute phase of cerebral infarction and trauma, as well as a novel treatment for retinal pigment epithelium (RPE) tear using iPS cell-derived RPE cells (development lead transferred to Sumitomo Pharma), and a new cancer immunotherapy using eNK cells. Of these, the Company intends to target management resources on the development of HLCM051 for ARDS for now, aiming for rapid launch.

Development pipeline

	Development Code	Therapeutic Area	Therapy	Region	Discovery	Pre-Clinical	Clinical P1	Clinical P2	Clinical P3	Comments
Inflammatory Conditions	HLCM051	ARDS	MultiStem®	Japan			Preparing for approval			Scheduled to apply for Conditional and Time-Limited Approval Orphan designation
			MultiStem®	Global (USA)			Preparing for Phase 3			Agreed with FDA on Global Phase 3 trial design in the U.S. Fast Track and RMAT designation (USA)*1
	HLCM051	Ischemic Stroke	MultiStem®	Japan			Phase 2/3			Consulting with regulatory authorities on application policy in Japan based on clinical trial data from the U.S. and Japan. SAKIGAKE designation (Japan) Fast Track and RMAT designation (USA)
				Global (USA)			Phase 3			
	HLCM051	Trauma	MultiStem®	Global (USA)			Phase 2			Funded by MTEC (United States Department of Defense) and the Memorial Hermann Foundation

*1 Fast Track and RMAT designations relate to a system that allows for expedited approval of drugs (RMAT is for cellular processed products) that meet certain conditions for the development of new drugs for serious or life-threatening diseases or diseases for which no treatment is available.

	Development Code	Therapeutic Area	Therapy	Region	Discovery	Pre-Clinical	Clinical P1	Clinical P2	Clinical P3	Comments
Replacement Therapies	HLCR011	RPE tear AMD	RPE*2	Japan			Phase 1/2			Joint research with Sumitomo Pharma Co., Ltd. Scheduled to be launched in FY2028 First subject enrollment initiated
Immuno-Oncology	HLCN061	Solid Tumors*3	eNK	Global						Pre-IND started IND: 2025 planned
	–	Solid Tumors	CAR-eNK	Global						

*2 Retinal Pigment Epithelium

*3 Gastric cancer, Mesothelioma, Lung cancer and Hepatocellular carcinoma

Note: Excludes pipeline assets scheduled to be carved out

Source: The Company's materials

Plans to conduct Phase 3 study of ARDS treatment in the U.S., apply for conditional and time-limited approval in Japan

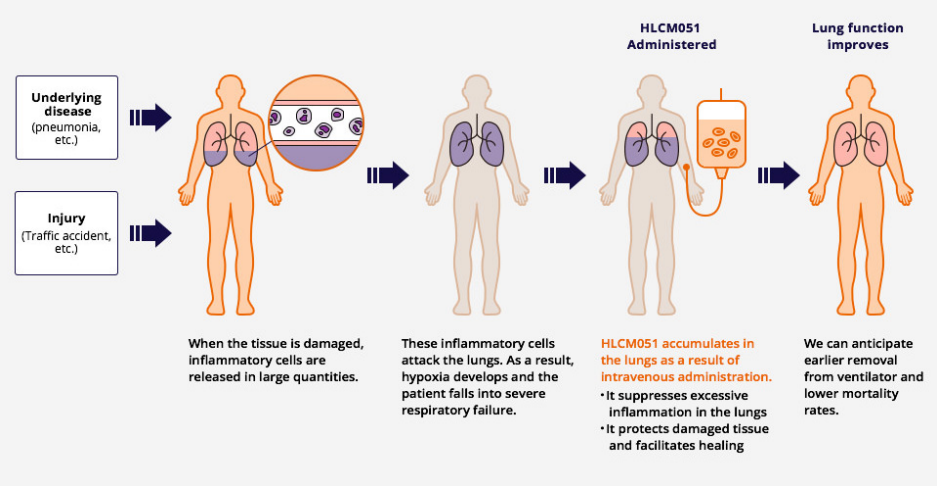
1. HLCM051 (ARDS treatment)

Acute respiratory distress syndrome (ARDS) is a general term for the symptoms of acute respiratory failure arising from a number of conditions, including severe pneumonia and trauma. Inflammatory cytokines are activated in response to these diseases or injury, causing damage to the alveoli and capillaries that make up the tissue of the lungs. As a result, water accumulates in the lungs, leading to acute respiratory failure. With a mortality rate of approximately 30-58%*, ARDS is a condition with a very poor prognosis. Currently, there is no complete treatment for ARDS. Patients are treated by ventilatory management in intensive care units, requiring the development of a novel therapy that can improve patient symptoms and vital prognosis. According to the Company's results briefing materials, the annual number of ARDS patients is estimated to be 28,000 in Japan, 262,000 in the U.S., 133,000 in Europe and 670,000 in China, for a global total of more than 1.1 million.

* From Company's website; source: ARDS Diagnostic Guidelines 2016

Applied intravenously to ARDS patients, HLCM051 is expected to reduce inflammatory cytokines that have accumulated in the lungs, as well as protect damaged tissue and facilitate healing, potentially leading to improvement in lung function. This is anticipated to facilitate earlier removal from ventilation and reduce the mortality rate.

HLCM051 expected mechanism of action against ARDS (image)



Source: The Company's website

A Phase 2 study conducted by Healios in Japan (2019-2021; 30 patients enrolled, including 20 in HLCM051 group and 10 in placebo group), yielded positive results, with the number of ventilator-free days during the first 28 days after treatment approximately double that of the placebo group (20 days for HLCM051 group vs. 11 days for placebo group), and a reduction in the mortality rate during the first 90 days after treatment (26.3% vs. 42.9%). Due to the small sample size of 30 patients, the Company was in discussion with Japan's Pharmaceuticals and Medical Devices Agency (PDMA) to conduct a Phase 3 trial. However, as noted above, the Company decided to change the development policy for HLCM051 following the bankruptcy of Athersys, which allowed it to acquire almost all related assets, including overseas clinical trial data, investigational drugs, and development rights. Specifically, the Company now plans to conduct a Phase 3 study (300-550 patients) in the U.S. and apply for a conditional and time-limited approval in Japan, based on the assumption that data from the Phase 3 study will be used as validation data. Athersys also conducted a Phase 2 study in the U.S. and obtained generally similar results to the Company's study in Japan, so we expect the new Phase 3 study in the U.S. to yield positive results.

The Company has already agreed the design of the Phase 3 study in the U.S. with the Food and Drug Administration (FDA). The primary endpoint will be the same as for the Phase 2 study conducted in Japan—the number of days a patient does not require mechanical ventilation out of 28 days post administration, compared with the placebo group. Interim analyses will be conducted at the 300 and 400 patient stages, and the Company can apply to end the study if statistical significance is confirmed at either stage. If the study is continued, the maximum number of patients is 550. Healios is also preparing to file an investigational new drug (IND) application in 2025, with the study expected to last 2-3 years (several hundred investigational agents were acquired from Athersys in April 2024). If the studies proceed smoothly, Healios could apply for approval in 2027 and begin sales in 2028. In the U.S., HLCM051 has received Fast Track and RMAT designation from the FDA, which allows for expedited approval.

The Company plans to fund the cost of the clinical study in the U.S. through the exercise of its 21st and 22nd stock acquisition rights*1 and proceeds from sales of medical products utilizing cell culture supernatants, scheduled to start in 2H 2025. In the event of a funding shortfall, the Company intends to raise funds through royalty investments*2 by U.S. subsidiaries or newly established subsidiaries, third-party share allotments, or other means.

> *1 Exercise prices are ¥174.2 for the 21st stock acquisition rights and ¥180 yen for the 22nd. Full exercise of rights would generate roughly ¥4.7bn.
> *2 A method of raising advance funding from investment funds by pledging sales royalties after the product is launched.

If HLCM051 is successfully developed in the U.S., Healios estimates sales would peak at around US$3-5bn. This assumes a drug price of US$100k, 262,000 patients and a usage rate of 10-20%. For its drug price calculation, Healios believes US$100k is a realistic figure, based on pharmacoeconomic analysis that takes into account the overall benefit to patients and the impact on health care costs in the U.S., assuming a shortened ventilator treatment period (5-9 days) if HLCM051 is administered.

The Company is already negotiating license agreements with several companies outside Japan and the U.S. (Europe, South Korea, Taiwan, China) to achieve early monetization.

Expects sales of medical materials using cultured supernatant to grow to several billion yen by FY12/26

2. Joint research agreement with AND medical group

In April 2024, the Company entered into a joint research agreement with AND medical group. Specifically, the Company is to supply cosmetic surgery clinics and other such enterprises* operated by AND medical group with medical materials that the Company develops using culture supernatant generated during the process of producing Healios-owned regenerative medical products. The Company is to receive ¥180mn, which consists of ¥60mn in upfront payments and compensation for milestones paid in alignment with research progress. Moreover, the Company intends to enter into an agreement to supply raw materials to AND medical Group upon having established a raw materials manufacturing method and system as well as having achieved the joint research objectives.

> * As of the end of September 2024, the AND medical group brand operates 26 clinics specializing in cosmetic dermatology, cosmetic surgery, plastic surgery, and urology services, making it the third-largest operator of clinics in Japan's beauty sector.

The Company received upfront payments in April 2024, and will furthermore receive ¥60mn in 4Q FY12/24 upon having achieved the first milestone associated with research progress. In alignment with demand from AND medical group going forward, the Company plans to start providing 25 liters of culture supernatant per month in 2025, and will progressively increase production to meet demand. With respect to unit price, whereas most commercial products sell for ¥10,000 to ¥30,000 per cubic centimeter, the final sales price is to be determined after confirming the quality required by the AND medical group.

The Company estimates the Japanese market for cell culture supernatant, which is used in settings such as beauty clinics and also used as a component in cosmetic products, will range from several billion yen to ten billion yen. Whereas the market environment surrounding this business sector is intensively competitive given factors such as imports from South Korea, the Company contends that it will gain momentum as a result of it already meeting standards of the Ministry of Health, Labour and Welfare (MHLW), which requires that culture supernatant also satisfy pharmaceutical-level manufacturing quality control standards. In fact, cosmetics product manufacturers and other beauty clinics have apparently been expressing interest, indicating the possibility that the Company may encounter growth in its number of customers going forward.

Exploring options with respect to ischemic stroke for design of clinical trials that are highly likely to result in approval, enlisting analysis of clinical trial data from Japan and the U.S.

3. HLCM051 (ischemic stroke treatment)

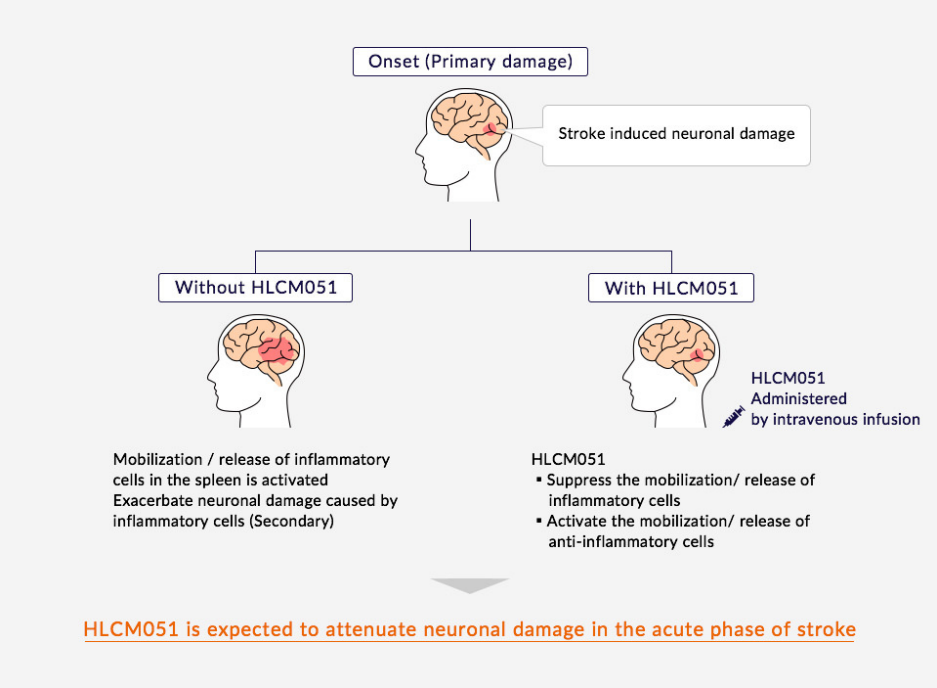
Ischemic stroke refers to a condition where a blood vessel in the brain becomes blocked, which prevents nutrients from reaching downstream cells and consequently disrupts brain function. Whereas symptoms vary depending on the location of the blocked blood vessel, paralysis, speech impairment, and other such aftereffects often linger even when the patient survives. According to the Company's results briefing materials, the annual number of stroke patients is estimated to be 330,000 in Japan*, 690,000 in the U.S., 840,000 in Europe, and 3.4 million in China, with a worldwide total of over 5.26 million.

* HLCM051 is intended for patients who have been admitted to a medical institution within 36 hours of symptom onset. The Company accordingly estimates that approximately 62,000 patients will meet such criteria in Japan.

Treatments commonly used for acute cerebral infarction include thrombolytic treatment, which entails dissolving blood clots that have blocked vessels in the brain, and mechanical thrombectomy, which entails restoring blood flow by directly removing blood clots from obstructed cerebral arteries. However, thrombolytic treatment may only be administered within 4.5 hours of symptom onset and mechanical thrombectomy may only be performed within 8 hours. As such, there is substantial need for development of new drugs that enable effective treatment even after a certain amount of time has elapsed since the initial onset of ischemic stroke.

When intravenously administered within 36 hours of onset of ischemic stroke, HLCM051 is expected to have neuroprotective effects by reducing nerve cell damage as a result of inhibiting the activation of inflammatory immune cells in the spleen, the site of immune response, thereby suppressing inflammation and immunoreaction, and furthermore by inducing proliferation of anti-inflammatory cells and releasing nutrient factors.

Effects of HLCN051 in treating acute ischemic stroke



Source: The Company's website

In terms of progress achieved in drug development, the Company conducted Phase 2/3 clinical trials in Japan and released the results in November 2022. Additionally, Athersys released interim analysis results of a Phase 3 trial in the U.S. in October 2023. In Japan, 220 patients within 18 to 36 hours of ischemic stroke onset were divided into two groups of 110 patients each consisting of an HLCM051 group and a placebo group, with the extent of improvement compared at 90 days and 365 days after administration. Comparisons were made with respect to the primary endpoint constituting the number of subjects achieving an Excellent Outcome (EO), defined as minimal or no difficulty in daily life. Comparisons were also made with respect to the secondary endpoints constituting the number of subjects achieving a Global Recovery (GR) score indicating daily life independence and the number of subjects achieving 95 or higher on the Barthel Index (BI) quantifying activities of daily living. Although results did not indicate presence of a statistically significant difference against the placebo group either 90 days or 365 days after administration, the primary endpoint, significant difference was confirmed with respect to GR (p-value of 0.037) and BI (p-value of 0.045) 365 days after administration, and safety after administration of HLCM051 was also confirmed.

Results of Phase 2/3 trials in Japan
Comparison of results of the HLCM051 group and the placebo group at 90 days and 365 days after administration (110 subjects for each)

	90 days			365 days		
	HLCM051 group	Placebo group	P-value*4	HLCM051 group	Placebo group	P-value*4
EO*1	12 subjects (11.5%)	10 subjects (9.8%)	0.903	16 subjects (15.4%)	11 subjects (10.8%)	0.431
GR*2	20 subjects (19.2%)	16 subjects (15.7%)	0.762	29 subjects (27.9%)	16 subjects (15.7%)	0.037
BI*3≧95	31 subjects (29.8%)	24 subjects (23.5%)	0.437	37 subjects (35.6%)	23 subjects (22.5%)	0.045

*1 Excellent Outcome (EO): EO is defined as achieving scores of mRS*5≤1, NIHSS*6≤1, and BI≥95, with mRS, NIHSS, and BI serving as the primary benchmarks used for functional assessment of stroke patients. It constitutes a scenario where patients encounter minimal or no difficulty in daily life.
*2 Global Recovery (GR): GR is defined as achieving scores of mRS≤2, NIHSS≥75%, and BI≥95. It constitutes a scenario of daily life independence (without need for long-term care).
*3 Barthel Index (BI): The BI involves evaluating an individual on the basis of a maximum score of 100 points constituting the sum of scores for 10 Activities of Daily Living (ADLs; eating, walking, getting dressed, etc.) in terms of the extent to which the individual is able to remain independent or otherwise needs long-term care.
*4 A p-value of p<0.05 is interpreted as indicating a statistically significant difference.
*5 Modified Rankin Scale (mRS): The mRS is a scale for measuring degree of disability on a graded scale of impairment as follows: 0 (no symptoms), 1 (no significant disability despite symptoms), 2 (slight disability), 3 (moderate disability), 4 (moderately severe disability), 5 (severe disability), and 6 (dead).
*6 National Institutes of Health Stroke Scale (NIHSS): The NIHSS involves assessing the neurological severity of a stroke by assigning separate scores to individual categories and then evaluating such severity enlisting the total score (ranging from 0 to 42 points), with a higher score indicating more severe symptoms. Meanwhile, findings of the Phase 3 trial (planned enrollment of 300 subjects) initiated by Athersys in the U.S. in 2018 indicated no statistically significant difference in the number of patients achieving Excellent Outcome on day 90 after administration, which was set as the primary endpoint. However, the findings confirmed statistically significant difference with respect to GR and BI on day 365, which was generally consistent with results obtained in the clinical trial conducted in Japan. Moreover, findings indicated that larger infarct volume of a subject correlates with greater therapeutic effect in comparison with the placebo group, as well as greater efficacy in patients aged 64 and younger.
Note: The table constitutes a summary of materials released on November 2, 2022.
Source: Prepared by FISCO based from IR news releases

With respect to its development policy going forward, the Company has indicated that it intends to explore options in terms of clinical trials designed for greater likelihood of gaining manufacturing and marketing approval, which will entail integrating data from clinical trials conducted in Japan and the U.S. and proceeding with further analysis. A key point in this regard is that of whether or not it will be possible to designate GR and BI at day 365 after administration as the primary endpoint. Meanwhile, with HLCM051 designated under the SAKIGAKE Designation System in Japan, the Company may seek conditional and time-limited approval based on the secondary endpoints with statistically significant results, following discussions with the PMDA.

Lower priority will be assigned to development of HLCM051 for use in treating ischemic stroke in the U.S. for the time being given that resources will be focused on its development for treatment of ARDS. However, the Company hopes progress in developing HLCM051 for use in treating ischemic stroke will be achieved in the future because the market for such application is larger than that for its use in treating ARDS, and given the prospect of rising demand for the product accompanying further aging of society going forward. In covering development costs associated with conducting clinical trials, the Company plans to raise funds in part through royalty investment and third-party allotment of shares through its U.S. subsidiary and newly established subsidiaries, which is similar to the approach taken with respect to use of the product as a drug for treating ARDS. Meanwhile, the Company has been enlisting a license-out approach in geographic regions outside of the U.S. and Japan, and has apparently been contacted by pharmaceutical companies regarding such possibilities.

Phase 2 clinical trial of HLCM051 for treatment of trauma currently underway, funded by the U.S. Department of Defense

4. HLCM051 (trauma treatment)

HLCM051 is under development in the U.S. as a trauma treatment drug, with the U.S. Department of Defense and the Memorial Hermann Foundation acting as sponsors. The Phase 2 trial (enrollment of 156 patients) was temporarily suspended due to bankruptcy of Athersys, but was resumed in October 2024. With approximately 20% of its enrollment target having been achieved, the trial is expected to reach completion by the end of 2025. The trial will proceed to the Phase 3 trial if the Phase 2 trial yields a favorable outcome, continuing with sponsors that expected to include the Department of Defense. Amid a situation where the Company itself does not assume financial burden with respect to the trial, developments going forward warrant attention given potential for mass adoption of HLCM051 by the U.S. military if development of the drug achieves a successful outcome.

Instances of death attributable to trauma caused by traffic accidents, industrial accidents, gunshot wounds, and other such incidents are prevalent in the U.S., where trauma is the leading cause of death among those under 45 years old, the third leading cause of death overall, and the leading cause of reduced quality of life (QOL), according to the Company's results briefing materials. There are 220,000 trauma-related deaths annually in the U.S., of which 55% are attributable to general trauma and 45% are attributable to trauma or acute poisoning under the influence of drugs. When a patient develops systemic inflammatory response syndrome (SIRS) due to trauma, the inflammatory response initially serves as a defense mechanism for the body, but eventually culminates in uncontrollable cytokine storm that triggers a massive inflammatory cascade resulting in renal failure and other such organ damage, which potentially leads to death. Given the current lack of effective drugs for treating patients who reach this stage, health-care providers are limited to providing treatment that addresses specific symptoms. It is hoped that administration of HLCM051 will suppress the cytokine storm, thereby having a positive effect with respect to patient prognosis.

The Phase 2 clinical trial enlists a double-blind, placebo-controlled comparison study focused on multiple organ failure/systemic inflammatory response syndrome (SIRS) attributable to trauma, while also comparing the placebo group to the HLCM051 group in terms of improvement in renal function achieved 30 days after administration, the primary endpoint. The trial also involves assessment of mortality rates and other such benchmarks that serve as secondary endpoints. Participants of the study consist of patients with severe traumatic injuries who were initially resuscitated within several hours of hospital admission. Developments going forward warrant attention given potential for mass adoption of HLCM051 by the U.S. military if development of the drug achieves a successful outcome.

Aiming to embark on clinical trial of immuno-oncology therapy using eNK cells in 2025

5. HLCN061 (next-generation immuno-oncology therapy)

The Company is making progress in carrying out joint research with multiple academic institutions on immuno-oncology therapy using iPSC-derived eNK cells independently developed using gene-editing technology, with the aim of embarking on clinical trials in 2025.

A distinguishing characteristic of eNK cells relative to NK cells is their enhanced cytotoxicity and ability to infiltrate tumor sites enlisting gene-editing technology. Findings of the Company's research to date confirm that eNK cells exhibit anti-tumor effects on orthotopic engraftment mouse models of lung cancer, subcutaneous xenograft mouse models of liver cancer, mouse models of gastric cancer peritoneal metastasis, and subcutaneous xenograft mouse models of mesothelioma. Findings of the Company's research also confirm that eNK cells exhibit similar anti-tumor effects on tumor organoids* derived from lung cancer patients, which have a similar environment as cancer in vivo.

* An organoid is a tissue or cell that has a three-dimensional structure with characteristics quite similar to those of tissues and organs present in organisms.

The Company's involvement in joint research projects has involved working with National Cancer Center Japan (NCC) in evaluating anti-tumor effects of eNK cells using patient-derived xenograft (PDX) mouse models derived from multiple cancer strains held by NCC. The Company has also been advancing joint research on hepatocellular carcinoma with the Graduate School of Hiroshima University and also advancing joint research on immuno-oncology therapy for mesothelioma with Hyogo Medical University. In 2024, the results of these studies were presented at academic conferences and other such forums.

With respect to research and development, the Company plans to have its subsidiary eNK Therapeutics take the leading role in advancing such projects going forward, while funds will be raised in part through royalty investment and third-party allotment of shares in cases where development costs for clinical trials and other such initiatives become necessary. The Company contends that this fundraising will help reduce its annual development cost burden by approximately ¥1.0bn.

Business alliances and license agreements

Business alliance with Alfresa and non-exclusive license agreement with an Astellas subsidiary

1. Business alliance with Alfresa

In June 2024, the Company entered into a basic business alliance agreement with Alfresa, a leading pharmaceutical distributor in Japan, regarding the distribution and sales of products handled by the Company. The Company also entered into a bond purchase agreement for ¥1.6mn in corporate straight bonds (first series and second series).

Three aspects of the business alliance are described as follows.

1) Exclusive rights for wholesale distribution of the Company's pipeline products within Japan, including HLCM051, as well as exclusive rights associated with transportation and delivery of investigational drugs associated with this pipeline within Japan
2) Rights for commercialization of HLCM051 culture supernatant and raw material products derived from the culture supernatant, along with rights as the sole distributor or exclusive seller of these products within Japan
3) Rights for commercialization of the Secure Integrated Freezer Unit (SIFU) automated freezing and thawing inventory management system within Japan, and rights for exclusive sales of such products within Japan

A separate contract will be concluded per discussions going forward regarding specific details of such business operations. This business alliance will address logistical concerns, thereby facilitating expansion of business in Japan.

2. License agreement concluded with Astellas Pharma subsidiary

In June 2024, the Company entered into a license agreement with Astellas Institute for Regenerative Medicine (AIRM), a U.S.-based subsidiary of Astellas Pharma that conducts research in the field of regenerative medicine. The license agreement grants non-exclusive rights worldwide outside of Japan to a patent on a method for manufacturing iPSC-derived RPE cells* that the Company shares with RIKEN and Osaka University, and to a patent on a method for purification of RPE cells shared with Osaka University. On July 2024, the Company received upfront payment amounting to US$3mn. Meanwhile, the Company may receive additional milestone payments of up to US$8mn upon manufacturing and marketing approval in the U.S. with respect to the product developed and manufactured by AIRM enlisting the patents.

* Retinal Pigment Epithelial (RPE) cells are cells that form the retinal pigment epithelium outside the neural retinal layer. RPE cells come into contact with photoreceptor cells and exert physiological functions to maintain and protect the functions of the photoreceptor cells. Upon depletion of RPE cells, visual function is subject to permanent impairment given that such cells do not regenerate. Research on the transplantation of iPSC-derived RPE cells has accordingly been attracting attention as a treatment for age-related macular degeneration and other such conditions.

Results trends

Revenue increased substantially in 1H FY12/24 as a result of having recorded upfront payments

1. 1H FY12/24 results

In the 1H FY12/24 consolidated results, revenue increased 372.4% YoY to ¥508mn (¥401mn higher YoY), operating loss was ¥1,331mn (operating loss of ¥1,555 in 1H FY12/23), loss before tax of ¥2,968mn (loss of ¥1,321mn in 1H FY12/23), and loss attributable to owners of parent of ¥2,958mn (loss attributable to owners of parent of ¥1,392mn in 1H FY12/23).

1H FY12/24 results (IFRS)

(¥mn)

	1H FY12/23 Results	1H FY12/24	
		Results	Change
Revenue	108	508	401
Gross profit	95	440	345
Research and development costs	1,047	1,119	72
SG&A expenses	602	689	87
Operating profit (loss)	-1,555	-1,331	224
Profit before tax (loss)	-1,321	-2,968	-1,647
Profit attributable to owners of parent (loss)	-1,392	-2,958	-1,566
No. of employees	63	59	-4

Source: Prepared by FISCO from the Company's financial results and results briefing materials

The increase in revenue is attributable to US$3mn in upfront licensing payments received from a subsidiary of Astellas Pharma and ¥60mn in upfront payments received from AND medical group. Although research and development costs increased by ¥72mn as a result of the Company having promoted R&D associated with HLCM051, HLCN061 and other candidates in the development pipeline, and SG&A expenses gained by ¥87mn, the increase in revenue served as a factor in reducing the amount of operating loss.

The increase in loss before tax is attributable to escalation of finance costs, which increased by ¥2,025mn to ¥2,100mn, against an increase of ¥155mn in finance income to ¥463mn. However, this primarily consists of non-cash profit and loss items, the impact on cash on hand of which is minimal. The finance income mainly consists of profit or loss transferred to equity interests held by external investors in Saisei Fund*1 amounting to ¥431mn and interest income amounting to ¥29mn, with the YoY increase primarily attributable to a YoY increase in profit and loss transferred to equity interests held by external investors of ¥201mn. Meanwhile, the finance costs mainly consist of loss on remeasurement of derivatives*2 of ¥1,692mn, loss on remeasurement of investment securities of ¥293mn, interest expenses on bonds*3 of ¥56mn, and share acquisition rights issuance costs of ¥55mn, with the increase primarily attributable to the YoY increases in loss on remeasurement of derivatives and loss on remeasurement of investment securities.

*1 Profit or loss transferred to equity interests held by external investors in Saisei Fund refers to the amount of profit and loss of the Company's consolidated subsidiary Saisei Bioventures, such that has been transferred to partners that have invested in Saisei Bioventures other than the Company.
*2 Loss on remeasurement of derivatives has arisen primarily from remeasurement at fair value of the 21st and 22nd stock acquisition rights issued by the Company, recognized in accordance with the International Financial Reporting Standards (IFRS). Under IFRS, the paid-in amount for share acquisition rights is recorded as a liability, and the fair value is measured at the end of each fiscal period with the gains or losses recorded as finance income or finance costs.
*3 Of the ¥56mn in interest expenses on bonds, ¥36mn was recorded as an expense using the amortized cost method (non-cash expense). Under IFRS, net proceeds calculated by deducting issuance fees from the bond issuance amount are recorded as a liability, thereby resulting in a difference between the face value of bonds and the amount recorded as a liability. The difference is then amortized (expensed) as interest expenses on bonds each fiscal period.

Meanwhile, the Company has not disclosed its consolidated results forecast for FY12/24 due to difficulty inherent in calculating appropriate and reasonable figures given the presence of numerous uncertainties at this point in time, such that include possibilities of new business alliances and acquisition of new seeds. On the expense side, research and development costs and SG&A expenses are poised to remain largely at the same level as the amounts in the previous fiscal period.

Fundraising going forward is to involve exercising outstanding share acquisition rights, royalty investment and third-party allotment of shares

2. Financial position

In terms of the Company's financial position, total assets as of the end of 1H FY12/24 were up ¥2,656mn from the end of the previous fiscal year to ¥17,811mn. Cash and cash equivalents increased by ¥2,172mn in current assets in part due to issuance of bonds, and other financial assets were up ¥325mn in non-current assets.

Meanwhile, total liabilities were up ¥3,258mn from the end of the previous fiscal year to ¥14,546mn. Other financial liabilities increased by ¥1,969mn in current liabilities in part due to fair value reassessment of share acquisition rights, and bonds and borrowings were up ¥1,599mn in non-current liabilities. Meanwhile, total equity was down ¥602mn from the end of the previous fiscal year to ¥3,266mn. Whereas issuance of new shares had a positive effect on equity of ¥2,181mn, the Company recorded a loss of ¥2,951mn.

Net cash (cash and cash equivalents – bonds and borrowings) amounted to ¥2,851mn. The Company will raise funds for its business activities going forward by exercising its outstanding 21st and 22nd share acquisition rights (estimated at approximately ¥4.7bn if all such share acquisition rights are exercised) and it will furthermore cover such costs in part with proceeds from sales of culture supernatant and upfront licensing payments. In the event of a shortfall, however, the Company plans to raise funds from investment funds and other such sources in part by enlisting royalty investment through its subsidiaries and third-party allotment of shares. The Company seeks to rapidly achieve profitability by promoting its hybrid strategy of prompting development of the field of medical materials, in addition to the fields of bone marrow-derived cells and iPSC regenerative medicine.

Consolidated balance sheet

(¥mn)

	End of FY12/21	End of FY12/22	End of FY12/23	End of 1H FY12/24	Change
Current assets	16,429	8,462	7,683	9,860	2,177
Cash and cash equivalents	15,126	7,247	6,722	8,894	2,172
Non-current assets	7,543	6,571	7,471	7,951	480
Total assets	23,971	15,033	15,155	17,811	2,656
Current liabilities	6,042	3,808	5,169	7,112	1,943
Non-current liabilities	9,284	6,842	6,118	7,433	1,315
Total liabilities	15,326	10,650	11,287	14,546	3,258
Bonds and borrowings	11,552	6,887	4,408	6,043	1,635
Total equity	8,645	4,382	3,867	3,266	-602
[Stability]					
Ratio of equity attributable to owners of parent	36.0%	29.2%	25.4%	18.2%	-7.2 pp
Interest-bearing debt ratio	133.7%	157.2%	114.3%	186.3%	72.0 pp
Net cash (¥mn)	3,574	360	2,314	2,851	537

Note: Net cash = Cash and cash equivalents – bonds and borrowings
Source: Prepared by FISCO from the Company's financial results

3. Growth strategy

Under its growth strategy, the Company plans to persist with development efforts in the fields of bone marrow-derived cells (HLCM051) and iPSC regenerative medicine, while also promoting a hybrid strategy aimed at rapidly achieving profitability by venturing into the medical materials business.

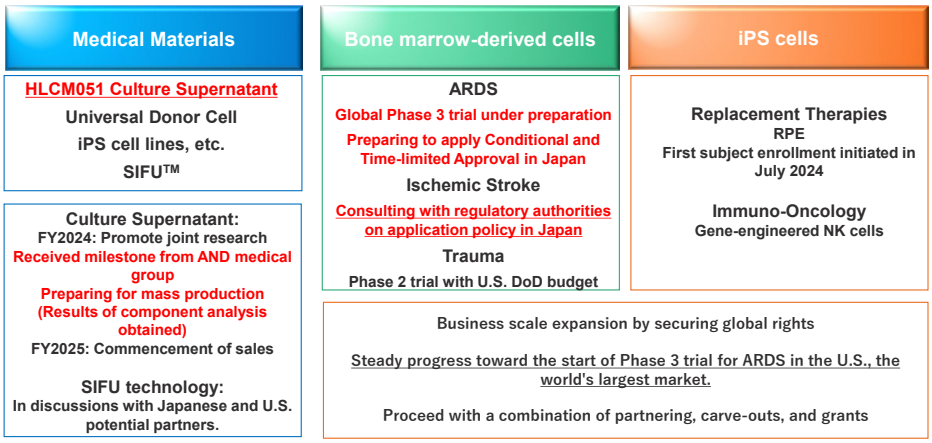
In regard to HLCM051, the Company's acquisition of global rights to the product has greatly amplified its growth potential. The Company initially plans to place top priority on gaining conditional and time-limited approval in Japan for its use as a drug for treatment of ARDS and initiating Phase 3 trial in the U.S. At the same time, the Company will proceed with licensing negotiations in Asia and Europe.

In the field of iPSC regenerative medical products, the Company is proceeding with development of next-generation immuno-oncology therapy using eNK cells through its subsidiary, and plans to raise development funds largely through royalty investments, third-party allotment of shares, and joint development agreements. In addition, the Company has embarked on Phase 1/2 clinical trials with its joint development partner Sumitomo Pharma with respect to treatment using RPE cells for patients with retinal pigment epithelium tear in the field of ophthalmology (planned enrollment of 21 subjects). Although the first subject was enrolled in 2024, this is not likely to affect the Company's results for the time being. However, the Company may enter into a new non-exclusive license agreement overseas.

In the medical materials business, in addition to anticipated expansion of cultured supernatant previously mentioned, the Company also plans to promote sales of research and development materials such as UDC and iPS cell lines, as well as sales of the SIFU automated freezing and thawing inventory management system for cellular pharmaceuticals acquired from Athersys.

Specifically, if sales of culture supernatant achieve growth as planned, it will then be on a trajectory to achieve positive results with respect to operating profit by FY12/26. In addition, successful development of ARDS treatment in the U.S. would suggest potential growth in product sales peaking at around US$3-5bn. With the Company having acquired 3D bioreactors capable of mass production along with manufacturing expertise from Athersys, it will augment its facilities and export products from Japan to overseas markets if it achieves progress with respect to commercialization. In so doing, the Company seeks to help reduce Japan's trade deficit in pharmaceuticals.

Hybrid strategy



Source: The Company's materials

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