COMPANY RESEARCH AND ANALYSIS REPORT

# SymBio Pharmaceuticals Limited

## 4582

Tokyo Stock Exchange Growth Market

23-Jan.-2023

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https://www.symbiopharma.com/ir_e/

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# Summary

## Significant increases in sales and profits expected in FY12/22 and BCV to see even higher growth potential with an expanded field of development

SymBio Pharmaceuticals Limited <4582> (hereafter, also "the Company") is a bio-venture progressing developments from the clinical trial stage, targeting indications for oncology, hematology, and rare diseases for which there are few patients but medical needs are high. Through a "no lab or fab" strategy, the Company is pursuing efficient business management. The pipeline includes TREAKISYM®, which has already been commercialized as a treatment for malignant lymphoma, along with the antiviral drug brincidofovir (BCV) in-licensed from Chimerix Inc. <CMRX> (hereafter, Chimerix) (U.S.) and rigosertib, which it in-licensed from Onconova Therapeutics, Inc. <ONTX> (hereafter, Onconova) (U.S.). With the start of operations of a subsidiary to lead its global development strategy in the U.S., the Company began reporting consolidated financial results from FY12/22. The Company has transitioned to the Tokyo Stock Exchange Growth Market in connection with the market restructuring of the Tokyo Stock Exchange in April 2022.

### 1. Overview of the 3Q FY12/22 results

In the 3Q FY12/22 (January to September 2022) results, the Company posted significant increases in sales and profits. Consolidated net sales increased 32.5% to ¥7,355mn, in comparison to the non-consolidated result for the same period of the previous fiscal year, and operating profit was up 274.5% to ¥1,588mn on the same basis. The main reason for the increase in net sales was that in March 2021, the Company expanded the indication areas for TREAKISYM® by obtaining approval for the manufacturing and marketing authorization, allowing the product to be used in the bendamustine-rituximab (BR) therapy and in the polatuzumab vedotin plus bendamustine-rituximab (P+BR) therapy to treat recurrent/refractory diffuse large B-cell lymphoma (hereafter, r/r DLBCL). The Company booked ¥550mn in sales milestone payments, and R&D expenses rose ¥277mn. However, the Company made progress in switching to the RTD formulation (liquid type) from FD formulation (lyophilized powder intravenous type), causing the gross profit margin to improve, and progress was also made on curtailing SG&A expenses. As a result, the operating profit margin rose significantly, from 7.6% in the same period of the previous fiscal year to 21.6%. One company began selling a generic version of TREAKISYM®, but it appears that the effect on the Company was negligible.

### 2. Trends in the development pipeline

In February 2022, the Company received marketing approval for TREAKISYM® Liquid Formulation Rapid Infusion (RI) administration (which reduces the infusion time from the original 60 minutes to 10 minutes). The Company has been working to switch from the RTD formulation to RI administration and expects that the switch will be almost fully completed sometime around March 2023. The Company is also advancing joint research with academia to explore the possibility of expanding to new applications through combination therapy with rigosertib. In February 2022 four pharmaceutical companies announced that they had received manufacturing and marketing approval for generic versions of RTD formulation products. In November 2022, two of those companies announced that they had also received authorization for RI administration. TOWA PHARMACEUTICAL CO., LTD. <4553> launched sales in June 2022, while Pfizer Japan Inc. did so in December 2022. Together with U.S. company Eagle Pharmaceuticals, Inc. <EGRX> ("Eagle"), the license holder, on December 16, 2022 the Company filed a patent infringement lawsuit against TOWA PHARMACEUTICAL CO., LTD., which had launched advance sales. On December 26, 2022, it also filed a patent infringement lawsuit against Pfizer Japan Inc., which had also launched advance sales.

Summary

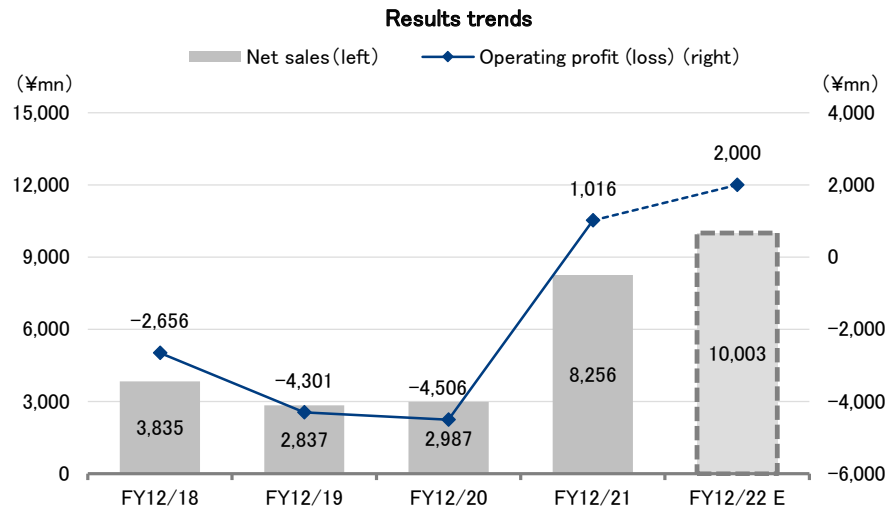
As for BCV (intravenous formulation), the Company's primary focus of current development, the Company is expanding joint research with major overseas academic institutions. This research has been possible because BCV is characterized by highly effective antiviral activity against a wide range of DNA viruses. At this time, the possibilities for development are growing for treatments for conditions with high unmet medical needs such as intractable cranial nerve disease and cancer. In terms of the status of development, the Company is conducting a phase II global joint clinical trial indicated for adenovirus (AdV) infections that develop after hematopoietic stem cell transplantation. Also, in December 2022, the Company started a phase II global joint clinical trial indicated for BK virus (BKV) infections after kidney transplantation. The prospect of launching clinical trials for EB virus (EBV) positive lymphoma in 2023 has emerged as a result of various joint research studies conducted with major overseas academic institutions. Apart from this, progress is being made on non-clinical studies indicated for conditions such as glioblastoma and multiple sclerosis. If the Company succeeds at development in these areas, future trends will be given attention all the more because the market value of BCV may surpass ¥100.0bn.

### 3. Outlook

In FY12/22 results, the Company is forecasting increases in sales and profits based on increased sales of TREAKISYM®, with net sales increasing 21.1% year-on-year (YoY) to ¥10,003mn, and operating profit increasing 96.9% to ¥2,000mn. The increase in net sales will largely result from the full-year contribution from net sales of TREAKISYM® for r/r DLBCL and growth in market share. In FY12/23, the major risk factors will be the drug price of TREAKISYM® and sales trends for generic drugs. The Company foresees an increase in the number of potential patients and higher demand from the penetration of BR therapy and P-BR therapy. However, partly because the price of generic drugs was set at approximately 43% of the price of the brand-name drug, the Company's net sales may decrease depending on future trends.

### Key Points

- TREAKISYM® achieved growth through expanded indications to r/r DLBCL and increased market share, but trends in generic drugs emerged as risk factors
- The growth potential for BCV has increased significantly as the possibilities for development have expanded to conditions such as malignant lymphoma, brain tumors, and multiple sclerosis, in addition to viral infectious diseases
- For its FY12/22 results, the Company expects continued increases in sales and profits due to growth in TREAKISYM®, and it aims to remain profitable in FY12/23




Note: Figures for FY12/21 and prior fiscal years represent non-consolidated results.
Source: Prepared by FISCO from the Company's financial results

# Company profile

## A bio-venture that conducts developments from the clinical trial stage, targeting the fields of oncology, hematology, and rare diseases

SymBio Pharmaceuticals is a bio-venture founded by the current Representative Director and President Chief Executive Officer Fuminori Yoshida in March 2005. For its business strategy, its basic policy is to conduct development and provision of new drugs for underserved therapeutic areas in which development has not been progressed due to the small numbers of patients. One of its features is a business model that aims to achieve highly efficient and rapid drug discovery within the areas targeting oncology, hematology, and rare diseases, which are fields with high medical needs, by in-licensing development candidates for which POC* for humans has been obtained, and conducting development from the clinical trial stage.

* POC (proof of concept): when the usefulness and efficacy of a new drug candidate compound is recognized following its administration to animals or humans during research and development.

The first development candidate to be in-licensed was the anticancer agent bendamustine hydrochloride (hereafter, bendamustine hydrochloride; product name in Japan: TREAKISYM®) indicated for malignant lymphoma that was developed by Astellas Pharma GmbH (Germany), for which the Company concluded an exclusive development and marketing rights agreement for Japan in December 2005. With the development code SyB L-0501 (FD formulation), the Company began the phase I clinical trial in 2006 for indications for recurrent/refractory low-grade non-Hodgkin's lymphoma (NHL) and mantle cell lymphoma (MCL), and in 2010, it acquired manufacturing and marketing approval. It progressed licensing activities during this time, and in 2007, it expanded the target areas for the exclusive development and marketing rights in China, South Korea, Taiwan, and Singapore. Then with Eisai Co., Ltd. <4523> it concluded licensing agreements for Japan in 2008 and for South Korea and Singapore in 2009. The domestic licensing agreement with Eisai Co., Ltd. was terminated on the deadline of December 9, 2020, and the Company transitioned to its own sales system. In addition, the Company terminated the marketing agreements for Asia during FY12/21.

The Company launched TREAKISYM® in the Japanese market in December 2010, and since then, the Company has progressed its development to expand its indications. It has made efforts to increase the number of patients for which TREAKISYM® is indicated. In 2016, the Company acquired marketing approval for chronic lymphocytic leukemia (CLL) and untreated (first line of treatment) low-grade NHL/MCL, and then in March 2021, it acquired approval for r/r DLBCL. In 2017, it concluded an exclusive development and marketing rights agreement for Japan with Eagle Pharmaceuticals, Inc. <EGRX> (U.S.) for the TREAKISYM® liquid type RTD formulation/RI administration (development codes: SyB L-1701/SyB L-1702)*. The Company obtained marketing authorization for the RTD formulation in September 2020, and has been working to switch from the FD formulation to the RTD formulation since 2021. Following the receipt of authorization for RI administration in February 2022, the Company is presently in the process of switching to RI administration.

> * The FD formulation, which the Company has purchased from Astellas Pharma up to the present time, has to be dissolved at a medical site at the time of use (which requires about 3 hours, including the adjustment time). But this work is not required with the liquid formulation, so it has the advantage of greatly reducing the burden placed on medical practitioners. Also, the only difference between the RTD formulation and the RI administration is the volume of diluted physiological saline, which is diluted to 250ml in the RTD formulation and to 50ml in the RI administration. Therefore, for the intravenous injection time, the RTD formulation takes the same time as the FD formulation, which is 60 minutes, but the RI administration reduces this to only 10 minutes, greatly reducing the burden on the patient.

Also, as the second in-licensed product, the Company concluded an exclusive development and marketing rights agreement in 2011 for Japan and South Korea with Onconova for rigosertib (development codes: SyB L-1101 (intravenous formulation) / SyB C-1101 (oral formulation)) as a development candidate indicated for myelodysplastic syndrome (MDS)*. Moreover, in September 2019, it concluded an exclusive global development, manufacturing, marketing, and licensing agreement with Chimerix for BCV for all viral diseases excluding smallpox. The features of BCV are that compared to cidofovir (CDV; unapproved in Japan), it has high antiviral efficacy and safety and is effective against a wide range of DNA viruses, and will become a mainstay drug for the Company.

> * MDS is a disease in which the patient cannot produce normal blood cells due to abnormalities in the hematopoietic stem cells in their bone marrow, causing a decrease in normal blood cells and symptoms such as anemia, infection, and hemorrhage. It is also an intractable disease that is highly likely to transition to acute myeloid leukemia, and frequently occurs in the elderly.

## History

| Date | Summary |
|---|---|
| March 2005 | Established SymBio Pharmaceuticals Limited at Minato-ku, Tokyo |
| December 2005 | Concluded a license agreement with Astellas Pharma GmbH (Germany) to acquire exclusive development and marketing rights in Japan for anti-cancer agent Bendamustine Hydrochloride |
| March 2006 | Obtained manufacturer's license (packaging, labeling and storage) from Tokyo Metropolitan Government |
| March 2007 | Concluded a license agreement with Astellas Deutschland GmbH (Germany) to acquire development and marketing rights in China, Taiwan, South Korea and Singapore for anti-cancer agent SyB L-0501 |
| August 2008 | Concluded a license agreement with Eisai Co., Ltd. to grant co-development and marketing rights in Japan for anti-cancer agent SyB L-0501 |
| March 2009 | Concluded sublicense agreement with Cephalon, Inc. (U.S.) to grant development and marketing rights in China for anti-cancer agent SyB L-0501 |
| May 2009 | Concluded a license agreement with Eisai to grant co-development and marketing rights in South Korea and Singapore for anticancer agent SyB L-0501 |
| September 2010 | Launched SYMBENDA® (generic name: bendamustine hydrochloride) in Singapore for the treatment of low-grade non-Hodgkin's lymphoma and chronic lymphocytic leukemia |
| October 2010 | Acquired manufacturing and marketing approval of anti-cancer agent for malignant lymphoma TREAKISYM® in Japan (launched in December 2010) |
| July 2011 | Concluded a license agreement with Onconova Therapeutics, Inc. for anti-cancer agents SyB L-1101/SyB C-1101 |
| October 2011 | Launched SYMBENDA® (generic name: bendamustine hydrochloride) in South Korea for the treatment of chronic lymphocytic leukemia and multiple myeloma |
| October 2011 | Listed on Osaka Securities Exchange JASDAQ Growth Market |
| February 2012 | Launched INNOMUSTINE® in Taiwan for the treatment of low-grade non-Hodgkin's lymphoma and chronic lymphocytic leukemia |
| October 2015 | Concluded a licensing agreement with The Medicines Company (U.S.) to acquire exclusive development and marketing rights in Japan for post-operative, self-administered pain-management medication, SyB P-1501 (the agreement ended in November 2017) |
| May 2016 | Established SymBio Pharma USA, Inc. at Menlo Park, California, USA |
| August 2016 | Acquired manufacturing and marketing approval of anti-cancer agent for malignant lymphoma TREAKISYM® in Japan for the additional indication of chronic lymphocytic leukemia |
| December 2016 | Acquired manufacturing and marketing approval of anti-cancer agent for malignant lymphoma TREAKISYM® in Japan for the additional indication of first-line treatment of low-grade non-Hodgkin's lymphoma and mantle cell lymphoma |
| September 2017 | Concluded a license agreement with Eagle Pharmaceuticals, Inc. to acquire development and marketing rights in Japan for bendamustine liquid formulations (RTD formulation and RI administration) *RTD: Ready-to-dilute, RI: Rapid Infusion |
| October 2017 | Filed for arbitration for damages against The Medicines Company (U.S.) due to the non-fulfillment of the licensing agreement |
| July 2018 | TREAKISYM® was newly listed as the standard treatment for malignant lymphoma in the 2018 edition of the Japan Society of Hematology's Guidelines for the Treatment of Hematopoietic Tumors, |
| September 2019 | Concluded an exclusive global license agreement with Chimerix Inc. (U.S.) concerning the rights to develop, manufacture, and commercialize the antiviral drug, brincidofovir (excluding smallpox) |
| September 2020 | In the final arbitration ruling for the claim for damages filed against The Medicines Company (U.S.) due to the non-fulfillment of a licensing agreement, the Company will receive from the Medicines Company 50% of its expenses relating to the arbitration proceedings, including attorneys' fees. |
| December 2020 | Start of own sales of TREAKISYM® |
| January 2021 | Concluded a joint research agreement with The Institute of Medical Science, The University of Tokyo to search for new indications for bendamustine and rigosertib |
| March 2021 | Submitted an IND application to the FDA in the U.S. for a global joint clinical trial indicated for adenovirus infections (in infants) after hematopoietic stem cell transplantation |
| March 2021 | Acquired marketing approval for a TREAKISYM® and rituximab combination therapy (BR therapy) and TREAKISYM®, rituximab, and polatuzumab vedotin combination therapy (P-BR therapy) indicated for r/r DLBCL |
| April 2021 | Obtained marketing approval of the RTD formulation of TREAKISYM® for its use in BR and P+BR therapy for the treatment of r/r DLBCL |
| August 2021 | Reached First Patient In (FPI) in a phase II global joint clinical trial of BCV indicated for adenovirus infections after hematopoietic stem cell transplantation |
| February 2022 | Obtained approval for a partial change to the manufacturing and marketing approval for the RI administration of TREAKISYM® |
| June 2022 | Submitted a clinical trial plan notification to the PDMA for a phase II global joint clinical trial of BCV indicated for patients with BKV infection after kidney transplantation (also submitted to the TGA of Australia in August 2022) |

Source: Prepared by FISCO from the Company's securities report and website

# Trends in the development pipeline

## TREAKISYM® achieved growth through expanded indications to r/r DLBCL and increased market share, but trends in generic drugs emerged as risk factors

### 1. TREAKISYM® (generic name: bendamustine hydrochloride)

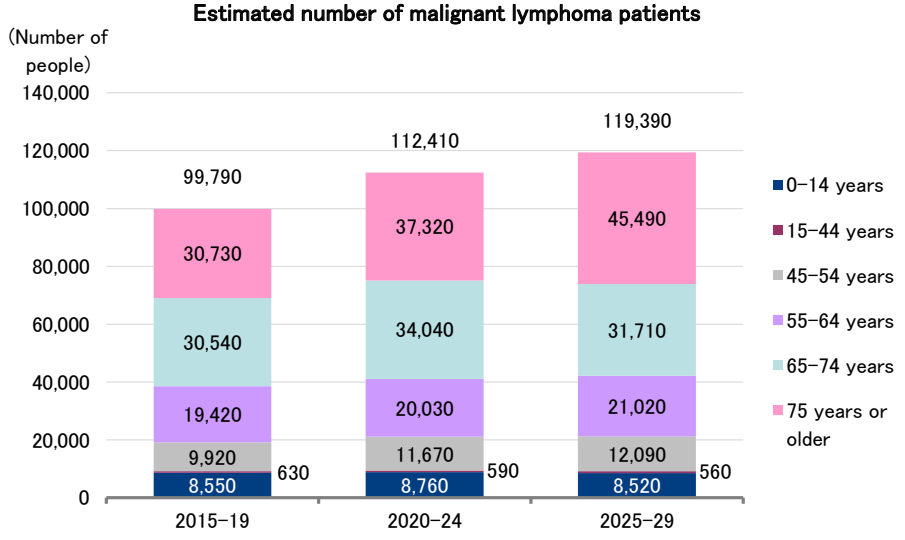
TREAKISYM® is an anticancer agent for malignant lymphoma. Malignant lymphoma is a disease in which lymphocytes, which are a type of white blood cell, undergo canceration (tumorification) and lumps (masses) can grow in lymph nodes distributed throughout the body and organs other than lymph nodes (such as the stomach, intestines, thyroid, spinal cord, lung, liver, skin, and eyes). It is the most frequent disease among blood cancers, with patients in Japan surpassing 30,000 annually, and the number of patients requiring treatment is predicted to increase gradually going forward as the elderly population grows. Malignant lymphoma is mainly divided into Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL), with about 90% of cases in Japan being NHL. It is classified into low-grade, medium-grade, and high-grade according to the progression rate of the symptoms, and there are various disease types.

**Types of non-Hodgkin's lymphoma**

| Type according to grade | Non-Hodgkin's lymphoma type (disease type) |
|---|---|
| Low grade: Indolent lymphoma (progresses yearly) | Follicular lymphoma (grade 1, 2), MALT lymphoma, lymphoplasmacytic lymphoma<br>Mycosis fungoides, Sezary syndrome, chronic lymphocytic leukemia / small lymphocytic lymphoma, etc. |
| Medium grade: Aggressive lymphoma (progresses monthly) | Follicular lymphoma (grade 3), mantle cell lymphoma, diffuse large B-cell lymphoma<br>Peripheral T cell lymphoma, extranodal NK / T cell lymphoma, adult T cell leukemia / lymphoma (chronic type), etc. |
| High grade: Highly aggressive lymphoma (progresses weekly) | Burkitt's lymphoma, acute lymphocytic leukemia / lymphoblastic lymphoma<br>Adult T-cell leukemia / lymphoma (acute type, lymphoma type), etc. |

Source: Prepared by FISCO from National Cancer Center Japan materials

**Estimated number of malignant lymphoma patients**




Note: Number of patients who required treatment during these periods
Source: Estimations by the Company based on cancer information service data from the National Cancer Center Japan

**(1) Expansion of indications**

As its sales strategy for TREAKISYM®, the Company has been working to sequentially expand its indications. It acquired marketing approval for recurrent/refractory low-grade non-Hodgkin's lymphoma (NHL) and mantle cell lymphoma (MCL) in October 2010, chronic lymphocytic leukemia (CLL) in August 2016 and untreated (first line of treatment) low-grade NHL/MCL in December 2016. Also, in July 2018, TREAKISYM® and rituximab combination therapy (BR therapy) was newly listed in the Japan Society of Hematology's Guidelines for the Treatment of Hematopoietic Tumors, and it has come to be recommended as the standard treatment option for all indications for which it has been approved. So TREAKISYM® has come to be positioned as the standard treatment for malignant lymphoma in both name and reality.

Other than the above, for CD20-positive follicular lymphoma (FL), which is a typical type of low-grade NHL, the Company acquired approval in July 2018 for partial changes relating to combination use with a new anti-CD20 antibody formulation, in addition to rituximab, and combination therapy with obinutuzumab*1 was added as a therapy option. Furthermore, in March 2019, it acquired approval for partial changes relating to pre-treatment with tumor-specific T-cell infusion therapy*2, and for the first time in Japan, TREAKISYM® can be used as a pre-treatment for the CAR T-cell therapy*3 Kymriah® intravenous drip*4.

*1 Obinutuzumab (GAZYVA®; sold by Chugai Pharmaceutical Co., Ltd. <4519>): similar to rituximab, which is recommended in the treatment guidelines domestically and overseas as a therapeutic drug for NHL, it is a glycosylated modified type II anti-CD20 monoclonal antibody that binds to CD20, a protein that expresses on B cells other than stem cells and plasma cells, and it directly attacks and destroys the B cells it targets together with the body's immune system.

*2 Tumor-specific T-cell infusion therapy: a therapy administered to patients after artificially applying and multiplying cancer specificity outside the body to the cancer patient's own T cells (a type of lymphocyte).

*3 CAR T-cell therapy (chimeric antigen receptor T-cell therapy): among tumor-specific T-cell infusion therapies, this is a therapy to introduce, amplify, and infuse into the gene-coding T cells the chimeric antigen receptors (CAR) that combine the antigen-binding site of the antibody that recognizes the membrane antigen on the tumor cell and the T-cell receptor's intracellular domain.

*4 Kymriah® intravenous drip (generic name: tisagenlecleucel): sold by Novartis Pharma KK as the first CAR-T therapy approved in Japan. In March 2019, it acquired manufacturing and marketing approval indicated for recurrent/refractory CD19-positive B cell acute lymphoblastic leukemia (B-ALL) and recurrent/refractory CD19 positive DLBCL.

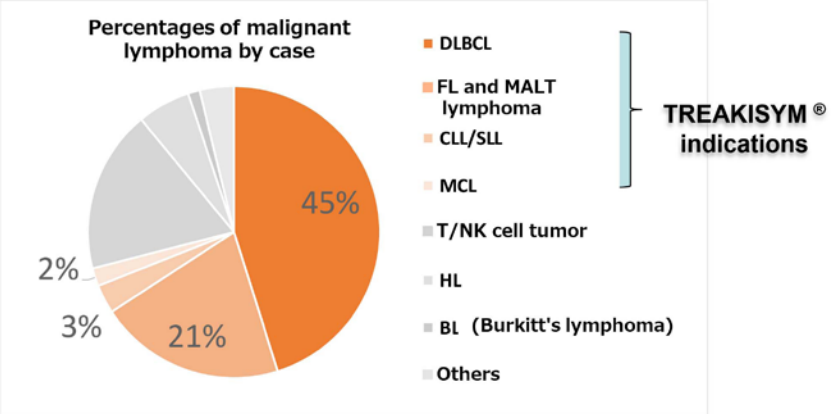
Then in March 2021, it announced the acquisition of marketing approval for r/r DLBCL *1. In addition to the combination therapy (BR therapy) with rituximab developed by the Company, the combination therapy with polatuzumab vedotin (P-BR therapy)*2 developed by Chugai Pharmaceutical Co., Ltd. <4519> was also approved. Through these marketing approvals, the number of patients TREAKISYM® is indicated for has greatly expanded (actual sales started from 2Q FY12/21).

*1 The standard treatment for untreated DLBCL is to provide a combination therapy of rituximab and chemotherapy, but recurrence is seen in approximately 40% of patients. Also, autologous stem cell transplantation (ASCT) is recommended as one treatment for r/r DLBCL, but for approximately half of patients, the relief chemotherapy provided prior to ASCT is not successful and ASCT cannot be provided. Moreover, there are many patients for whom ASCT is not suitable as a treatment, such as due to their age or complications, and it has yet to be established as the standard treatment.

*2 Polatuzumab vedotin: an anti-CD79b antibody drug compound developed by Roche <ROG>using the antibody drug conjugate technologies of Seattle Genetics Inc. (U.S.), in which humanized anti-CD79b monoclonal antibodies and tubulin polymerization inhibitors are combined with a linker. CD79b proteins are expressed specifically on many B cells, and this is a promising target in terms of developing new therapies. It is considered that polatuzumab vedotin binds with CD79b while suppressing the effects on normal cells and destroys B cells through the delivered chemotherapy agent.

Trends in the development pipeline

Details of malignant lymphomas




Source: Prepared by SymBio Pharmaceuticals based on Chihara D, et al. Br J Haematol 164:536-545,2014

Source: Reprinted from the business plan and items relating to growth potential

The results of the phase III clinical trial for BR combination therapy indicated for r/r DLBCL announced by the Company were excellent, with a complete response rate of 47.4% and an overall response rate of 76.3%. In particular, it seems that medical specialists were surprised by the level of the complete response rate for persons aged 76 years and older, which was 36.4%. There was no effective treatment for r/r DLBCL until now, and a multi-drug combination therapy that combines multiple anticancer agents (3 to 6 types) was administered as relief chemotherapy. However, it had strong side effects and little effectiveness. For these reasons, it is highly likely that the use of BR therapy and P-BR therapy, which have few side effects and high effectiveness, will spread as the standard therapies and sales of TREAKISYM® are forecast to further increase due to an increase in the number of patients and growth in market share. The choice of whether to use BR therapy or P-BR therapy depends on the doctor's decision, based on factors such as the patient's symptoms and gene type*.

* In BR therapy, TREAKISYM® 120mg/m2 (body surface area) is administered once a day for 2 consecutive days, and then not administered for 19 days. This constitutes one cycle, and it is administered for a maximum of six cycles while observing the patient's condition. In P-BR therapy, the dosage is 90mg/m2.

**(2) RTD formulation /RI administration**

Sales of the RTD formulation, which is the TREAKISYM® liquid type, began in January 2021, and the full switch from the FD formulation was completed in December of the same year. The switching rate has advanced in stages, increasing from approximately 20% in March 2021 to slightly less than 50% by June, and increasing to slightly less than 60% as of September. This was mainly because sales were started initially for existing indications except for r/r DLBCL, but it acquired marketing approval for r/r DLBCL in April 2021, so it can now be sold for all existing indications.

The Company also received marketing approval for RI administration in February 2022. As of the end of September 2022, it had confirmed that more than 94% of the medical institutions with which it conducts business intend to switch to RI administration, and expects that the switch will be almost fully completed sometime around March 2023. RI administration reduces the infusion time from the original 60 minutes to 10 minutes, thereby making it possible to significantly reduce the burden on healthcare professionals and patients. In particular, outpatients can be treated in a shorter time period, providing them with a major advantage. Therefore, at FISCO we believe that there is a high likelihood that the use of RI administration will spread even more at medical facilities conducting multi-drug combination therapy, leading to growth in market share.

**Sales progress of TREAKISYM®**

| Drug | Indication | Progress |
|---|---|---|
| SyB L-0501<br>(FD lyophilized powder formulation) | r/r low-grade NHL/MCL<br>CLL<br>First-line low-grade NHL/MCL<br>r/r DLBCL | Marketing approval in October 2010<br>Marketing approval in August 2016<br>Marketing approval in December 2016<br>Marketing approval in March 2021 |
| SyB L-1701<br>(RTD liquid formulation) | Already approved indications | Marketing approval in September 2020<br>(Marketing approval for relapsed and refractory DLBCL in April 2021) |
| SyB L-1702<br>(RI liquid formulation) | Already approved indications | Marketing approval in February 2022 |

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

### (3) Impact of generic drugs

In February 2022, it was announced that four companies (TOWA PHARMACEUTICAL CO., LTD. <4553>, Pfizer Japan Inc., Meiji Seika Pharma Co., Ltd., and KOA ISEI CO., LTD.) had received marketing approval for generic drugs using the RTD formulation of the brand-name drug. Of these companies, TOWA PHARMACEUTICAL CO., LTD. and Pfizer Japan Inc. have announced that they received marketing approval for RI administration in November 2022. There are three indications, which are low-grade NHL/MCL, recurrent/refractory DLBCL, and pre-treatment with tumor-specific T-cell infusion therapy. This means that with the exception of CLL, the generic drugs will cover all of the indications of the brand-name drug. Following on from the launch of sales by TOWA PHARMACEUTICAL CO., LTD. in June 2022, Pfizer Japan Inc. launched sales in December 2022. Although generic drugs had almost no impact on the Company's sales through 1H FY12/22, there could be an impact in the future because the drug price of the generic drugs is set at a low level of approximately 43% of the brand-name drug and Pfizer Japan Inc. has launched sales. Eagle, which is the original developer of the brand-name drug, holds a formulation patent and several use patents related to the RTD formulation and RI administration. The Company, which holds exclusivity rights for these patents domestically, had sent a written notification to the four companies regarding its concerns over potential patent infringement. On December 16, 2022, the Company filed a lawsuit against TOWA PHARMACEUTICAL CO., LTD., which had begun advance sales, in the Tokyo District Court, on the grounds that it had infringed upon the relevant patents. Specifically, the Company is claiming an injunction against the manufacture and sale of the generic drugs and compensation for damages based on patent infringement. Thereafter, the Company also filed a similar lawsuit against Pfizer Japan Inc. on December 26, 2022.

The formulation patent for RTD formulation determines the density of components (bendamustine, glycol, and antioxidants) and the component ratio, among other things. Although the components of the generic drugs made by the four companies differ from what is listed in the patent, it is not necessarily the case that this difference alone clears them of patent infringement, and it appears that judgement will be made based on a comprehensive view including use patents. In fact, in the U.S., Mylan <MYL> and three other companies had tried to sell generic drugs for RTD formulation, but at a trial held in August 2021, the court ruled in favor of Eagle and declared that its patent was valid until 2031. However, it cannot be denied that a different ruling may possibly be made in Japan, so the Company must be mindful of business risks. Although RTD formulation/RI administration are products subject to price maintenance premiums*, and the prices are being maintained, if sales of generic drugs are launched, it is possible that they will no longer be applicable starting from FY2023, the next drug price revision year, and that the price of the drugs will be reduced.

* Price maintenance premiums (premium to promote the development of new drugs and eliminate off-label use) are premiums applied to new drugs that meet certain criteria during the period of drug price revisions. This is a system in which drug prices are maintained or made difficult to lower until the patents expire in an aim to promote the creation of innovative new drugs and the development of unauthorized or off-label drugs.

**(4) Future development plans**

For TREAKISYM®, the Company is advancing joint research with academia to search for new indications, and its policy is to work to further increase business value. Specifically, in January 2021 it concluded a joint research agreement with The Institute of Medical Science, The University of Tokyo, and they are conducting research into new treatments through possible developments not only for blood cancer, but also for solid cancers and other types of cancer, and also through combinations with other drugs, while utilizing AI technologies. In addition, in August of the same year it concluded a joint research agreement with Kyoto University, and they are progressing research into its inhibitory effect on LUBAC, which it has been suggested is involved in refractory activated B cell type (ABC) DLBCL. Furthermore, the Company started an investigator-led phase II clinical trial indicated for autologous hematopoietic stem cell transplantation in patients with r/r DLBCL through BR therapy at Saitama Medical University in January 2022.

## The growth potential for BCV has increased significantly as the possibilities for development have expanded to conditions such as malignant lymphoma, brain tumors, and multiple sclerosis, in addition to viral infectious diseases

### 2. Brincidofovir (BCV) (intravenous formulation/oral formulation)

**(1) Overview and licensing agreement**

BCV's features are that it can provide a higher antiviral activity and efficacy than cidofovir (CDV), which is known as a treatment of cytomegalovirus (CMV) retinitis, and that it exhibits antiviral activity against a wide range of DNA viruses. Moreover, academic research has uncovered that BCV has high anti-cancer activity, and it is gaining attention as a development candidate to enhance a niche area with high unmet medical needs where treatments have not yet been established.

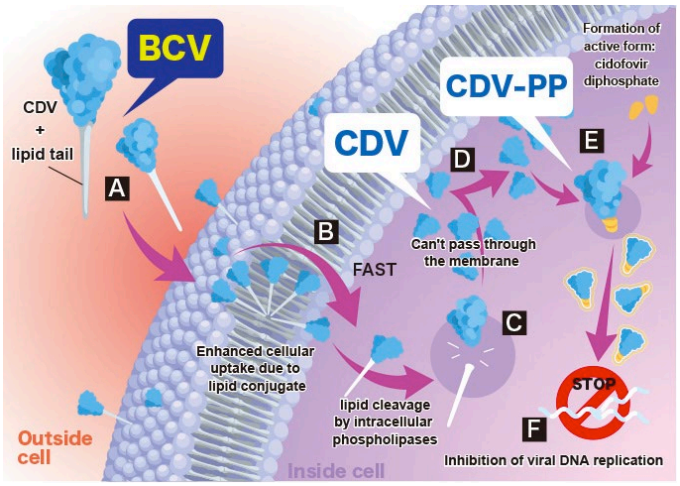
**Comparison of antiviral activity (EC50)**

| Virus | BCV | CDV | Maribavir | Letermovir | Ganciclovir | Foscarnet | Acyclovir |
|---|---|---|---|---|---|---|---|
| ADV | 0.02 | 1.3 | - | >10 | 4.5-33 | Inactive | >100 |
| BKV | 0.13 | 115 | - | - | >200 | Inactive | >200 |
| EBV | 0.03 | 65.6 | 0.63 | >10 | 0.9 | <500 | 6.2 |
| CMV | 0.001 | 0.4 | 0.31 | 0.005 | 3.8 | 50-800 | >200 |

Note: EC50 (the concentration at which a drug or antibody shows a 50% maximum response from the lowest value) indicates that the lower the value, the higher the activity. BCV possesses high antiviral activity for all viruses.
Source: Prepared by FISCO from the Company's results briefing materials

BCV has a structure that conjugates a lipid chain into CDV, which allows for more efficient uptake of BCV into cells than CDV alone. Once inside target cells, the lipid chain is cleaved, releasing CDV, which is then converted to its active form of cidofovir diphosphate (CDV-PP), which fulfills the role of inhibiting viral DNA replication. Data obtained from in vivo tests and other studies shows that BCV has a much higher antiviral replication effect than CDV and other antiviral drugs through these action mechanisms. In terms of the safety profile, CDV has risks for side effects such as strong nephrotoxicity, including renal dysfunction caused by the accumulation of CDV in renal tubular epithelial cells. However, because the lipid conjugation of BCV brings no accumulation of CDV in renal tubular epithelial cells, BCV has the outstanding feature of reducing the risk of nephrotoxicity associated with CDV. CDV has been granted fast-track designation by the FDA for the prevention of cytomegalovirus and the treatment of adenovirus, while in Europe, the EMA has granted orphan drug designation for the same viruses.

How BCV works




Source: Reprinted from the Company's website

Chimerix had been developing an oral formulation of BCV, but it discontinued development because it did not obtain statistically significant results in the phase III clinical trials, and as there were some side effects, including diarrhea. Subsequently, Chimerix was looking for a partner to whom it could out-license BCV to concentrate its management resources in the anticancer agent field, and in September 2019, the Company and Chimerix concluded a licensing agreement for the global manufacture, marketing and development (excluding smallpox) of BCV. The key point for the Company's decision to in-license BCV was that it has excellent safety and functionality (high antiviral activity against a wide range of viruses), and it judged that its development was highly likely to be a success. Also, its target diseases are "rare diseases," and "niche areas with high unmet medical needs," are not only consistent with the Company's development targets, but are also the same blood disease areas targeted by TREAKISYM®, so it judged that synergies for sales would be easier to obtain.

In terms of the reason why Chimerix failed to develop an oral formulation, the Company thinks that as the drug absorption rate from the digestive organs was low, it was necessary to administer a large dosage. The Company believes that an intravenous formulation could have the same effect as an oral formulation at just 10% of the dosage, so it thinks there is a lower risk of side effects and a higher probability of success. The agreement covers not only an intravenous formulation, but also an oral formulation, allowing for the possibility of developing the oral formulation in the future. Of the viral infectious diseases, the reason why smallpox alone is excluded from the agreement is that the U.S. government needs to maintain its ability to manufacture and stockpile a smallpox treatment independently within the country as a measure to counter bioterrorism*.

* In June 2021, Chimerix announced that the U.S. FDA approved its New Drug Application (NDA) for BCV Oral as a medical countermeasure for smallpox.

This licensing agreement is noted for being a global licensing agreement and for covering manufacturing rights. The use of a licensing agreement covering manufacturing rights stems from a TREAKISYM® quality defect issue that occurred in 2019. The Company understands that controlling manufacturing rights on its own and constructing systems to limit business risks to the best of its ability benefit all stakeholders, including patients, and is critical in order to aim for growth as a global specialty pharmaceutical company. The Company has already found a manufacturing contractor, and when the chances for launching the product become clear, the Company intends to transfer the technology and outsource manufacturing to the contractor.

Target indications of these developments include viral infections after hematopoietic stem cell transplantation or organ transplantation, and based on university research findings, the Company indicates its intention to advance development of EBV* positive lymphoma, glioblastoma stemming from CMV infection, and multiple sclerosis, an intractable disease which has been revealed to largely be caused by EBV. In October 2021, the Company commenced operations of SymBio Pharma USA, which will serve as an integrated development base in the U.S. (the company was established in 2016, but had been in a dormant state). The Company hired a talented individual with the expertise and experience to smoothly advance clinical trials on a global scale as the vice president. It plans to double its workforce in 2023 from roughly 10 (including 5 full-time employees) as of September 2022 and to enhance its development systems.

> * EBV is a type of herpes virus. EBV is known for infecting roughly 50% of five-year olds and nearly 95% of adults. In infancy or early childhood, nearly all EBV infections are asymptomatic. EBV infections can cause transitory symptoms such as fever, sore throat, and swollen lymph nodes beginning in adolescence. EBV typically infects B lymphocytes and lies hidden within the cell, inactive, but becomes active due to some sort of environmental change. It has been found that EBV is linked to the onset of certain cancers, including some lymphomas and nasopharyngeal cancer.

Furthermore, in relation to the BCV licensing agreement, the Company paid a lump-sum contract payment of $5 million USD (approx. ¥540mn) to Chimerix, the original developer, in FY12/19. According to the agreement, as a future milestone, the Company will pay a maximum of $180 million USD (approx. ¥19.4bn) as a two-digit royalty payment corresponding to net sales of goods.

**(2) Development plans**

**a) Adenovirus infections after hematopoietic stem cell transplantation**

For the initial development target of BCV (formulation), the Company initiated a phase II global joint clinical trial in August 2021 indicated for infants (but including adults) with adenovirus infections after hematopoietic stem cell transplantation (scheduled number of patients: 24 cases) in the US. Adenovirus is a naturally existing virus that causes infectious diseases such as pharyngitis, tonsilitis, conjunctivitis, gastroenteritis, and hemorrhagic cystitis through the infection of areas including the respiratory organs, eyes, intestines, and urinary organs. Although cases of able-bodied individuals developing serious complications after being infected are rare, there is a high risk of serious complications when patients' immunity is lowered after hematopoietic stem cell transplantation, and there are still no treatments, so there is a strong desire for the development of treatments or preventative drugs. Every year, there are 35,000 cases of hematopoietic stem cell transplantation around the world, among which there are approximately 2,000 patients infected with adenovirus (Source: Bone Marrow Transplantation 2016, Bone Marrow Transplantation 2019).

In the phase II clinical trial, drug dosage is divided into four groups, and aspects such as safety, tolerability, and efficacy are evaluated and the recommended dosage for the next trial is determined. As of November 2022, the trial has advanced to Group III, with the trial expected to be completed sometime around spring 2023. If the trial progresses smoothly, it is predicted that the Company could start talks with the FDA in the second half of 2023 and enter phase III clinical trials in 2024. Furthermore, if the results of the phase II clinical trial confirm a high efficacy, it is also possible that the Company will conclude a partner agreement and advance to the phase III clinical trial.

**b) BK virus (BKV) infections after kidney transplantation**

As the second pipeline, the Company has started phase II global joint clinical trials indicated for BKV* infections after kidney transplantation. On December 13, 2022, the Company began dosing its first patient in Australia, with plans to advance the trial in Australia, Japan, and South Korea. The planned number of cases is 36. The trial will confirm safety, tolerability, and efficacy (changes in BKV levels in blood plasma after administration), as well as determine the suggested dosage for the next trial. The trial period is scheduled to last approximately two years.

> * BKV is a DNA virus that belongs to the polyomavirus family. For BKV, nearly 100% of even able-bodied individuals are infected during infancy, and although there are no notable symptoms as long as the individual is in healthy condition, in a state where immunity is lowered after organ or bone marrow transplantation, the virus becomes active, causing illnesses such as hemorrhagic cystitis and interstitial nephritis. Furthermore, if symptoms worsen, there are even cases in which failure of the newly transplanted kidney occurs and the organ is lost.

Kidney transplantation is the only definitive treatment for end-stage renal disease. It is FISCO's view that the number of patients worldwide who require transplantation surgery is approximately 100,000. Because immunity is lowered following kidney transplantation, cases of infection are frequent; the incidence rate is less than 15% for BKV, less than 20% for CMV, and less than 10% for the varicella-zoster virus. There are 8,000 patients with BKV infections every year (Source: International Report on Organ Donation and Transplantation Activities Executive Summary 2019, April 2021 & Transplantation 2012). Currently, immunosuppressive drugs and CMV anti-infective agents are prescribed as symptomatic therapy, but the results are limited, so BKV infection is a disease with a high level of unmet medical needs for which treatment has yet to be established. For this reason, the early development of an effective therapeutic medicine is desired.

**Potential needs for kidney and liver transplantation**

(Unit: people)

| | U.S. | EU | Japan | Other countries | Total |
|---|---|---|---|---|---|
| Kidney transplantation | 39,515 | 28,053 | 1,827 | 30,702 | 100,097 |
| Liver transplantation | 13,070 | 10,754 | 395 | 11,565 | 35,784 |

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

**c) EB virus (EBV) positive lymphoma**

As the third BCV pipeline, clinical trials for EBV positive lymphoma are increasingly anticipated to begin in 2023. This is because animal testing conducted by the National Cancer Center Singapore (NCCS), with whom the Company concluded a joint research agreement in September 2021, has confirmed clear anti-tumor activity against EBV positive NK/T-cell lymphoma*1. The principal investigator of the study announced the study's findings at the American Society of Hematology (ASH) Annual Meeting held in December 2022. In NK/T-cell lymphoma, a rapidly progressing form of lymphoma, for which no effective treatment is currently available, the study confirmed for the first time that BCV suppressed the expression of MYC*2, an oncogene that contributes to tumor malignancy, and the expression of a dominant gene cluster, and that BCV induced immunogenic cell death which is known to activate cancer immunity. In addition, BCV showed clear tumor growth inhibitory effect in a mouse model in which the tumor was transplanted. The principal investigator of the study said: "In this joint research, the anti-tumor activity of BCV against NK/T-cell lymphoma was newly confirmed. BCV has the potential to become a new therapeutic agent in the field of oncology, including lymphoma." This joint research suggests the possibility of expanding the areas targeted for BCV development. Malignant lymphoma is also a TREAKISYM® target disease. Therefore, if the Company succeeds in developing BCV, synergies can be expected, bringing even greater attention to future development trends.

*1 NK/T-cell lymphoma is a type of malignant lymphoma that originates from NK or T cells. NK/T-cell lymphomas are classified as low-grade (progressing yearly), intermediate-grade (progressing monthly), or high-grade (progressing weekly). They mainly present in the perinasal space or on the skin. This disease is characterized by its relatively high prevalence in Southeast Asia, including China.

*2 MYC, also known as c-Myc, is one of the oldest oncogenes, and abnormalities of this family of genes have been found in a wide range of cancer types, including translocations, mutations, and amplifications in hematopoietic tumors. It functions as a nuclear transcriptional regulator and is known to be a very important factor that controls the balance of proliferation and differentiation of hematopoietic cells by regulating the expression of dominant genes.

**d) CMV infection in brain tumors (GBM)**

The Company has announced that a non-clinical study has been conducted since September 2021 to investigate anti-tumor efficacy against brain tumors at the Brain Tumor Center within the Department of Neurological Surgery at the University of California, San Francisco in the U.S. Additionally, in March 2022, the Company also announced the initiation of a non-clinical study to investigate anti-tumor efficacy against brain tumors associated with CMV infections in collaboration with Brown University in the U.S.

There are approximately 30,000* incident cases of GBM (glioblastoma), which has a particularly high degree of malignancy among brain tumors, and CMV infections are discovered in nearly half of those cases. The reactivation of CMV causes inflammation in cells, and creates a hypoxic state, thereby increasing the VEGF which is a growth factor related to the formation of new blood vessels, and it has been indicated that this may accelerate the multiplication of cancer cells. The standard treatments for GBM are surgical operations, radiation therapy, and chemotherapy, but the average life expectancy is between 15 to 20 months, and the survival rate after five years is extremely low at under 5%, so it is becoming a field where there is a strong desire for the development of effective treatments. Although there are many GBM treatments in development, there are none which target both CMV and brain tumors, so if BCV is proven to be effective, it is predicted that its market value will increase further. The Company is examining the results of the two non-clinical studies under way at U.S. universities and working to determine whether or not it will progress to clinical trials.

* Company estimates based on GlobalData: Forecast of incident cases of GBM in US, 5EU, China and Japan (2027).

**e) Multiple sclerosis**

Research in recent years has found that EBV is involved in the cause behind the onset of multiple sclerosis, an intractable disease. Developing BCV as a treatment for this disease is now emerging as a possibility. Multiple sclerosis is one type of neurological disease that causes functional impairments in areas such as the brain, spinal cord, and optic nerve due to inflammation of the central nervous system or optic nerve for some reason or another. As resurgence and remission occur over and over in repeated cycles, vision, limb functions, and cognitive abilities will decline if symptoms develop further. There are many patients in North America and Europe, with approximately 3 million people around the world and approximately 18,000 in Japan.

Multiple items are being sold as treatments, with some predicting that the scope of overall sales of these treatments will grow from $24.0bn in 2021 to a scale of more than $30.0bn in 2027. However, because the cause of onset is unclear, there are only symptomatic treatments to prevent remission and hold back the progression of the disease, and root treatments have not yet been developed. For this reason, even now many companies are advancing development.

Against this backdrop, in August 2022, the Company entered into a collaboration agreement with the National Institute of Neurological Disorders and Stroke (“NINDS”), part of the National Institutes of Health (NIH) in the U.S., for the transfer of materials related to BCV. The purpose of the agreement is to conduct non-clinical studies to evaluate the potential antiviral activity of BCV against EBV, eyeing future development activities in the multiple sclerosis area. The studies will investigate how the progression of the disease changes by suppressing the activity of EBV with BCV. If positive results are obtained, it is highly likely that the Company will move forward with clinical trials. Given the large size of the market, BCV is expected to garner even greater interest.

**f) Polyomavirus infection**

In November 2022, the Company entered into a Material Transfer Agreement (MTA) for BCV materials with Penn State College of Medicine and started a non-clinical study to evaluate the efficacy of BCV in a mouse model of polyomavirus infection*. Polyomaviruses are known to cause serious diseases through their infection. As existing antiviral drugs show little efficacy, the development of an effective treatment is eagerly awaited, and future trends will be watched all the more closely.

> * Normally, polyomavirus infections such as BKV and JCV are asymptomatic. However, when the body’s immune system is significantly compromised for some reason, these viruses are reactivated and manifest as severe infections in the infected tissues (primarily in the genitourinary system, central nervous system, and hematopoietic cells).

**g) Cranial nerve diseases**

In December 2022, the Company announced that it has entered into a Sponsored Research Agreement (SRA) with Tufts University in the U.S. to conduct a non-clinical study that will evaluate the efficacy of BCV in a herpes simplex virus (HSV) infection model. Some DNA viruses such as HSV are directed against cranial nerve tissues and are known to cause serious diseases in various cranial nerve areas due to infection caused by their reactivation. This research will test the potential utility of BCV against HSV infection and reactivation using human-induced neural stem cells in a three-dimensional bioengineered brain model. The goal of this study is to pave the way for the development of new treatment methods for cranial nerve diseases such as Alzheimer’s disease, for which no treatment method has been established yet. BCV may be able to suppress the onset and progression of these diseases by directly inhibiting the causative virus, so progress on future development is anticipated.

**Status of progress on brincidofovir (BCV) development**

| Drug | Indication | Progress |
|---|---|---|
| SyB V-1901 (Intravenous formulation) | Adenovirus infections in patients with immunodeficiency, including immunodeficiency after hematopoietic stem cell transplantation (children and adults) | Phase II global joint clinical trial being conducted (U.S. and UK) |
| | BKV infection after kidney transplantation | Phase II global joint clinical trial being conducted (Japan, Australia, South Korea) |
| | EBV positive lymphoma | Pre-clinical study being conducted in collaboration with National Cancer Center Singapore (NCCS) |
| | GBM from CMV infections | Pre-clinical study being conducted in collaboration with Brown University in the U.S. |
| | Multiple sclerosis | Pre-clinical study being conducted at NIH in the U.S. |
| | Polyomavirus infection | Pre-clinical study being conducted at Penn State College of Medicine in the U.S. |
| | Cranial nerve diseases | Non-clinical study being conducted at Tufts University in the U.S. |

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

**h) Underlying market value of BCV**

In terms of antiviral treatments, maribavir (LIVTENCITY) from Takeda Pharmaceutical Company Limited <4502> received U.S. marketing approval in November 2021 as a treatment for refractory or resistant CMV infection* after organ or hematopoietic stem-cell transplantation. According to estimates by Takeda Pharmaceutical Company Limited, every year approximately 200,000 adults around the world undergo transplantation surgery, and it is understood that roughly 25% of these people face the risk of CMV infection. With the number of indicated patients, including those with first-line CMV infections after hematopoietic stem-cell transplantation, at 25,000, Takeda Pharmaceutical Company Limited projects net sales to reach between $700 and 800mn USD during the peak of maribavir. The number of patients indicated for BCV, which this company develops, is approximately 40,000 when including patients with brain tumors from CMV infections, and if patients with multiple sclerosis, cranial nerve diseases such as Alzheimer's disease, EBV positive lymphoma, and GBM (glioblastoma) are also included, BCV could grow into a blockbuster drug with a potential market value far surpassing $1.0bn, so future trends will be watched closely.

* Four types of antiviral treatments (ganciclovir, valganciclovir, foscarnet, and cidofovir) are indicated for refractory or resistant CMV infections

Due to its potent antiviral action against a wide range of DNA viruses, BCV has attracted the attention of leading overseas academic institutions. In response to this high degree of interest, the Company has signed various joint research and material transfer agreements with these institutions beginning in 2021. This shows that on the R&D front, the Company has taken full advantage of its adoption of an external resource-based "no lab" strategy. It is anticipated that the Company will expand its development areas by continuing to foster joint research with academia.

## Exploring the possibilities of developing rigosertib through combinations with other drugs, including TREAKISYM®

**3. Rigosertib (intravenous formulation/oral formulation)**

Rigosertib is an anticancer agent candidate that has unique multi-kinase inhibitory action (which causes cancer cells to die by inhibiting the multiple kinases involved in cancer cell proliferation, invasion, and metastasis). Its licensor, Onconova, has conducted the phase III global joint clinical trials (INSPIRE trial) for myelodysplastic syndrome (MDS). In August 2020, it was announced that the primary endpoint had not been achieved in comparison to the doctor-selected therapy.

The Company is responsible for clinical development in Japan, and its policy is to search for new disease targets, including from the findings obtained from the INSPIRE trial's additional analysis. Specifically, through the joint research agreements concluded with the Institute of Medical Science, The University of Tokyo, and Gunma University, they are creating new treatments through combination therapies for bendamustine and rigosertib and their combined use with other existing drugs, and searching for new disease targets, including in treatment areas other than the oncology area, while utilizing AI technologies. There do not appear to be any major developments on this front at this time.

# Results trends

## In the 3Q FY12/22 results, sales and profits increased significantly through the increase in sales of TREAKISYM®

### 1. Summary of 3Q FY12/22 results

In the 3Q FY12/22 consolidated results, sales and profits increased significantly. Net sales increased 32.5% YoY to ¥7,355mn, operating profit rose 274.5% to ¥1,588mn, ordinary profit increased 344.8% to ¥1,843mn, and profit attributable to owners of parent rose 378.9% to ¥1,555mn.

**3Q FY12/22 results (cumulative)**

(¥mn)

| | 3Q FY12/21 (cumulative) | | 3Q FY12/22 (cumulative) | | YoY change | YoY % change |
|---|---|---|---|---|---|---|
| | Results (non-consolidated) | vs. net sales | Results (consolidated) | vs. net sales | | |
| Net sales | 5,553 | - | 7,355 | - | 1,802 | 32.5% |
| Gross profit | 4,045 | 72.9% | 5,466 | 74.3% | 1,420 | 35.1% |
| SG&A expenses | 3,621 | 65.2% | 3,877 | 52.7% | 256 | 7.1% |
| R&D expenses | 1,286 | 23.2% | 1,563 | 21.3% | 277 | 21.6% |
| Other SG&A expenses | 2,335 | 42.1% | 2,314 | 31.5% | -21 | -0.9% |
| Operating profit | 424 | 7.6% | 1,588 | 21.6% | 1,164 | 274.5% |
| Ordinary profit | 414 | 7.5% | 1,843 | 25.1% | 1,428 | 344.8% |
| Extraordinary profit | 0 | - | 106 | - | 106 | - |
| Profit attributable to owners of parent | 324 | 5.9% | 1,555 | 21.2% | 1,230 | 378.9% |

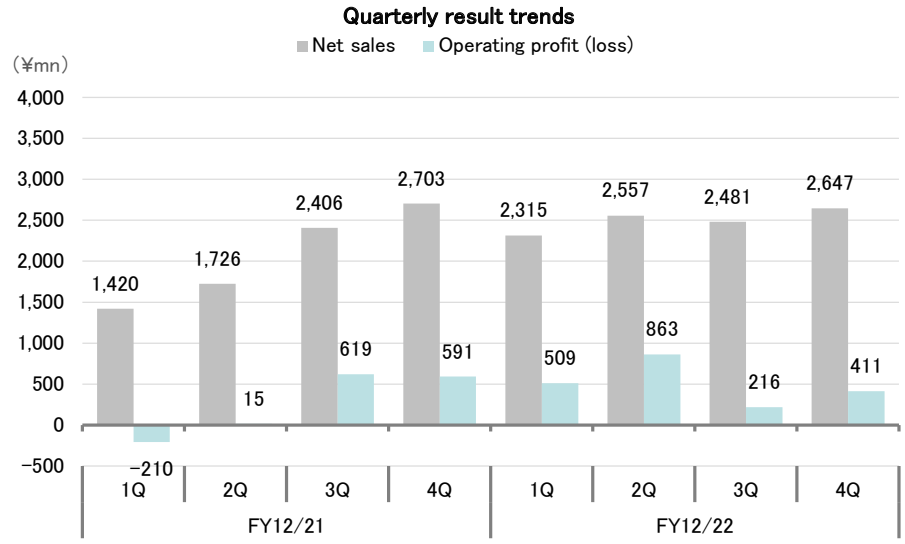
Source: Prepared by FISCO from the Company's financial results

The main reason for the increase in net sales was steady growth in the market share of TREAKISYM®, due partly to the approval of RI administration, which dramatically reduces the burden on patients and healthcare professionals, in addition to penetration of BR therapy and P-BR therapy for TREAKISYM®. The launch of sales of a generic product by one company seems to have had only a negligible impact.

The gross profit margin rose from 72.9% in the same period in the previous fiscal year to 74.3%. The Company recorded a sales milestone of ¥550mn under cost of sales in 3Q FY12/22. Excluding this impact, the gross profit margin would have been 81.8%, an increase of 8.9 percentage points. This increase was mainly due to the full switch from the FD formulation to the RTD formulation. In terms of the exchange rate, although the yen weakened rapidly in value, the impact was negligible because the Company had entered into foreign exchange forward contracts at just under ¥120 per U.S. dollar. Moreover, the TREAKISYM® sales milestone has concluded with the latest payment, and no further milestone payments will be incurred in the future.

Among SG&A expenses, R&D expenses increased 21.6% YoY to ¥1,563mn. The main reasons for this increase were increases in clinical trial expenses and joint research expenses related to BCV, along with costs at the Company's U.S. subsidiary. Other SG&A expenses decreased slightly by 0.9% to ¥2,314mn. The main reasons for this decrease were that sales activities for TREAKISYM® were shifted mainly online due to the spread of COVID-19, allowing the Company to reduce the number of CMRs (contract MRs) and that the Company worked to curtail other expenses. Non-operating income (expenses) improved ¥264mn YoY mainly owing to the recording of foreign exchange gains of ¥345mn in connection with the weaker yen.

Looking at how results trended on a quarterly basis, the Company recorded an increase in sales but a decrease in profits. In 3Q FY12/22, net sales rose 3.1% YoY to ¥2,481mn, while operating profit decreased by 65.1% to ¥216mn. Excluding the impact of the sales milestone, operating profit was firm, increasing 23.8% to ¥766mn.




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

# Cash on hand increased as the Company entered a monetization phase

### 2. Financial condition

As of the end of 3Q FY12/22, total assets were up ¥2,165mn compared to the end of the previous fiscal period to ¥10,618mn. Looking at the main change factors, in current assets, there were increases of ¥2,272mn in cash and deposits and ¥52mn in inventories. In non-current assets, there were decreases of ¥10mn in property, plant and equipment and ¥27mn in intangible assets in step with the recording of depreciation and amortization. In addition, deferred tax assets decreased ¥143mn.

Total liabilities were up ¥56mn compared to the end of the previous fiscal period to ¥1,763mn. The main change factors were an increase of ¥752mn in accounts payable-other, while there was no more provision for product changeover of ¥186mn, and a decrease in income taxes and consumption taxes payable. Moreover, net assets increased ¥2,108mn to ¥8,854mn. Retained earnings increased ¥1,464mn due to the recording of profit attributable to owners of parent. In addition, there were increases of ¥379mn both in share capital and capital surplus following the issuance of new shares and the 58th stock acquisition rights through a third-party allotment (CVI Investments, Inc.) conducted in June 2022. As a result, the equity ratio rose 5.9 percentage points, from 73.7% to 79.6%.

The exercise price of the stock acquisition rights is fixed at ¥785 and the number of dilutive shares is 2 million shares. The Company will allocate most of the ¥662mn procured through the issuance of new shares and the ¥1,568mn scheduled to be procured through the exercise of stock acquisition rights to development funds for BCV. It also plans to allocate some of the funds to new in-licensing and investment funds for M&As and other opportunities. Apart from this, at the end of March 2022, the Company renewed its syndicated loan (commitment line) agreement with three banks. The upper limit has been set at ¥3,150mn with the commitment period set to last until April 4, 2024. If there is a sudden need for funds, the Company's policy is to address the situation, even through borrowing from financial institutions.

**Balance sheet and management indicator**

(¥mn)

| | FY12/19 | FY12/20 | FY12/21 | 3Q FY12/22 | Change |
|---|---|---|---|---|---|
| Current assets | 4,887 | 5,815 | 6,747 | 9,095 | 2,348 |
| (Cash and deposits) | 3,910 | 3,848 | 3,860 | 6,133 | 2,272 |
| Non-current assets | 386 | 459 | 1,705 | 1,522 | -183 |
| Total assets | 5,273 | 6,274 | 8,452 | 10,618 | 2,165 |
| Total liabilities | 873 | 1,617 | 1,707 | 1,763 | 56 |
| (Interest-bearing debt) | - | - | - | - | - |
| Net assets | 4,400 | 4,657 | 6,745 | 8,854 | 2,108 |
| Management indicator | | | | | |
| Equity ratio | 71.7% | 64.3% | 73.7% | 79.6% | 5.9pt |

Note: Figures for FY12/21 and prior fiscal years are non-consolidated.
Source: Prepared by FISCO from the Company's financial results

# Outlook

## For its FY12/22 results, the Company expects continued increases in sales and profits due to growth in TREAKISYM®, and it aims to remain profitable in FY12/23

### 1. Outlook for FY12/22

For FY12/22 results, the Company has upwardly revised its forecasts announced in August 2022 at each profit level. The Company's forecast now calls for net sales to increase 21.1% YoY to ¥10,003mn, operating profit to increase 96.9% to ¥2,000mn, ordinary profit to increase 129.7% to ¥2,300mn, and profit attributable to owners of parent to decrease 18.8% to ¥1,650mn. The main reason for the increased forecast for operating profit is greater-than-anticipated progress on the streamlining of SG&A expenses. The forecast for ordinary profit was increased mainly because of the recording of foreign exchange gains.

**Outlook for FY12/22**

(¥mn)

| | FY12/21 | | FY12/22 (consolidated) | | | Change | % change |
|---|---|---|---|---|---|---|---|
| | Results (non-consolidated) | vs. net sales | Company forecast | Revised forecast | vs. net sales | | |
| Net sales | 8,256 | - | 10,003 | 10,003 | - | 1,746 | 21.1% |
| Operating profit | 1,016 | 12.3% | 1,770 | 2,000 | 20.0% | 983 | 96.9% |
| Ordinary profit | 1,001 | 12.1% | 1,750 | 2,300 | 23.0% | 1,298 | 129.7% |
| Profit | 2,032 | 24.6% | 1,480 | 1,650 | 16.5% | -382 | -18.8% |

Note: The Company forecasts for FY12/22 were announced in August 2022. The revised forecasts are based on figures announced in November 2022
Source: Prepared by FISCO from the Company's financial results

Net sales are expected to increase for three consecutive fiscal periods and reach an all-time high, as TREAKISYM® sales are continuing to perform firmly in 4Q FY12/22. The expected increase in sales is mainly supported by growth in sales of products for r/r DLBCL. Although monitoring net sales by target field is challenging, the Company estimates that sales of products for r/r DLBCL will be around ¥4.0bn in FY12/22, which is nearly double the level of sales in the previous fiscal year, given that sales began in earnest in 3Q FY12/21. Solid sales are also anticipated in other target fields. It appears that the impact of generic drugs has been limited.

The gross profit margin is forecast to rise from 70.2% in the previous period to around 76% (around 82% when excluding the impact of the sales milestone), because the switch to RTD formulation/RI administration has been fully completed since the beginning of the period. The exchange rate has been trending at around ¥140 per U.S. dollar, moving toward a weakened yen since the formulation of the plan when it was ¥110 per U.S. dollar. However, purchases from Eagle for the fiscal year under review have been hedged with the Company's U.S. dollar-denominated financial assets on hand and foreign exchange forward contracts (at just under ¥120 per U.S. dollar), so profits will largely be unaffected. For FY12/23, the Company has entered into foreign exchange forward contracts at just under ¥130 per U.S. dollar for the anticipated purchases. Purchase costs for TREAKISYM® and overseas development expenses for BCV are affected by foreign exchange rate movements. The Company estimates that an exchange rate movement of ¥1 per U.S. dollar will impact operating profit by approximately ¥20mn for the full year.

Among SG&A expenses, the Company projects R&D expenses to increase ¥764mn YoY to ¥2,500mn. The main factors behind this increase include expenses for BCV clinical trials in addition to the recording of expenses for the operation of its U.S. subsidiary that will serve as an integrated development base, and an increase in expenses for joint research with academia. The Company projects that other SG&A expenses will remain at around ¥3,100mn, mostly the same level as in the previous fiscal year. As a result of the streamlining of sales, the number of CMR personnel has decreased and will absorb other increases in expenses. The Company is forecasting a decrease in profit attributable to owners of parent because of a snapback decline from deferred tax assets recorded in the previous fiscal year.

The Company is currently formulating its results forecasts for FY12/23, and it aims to ensure positive operating profit. Generic drugs and drug price trends will be risk factors for net sales. However, the number of indicated patients has been increasing and product value has been rising as RI administration dramatically reduces the burden on healthcare professionals and patients. Considering these factors, the Company's market share in current target areas, which has remained at just under 50%, is expected to increase. Due in part to these positive factors, it is difficult to forecast the trend in net sales at this time.

Meanwhile, the Company anticipates an increase in expenses of just over ¥1.0bn to roughly ¥3.6bn. While there will be no more ¥550mn sales milestone, the increase in expenses is due in part to an increase in expenses for BCV clinical trials under R&D expenses, as well as plans to increase personnel at the subsidiary in the U.S. that will serve as its integrated development base. If a development project for AdV infection after hematopoietic stem cell transplantation enters phase III clinical trials within 2023, the Company will incur a development milestone payment of ¥550mn. Based on current progress, it is highly likely that this payment will be pushed back to 2024. In other SG&A expenses, the Company plans to continue to curtail these expenses in FY12/23.

## Advance development of BCV and aim for growth as a global specialty pharmaceutical company

### 2. Long-Term Strategy

In the long term, the Company is forming a policy to aim for growth as a global specialty pharmaceutical company. Specifically, in addition to initiatives aimed at expanded sales of TREAKISYM®, the Company's strategy involves establishing POC in multiple niche areas with high unmet medical needs through BCV, and expanding its overseas business while considering entering partnership agreements. As for BCV, in order to carry out a stable supply of high-quality products, the Company plans to maximize profit by conducting in-house manufacturing (manufacturing consignment) and also uncover fundamental business values contained by each pipeline while advancing joint research with academia and others, and bridging that to maximization of business values, while simultaneously working on enhancing pipelines by in-licensing new development candidates.

The Company has set "Local & Global" and "50 and 50 in 30" as the management keywords. These keywords signify taking a dramatic leap forward as a global pharmaceutical company by successfully guiding the development of BCV with the aim of increasing the percentage of total sales from overseas sales to 50% by 2030. At FISCO, we expect that the Company's corporate value will substantially improve if it succeeds at developing BCV as a treatment for viral infection after hematopoietic stem-cell transplantation or organ transplantation, and as a treatment for brain tumors or multiple sclerosis caused by viruses, and are focused on future development trends.

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