SymBio Pharmaceuticals Ltd

(4582 GROWTH) Issued July 14,2023

Aiming to become a truly global specialty pharma

2023 likely to be a climacteric

2023 is shaping up to be a critical year for SymBio, with the market for Treakisym®, long its major earner, starting to be eroded by generics. At the same time, in May 2023, brincidofovir (BCV), which SymBio has positioned as a pillar of future global expansion, has established POC for humans in is first indication (disseminated adenoviral infection after hematopoietic stem cell transplantation). Subsequent indications (BK virus infection after kidney transplantation, resistant/refractory CMV infection after hematopoietic stem cell transplantation or organ transplantation) are also providing opportunities to promote in-house development. Additionally, in 2023 SymBio has concluded cooperative research and development agreements (CRADA) with two institutes within the National Institutes of Health (NIH), the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of Allergy and Infectious Diseases (NIAID). This means that research can be pursued using the US national budget, and facilities, intellectual property, and human resources owned by NINDS and NIAID. That is why CRADA can only be concluded for projects that may lead to a paradigm shift, concluding these two CRADA is quite epoch-making. SymBio retains sole ownership of any licenses stemming from the research results.

BCV market estimated at JPY45 billion

The BCV market for disseminated adenoviral infections after hematopoietic stem cell transplantation, which is expected to be launched in 2028, is estimated at JPY6 billion. The BCV market for BK virus infections after kidney transplantation, which is being developed, is JPY24 billion. Then there is the BCV market for resistant/refractory CMV infections after hematopoietic stem cell transplantation or organ transplantation, estimated at JPY15 billon. The total market size, therefore, is JPY45 billion, and the BCV pipeline value for these markets alone we posit at between JPY41.9 billion and JPY60.4 billion. The company's next targets are cancers caused by viral infections (NK/T cell lymphoma, glioblastoma, etc.) and neurodegenerative diseases caused by viral infections (multiple sclerosis, Alzheimer's dementia). It goes without saying that the market for these is extensive.

Global specialty pharma status by 2030

For the time being, while the Treakisym® market contracts, SymBio will focus on its own global development of BCV for infectious diseases after hematopoietic stem cell transplantation or organ transplantation. However, if neurodegenerative disease research is successful, a global partnership is possible around 2024 or 2025. Looking further ahead, after 2030 the company plans to enter into full-scale development in the area of cancers caused by viral infections and neurodegenerative diseases caused by exposure to viral infections. It will not be easy to do all of this at the same time, but if successful, there is no doubt that a very large market awaits. The support of investors who approve of SymBio's strong development drive will be essential.

Revised Basic Report

Fair Research Inc

Tsuyoshi Suzuki

Company Outline	
Location	Tokyo
President	Fuminori Yoshida
Established	March 2005
Capital	JPY 17,568 mil
Listed	Oct. 2011
URL	www.symbiopharma.com
Industry	Pharma
Employees	121 (consol.)
Key Indicators (July 13, 2023)	
Share Price	JPY422
52-week high	JPY881
52-week low	JPY357
Shares outstanding	39,827,256
Trading unit	100 shares
Market cap	JPY16,807 mil
Dividend (est)	0.0
Forecast EPS	JPY-9.36
Forecast PER	NM
Actual BPS	JPY205.4
Actual PBR	2.05X

Note: EPS, PER, BPS and PBR based on shares outstanding, excl. treasury shares

Results	Revenues JPY mil	YoY %	Op. Income JPY mil	YoY %	Rec. Profit JPY mil	YoY %	Net Income JPY mil	YoY %	EPS JPY	Stock Price JPY	
										High	Low
2018/12 Actual	3,835	11.4	-2,656	NA	-2,748	NA	-2,752	NA	-165.5	289	115
2019/12 Actual	2,837	-26.0	-4,301	NA	-4,376	NA	-4,376	NA	-189.0	275	150
2020/12 Actual	2,987	5.3	-4,506	NA	-4,615	NA	-4,090	NA	-124.1	653	243
2021/12 Actual	8,256	176.4	1,016	NA	1,001	NA	2,032	NA	53.0	2,423	387
2022/1 Actual	10,008	NM	1,963	NM	1,999	NM	1,179	NM	30.2	1,284	610
2023/1 Forecast	7,000	-30.1	-331	NA	-351	NA	-370	NA	-9.4		

Company overview and management philosophy

＜Business model＞

The company is a pharmaceutical venture business with ambitions to become a global specialty pharma, aiming for high returns and operating in a niche sector without labs or manufacturing facilities to reduce risk

SymBio Pharmaceuticals Ltd. is a global specialty pharma with a focus on rare conditions with strong medical need in the areas of cancer and hematology, to which the major pharmaceutical companies have paid little attention. The company's involvement extends from clinical trials, rather than from the high-risk area of drug discovery, through to sales activity undertaken by the company itself. The company's business model has three characteristics:

① Post-POC strategy

The company does not itself undertake drug discovery research but investigates new drug candidates developed by drug discovery ventures and pharmaceuticals companies around the world. Usually, proof of concept has already been established. By insisting on prior evidence of efficacy and safety in human subjects the company reduces the development risks of new drug candidates.

② A specialty pharma using a high return, high market share niche strategy

The company focuses its efforts on drugs for relatively rare conditions in, for example, cancer and hematology, where the need is high, but where the major pharmaceuticals companies are relatively unrepresented. Using this niche strategy, the company seeks high market share and high returns. Until 2020, the company's business model involved entering into licensing agreements covering new drug candidates it had selected, developing them in Japan and then licensing out to other pharmaceuticals companies. Since 2021, however, it has set up its own sales function in Japan and has established itself as a pharma specialising in hematology.

③ Global licensor

Further, in September 2019, SymBio acquired exclusive rights (development, production and sales) to brincidofovir (BCV), a product with global applications. SymBio has thus evolved from a company seeking licenses in Japan to one providing licenses around the world, firstly in Asia, including China, and also the US and Europe.

The key to returns is the company's network of drug discovery companies, and the company's own expertise

The success of this business model owes much to the company's network of pharma-collaborators around the world and the company's own expertise. Hence, the company's track record. Normally, it takes some 10-20 years to bring a drug from basic research to the market. In terms of the probability of success, some estimates suggest that, counting from the chemical compound stage, it is less than 1/30,000, and even from the POC stage, it is only around 7-8%. In the case of SymBio's first product, Treakisym® it took only five years or so to go from licensing-in (in 2005) to manufacturing and sales approval (in 2010). In July 2018 it became the preferred drug for the treatment of malignant lymphomas. In the 17 years since the company was founded SymBio has introduced 6 products, 3 of which are now under development or at the development planning stage.

SymBio is a rare bio-venture in that it already has a product on the market, which took only five years from inception to regulatory approval

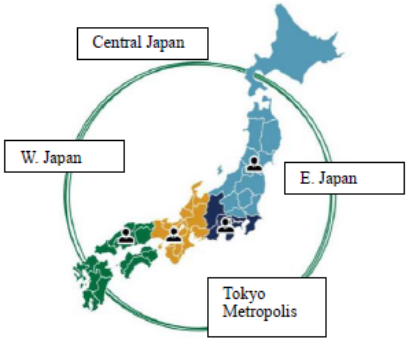
The elements which underpin this track record are the company's human resources and organisation. Hence, one-third of its 121 employees are engaged in research and development, and the company also boasts a Scientific Advisory Board consisting of specialists, including Nobel Prize candidates, to support its drug search and scrutiny activities. Needless to say, the role and professional network of the company founder and current president, Fuminori Yoshida, are pivotal.

Focus on human capital and company organisation to support networking and expertise

Establishment of an in-company sales structure

The company's sales sysem

- Has a regionally based sales system made up of four regions nationwide
- Stationing haematology experts (HE's) in each region to provide technical support



Nationwide distribution network

Suzuken

+Toho Pharmaceutical

+S.D. COLLABO

Source: SymBio: "Matters pertaining to the management plan and company growth potential", April 2022

SAB (Scientific Advisory Board) Members

	George Morstyn (Chair)	Previously Senior Vice Pres.. (Global Development) of Amgen and CMO		Robert Lewis	Former Senior Vice President at Aventis, and CEO of Bridgewater Research Institute
	Tomomitsu Hotta	Chairman, Foundation for Promotion of Cancer Research Honorary President, National Cancer Center, Honorary Director, NHO Nagoya Medical Center		Makoto Ogawa	Honorary President, Aichi Cancer Center
	Tatsutoshi Nakahata	Emeritus Professor, Kyoto University Director, Central Institute for Experimental Animals		Toshio Suda	Professor Internatinal Research Center for Meical Science, Kumamoto Univ, Professor at Singapore National University's cancer research insitute
	Tsutomu Takeuchi.	Emeritus Professor, Keio University, Vice Chancellor, Saitama Medical University.		Toshio Heike	Director of Hyogo Prefectural Amagasaki General Medical Center, Emeritus Professor, Kyoto University
	Yasukazu Takahashi	MD, Texas university Anderson Cancer Centre Leukemia Dept. Assistant Professor, Dept. of genomic medicine			

Senior Advisor

	Matius J Rumel	Medical Director Clinic for hematology and Medical Oncology, Justus-Liebig University

Source: SymBio

Significant events

2005/3	SymBio established
2005/12	Acquires from Astellas in Germany the exclusive rights in Japan for the development and sale of bendamustine
2008/8	Concludes with Eisai an agreement on the sale in Japan of freeze-dried bendamustine
2010/10	Acquires approval for manufacture and sale of Treakisym® (freeze-dried bendamustine) in Japan
2010/12	Starts sales of Treakisym®
2011/7	Concludes rigosertib licensing agreement with US company Onconova Therapeutics Inc.
2011/10	Listed on JASDAQ
2015/8	Onconova re-designs rigosertib tests and starts joint international Phase 3 (INSPIRE) trials
2015/10	The Medicines Company in the US acquires sole development and sales rights in Japan for IONYS® post operative self-administered pain medicine
2016/5	Treakisym® approved for additional indication in Japan - chronic lymphocytic leukemia
2016/8	Approval given for expanded indications in Japan for low-malignity non-Hodgkin's lymphoma and mantle cell lymphoma
2017/9	Acquires from US company Eagle Pharmaceuticals the sole rights in Japan to develop and sell bendamustine liquid formulation (RTD and RI preparations)
2017/10	Petition seeking arbitration for damages due to non-performance of The Medicines Company's agreement on license for IONSYS®
2017/11	IONSYS® agreement cancelled
2018/7	Approval of Treakisym® and Gazaiba® combined treatment for follicular lymphoma (CD20 positive)
2018/7	Treakisym® listed for the first time in the Hematopoietic Tumor Clinical Practice Guidelines (2018 Edition) as a first-line treatment for malignant lumphomas
2019/3	Treakisym® approved as pre-treatment for Kymriah CAR-T treatment of r/r acute lymphocytic leukemia
2019/9	Acquires sole global license for development, manufacture and sale of the anti-viral agent BCV from the US company, Chimerix (excludes smallpox)
2020/8	Top-line results of internatonal joint Phase 3 (INSPIRE) trials on rigosertib show no significant difference from physician-chosen treatment
2020/9	Approval given for the Treakisym® RTD formulation on existing indications
2020/9	IONSYS® arbitration handed down: SymBio to receive half the costs of arbitration-related costs
2020/12	SymBio takes over sales of Treakisym®
2021/1	Enters agreement with the Institute of Medical Science, Tokyo University on joint research into discovering new indications for which bendamustine and rigosertib night be indicated
2021/3	Phase 2 trials start in the US to test BCV targeting adenovirus infections following HSC transplants
2021/3	Combined Treakisym® and Rituxan® therapy approved for treatment of r/r DLBCL
2021/3	Combination of Treakisym® Rituxan® and Polivy® approved
2021/4	Treatisym RTD liquid formulation approved for r/r DLBCL treatment
2021/4	Development of BCV targeting adenovirus infections in children given fast track examination status
2021/5	Application submitted for approval of Treakisym® RI formulation
2021/8	Among the adenovirus targets of BSV was that for pediatric cases - Phase-2 FPI administrations
2022/2	Treakisym® RI formulation approved
2022/2	Treakisym® generics approved
2022/6	Towa pharm. starts sales of Treakisym generic targeing r/r DLBCL
2022/6	BCV: FPI in Australian Phase-2 for BK infection following kidney transplant
2022/11	Towa and Pfizer generics approved for Treakisym® RI administration
2022/12	BCV: Research results of effect of BCV on NK/T-cell lymphoma published by ASH
2022/12	Filed a lawsuit against Pfizer and Towa Pharmaceuticals seeking an injunction to stop the manufacture and sale of generics and compensation for damages
2022/12	BCV: Concluded a research agreement with Tufts University to verify the effects of BCV on Alzheimer's disease caused by HSV-1 infection using a 3D brain model
2023/3	BCV: Concluded a joint R&D agreement with the National Institute of Neurological Disorders and Stroke (NINDS) Target: multiple sclerosis caused by EBV
2023/4	BCV : Concluded a behavioral R&D agreement with the US National Institute of Allergy and Infectious Diseases. Subject: Treatment effect on EBV disease
2023/5	BCV: Establishes human POC for AdV infection after hematopoietic stem cell transplantation

Source: Compiled by Fair Research Inc. using SymBio's securities reports and other filings

＜Product pipelines＞

1. Brincidofovir（SyB V-1901）

Next leading product candidate: brincidofovir (BCV)

SymBio's next mainstay product pipeline is the antiviral agent, brincidofovir (BCV), a highly active agent for multi-viral infections developed by the US company Chimerix. SymBio plans to develop BCV to target diseases in four areas. Firstly, in the area of hematopoietic stem cell transplantation, adenoviral infections and cytomegaloviral infections following such transplantations. Secondly, in the area of organ transplantations, BK viral infections following kidney transplantations. Thirdly, in the area of cancers caused by viral infections, NK/T-cell lymphoma, cytomegalovirus-infected GBM, etc. And fourthly, in the area of brain neuro-degenerative diseases caused by exposure to viruses, such as EB virus-associated multiple sclerosis and herpes simplex virus type 1 (HSV-1) infection Alzheimer's dementia.

[Brincidofovir]

Pipeline	Indication(s)	Clinical Trial			NDA※1	MA※2
		Phase 1	Phase 2	Phase 3		
SyB V-1901 Antiviral Drug (IV)	AdV infection Immunocompromised patients including post hematopoietic stem cell transplantation		Phase II study on going			
	BKV infection Post kidney transplantation		Phase II study on going			
	CMV infection Post hematopoietic stem cell transplantation	Phase Ib study in preparation				
	EB virus-related diseases Multiple Sclerosis	Preclinical study on going				
	HSV-1 Alzheimer's disease	Preclinical study on going				
	CMV infection GBM	Preclinical study on going				

NDA: New Drug Application, MA: Marketing Approval

Source: SymBio Pharmaceuticals website

In 2019 the company licensed in the highly active anti-multiviral agent BCV from the US company, Chmerix

As a strategic product to succeed Treakisym®, SymBio announced on October 1st 2019 that it had acquired exclusive global licensing rights (development, manufacturing and sales) to BCV from Chimerix, Inc. for all diseases except smallpox. Until this time SymBio's business had involved acquiring licenses overseas and undertaking development mainly for the Japanese market. This contract, however, allows it to evolve into a provider of licenses for development globally. (Subsequently, on May 16th 2022, Chimerix announced that it would transfer the license for BCV to Emergent BioSolutions Inc. However, the rights acquired by SymBio will not be affected.)

① Disseminated adenoviral infection after hematopoietic stem cell transplantation

First target indication for BCV is disseminated adenoviral infection after hematopoietic stem cell transplantation

Adenovirus infections after hematopoietic stem cell transplantation and BK virus infections after kidney transplantations are currently in Phase-2. It is generally the case that in hematopoietic stem cell transplantation and organ transplantation, irradiation and immunosuppressive agents are used to suppress rejection, which

	makes patients susceptible to infection from viruses. Conventionally, other antiviral agents such as cidofovir (CDV) and foscarnet (FOS) have been used, but there have been concerns about nephrotoxicity as a side effect. BCV has low nephrotoxicity and is therefore an important product that will support SymBio's goal of becoming a specialty pharma in the hematology field.
	Development recap
Decision reached in August 2020 that the first target should be adenovirus infections following hematopoietic stem cell transplantation	(a) Decision on development policy After the Global Scientific Advisory Board meetingheld in February 2020, SymBio decided to prioritise adenoviral infections after hematopoietic stem cell transplantation as the first development target in August 2020 and that tests on children would be given priority. In addition, since safety had already been confirmed using data from Chimerix, it was decided to start with a Phase-2 dosage study (development for adults to begin once POC in the pediatric trials was established.)
IND application for Phase 2a clinical trlials in March 2021, FDA fast-track designation in April, FPI in August	(b) Clinical trials IND application to conduct Phase-2a joint international trials made on March 10th 2021 and the development program for pediatric adenovirus infections accorded fast-track designation by the FDA on April 26th. FPI (first-patient-in) was on August 16th 2021. IND application for UK clinical trials made in January 2022.
Structure: 4 groups, about 6 cases each	The clinical trial was designed to study (Phase-2a ATHENA study; 4 cohorts, about 6 subjects in each cohort) and confirm safety and tolerability by successively increasing the doses. 1st cohort BCV 0.2mg/1kg body weight. Twice per week for at least 4 weeks 2nd cohort BCV 0.3mg/1kg body weight. Twice per week for at least 4 weeks 3rd cohort BCV 0.4mg/1kg body weight. Twice per week for at least 4 weeks 4th cohort BCV 0.4mg/1kg body weight. Once per week for at least 4 weeks
Confirmed POC in human subjects in 24 cases up to the third cohort in May 2023 Starts discussions with FDA as Phase-3 approaches	(c) POC in humans established On May 29th, 2023, SymBio submitted to the FDA clinical data for a total of 24 patients (8 in the first cohort, 9 in the second cohort, and 7 in the third cohort) and announced that, as a result, POC (proof of concept) had been confirmed. Consequently, with the 3rd cohort completed, the administration schedule for the 4th cohort is being considered, and discussions are underway with the FDA prior to the start of a Phase-3 clinical trial.
Phase-3 to start in 2024 with market launch around 2027-2028	If all goes well, Phase-3 (several hundred cases) will start in the first half of 2024, an application for approval will be submitted to the FDA in 2026-2027, and market launch will be in 2027-2028.

SymBio's second target indication is BK viral infections after kidney transplantation

In June 2022, the company submitted a clinical trial protocol for international joint Phase-2 to the PMDA. In August, it also submitted a clinical trial protocol to the Australian authorities

First administrations in Australia started in December 2022

Protocol: 3 groups
Phase-2 completion H1/2025

Promoting in-house product development

② BK viral infection after kidney transplantation

SymBio plans to move development beyond viral infections following haematopoietic stem cell transplantation to viral infections after organ transplantation. Organ transplants are more common in Europa and North America than in Japan. For example, while some 1,600 kidney transplantations are carried out annually in Japan, 20,000 are carried out in the US and around the same number in the five major European countries. Of these, an estimated one-third contract the BK virus or the CMV (cytomegalovirus). While the number of infections is quite low (560) in Japan, in the US + 5 main countries of Europe the total is around 15,000 cases annually.

SymBio is planning to begin product development in Australia, Japan and one other country and on June 14th 2022, submitted to the PMDA an application to conduct Phase-2 joint international clinical trials of BCV on BK viral infections after kidney transplantations. Additionally, on August 22nd 2022, the company submitted the application for clinical trials plan to the Australian Therapeutic Goods Administration (TGA). In these joint international trials, dose-setting tests are first carried out, and the plan is to have 3 groups of 12 cases each. The beginning of administrations in Australia was announced on December 13th 2022. Phase-2 is scheduled for completion in the first half of 2025.

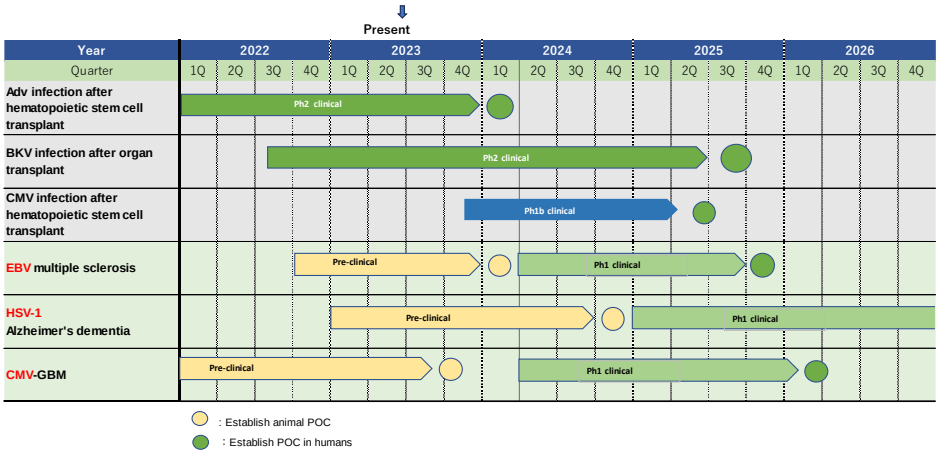
1st cohort BCV 0.3mg/1kg body weight. Twice/week, 8-14 weeks

2nd cohort BCV 0.4mg/1kg body weight. Twice weekly, 8-14 weeks

3rd cohort (expanded cohort) BCV recommended dose twice weekly, 8-14 weeks

The company plans to promote its own in-house product development, but organ transplantations are outside SymBio's s area of expertise, and there are not enough cases in Japan. For these reasons, it is thinking of partnering with a European or US pharmaceutical company to promote development and sales in the area of organ transplantations.

BCV injections: planned development timeline



Source: SymBio company briefing, February 2023

CMV infection following haematopoietic stem cell transplantation has emerged as the next target indication

Restance emerges in almost half the cases treated with maribavir

③ CMV infections after hematopoietic stem cell transplantation

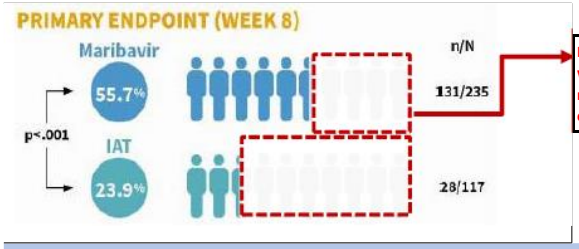
SymBio is considering starting Phase-1b trials for cytomegalovirus infection after haematopoietic stem cell transplantation by the end of 2023. Development of the drug had already been put on the back burner because of the earlier development of Takeda's maribavir for the same CMV indication, but physicians who conducted the clinical trials on maribavir requested a BCV trial for those patients (44.3%) who showed resistance to maribavir, and the decision was made to pursue development in relapsed and refractory CMV infection.

Maribavir efficacy

- Limited effectiveness of existing antivirals, including maribavir
- Problems include possible toxicity, resistance and cross tolerance

Maribavir international Phase-3 clinical trials

2021 Nov. SOLSICE study: Approved by FDA for r/r CMV infection after SOT



Trial results

- Achieved the required proportion of patients who saw clearance of CMV 8 weeks after administration
- But 44.3% were resistant and showed no effect
- Even after the virus became undetectable resistance devleloped, 23% relapsed after 6 weeks and 30% afer 12 weeks

Source: SymBio company briefing, February 2023

Unlike maribavir, BCV is regarded as unlikely to cause resistance mutations

Unlike maribavir, BCV is thought to be resistant to mutations. The target molecule of maribavir is a protein kinase called U97, which is prone to resistance mutations, whereas the target molecule of BCV and CDV is a virus-derived DNA polymerase called UL54, which is essential for viral replication, so resistance mutations are unlikely to occur. In fact, clinical trials of BCV have not detected mutations associated with resistance.

④Hematological malignancies (NK/T-cell lymphoma, etc.) and solid tumors (GBM, etc.)

(a) Hematological malignancies

The EB virus is linked to blood tumours

The EB virus was the first human cancer virus isolated from Burkitt's lymphoma, a type of blood tumor (1964), and is known to be associated with various cancers. Its involvement in nasopharyngeal cancer, Hodgkin's lymphoma, NK/T-cell lymphoma, etc. has been documented. However, instead of infection = carcinogenesis, changes in the genes of infected cells by EB virus are involved in carcinogenesis.

Therapeutic effect of BCV against NK/T cell lymphoma etc. was announced by ASH in 2022

As a result of joint research by SymBio and the National Cancer Center of Singapore, the therapeutic effect of BCV (non-clinical) for rapidly progressing NK/T cell lymphoma, for which no effective treatment has been established so far, was released by ASH (the American Society of Hematology) in December 2022.

NK/T cell lymphomas occur

NK/T-cell lymphoma is a malignant lymphoma derived from NK cells or T cells. It occurs primarily in the perinasal and cutaneous areas as extranodal NK/T-cell lymphoma. This disease is more common in East Asia and South America than in Europe and the United States. In Europe and the United States, it accounts for less

frequently in East Asia and South America

than 1% of non-Hodgkin's lymphoma, while in East Asia (China) it accounts for about 10%. Most NK/T-cell lymphomas are EB virus-positive.

Most patients are EB virus positive

Distribution of NK/T lymphoma patients

	Japan	US	EU	China	
# NHL (2020)	34,792[11]	80,160[5]	67,988[6]	68,500[7] (est. 2016)	Nationwide
% NK/T lymphoma	0.8%	<< 1%[4]	<< 1%[4]	12%[8]	5 major hospitals in Beijing, Chengdu, and Shanghai
# NK/T lymphoma	283[1]	<< 802	<< 680	8,220	
% EBV+	100%[2-3]	100%[3]	100%[3]	94 - 100%[9, 10]	
# EBV+ NK/T	283	<< 802	<< 680	7,727 – 8,220	

Source: ASH, December 2022

The EB virus is involved in tumor malignancy via various pathways

While by no means fully elucidated, the carcinogenic mechanism probably goes as follows. In NK/T-cell lymphoma cancer cells, the EB virus is latently infectious and expresses a variety of EB virus proteins such as EBNA-1, EBNA-2, LMP-1 and LMP-2. When EBNA-1 is expressed, p53 is inhibited and apoptosis of cancer cells is suppressed. LMP-1activates NF-κB and this also suppresses apoptosis. It is thought that LMP-2 is involved in carcinogenesis via the P13K or MAPK pathways.

EBV promotes maligancy

EBNA-1＝＞P53 instability＝＞apoptosis

EBNA-2＝＞MYC、LMP-1/2 promotion of expression＝＞cell mmortalised

LMP-1 ==＞NF-κB activation ＝＞apoptosis suppression

LMP-2 ＝PI3K pathway /MAPK pathway activation

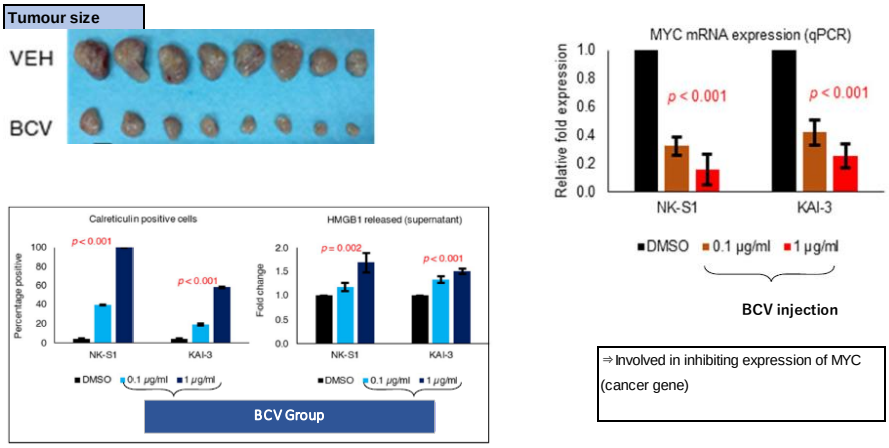
=>involvement in carcinogenesis

BCV not only suppresses the expression of a group of genes that promote tumour malignancy, but also induces immunogenic cell death

BCV has been found not only to suppress the expression of a group of genes (MYC) that promotes tumour malignancy by the EB virus, but also to destroy tumour cells and induce immunogenic cell death, which activates cancer immunity. This could also lead to a beneficial effect in combination with immunotherapy, such as with anti-PD-1 inhibitors.

Therapeutic efficacy of BCV

The effect of a therapy combining BCV with immunotherapy, such as anti-PD-1 inhibitor, could be promising



Source: SymBio company briefing, February 2023

Note: Immunogenic cell death

When cancer cells die, the cells are destroyed and their contents are released, which signals to dendritic cells, a type of immune cell, that cancer cells have been destroyed, teaching effector memory T cells how to recognise cancer cells and allowing the immune system to act. This type of cell death is called 'immunogenic cell death'.

The International Conference on Malignant Lymphoma in June 2023 also confirmed the effectiveness of BCV

In addition, a presentation at the International Conference on Malignant Lymphoma in June 2023 demonstrated that high sensitivity to BCV is highly correlated with low expression of TLE1 (cancer suppressor), worse prognosis in patients with NK/T-cell lymphomas, and increased expression of oncogenes such as MYC.

In April 2023, SymBio completed a CRADA with NIAID in the US to examine the effect of BCV on EB virus-associated lymphoproliferative disorders

Further, in April 2023, SymBio concluded a joint R&D agreement (CRADA) with the US National Institute of Allergy and Infectious Diseases (NIAID) to conduct non-clinical studies to evaluate BCV's effect on EB virus-associated lymphoproliferative disorders.

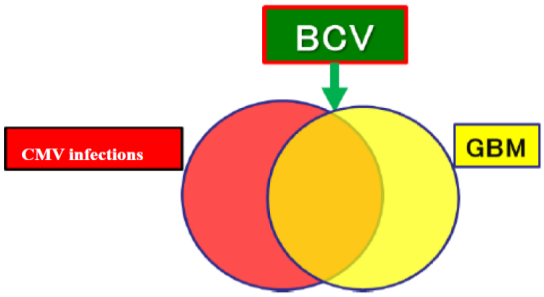
(b) Solid tumours (GBM)

Half of all glioblastoma (GBM) patients test positive for CMV

Glioblastoma (GBM) is the most common malignant brain tumour and an area of seriously unmet medical need. It has a survival time of only 15-20 months and a 5-year survival rate of less than 5%. Approximately 50% of patients are known to be CMV positive. Various therapeutic agents are currently under development, but there are no therapeutic drug candidates targeting CMV.

Research at Brown University in the US has demonstrated a mechanism by which CMV infection promotes the growth of GBM cancer cells

Although the CMV-brain tumour mechanism is not fully understood, research at Brown University, has demonstrated in a mouse model that CMV infection enhances NF-κB signaling, leading to increased expression of the angiogenic PDGF-D factor, which promotes GBM cancer cell growth. It has also been found experimentally that the antiviral drug cidofovir (CDV) inhibits CMV reactivation and improves survival in CMV-infected mice（The Journal of Clinical Investigation 2019, Sean E. Lawler Sean et al.).



BCV may have an anti-tumour effect and the ability to inhibit malignancy growth

The possible mechanisms of action of BCV on GBM include an anti-tumour effect, in which BCV changes intracellularly into CDV-PP and inhibits the replication cycle of tumour cells, inducing apoptosis, and a malignant growth suppression effect, in which BCV inhibits CMV reactivation and suppresses tumour growth.

Now conducting non-clinical studies, with Phase-1 due to begin in 2024

SymBio is currently evaluating the anti-tumour potential of BCV in collaboration with the University of California and is also working with Brown University to evaluate the anti-tumour effect and the effect on tumour malignancy of BCV, with results expected by the end of 2023. Thereafter, a Phase-1 is planned to start in 2024.

Some neurodegenarative diseases thought due to inflammation due to viral infection

Now conducting non-clinical studies on multiple sclerosis (MS) and Alzheimer's dementia

⑤ Expansion into the field of neurodegenerative diseases.

Some neurodegenerative brain diseases are thought to be caused by inflammation due to viral infection. SymBio is currently conducting pre-clinical studies on multiple sclerosis and Alzheimer's dementia.

Schedule for development of treatment for neurodegenerative diseases

Multiple sclerosis

Trial type	Tester	Protocol
Basic	NIH/Symbio	Q3/2022（underway）
Animal model	NIH/SymBio	2023/Q3～
Clinical (human)	NIH/SymBio	2024/Q2～

Alzheimer's dementia

Trial type	Tester	Protocol
3D brain model	Tufts Univ.	2022/Q4（underway）
Animal model	SymBio	2023/Q4～
Clinical (human)	Jointly with partner	2025/Q1～

Alzheimer's dementia

Trial type	Tester	Protocol
3D brain model	Tufts Univ.	2022/Q4（underway）
Animal model	SymBio	2023/Q4～
Clinical (human)	Jointly with partner	2025/Q1～

Source: SymBio company briefing. February 2023

MS considered a new target since February 2022

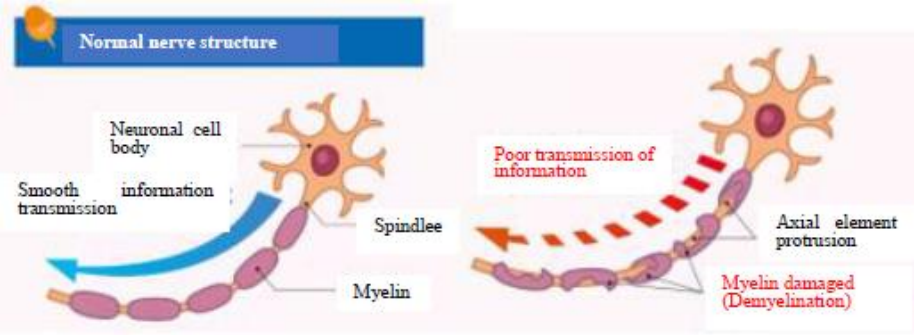
CRADA concluded with NINDS in 2023

Development will proceed to animal models from late 2023 and to human Phase-1clinical trials in 2024, at which point a potential global partnership is in the offing

(a)Multiple sclerosis

In February 2022 the company announced that it was considering MS, an autoimmune disease, as a new target indication for BCV. In August 2022 it concluded a cooperative research and development agreement (CRADA) with NINDS, which belongs to the National Institutes of Health in the US, to evaluate the antiviral effect of BCV against the EB virus. Under this agreement, Symbio was to provide NINDs with BCV to conduct non-clinical tests for evaluation of potential effect of BCV against diseases caused by EB. Further, in March 2023, SymBio concluded a CRADA with the National Institute of Neurological Disorders and Strokes (NINDS) to test the efficacy of BCV in-vitro and in animal models using cells derived from patients with multiple sclerosis with EB virus infection. In the second half of 2023, more advanced experiments using animal models (marmosets) is scheduled, with plans to start clinical trials (Phase-1) in the second half of 2024. It is expected that at this stage the major pharmaceutical companies will pay closer attention.

Reference: Multiple sclerosis
An autoimmune disease subject to repetitive relapses and remissions in which lymphocytes attack the myelin covering the axons of nerve cells and demyelinate them, causing various neurological symptoms (e.g. motor, visual, sensory and urinary disorders) as information is not transmitted smoothly in the demyelinated nerves. Lesions occur sporadically in the brain, spinal cord, and optic nerve, and recur at intervals of one month or longer. The number of patients in Japan, including neuromyelitis optica patients, is about 18,000, but it is said that there are 3 million cases worldwide, mainly in Europe and the United States. There is no fundamental treatment, and steroid pulse therapy which suppresses inflammation with steroids and immunomodulators that suppress the activity of lymphocytes are used.



Source: multiple sclerosis.jp

The mechanism by which EB virus causes multiple sclerosis (MS) is not fully understood, but an association with EB virus is supported by epidemiological studies. A Harvard University research team analyzed a sample of more than 10 million U.S. military service adults and found that 955 were diagnosed with MS during military service. Studying these 955 cases it was found that the incidence of post-EB virus infections were 32-times greater than with other viral infections. (Science Magazine, January 13, 2022:,"Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis")

A research team at Stanford University has recently put forward a powerful new hypothesis explaining the mechanism of MS onset by the EB virus (Nature, January 24 2022: "Clonally Expanded B cells in Multiple Sclerosis Bind EBV EBNA1 and Glial CAM") According to this hypothesis, the EB virus transcription factor, EBNA1, and the glial cell adhesion molecule, GlialCAM, in the brain are structurally similar, leading the lymphocytes that produce autoantibodies which recognize both to migrate to the center, accidentally damaging their own myelin, leading to the onset of multiple sclerosis. This hypothesis is supported by the effectiveness of blocking the transfer of lymphocytes into the central nervous system (sphingosin 1- phosphate receptor agonist) or blocking the migration of lymphocytes from the lymph nodes (anti-α4 integrin antibody) and the effectiveness of molecular-targeted drugs such as the anti-CD20 antibody (ocrevus) in targeting B-cells. SymBio believes that if our understanding of this mechanism is correct, the progression of MS can be inhibited by promptly eliminating the EB virus with BCV after the onset of MS. Currently, the scale of the market for multiple sclerosis drugs is about JPY1.5 trillion, and perhaps JPY 2 trillion if steroids are included. SymBio expects that BCV will be added as a combination drug offering a new mechanism.

Major Multiple Sclerosis Drugs (2020)

(JPYbillion)

Mechanism	Product	Company	Worldwide Sales
Anti-CD20 antibody	Ocrevus	Biogen/Roche/Genentech	492.2
Activation of Nrf2 pathway	Techfidera	Biogen	422.2
S1P receptor activation	Gilenya/Imusera	Novartis/Tanabe-Mitsubishi Pharm	324.6
DHOD inhibition	Aubagio	Sanofi	249.1
Anti-α4 integrin antibody	Tysabri	Biogen/Biogen Japan	207.8

Source: SymBio results meeting materials, February 2022

(b) Alzheimers dementia disease

VSV activates herpes simplex virus type-1 and amyloid β accumulates

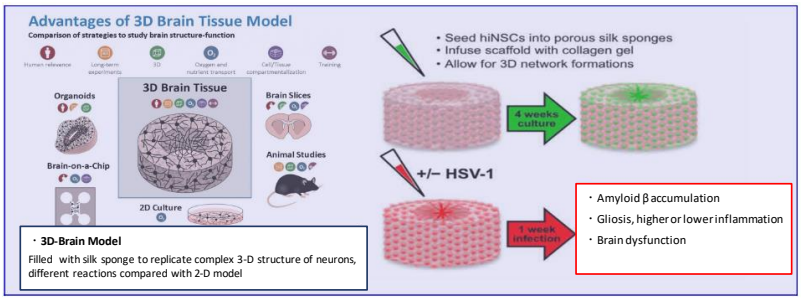
Recently, evidence has been accumulating that herpes simplex virus type 1 (HSV-1) is involved in the onset of Alzheimer's disease (Nikkei-FT Conference on Infectious Diseases: October 24th 2022: Nikkei News Paper). According to the article, research at Tufts University has raised the possibility that the VSV (varicella-zoster virus) activates HSV-1 and leads the tau protein and amyloid β to accumulate, reducing the functioning of nerve cells. In particular, it has been pointed out that carriers of the APOE4 gene are receptive. Research at Oxford University has also shown that when HSV-1 is present in the brain the combination with APOE4 increases susceptibility to Alzheimer's.

Pre-clinical trials underway to test the effectiveness of BCV using the Tufts University 3-D brain model

On 19th December 2022, SymBio concluded a contract research agreement with Tufts University and began a pre-clinical study to test the effect of BCV using Tufts University's 3-D brain model of the herpes simplex virus (HSV). Longer term the aim is to develop anti-viral drugs to treat Alzheimer's. Anti-amyloid-β fibre antibodies such as Lecanemab are currently under the spotlight as a treatment for

Alzheimer's disease, but SymBio is hoping BCV can respond a wider variety of stages than those at which these antibodies are successful.

Note: 3-D Brain Tissue Model
An experimenting system in which human neural stem cells are cultured using collagen-filled porous silk protein sponge as a base material, and then proliferated and differentiated into a functional network of neurons and glial cells that are also susceptible to viral infection. In this system, electrophysiological functions, amyloid-β fibril formation due to HSV infection, neuroinflammation, etc. can be evaluated under conditions exclusive of other factors.



Source: SymBio company briefing. February 2023

Efficacy against illnesses caused by a variety of other viruses is also being examined

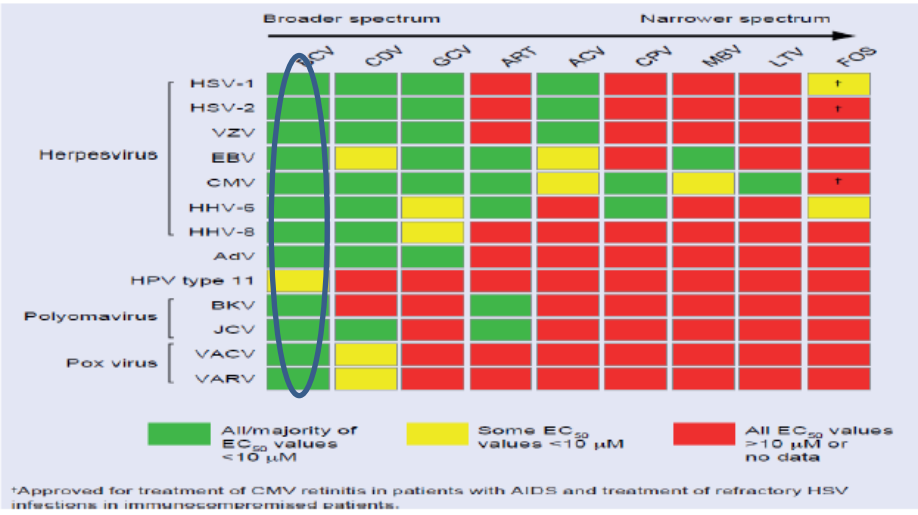
Additionally, in November 2022 SymBio concluded a material transfer agreement with Pennsylvania State University, and non-clinical trials have been started to test the effect of BCV on models of polyoma viral infections The polyomavirus is a double-stranded DNA virus that causes serious diseases. Existing antiviral drugs are mostly ineffective. The BK virus and the JC virus are both polyoma viruses.

Review 1: Characteristics of brincidofovir

BCV stands out against other agents because it is highly active and broad spectrum

Compared to other antiviral agents such as cidofovir (CDV) and foscarnet (FOS) BCV is highly active and effective against multiple viruses.

BCV - highly active and broad spectrum



Chemaly RF et al. Presented at ESCV 2018, Athens, Greece

Source: Chimerix Inc.

Note: the lower the EC50 (half maximal effective concentration of a drug or antibody) the higher the activity. In the chart, green indicates high activity and red indicates low activity. BCV on the far left is green for various viruses = has a broad spectrum.

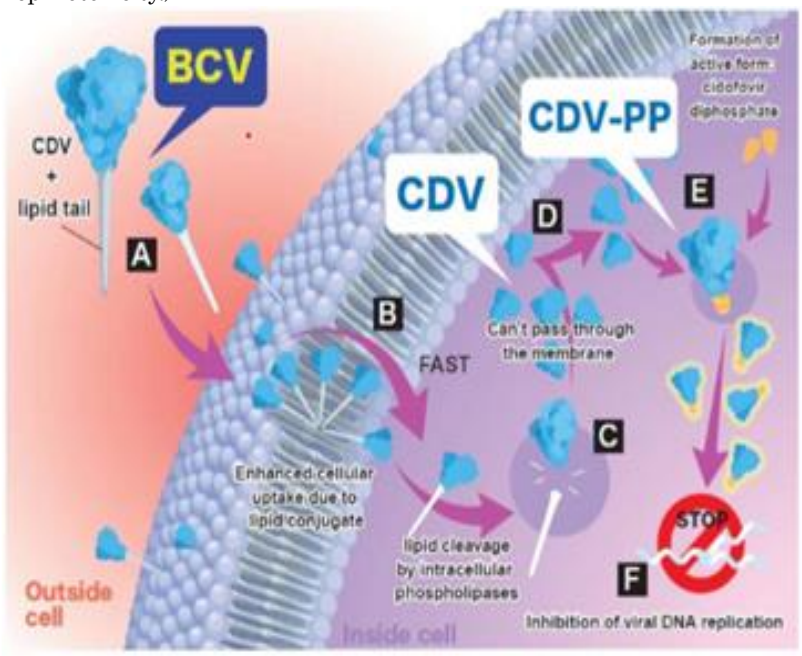
Also, BCV is very safe

Reference: Cidofovir - CDV

The FDA approved CDV in 1996 for the treatment of cytomegalovirus retinitis in AIDS patients. CDV is a cytosine nucleotide analog that inhibits the replication of not only herpesviridae but also DNA viruses such as adenovirus, papillomavirus, and polyomavirus. CDV is also effective against ganciclovir (GCV) resistance (UL97 gene mutation) and is considered useful when foscarnet (FOS) cannot be used when GCV resistance emerges. It has not been developed in Japan, where it is not approved. As is clear from the above chart, CDV is close to BCV in terms of activity level and spectrum width but is nephrotoxic and difficult to handle. BCV, meanwhile, has low toxicity and is safe despite its high activity.

Review 2: BCV's mode of action

Brincidofovir (BCV) has a structure in which a fatty chain (hexadecyloxypropyl: HDP) is attached to CDV, which is rapidly incorporated into the lipid bilayer and efficiently transferred into the cell, after which the fatty chain is detached by metabolism by intracellular phospholipase and the activated form (CDV-PP: CDV diphosphate) produced is retained intracellularly for a protracted period. This results in a compound with dramatically improved antiviral activity. Additionally, due to HDP binding, OAT-1 transporter-mediated accumulation in renal tubular epithelial cells does not occur, and the level of CDV released into the blood is low, thus avoiding the nephrotoxicity problem of CDV. (Since CDV does not have a fatty chain, it acts as a substrate for OAT-1 and accumulates in renal tubular epithelial cells, resulting in nephrotoxicity.)



Source: SymBio Pharmacueticals I.R documents

2. Development of rigosertib (SyB L-1101 injection and SyB C-1101 oral)

Rigosertib was being developed for myelodysplastic syndromes until it was discontinued. Consideration is now being given to development using a different mode of action

Onconova, the licensor, is focusing on rigosertib's RAS inhibitory function

Rigosertib was originally developed to target MDS (myelodysplastic syndromes), However, it failed to meet its primary endpoint in Phase-3 international joint trials (INSPIRE trials)) in August 2020.

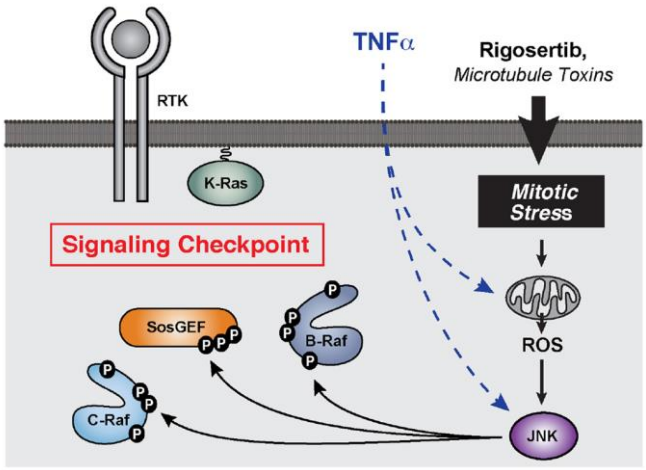
[Rigosertib]

Pipeline	Indication(s)	Clinical Trial			NDA※1	MA※2
		Phase 1	Phase 2	Phase 3		
SyB L-1101 Anti-cancer agent (IV)	Relapse/ refractory high risk MDS monotherapy	Global phase Ⅲ study completed				
SyB C-1101 Anti-cancer agent (oral)	Relapse/ refractory high risk MDS	Japan study completed				
	1st line high risk MDS Combination with AZA	Global phase Ⅰ/Ⅱ study completed				

Source: SymBio web page

Now, however, the focus has shifted to its function as a RAS inhibitor, with the rigosertib licensor, Onconova Therapeutics, pursuing the development of cancer drugs.

Rigosertib's action mechanism



Source: Daniel A Ritt et al, 「Inhibition of Ras/Raf/MEK/ERK Pathway Signaling by a Stress-induced Phospho-regulatory Circuit」 Mol Cell 2016 Dec
Rigosertib's microtubule inhibitory effect activates JNK and is thought to act on the Ras/Raf/MEK/ERK pathway.

In September 2021, Onconova released Phase-1 partial interim results of a study (Phase-1/2a) of a combination of rigosertib (oral) and anti-PD-1 antibody nivolumab (Optdivo®) for non-small cell lung cancer (NSCLC) with KRAS mutation.

The patient subjects were all KRAS mutation NSCLC patients who had at least one experience of treatment with anti-PD-1 antibody. For NSCLC patients, anti-PD-1 antibodies such as Opdivo® are targeted at patients with a PD-L1 expression rate of 50% or higher, but among patients with a PD-L1 expression rate of 50% or higher, only about 45% respond to anti-PD-1 antibodies. In other words, even if the anti-PD-1 antibody (Opdivo®) is indicated for treatment by genetic testing, it is not effective in 55% of patients receiving first-line therapy. There is an unmet medical need here, and it is also a field where pharma companies are competing.

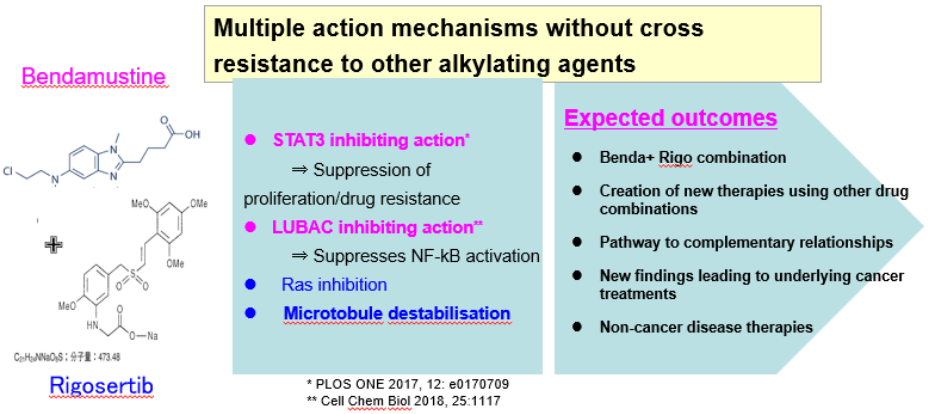
As a result, of the 12 subjects, 2 had not yet reached the evaluation stage, and 3 were discontinued due to side effects, etc., so 7 patients were available for evaluation, 2 of whom had a partial response (PR). 1 had stable disease (SD), with a disease control rate of 43%. Partial responses were observed in patients with mutations in the G12C segment as well as in the G12V segment among KRAS mutations. No unexpected or serious side effects were observed.

In NSCLC, KRAS mutations are observed in approximately 20% of patients, of which the most frequent (approximately 13%) are mutations in the G12C segment. LUMAKRAS (generic name sotorasib, AMGEN accelerated approval in May 2021), the world's first approved KRAS inhibitor, is an inhibitor of the G12C mutation. US-based Mirati is also developing the KRAS (G12C) inhibitor adagrasib for NSCLC, and has also begun developing a KRAS (G12D) inhibitor for pancreatic cancer. However, both AMGEN's drug and Mirati's drug bind to a specific mutated portion of KRAS and act only on that mutation. On the other hand, rigosertib is thought to have multiple mechanisms of action, such as RAS signal inhibition and microtubule destabilization.

SymBio is cooperating with academic institutions (such as Tokyo University and Kyoto University) on further research into new modes of action for rigosertib and Treakisym® (bendamustine) and seeking out novel uses and new indications.

SymBio is collaborating with academia in research on new modes of action

Possibilities for t combining rigosertib and Treakisym® (bendamustine)



Source: SymBio company briefing

3. Treakisym® (SyB L-0501 (freeze-dried injection formulation/SyB L-1701 (RTD liquid formulation)/ Treakisym® (SyB L-1702 liquid formulation)

Symbio guided Treakisym® to its status as a standard drug for malignant lymphomas in Japan

Treakisym® (generic name: bendamustine) developed by SymBio was the first drug for malignant lymphoma in Japan. Treatment using Treakisym® is now established as one of the standard therapies for malignant lymphoma.

[TREAKISYM®]

Pipeline	Indication(s)	Clinical Trial			NDA※1	MA※2
		Phase 1	Phase 2	Phase 3		
SyB L-0501 Anti-cancer agent	r/r Low-grade NHL/MCL				Approved October, 2010	
	CLL				Approved August, 2016	
	1st line Low-grade NHL/MCL				Approved December, 2016	
	r/r DLBCL				Approved March, 2021	
SyB L-1701 (RTD)※	All except for r/r DLBCL				Approved September, 2020	
	r/r DLBCL				Approved April, 2021	
SyB L-1702 (RI)※	All				Approved February, 2022	

※ On September 20, 2017, SymBio obtained the exclusive rights from Eagle Pharmaceuticals, Inc. (New Jersey) for its patent-protected bendamustine liquid formulations (RTD and RI). SymBio plans to market the RTD formulation on January ,2021 and launch the RI formulation on the subsequent date.

RTD: Ready-To-Dilute; RI: rapid infusion

Source: SymBio home page

Treakisym® is indicated for low-grade B-cell non-Hodgkin's lymphoma, mantle cell lymphoma, chronic lymphocytic leukemia, and relapsed/refractory DLBCL

Treakisym® is indicated for the following four malignant lymphomas:

- ○ Relapsed/refractory indolent-B-NHL and MCL (approved Oct. 2010)
- ○ Treatment-naïve indolent B-NHL and MCL (approved Dec. 2016)
- ○ Chronic lymphocytic leukemia (CLL) (approved Aug. 2016)
- ○ Relapsed/refractory DLBCL (approved March 2021)

Note: naïve DLBCL: Not eligible for treatment

Reference: Types of malignant lymphoma
Lymphoma is a blood disease that occurs when lymphocytes (a type of white blood cell), which act as immune cells, become cancerous. Lymphoma is mainly divided into Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL). In the case of Japanese malignant lymphoma, 94% are considered to be NHL. NHL is classified according to the rate of progression of the disease into three categories:

- ○ Low-grade (indolent-B-NHL): Disease progresses on a yearly basis (such as MALT and FL (up to grade 3a):

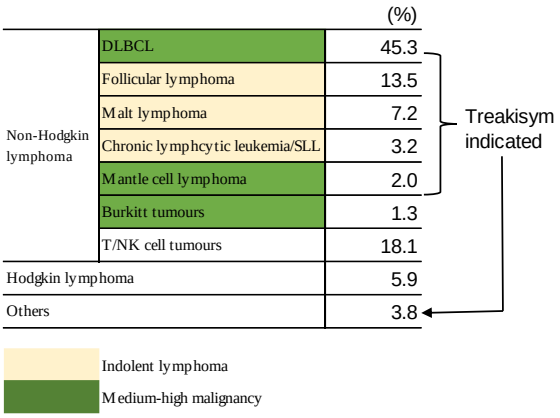
  FL: Follicular lymphoma, MALT: MALT lymphoma

  Follicular lymphoma accounts for about 80% of low-grade B-cell non-Hodgkin's lymphoma
- ○ Intermediate grade: progression of disease on a monthly basis (MCL, DLBCL, etc.)

  MCL: mantle cell lymphoma, DLBCL: diffuse large B-cell lymphoma
- ○ High grade: Weekly progression (such as Burkitt lymphoma)

Diffuse large B-cell lymphoma (DLBCL) is the most common type of NHL, but it has a poor prognosis and a high rate of relapse/refract (r/rDLBCL).

Distribution of malignant lymphoma by type (Japan)



Note: Among DLBCL's indicated for r/r DLBCL, 1st-Line DLBCL - off-label
Further, splenic green band B-cell lymphoma, lymph plasma cell lymphoma, and nodal line green band B-cell lymphoma belonging to other categories are also indicated.

Source: Compiled from Chihara D et al, "Differences in incidence and trends of haematological malignancies in Japan and the United States" British Journal of Haematology. 2014

SymBio introduced Treakisym to Japan in December 2005

Acqured first indication approval five years after licensing in

Established as a standard therapy in 2018

Sales boost in 2021 from approval of r/rDLBCL

① History of development

Looking back briefly at the history of development, Treakisym® was developed in Germany in 1971. In December 2005, SymBio acquired exclusive development and marketing rights in Japan from Astellas Pharma's European subsidiary, Astellas Pharma (current name: Astellas Deutschland GmbH) and conducted clinical trials. In October 2010, just five years after its introduction, it was approved for the indication of relapsed/refractory indolent-B-NHL and MCL, and sales began in December. In August 2016, it was approved for chronic lymphocytic leukemia (CLL), and in December 2016, it was additionally approved for treatment-naïve indolent-B-NHL and MCL. Furthermore, in July 2018, indolent-B-NHL, MCL, and CLL, for which Treakisym® had been approved, were newly included as standard treatment options in the 2018 edition of the Clinical Practice Guidelines for Hematopoietic Malignancies (edited by the Japanese Society of Hematology). Market penetration of Treakisym® increased as it was established as one of the standard therapies, completely surpassing the R-CHOP therapy, which had been the conventional standard therapy, and domestic sales in 2018, the eighth year since its launch, expanded to JPY8.5 billion (NHI drug price basis). There was subsequently some temporary stagnation in sales due to quality issues at the manufacturer and inventory fluctuations as the company switched to its own sales system (domestic sales in 2020: JPY8.1 billion, NHI drug price basis), but in March 2021, approval was given for the B-R therapy and P-BR therapy (Polivy® + B-R therapy) for diffuse large B-cell lymphoma (r/rDLBCL), opening the way for sales to again expand.

SymBio has been developing user-friendly dosing formulations

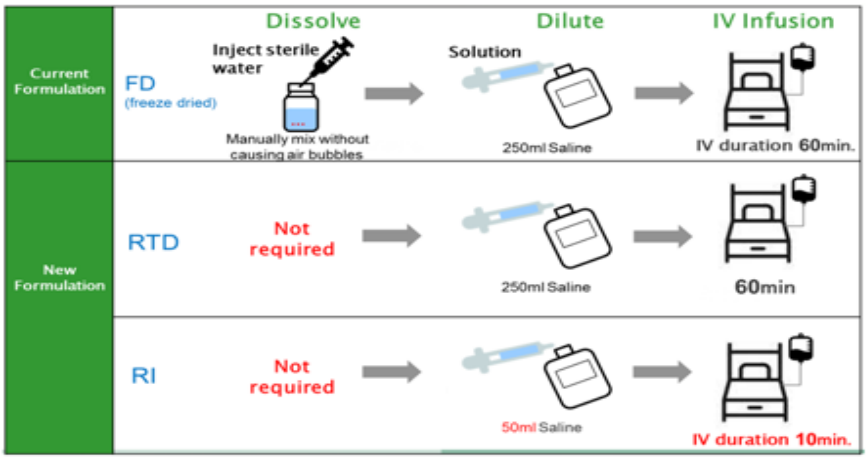
RTD formulation approved in September 2020, leading to signficant cut in costs

SymBio has also been developing more user-friendly formulations. Until December 2020, Treakisym® was a freeze-dried formulation (FD formulation) manufactured by Astellas Deutschland GmbH. In September 2017, SymBio announced the licensing-in of a Treakisym liquid formulation (RTD - Ready to Dilute) from Eagle Pharmaceuticals Inc. in the United States. Although the conventional FD formulation has the advantage of storage at room temperature, it requires the work of dissolving in a solvent and dilution with physiological saline before administration, which takes time and effort. On the other hand, liquid preparations must be refrigerated, but they have the advantage of reducing the work-load by simple dilution with physiological saline, which shortens the preparation. Further, the switch to a liquid formulation can provide substantial savings of the sales-cost ratio. Since the efficacy and administration of the RTD formulation are the same as for the FD formulation, no additional clinical trials were necessary. Providing only

Approval given for time-saving RI administration in February 2022

formulation safety data an application was submitted in September 2019 and approval for the existing indications was received in September 2020, with sales beginning on January 12th 2021. In April 2021, the RTD formulation was also approved for r/rDLBCL. In addition, regarding the RI administration that can be administered in a shorter time, using Bendeka 10-minute administration licensed from Eagle Pharmaceuticals in the US, the concentration and administration time are different, so the company had to confirm safety and pharmacokinetics. Clinical trials were conducted, an application was filed in May 2021, and all indications were approved in February 2022. The administration time is shortened to 10 minutes and the salt content is low, so it is positioned as a formulation suitable for malignant lymphoma patients, many of whom are elderly.

Comparison of FD, RTD, and RI (10-minute administration) formulations



Source: SymBio results meeting

② **Emergence of generics and Symbio's response**

<Evolution of generics in the market>

In February 2022 a number of generics (RTD preparations) were given FDA approval

The entry of Treakisym® generics into the market started in February 2022. On February 15th 2022, Pfizer (Japan) Meiji Seika Pharma, Kowaisei and Towa Pharmaceutical received approval for the manufacture and sale of a generic Treakisym® intravenous dip (RTD formulation). It is relatively easy in Japan, which has a policy of encouraging the take-up of generic drugs, to have a generic approved through the inclusion of a different ingredient to the original drug's composition. However, this can create patent infringement problems.

Three of these companies decided to put off sales, but Towa went ahead

On February 25th 2022, SymBio notified the four companies of concerns about patent infringement. The patent in question, which has also been recognized in Japan, is the property of Eagle Pharmaceuticals Inc., a US company, which is the original licensor of the RTD formulation and RI administration. There was a previous instance in the US of patent infringement involving the Treakisym Bendeka® RI administration. The court in that case found for Eagle Pharmaceuticals (the licensor was Teva) and enjoined the generics makers from selling the product for a prescribed period. On February 28th 2022, approval was given for the RI formulation, which is even more convenient to administer than the RTD formulation, and SymBio began encouraging a switch. On May 11, Meiji Seika Pharma announced it was putting off the posting of drug prices scheduled for June and some generic makers followed Meiji Seika Pharma. With this, the risk posed by generics receded somewhat, however one company, Towa, got as far as posting prices and starting sales.

Indications approved for the

generics were expanded to include r/rDLBCL in June 2022

In November 2022, Towa and Pfizer received approval for generic RI administration, also approved for use in P-BR therapy

In December 2022, SymBio filed a lawsuit against Towa and Pfizer for patent infringement

The indications approved for the four generics makers in February covered indolent B-NHL and MCL, but not r/r DLBCL. In June, Towa received approval for the additional indication of r/r DLBCL. Meanwhile, CLL is covered by exclusive protection during the reexamination period (until 2026) and cannot be included in the indications for generic products. At that time, the P-BR therapy was not approved for the treatment of r/r DLBCL.

However, on November 9th 2022 Towa Pharmaceuticals and Pfizer (Japan) received approval for an RI generic, and Pfizer began sales on December 16th. The indications approved for Pfizer included P-BR for r/r DLBCL (in February 2023 Towa was also permitted to use it in P-BR therapy). In response, SymBio filed a lawsuit against Towa Pharmaceutical on 16th December 2022 for an injunction against the manufacture and sale of generic products, and compensation for damages, claiming possible patent infringement with regard to the RI administration. In addition, on 26th December, a similar lawsuit was filed against Pfizer.

<Effect on sales>

As of 2022 the effect of generics on sales was around JPY200 million

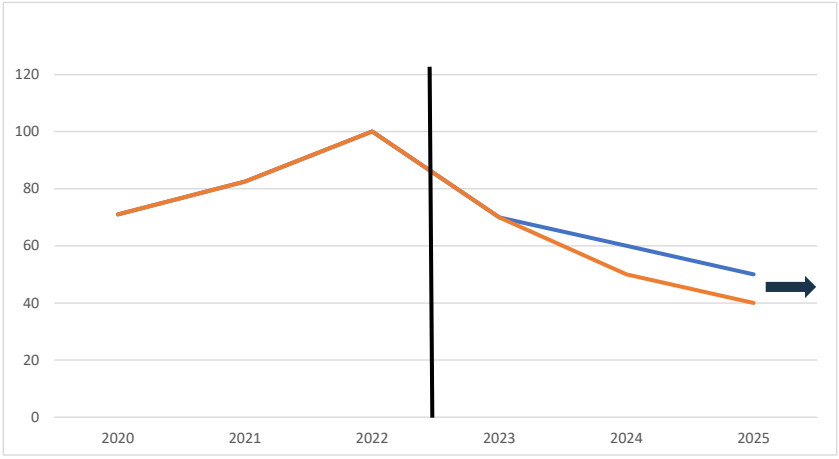
However, due to the entry of Pfizer with its stong brand power into the market, and to the approval for use in P-BR therapy, which has become the mainstream therapy for r/rDLBCL, sales in 2023 are expected to fall 30% to JPY7 billion

As for 2022, the impact on sales due to the entry of generics seems to had been limited to about JPY200 million. In August 2022, SymBio lowered its initial sales forecast of JPY10,992 million by about JPY990 million to JPY10,003 million, estimating the effect of generics on sales at only around JPY200 million. SymBio made its forecast based on details of each medical facility's generic adoption level, the use of new anticancer drugs, inpatient-outpatient ratio, parent organization of the facility (public hospitals are under pressure to adopt generics), the existence or otherwise of accounts for freeze-drying agents (FD formuation), pharmacy department sensitivity to distributors' recommendations, medical facility sensitivity to proposals by MRs (Treakisym Manager – TM), in addition to RI administration usage level and timing of switch to RTD. The sales forecast for the third quarter was JPY2,476 million and for the fourth quarter was JPY2,654 million, but the actual sales for the third quarter was JPY2,481 million, demonstrating, as expected, the accuracy of the estimates. As of mid-October, some 20 medical facilities had confirmed delivery of generics, suggesting a cautious stance toward their adoption.

With the gradual penetration of generics and official dug price revisions sales in 2024 are forecast to come in at JPY4-5 billion, and in 2025 at JPY4-5 billion

In December 2022, however, Pfizer with its strong brand power, entered the market. Additionally, Treakisym® RI administration and generics were approved in the mainstream P-BR treatment of r/rDLBCL. This has necessitated a more cautious view of Treakisym® sales. SymBio expects sales of Treakisym® in 2023 to drop 30% year-on-year to around JPY7 billion. In addition, it seems that sales in 2024 are expected to come in at around JPY5-6 billion yen due to drug price revisions, and sales in 2025 are expected to be JPY4-5 billion yen.

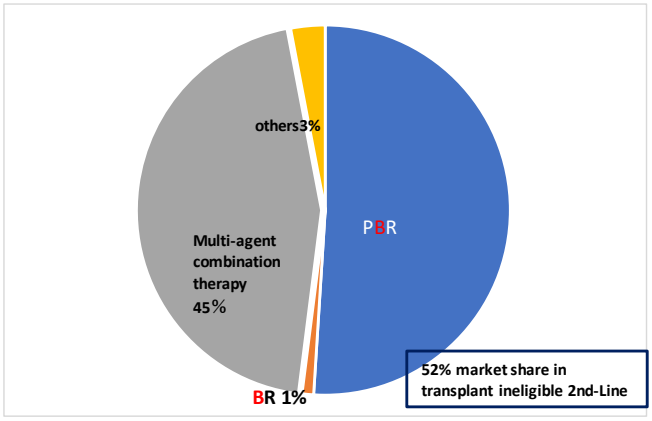
Sales forecast of Treakisym®



Source: Compiled by Fair Research Inc. from interviews

SymBio's plan is to stabilise sales by focusing on expanding Treakisym's share in the r/rDLBCL area	Of course, in the field of hematology and oncology, there is a deep-rooted, relatively cautious attitude toward generics that have a slightly different composition to Treakisym®. In addition, the market share of the B-R therapy and P-BR therapy targeting r/rDLBCL is still only about half, so we can expect an increase in prescriptions due to market share expansion. More specifically, in the treatment of r/rDLBCL, the B-R therapy and P-BR therapy began making inroads in late-line 3rd and 4th line stages but came to be increasingly used in the 2nd line and earlier stages. The company's sales force is focusing on expanding market share in the r/rDLBCL field. Through these efforts, it is hoped that sales of Treakisym® will stabilise at the JPY4 billion level from 2026 onwards.

r/rDLBCL market



Source: SymBio company briefing, February 2023

B: bendamustine=Treakisym®

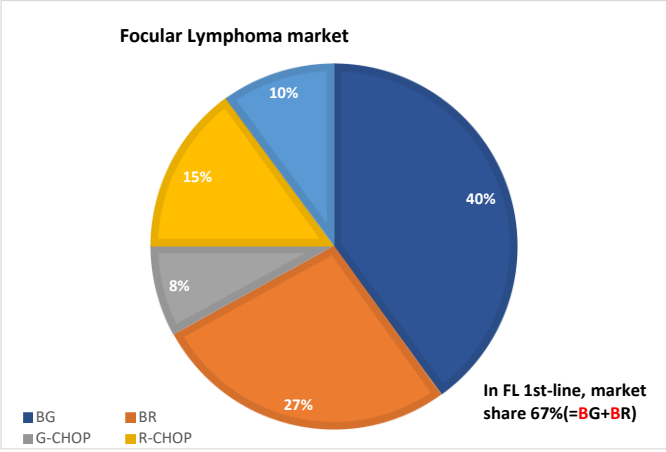
Reference:

No. of cases for treatment with Treakisym® (annual)

①	r/r indolent-B-NHL	around 9,000 cases
②	CLL	around 600 cases
③	1st-Line indolent-B-NHL	around 6,000 cases
④	r/r DLBCL	around 10,000 cases

Source: Compiled by Fair Research Inc. from interviews

In the area of follicular lymphoma (FL), which accounts for about three-quarters of ③1st-Line indolent-B-NHL, Treakisym®'s market share is around 70%.



Source: SymBio company briefing, February 2023

<Potential market size for next major product>

Brincidofovir (BCV) market size

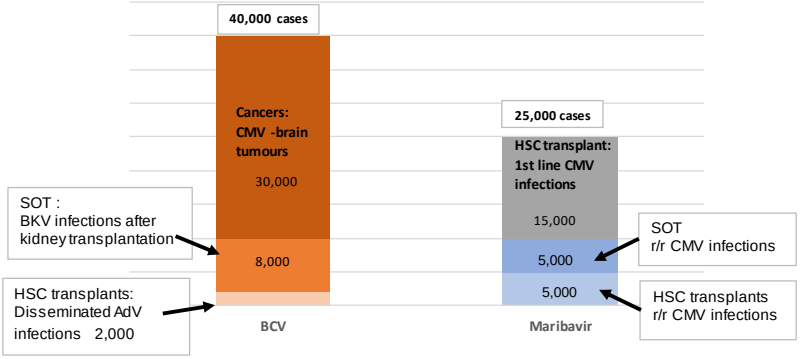
We will here look at the size of three areas which demonstrate SymBio's in-house development policy: ① Disseminated adenoviral infection after hematopoietic stem cell transplantation; ② BK virus infection after renal transplantation; ③ Resistant/refractory CMV infection after hematopoietic stem cell or organ transplantation. The company also plans to develop for blood cancers, such as NK/T-cell lymphoma, in-house, but we do not speculate on size of market because the development plan is not yet clear. Glioblastoma (GBM), a type of solid cancer, is calculated only for reference.

On the other hand, neurodegenerative diseases (multiple sclerosis and dementia of the Alzheimer's type) are outside SymBio's current area of expertise. Collaboration with leading external pharmaceutical companies would be essential and we are currently not including such diseases in our calculation.

The number of target patients is 2,000 for disseminated AdV infection, 8,000 for BKV infection, and 10,000 for resistant/refractory CMV infection

The number of patients in the fields targeted by BCV is approximately 2,000 for ① disseminated adenoviral infection after hematopoietic stem cell transplantation, ② approximately 8,000 for BK virus infection after kidney transplantation, and ③ an estimated approximately 5,000 people each with refractory CMV infection and resistant/refractory CMV infection after organ transplantation.

Target patient population comparison between brincidofovir and maribavir



Figures for Maribavir based on IR Material by Takeda Pharm. 2019 Nov 21
Global data for GBM is based on forecast incidence of cases of GBM in US, EU5, China and Japan (2027)
HCT data based on Bone Marrow Transplantation 2016, Bone Marrow Transplantation 2019
SOT data is based on International Report on Organ Donation and Transplantation Activities, executive summary 2019, April 2021 and Transplantatio

Source: SymBio company briefing, February 2022

BCV's target patients for resistant/refractory CMV marivavir-resistant patients are 5,000

Of the CMV infections after hematopoietic stem cell transplantation, the first-line portion (approximately 15,000 patients) is not indicated for BCV. BCV's target is resistant/refractory CMV infections. About half of the patients with resistant/refractory CMV infection after hematopoietic stem cell transplantation or after organ transplantation (approximately 10,000 in total) show maribavir resistance. Therefore, BCV's target patients for resistant/refractory CMV are approximately 5,000.

Assuming the drug cost per case is JPY3 million, then for three viral infectons the total value comes to JPY45 billion

Assuming, by referencing other antiviral agents, that the drug cost for one case is JPY3 million, then:

① Disseminated adenoviral infection after hematopoietic stem cell transplantation: 2,000 patients×JPY3 million＝JPY6 billion

② BK virus infection after kidney transplantation:
8,000 patients×JPY3 million＝JPY24 billion
③Resistant/refractory CMV infection after hematopoietic stem cell or organ transplantation: 5,000 patients×JPY3 million＝JPY15 billion

From the above we posit a total value for ①～③ of JPY45 billon. However, worth noting is that there is a lot of room for expanded indications in other areas.

For reference purposes, we estimate a value for GBM of JPY90 billion
We infer a very large market for cancers and neurodegenerative diseases caused by viruses

Reference:
Glioblastoma（GBM）: 30,000 patients×JPY3 mil＝JPY90 billion.
Multiple sclerosis (MS): Current market valued at JPY2 trillion

Reference: Pipeline value

<Pipeline Value>

On the basis of a number of variables we accord a tentative 10% discount rate

Here we calculate estimated pipeline values for Treakisym® and for brincidofovir using the DCF methodology. Given inroads made by generics, and hence reduced earnings power, we accord Treakisym® a discount rate of 10% (8% in our previous report).

(a) Preconditions for the Treakisym® pipeline value calculation

Treakisym® sales outlook must take into account the entry of generics

The size of the Treakisym® market will decrease to JPY7 billion in 2023, JPY5-6 billion yen in 2024, and JPY4-5 billion yen in 2025 due to the impact from the emergence of generics. Thereafter, it will continue to decline slightly until 2031, from which point it is assumed that it will shrink rapidly (annual rate of 10%).

Sales promition costs for the year set at JPY1 billion

It is assumed that the sales structure went in-house from 2021, and will mostly switch to liquid formulations (RI administration) from 2023 onwards. In addition, we assume that the unit cost rate for liquid formulations would be around 20%, even with royalties paid to Eagle Industries. Milestone payments to Eagle have already been completed. Sales promotion costs are posited at around JPY1 billion per year due to streamlining of the sales system.

(b) Preconditions for brincidofovir (BCV)

There are too many uncertainties in the BCV pipeline to make a value estimate

It is difficult to calculate for BCV because of the number of uncertain elements. Therefore, for reference purposes only, our calculation relates to: ① disseminated adenoviral infection after hematopoietic stem cell transplantation; ② BK virus infection after kidney transplantation; and ③ resistant/refractory CMV infection after hematopoietic stem cell transplantation or organ transplantation.

<Value of markets targeted>

Target diseases are restricted to AdV infection after hematopoietic stem cell transplantation, BKV infection after kidney transplantation, and resistant/refractory CMV

The foregoing are given values of: ①JPY6 billion; ②JPY24 billion; and ③ JPY15 billion.

<Development schedule and development costs>

Since SymBio has not disclosed actual development cost figures or the timing of regulatory approval or market launch, Fair Research Inc. has made its own predictions (below). Investors should bear in mind that changes may be made.

infection after hematopoietic stem cell transplantation or organ transplantation

Assumptions for BCV development costs and development schedule

(JPY-100mil)

		2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	Image of Ph-3 scale
AdV	SOT－AdV	Ph2 5	Ph3 start 5	Ph3 10	Ph3 10	Applic.& approval	Launch							Ph3:100 cases ＋Historical data
BKV	ZOT-BKV	Ph2 11	Ph2 7	Ph2 finish 4	Ph3 10	Ph3 15	Ph3 15	Applic. & approval	Launch					Ph3:200 cases+Historical data
CMV	SOT-r/rCMV	Ph1b 1	Ph1b 5	Ph1b-Ph2 5	Ph2 5	Ph2 5	Ph2-Ph3 10	Ph3 10	Ph3 10	Applic.& approval	Launch			Ph3:150 cases ＋Historical data
	ZOT-r/rCNV			Ph1b 1	Ph1b 5	Ph1b-Ph2 5	Ph2 5	Ph2 5	Ph2-Ph3 10	Ph3 10	Ph3 10	Applic. & approval	Launch	
	Sub totals	1	5	6	10	10	15	15	20	10	10			
BCV Total		**17**	**17**	**20**	**30**	**25**	**30**	**15**	**20**	**10**	**10**			

Source: Fair Research Inc.

Assuming BCV targeting AdV infections after hematopoietic stem cell transplantation is launched in 2028 and further launches are made in succession

<Milestones>

There are still USD175 million in milestone payments outstanding to Chimerix

SymBio is to pay Chimerix a total of $180 million in milestone payments (including a $5 million contract fee) and royalties. Details of the timing and amounts of milestone payments have not been disclosed, but for the purposes of the calculation we are assuming that payments will be made at the time each clinical indication is launched, and when sales reach a certain level.

<Royalties and manufacturing costs>

We are assuming that royalties of 12% will be paid to Chimerix

The company has simply said that sales royalties to Chimerix will be at the double-digit percentage level. For the purpose of this calculation, we are assuming12%. The manufacturing cost rate has also not been released, so for calculation purposes we are assuming a conservative 20%.

<Sales costs>

Aiming to establish in-house sales structure for Europe and the US

Sales Promotion costs in Europe and the US would come to JPY1 billion for each region, and an additional JPY500 million for Japan

In addition, SymBio is considering a plan to set up a sales structure in Europe and the US in order to establish itself also as a specialty pharmaceutical company overseas. The alternative would be out-licensing the sales rights after in-house development. The number of transplant centers to be covered is about 35 in Japan, while there are around 75 in the US and about 90 in Europe. In order to build and maintain such a sales structure, we posit annual sales promotion expenses of approximately JPY 1 billion in both regions. In Japan this would mean adding about JPY500 million to current Treakisym® sales promotion expenses of JPY1 billion. Finally, since BCV efficacy in humans has already been established we posit probability of success at 60-80%.

Finally, it is necessary to consider company-wide costs, such as new drug candidate discovery and basic R&D, and general admin costs. We posit JPY2.5 billion for R&D costs related to routine discovery and company management.

(c) Results of trial calculation

Treakisym® value: JPY18.7 billion (before tax)

BCV value adjusted for probability of success: JPY41.9-60.4 billion

Calculating the discounted present value under the above preconditions yields the results shown in the table below. The value of Treakisym® (before tax) is estimated at JPY18.7 billion, a significant decrease from the previous estimate (JPY55.7 billion) due to the impact of generics and changes in the discount rate. The value of BCV is estimated at JPY41.9 billion with a success probability of 60% because the underlying premise has been changed to in-house development and in-house sales.

After deducting comapany-wide costs value still comes to JPY35.6-54.1 billion

The value will further increase on expansion into the fields of maligant brain tumours and cranial nerve disorders

The combined value of Treakisym® and BCV comes to an estimated JPY60.6 billion, but if company-wide costs are subtracted, the pipeline value (before tax) comes to an estimated JPY35.6 billion. Assuming an 80% probability of success, the value of brincidofovir is JPY60.4 billion, resulting in: Treakisym® + BCV - company-wide costs = JPY54.1 billion. Although not included in the trial calculations on this occasion, the value of the pipeline will further increase as further indications for BCV are added (GBM, multiple sclerosis, etc.) and applications such as rigosertib are factored in. Even after considering factors such as the tax rate, SymBio's market capitalisation of under JPY20 billion as of July 03, 2023 is probably too low.

Pipeline trial calculation (before tax)

(JPY-100 mil)

	Prob. Of success 100%	Prob. of success 80%	Prob. of success 60%
Treakisym®	**187**	---	---
BCV	788	**604**	**419**
Sub-total	975	791	606
company-wide costs	-250	-250	-250
Total	725	**541**	**356**

Discount rate set at 10%

BCV targets: SOT-AdV、ZOT-BKV、SOT-r/rCMV and ZOT-r/rCMV

Source: Fair Research Inc.

Note: No direct comparison of pipeline value and market capitalisation is possible

<Medium term outlook>

Medium term earnings trajectory

Achieved profitability in 2021, but profit declined in 2022 due to emergence of generics and expansion of BCV development

SymBio achieved profitability in 2021. In 2022, however, the appearance in the market of generic versions of Treakisym®, the company's mainstay product, cast doubts on the idea that it could secure profit growth from expanded sales of Treakisym® while pursuing development of its next mainstay, BCV. Sales for the first indication of BCV (disseminated AdV infection after hematopoietic stem cell transplantation) are expected around 2028, and sales other than Treakisym® cannot be expected until then. It is therefore probably better to consider the profit trajectory not only for 2023 but for the three years to 2025.

The company forecasts an operating loss of JPY330 million in 2023. However, since this is based on conservative assumptions, there is the possibility of a better outcome

First, in the company's forecast for 2023, sales are expected to decline to JPY7 billion, and operating income is expected to turn into a deficit of JPY331 million. The main factors at work here are a sharp drop in sales, an increase in SG&A expenses, and higher production costs. R&D expenses will increase by about JPY825 million, mainly related to BCV, and although SG&A expenses other than R&D expenses will be reduced, overall SG&A expenses will increase by JPY220 million. However, amid concerns about the future of Treakisym®, it is essential to strengthen development of the next mainstay product, BCV. The company expects the cost of sales ratio in 2023 to come in at 21.1%. The ratio in 2022 is ostensibly 24.1%, but this includes the sales milestone payment of JPY550 million to Eagle. Excluding this, the ratio is 18.6%. In addition, the cost ratio in the first quarter of 2023 was 19.5%. The company expects the cost of sales ratio to rise due to falling drug prices, but this appears to be a somewhat conservative expectation. In addition, it is expected that there will be room for further reductions in SG&A expenses, and in the final analysis, it is possible that operating profit will be close to zero.

2023 Company management plan

(JPY mil) (JPY mil)

	2021	2022	2023 (company forecast)	2022 Jan-March	2023 Jan-March
Sales	8,256	10,008	7,000	2,315	1,544
Cost of goods	2,456	2,408	1,474	417	301
COGS ratio	29.7%	24.1%	21.1%	18.0%	19.5%
excl. milestone payments		18.6%			
		Greatly reduced by the change to liquid formulation	deteoriation due to NHI price revision		
SG&A	4,784	5,636	5,857	1,388	1,192
of which, R&D	1,736	2,554	3,380	495	549
(BCV related)	NA	1,111	1,739		
Op. revenues	1,016	1,963	-331	509	51
Net profit	2,032	1,179	-370	163	4

Source: Fair Research Inc., using company earnings reports

From 2024, Treakisym® sales will decline and BCV development will be in full swing. There is an expectation that in 2024-2025 there will be revenues from the global partnership targeting neurodegenerative disorders

For 2024, it appears that further inroads made by generics and revisions to official prices will depress sales to the JPY5-6 billion level. Meanwhile, in terms of R&D expenses, there will be further progress in BCV development (such as Phase-3 clinical trials for AdV infections), while the cost of establishing clinical facilities for BKV infection after kidney transplantation will level off. It seems likely therefore that there will be no change on 2023 levels. By the end of 2024, or at the latest by 2025, SymBio aims to conclude a joint research and development agreement with a global mega-pharmaceutical company in the area of neurodegenerative diseases based on the results of non-clinical trials to date. SymBio expects JPY10 billion in development cooperation funds through this global partnership.

Assuming that development cooperation funds from the global partnering are JPY2 billion for 5 years, there is a possibility that the company will avoid falling deeply into the red in 2024 and 2025

Sales of BCV for its first indication, disseminated AdV infection after hematopoietic stem cell transplantation, are expected in 2028, until which time sales of products other than Treakisym are unlikely. The prospective development collaboration fee is therefore essential to complete the in-house development of BCV (for purposes other than neurodegenerative diseases).

It is not possible to predict how many billions of yen will be disbursed in increments of JPY100 million from this development cooperation fund. However, if we assume that JPY2 billion will be paid in 5-year increments (2024-2028), the company should not encounter serious losses in in 2024 and 2025.

Medium term earnings JPY100-mil

Medium term	2023	2024	2025
Sales			
Treakisym	70.0	50～60	40～50
Development fees from partnering		20	20
Gross profit	0.0	59～67	51～59
R&D	33.8	32	35
BCV : infections following SOT,ZOT	17.4	17	20
Others	16.4	15	15
Sales costs	24.6	24	24
Milestone payments to Chimerix	0.0	0	0
Operating revenues	-3.3	4～12	-6～4

Close to zero

Source: calculations by Fair Research Inc.

However, if BCV development targets are expanded beyond expectations, or if BCV development accelerates, then losses for the company could also grow

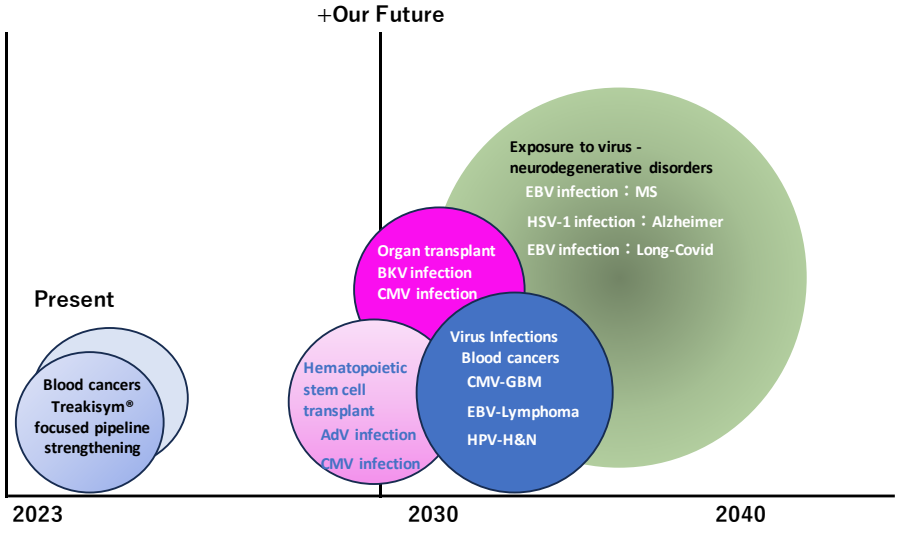
However, if the scope of BCV development expands or accelerates more than expected, the deficit will increase. Please note that the amount will vary depending on the scale and timing of development cooperation funds from the global partnering. From 2026 onwards, there are many uncertain factors, such as the expansion of BCV development and whether sales of Treakisym® will stabilize, making it difficult to forecast earnings over the medium term.

Given SymBio's strong product development drive available funds may not be sufficient

Currently (as of the end of March 2023), cash and deposits on the balance sheet stand at around JPY5,939 million, and we can expect development cooperation funds of about JPY10 billion through the global partnering. However, for SymBio, which has a strong drive to develop products, it is not possible to predict whether these funds will be sufficient.

＜Conclusion＞	Conclusions
2023 repesents a major climaceric for SymBio Major inroads being made by generics POC achieved for IV BCV in humans	2023 could turn out to be a major turning point for SymBio. The company has for many years nurtured the market for Treakisym®, which has become its biggest earner, but generics have begun eating into this in a big way in 2023. Meanwhile, the company has positioned BCV as its next pillar of global growth and, in May 2023, established POC in humans for BCV's first indication, disseminated adenovirus infection following hematopoietic stem cell transplantation. Subsequent indications (BK virus infection after kidney transplantation, resistant/refractory CMV infection after hematopoietic stem cell transplantation or organ transplantation) are also providing opportunities for in-house development.
Research can now be promoted using US state funding and using the facilities, intellectual properties and personnel of NINDS and NIAID	In 2023, SymBio concluded cooperative research and development agreements (CRADA) with two research institutes belonging to the National Institutes of Health (NIH), the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of Allergy and Infectious Diseases (NIAID). Signing CRADA with two institutes coming under the aegis of NIH, he world's largest life sciences and medical research institute, means that research will be promoted using the US national budget, research facilities, intellectual property, and human resources owned by NINDS and NIAID. That is why CRADA can only be concluded with projects that will lead to paradigm shifts. In addition, the licenses ensuing from the research are controlled solely by SymBio.
For the time being, the company will pursue global development targeting post-transplantation infectious diseases From 2030 onwards, it will participate fully in the area of cancers and neurodegenerative disorders caused mainly by exposure to viral infections	For the time being, SymBio plans to concentrate on developing BCV for infectious diseases after hematopoietic stem cell transplantation or organ transplantation for the global market. After 2030, the company then plans to enter into full-scale development in the area of cancers caused by viral infection and in the area of neurodegenerative diseases caused by exposure to viral infection. It will not be easy to pursue these targets simultaneously, but if successful, there is no doubt that a very large market awaits. The support of investors who value SymBio's development ambitions is essential.

SymBio business development - image



Source: company briefing, February 2023

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