SymBio Pharmaceuticals Ltd.

(4582 GROWTH) Issued: 30 September 2024

BCV: Heading for a global partnership in 2025

Two clinical trials to expand BCV's indications have begun

SymBio now stands at an important crossroads. The market for Treakisym®, which for many years has been the company's main source of income, has been seriously eroded by generics. Meanwhile, it was announced in May 2023 that Brincidofovir (BCV), had established proof-of-concept in humans for its primary indication (disseminated adenovirus (AdV) infection after hematopoietic stem cell transplantation), and was the subject of promising Phase 2 data presented at the American Society of Hematology (ASH) in December 2023. The design of Phase 3 is currently under consideration. Following this, a clinical trial (Phase 2) targeting cytomegalovirus (CMV) infection after hematopoietic stem cell transplantation was initiated in February 2024, with the first patients enrolled in June. Consideration is also being given to resumption of Phase 2 for BK virus infection after kidney transplantation. The company has thus been developing BCV to target infections after hematopoietic stem cell transplantation (HSCT) or organ transplants, but as the next step, in August 2024, the company began prioritising clinical development (Ph1b/2) targeting malignant lymphomas, which are blood tumors (NK/T cell lymphomas, PTCL, etc.)

The market for BCV for infections following HSCT and organ transplantations is valued at JPY256 billion

The market for BCV targeting disseminated adenovirus infections after HSC transplantation, which is expected to be launched around 2028, is estimated at JPY16.8 billion, followed by the market for BK virus infections after kidney transplantation, currently under development, which is estimated at JPY67.2 billion, and the market for BCV targeting resistant/refractory CMV infections after HSC transplantation or organ transplantation, which is estimated at around JPY42 billion. Penetration into the JPY126 billion market for first-line CMV infections after HSC transplantation is also expected. In total, a market of JPY252 billion is in sight. Furthermore, the markets for the next targets, cancer caused by viral infections (NK/T cell lymphoma, glioblastoma GBM, etc.) and neurodegenerative diseases caused by exposure to viral infections (multiple sclerosis and Alzheimer's dementia), are also likely to be significant.

All-out efforts for early commercialization of BCV and global partnering

Results of studies examining the efficacy of combining BCV with immune checkpoint inhibitors are expected to become available in 2024. Two programs, one for adenovirus (AdV) and one for cytomegalovirus (CMV), are expected to move into late-stage development in 2025. Progress in clinical development (Phase 1b) for hematological malignancies is also expected. In addition, clinical trials (Phase 1) in the field of solid tumors may start in 2025.Further, it is clear that SymBio is currently discussing a global partnership with several companies, and hopefully in 2025 will conclude a partnership with one of them.

Note: This report is the English-language version of the original Japanese-language report issued on September 30th, 2024, to which you should refer for precise details.

Basic Report (revised)

Fair Research Inc.

Tsuyoshi Suzuki

Company Outline	
Location	Tokyo
CEO	Fuminori Yoshida
Established	March 2005
Capital	JPY18,328 mil
Listed	Oct 2011
URL	www.symbiopharma.com
Industry	Pharma
Employees	110 (consol)
Key Indicators (Sep. 27 2024)	
Share Price	257
52-week high	450
52-week low	149
Shares outstanding	45,910,081
Trading Unit	100 shares
Market cap	JPY11,799 mil
Dividend (forecast)	0.0
EPS (forecast)	-84.1
Forecast PER	NM
Actual BPS	JPY134.3
Actual PBR	1.91X

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	Stock Price JPY Low
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
2022/12 Actual	10,008	NM	1,963	NM	1,999	NM	1,179	NM	30.2	1,284	610
2023/12 Actual	5,589	-44.1	-811	NA	-736	NM	-1,962	NM	-49.1	651	229
2024/12 Forecast	2,623	-53.1	-3,702	NA	-3,524	NA	-3,628	NA	-84.1		

Company Philosophy and Outline

＜Business Model＞

The company is a pharmaceutical venture business with global ambitions aiming for high returns using a niche strategy. Operating without laboratories or manufacturing facilities reduces much of the risk inherent in drug discovery

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 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 SymBio is a specialty pharma using a high return, high 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 mainly in hematology.

③ Global licensing
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 its 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

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

The elements which underpin this track record are the company's human resources and organisation. Hence, one-third of its 141 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.

＜Product Pipeline＞

1. Brincidofovir (SyB V-1901)

Next flagship product candidate: brincidofovir (BCV), an antiviral drug targeting various diseases

SymBio's next flagship product candidate, the antiviral drug brincidofovir (BCV), is currently under development to target various disease areas. The diseases SymBio is targeting for development are, firstly, infections caused by immunodeficiency following, for example, transplantation (adenovirus, cytomegalovirus, BK virus), and secondly cancers caused by viral infections (NK/T-cell lymphoma, GBM etc.,) and thirdly, areas of brain neurodegenerative diseases caused by exposure to viral infections (EB virus-related diseases such as multiple sclerosis, herpes simplex virus type-1 (HSV-1)) infections, such as Alzheimer's-type dementia)).

Promising results announced by ASH in December 2023

Pipeline	Indication(s)	Clinical Trial Phase 1	Clinical Trial Phase 2	Clinical Trial Phase 3	NDA*1	MA*2
SyB V-1901 Antiviral Drug (IV)	AdV infection Immunocompromised patients including post HSCT		Phase 2 study on going			
	Cytomegalovirus infection Post HSCT		Phase 2 study on going			
	NK/T-cell Lymphoma	Phase 1b study on going				
	BKV infection Post kidney transplantation		Phase 2 study on going			
	Preclinical studies ongoing for EB virus/multiple sclerosis, HSV-1/Alzheimer's disease、Cytomegalovirus/GBM					

Source: SymBio Pharmaceuticals home page

NDA:New Drug Application MA: Marketing Approval

Reference: Background to product licensing-in

BCV is a highly active multiviral drug originally developed by Chimerix Inc. in the United States. On October 1, 2019, SymBio announced the acquisition from Chimerix of exclusive global licensing rights (development, manufacturing and sales) for BCV to target all diseases except Orthopox (smallpox and monkeypox amongst others) as a strategic product to succeed Treakisym. Until this point, SymBio had been licensing in products from overseas and developing them mainly for the Japanese market, but with this agreement they are now in a position to license out developed products globally. (In September 2022, Chimerix transferred the license related to BCV to Emergent BioSolutions Inc., but the rights acquired by SymBio are not affected)

BCV is a highly active, broad-spectrum antiviral agent

It is very safe

(1) Special characteristics of brincidofovir

Compared to other antiviral drugs such as citodofovir (CDV) and foscarnet (FOS) brincidofovir is a highly active multiviral drug. A broad-spectrum drug similar to brincidofovir (BCV) is cidofovir (CDV), but cidofovir is nephrotoxic and difficult to administer. In contrast, brincidofovir (BCV) has low toxicity and an excellent safety profile despite its greater level of activity.

BCV's three advantages:

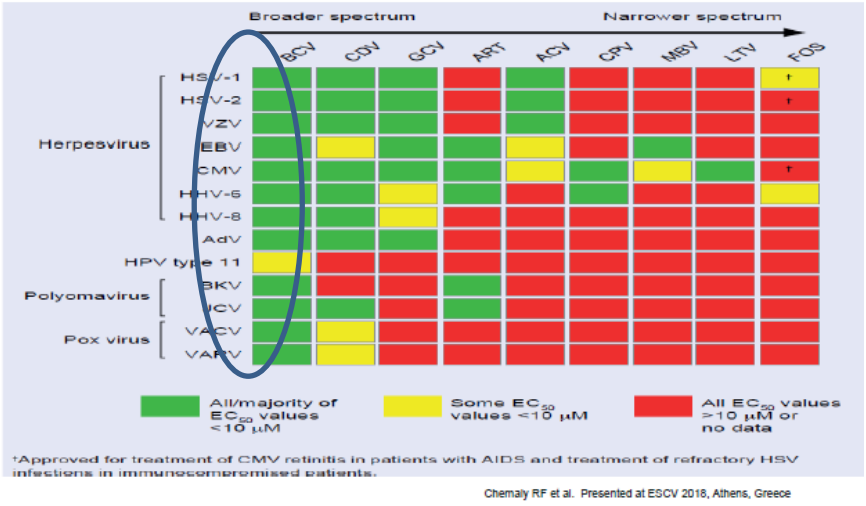
◎ Superior antiviral effect against a wide range of double-stranded DNA viruses

It has high blood-brain permeability

◎ Has none of the serious side effects of other antiviral drugs, such as nephrotoxicity or bone marrow suppression

◎ Has high blood-brain barrier (BBB) permeability

Highly active and broad-spectrum brincidofovir (BCV)



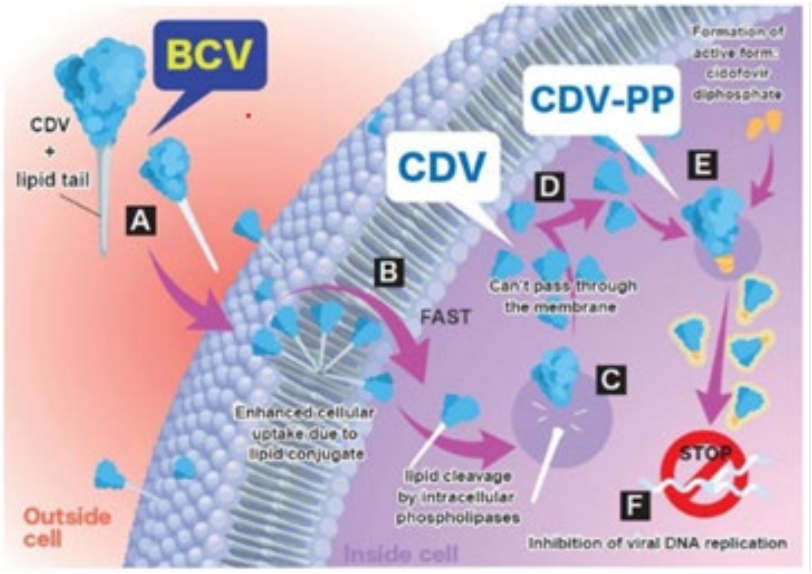
Chemaly RF et al. Presented at ESCV 2018, Athens, Greece

Source: Chimerix Inc.

Note: The lower the EC50 (the concentration at which a drug or antibody exhibits a maximum response of 50% above the lowest value), the higher the activity. The above diagram is color-coded according to high and low EC50, with green indicating high activity and red indicating low activity. The BCV reading on the far left is green for various viruses = broad spectrum.

Reference: Brincidofovir mechanism of action

Brincidofovir (BCV) is a compound in which cidofovir (CDV) is bound to a fatty chain (hexadecyloxypropyl: HDP). After being rapidly incorporated into the lipid bilayer and efficiently transferred into the cell, the fatty chain is cleaved by metabolism with intracellular phospholipase, and the activated form (CDV-PP: CDV diphosphate) is retained in the cell for a long time, resulting in dramatically improved antiviral activity. In addition, the HDP binding prevents accumulation in renal tubular epithelial cells by the OAT-1 transporter, and the level of CDV released into the blood is low, thus avoiding the fundamental problem of CDV nephrotoxicity. (Since CDV does not have a fatty chain, it becomes a substrate for OAT-1 and accumulates in renal tubular epithelial cells, which easily causes nephrotoxicity.)



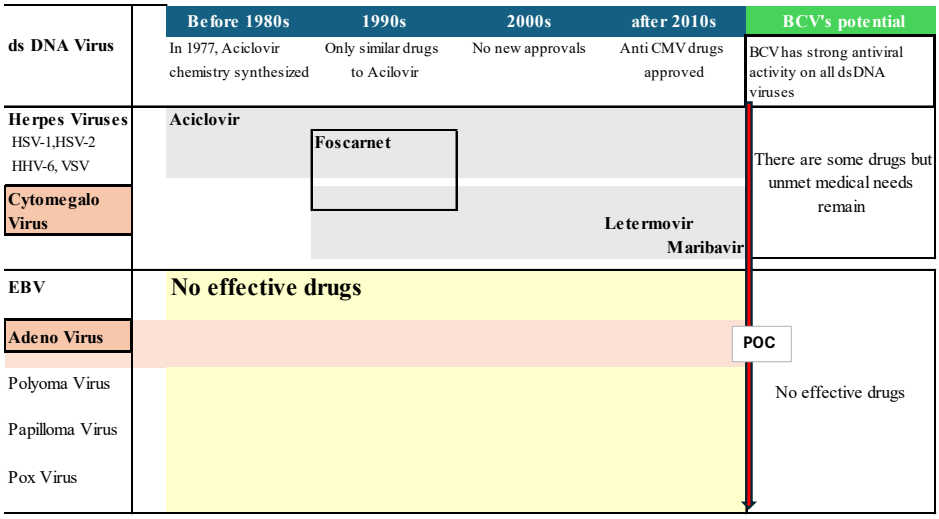
Source: SymBio IR materials

(2) Promising areas of BCV effectiveness

The development of BCV is expected to fill in gaps such as EB virus, adenovirus, and polyomavirus, for which no antiviral drugs have been developed

The first dsDNA virus drug was Aciclovir (ACV) in 1977. In the 1990s, similar drugs such as Forscarnet (FOS) and Ganciclovir (GCV) were developed. No new drugs appeared in the early 2000s until, in 2017, Letermovir (LTV), which Merck acquired from AiCuris, was approved and released. Maribavir, which Takeda acquired when it bought Shire, was approved. Thus, there are not that many antiviral drugs for dsDNA viruses. In addition, the targets against which the existing antiviral drugs are active are herpes viruses and cytomegalovirus (CMV). Since there is nothing available for the treatment of EB virus, adenovirus, polyomavirus, human papilloma virus, etc., much is expected with the appearance of highly active, broad-spectrum BCV.

History of development of drugs to treat double-stranded DNA (dsDNA) viral infections



Source: SymBio company briefing, August 21, 2024

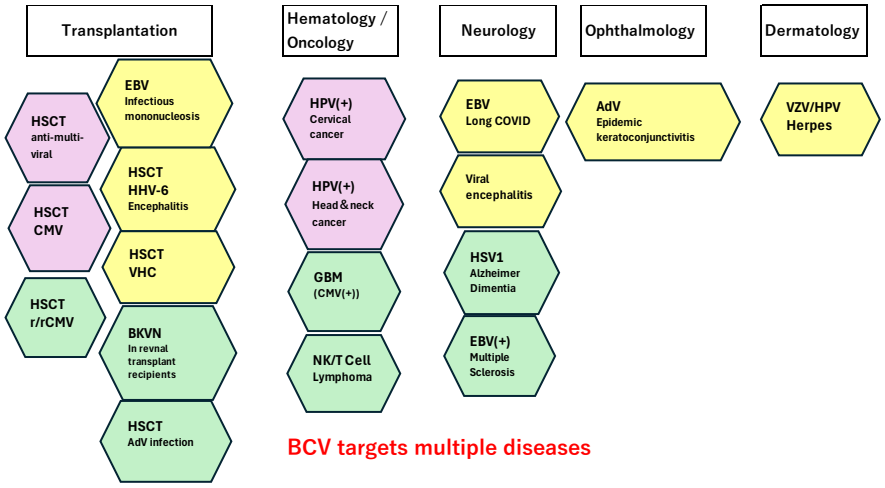
BCV is also expected to be effective in areas where there are concerns about side effects from, and resistance to, existing antiviral drugs

Although there are antiviral drugs to treat herpes viruses and cytomegalovirus, they come with problematic side-effects, such as nephrotoxicity, bone marrow suppression, and the emergence of drug resistance. BCV is expected to overcome these problems.

Target diseases include post-transplant infections, blood tumors, solid cancers, and neurological disorders

The viruses targeted by BCV are associated with a variety of diseases. Adenovirus, cytomegalovirus, and polyomavirus are usually present in many adults, but without showing symptoms (they are in a state of latent infection). However, immunosuppressants are administered to suppress rejection during hematopoietic stem cell transplants and organ transplants, and the reactivation of these viruses can cause serious infections during such immunosuppressed states. In addition, the EB virus has been linked to blood tumors such as NK/T cell lymphoma, and its link with multiple sclerosis has also been revealed. Human papillomavirus (HPV) is known to cause head and neck cancer and cervical cancer. In addition, in recent years, it has been pointed out that the cytomegalovirus is associated with brain tumors.

BCV commercialisation potential



Source: SymBio company briefing, August 2024

(3) Brincidofovir (BCV) development pipeline

① Disseminated adenovirus infection after HSC transplantation

The first target is disseminated adenovirus infection after hematopoietic stem cell transplantation

Generally, in hematopoietic stem cell transplantations, irradiation and immuno-suppressants are used to suppress rejection, but this leaves the patient susceptible to viral infection. Conventionally, antiviral agents such as cidofovir (CDV) and foscarnet (FOS) have been used, but there have been concerns about side effects such as nephrotoxicity. BCV, which has low nephrotoxicity, is therefore an important product that will support SymBio's goal of becoming a specialty pharma in the hematology field.

Looking back at the course of development;

(a)Decisions on development policy

In August 2020 the company selected adenovirus infections following hematopoietic stem cell transplantation as its first target

Following a Scientific Advisory Board meeting held in February 2020, SymBio announced in August 2020 that its first development target would be adenovirus infection after hematopoietic stem cell transplantation, with trials targeting children in particular being given priority. Additionally, since the safety of the drug had already been confirmed by data from Chimerix it was decided to start with a dose-finding study (Phase 2). Note that development for adults is scheduled to begin once POC is established in pediatric trials).

(b)Trials protocol

Filed for Phase2a clinical trials in March 2021 and received Fast Track designation from FDA in April, with FPI in August

An application for the international joint clinical trial Phase 2a (ATHENA trial) was submitted to the FDA along with a Fast Track designation application in the United States on March 10, 2021, and on April 26, the FDA granted Fast Track designation to the development program for pediatric adenovirus infection. The first patient enrollment (FPI) was achieved on August 16, 2021. A clinical trial application was submitted in the UK in January 2022.

Clinical trial designs involve increasing the dosage in stages to check safety and tolerability (Phase-2a ATHENA trial; 4 groups, approximately 6 patients in each group). Target patients are immunocompromised children with AdV (mainly allogeneic hematopoietic stem cell transplant patients).

In terms of design, 4 groups of around 6 cases per group

Cohort 1 BCV 0.2mg/1kg body weight, twice per week for min. 4 weeks
Cohort 2 BCV 0.3mg/1kg body weight, twice per week for min. 4 weeks
Cohort 3 BCV 0.4mg/1kg body weight, twice per week for min. 4 weeks
Cohort 4 BCV 0.4mg/1kg body weight, onc per week for min. 4 weeks

(c)Establishment of POC in human subjects

In May 2023 POC was established in 24 cases up to Cohort 3

On May 29, 2023, SymBio submitted clinical data to the FDA for a total of 24 cases (Cohort 1: 8 cases, Cohort 2: 9 cases, Cohort 3: 7 cases). As a result, POC (Proof of Concept) was confirmed.

(d) Promising ASH data released

Promising Phase 2 results were announced at ASH in December 2023

After establishing POC, observation of Cohort 3 continued, and an oral presentation was made at the American Society of Hematology Annual Meeting (ASH) in December 2023 based on data from a total of 27 cases. Here, it was confirmed that the results were positive regarding efficacy and that there were no serious concerns regarding safety.

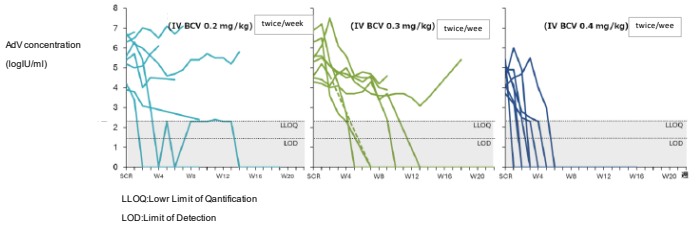
Efficacy: Antiviral activity

Confirmation of antiviral activity in a dose-dependent manner

Twice weekly administration of 0.4 mg/kg (Cohort 3): AdV cleared from blood in all cases (90% within 4 weeks).

Furthermore, from a comparison of Cohorts 1, 2, and 3, it can be inferred that antiviral activity increases in a dose-dependent manner.

	Cohort1 (n=8)	Cohort2 (n=9)	Cohort3 (n=10)
Mean duration of BCV IV treatment, Weeks(Range)	6.2(0.6-13.7)	8.8(1.0-13.4)	5.1(2.6-10.9)
Median duration of BCV IV treatment, Weeks(quartile range)	3.3(4.7)	8.0(6.0)	4.0((2.9)
Number of patients who achieved viral clearance(%)	2(25%)	3(33%)	10(100%)
Viral clearance uopon or before completion of the initial 4-week BCV IV(%)	1(13%)	1(11%)	9(90%)
Mean duration of BCV IV treatment, weeks(range)	8.6(3.4-13.7)	8.1(1.0-13.4)	5.1(2.6-10.9)
Median duration of BCV IV treatment, weeks(quartile)	8.6(5.1)	7.4(7.7)	4.0(2.9)



LLOQ:Lowr Limit of Qantification
LOD:Limit of Detection

In Cohort 3 there was a relatively rapid decrease of virus in the bloodstream in all cases

Source: SymBio IR materials, December 11 2023

Note: Quartile data
When data is sorted by size, the quartiles are the values that divide it into four equal parts. A large interquartile range suggests a large dispersion in the data

The line graphs above show changes in the amount of blood virus in each case. It can be observed that in Cohort 3, the amount of blood virus in all cases decreased to below the limit of detection (LOD) at a relatively early stage. On the other hand, in Cohorts 1 and 2, there were cases where the viral load did not decrease even after a prolonged treatment period. Inadequate doses resulted in low antiviral activity, prolonged administration in some cases, and widening of the interquartile range.

Safety

The treatment produced no serious adverse events

Among all 27 patients, there were no treatment-related serious adverse events (Grade 4 or higher), including gastrointestinal toxicity and hepatotoxicity, which were observed with oral BCV formulations. (The fact that SymBio focused on injectable drugs rather than oral drugs at the time of introduction is evidence of the company's judgement.) There were 6 patients for whom administrations were discontinued due to adverse events, of which 3 cases were due to treatment-related adverse events. Only one patient in Cohort 3 had a Grade 3 increase in AST, but this disappeared after discontinuing treatment. In all seven cases of treatment-related adverse events, the adverse events resolved after administration ceased. The mechanism of liver damage caused by BCV (e.g., increased AST and transaminase levels) is unknown, but it is temporary and reversible.

All treatment-related adverse events were temporary and reversible

	Cohort 1 0.2mg/Kg	Cohort 2 0.3mg/Kg	Cohort 3 0.4mg/Kg
No. of cases	8	9	10
Safety			
Adverse events related to treament	**2**	**3**	**2**
Administration stopped due to adverse event	3	2	1
of which, related to treatment	**1**	**1**	**1**
of which, grade 2	1		
of which, grade 3		1	1
	(diahrrhea)	(Transaminitis)	(Elevated AST)

Source: "Preliminary Results of a Phase2a Clinical Trial to Evaluate Safety, Tolerability and Antiviral Activity of Intravenous Brincidofovir in Immunocompromised Patients with Adenovirus Infection" Abstract from ASH 2023

AdV in stools also disappears in a dose-dependent manner

Additionally, the results of this Phase-2a study have been selected for study at the Pediatric Best Abstracts session of the 2024 Tandem Meetings (joint meetings of the American Society for Transplantation and Cell Therapy and the International Blood and Marrow Transplant Center) held in February 2024. Here, data was added on the antiviral effect against AdV in stools, and reports submitted on the disappearance of AdV in stools in a dose-dependent manner. Furthermore, AdV in stools is known to become positive in children prior to AdVemia and is monitored as an early indicator in routine clinical practice in Europe and elsewhere.

Based on the data accumulated so far, it has been determined that the selection of the recommended dosage is complete

(e)Current situation

Since one of the objectives of this study was to set the recommended dose, the top-line data from ASH (data up to Cohort 3) was regarded as able to verify the safety and efficacy of the drug, and the recommended dose (0.4 mg/kg, twice a week) was selected. In fact, based on the data up to Cohort 3, a patent for the use of injectable BCV for AdV infection was given accelerated approval in Japan (announced on January 19, 2024). The life of this patent is 20 years from the date of application, until August 2043. Looking ahead, SymBio plans to apply for the same patents in Europe, the United States, and elsewhere.

A usage patent (valid for 20 years) has actually been approved

Now considering the design of Phase 3 following completion of Cohort 4 observation

Additionally, administration and observation of seven cases in Cohort 4 has already been completed, and the design of Phase 3 trials (a randomized controlled trial with approximately 150 cases) is currently under consideration. Fair Research hopes that the next stage (outline of Phase 3) will become clear by 2024. Therefore, the plan for product launch in 2028 is unchanged.

② Cytomegalovirus (CMV) infection after hematopoietic stem cell transplantation

CMV infections following hematopoietic cell tranplantations has emerged as the next target

SymBio has begun developing a treatment for CMV (cytomegalovirus) infections following hematopoietic stem cell transplantations

Half the patients evidenced resistance to Maribavir, which had been approved earlier

Development of BCV had been put on the back burner because Takeda Pharmaceutical's Maribavir had already been developed for cytomegalovirus infections after hematopoietic stem cell transplantation. However, doctors who conducted clinical trials of Maribavir requested BCV for patients who showed resistance to Maribavir (44.3%). SymBio decided to also undertake development targeting CMV infections, and applied for a change to the ATHENA trials protocol to include CMV infections in the development of BCV for infections after HSC transplantation. The application was accepted by the FDA in February 2024, and the first patient was enrolled in June 2024.

BCV is thought to be less susceptible to resistance mutations than Maribavir

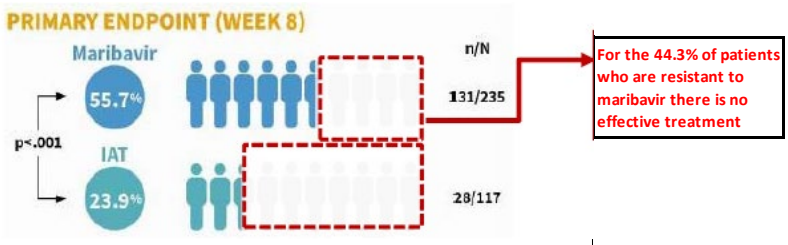
BCV is thought to be less susceptible to resistance mutations than Maribavir. Maribavir's target molecule is a protein kinase called U97, which is prone to resistance mutations, whereas BCV and CDV's target molecule is a viral DNA polymerase called UL54, which is essential for viral replication and therefore is thought to be less susceptible to resistance mutations. In fact, no resistance mutations have been detected in clinical trials of BCV.

Effectiveness of Maribavir

- 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 we

Source: SymBio company briefing, February 2023

Phase 2 will be a 3-cohort study to find optimal dosage

Top-line results for a targeted 18 subjects expected in 2025

However, this protocol change will not affect the development schedule for AdV infections. Phase 2 (ATHENA study) for CMV infections is a dose-finding study with three cohorts and a target case number of 18. Development is underway with the aim of obtaining top-line results by 2025. Several cases have already been enrolled, and high efficacy appears to be observed.

③ Polyomavirus infections

Polyomaviruses (BK virus, JC virus, etc.) also cause severe infections.

The main polyomaviruses that infect humans are the BK virus and the JC John Cunningham) virus (as well as the MCP virus, which causes Merkel cell carcinoma). Polyomavirus is mostly asymptomatic in healthy individuals, and mainly infects the urinary system and lymphatic tissue as a latent infection.

	However, when the immune system is weakened, the virus reactivates, leading to severe infection. BK virus infection after kidney transplantation results in graft rejection in approximately half of cases. JC virus is the causative agent of progressive multifocal leukoencephalopathy (PML), designated as an incurable disease. The median survival time for PML is only three months. Although it was once a very rare disease, cases of PML occurring in patients with immunodeficiency due to HIV infection are being reported.
BCV is expected to have a therapeutic effect in suppressing the proliferation of polyomavirus	In November 2022, SymBio entered a data provision agreement with the Pennsylvania State University School of Medicine for validation and testing of BCV on a mouse model infected with polyomavirus. In July 2024, the results of the research were published as a paper in the journal mBio, showing that BCV suppresses the proliferation of polyomavirus. **◎Primary culture studies using renal epithelial cells and cerebral cortical cells** **・BCV selectively suppresses virus production after polyomavirus inoculation** **・It was suggested that the suppression of virus production involves a reduction in viral T antigen (a viral protein)** **◎Tests using a mouse model** **・BCV suppresses polyomavirus production in the kidney and brain at relatively low doses** **・The inhibitory effect on virus production in chronic polyomavirus infections was also confirmed in immunodeficient mouse models**
The company has also started development of a treatment for BK virus infection after kidney transplantation An international joint Phase-2 clinical trial plan notification was submitted to the PMDA in June 2022, and a clinical trial plan notification to the Australian authorities was submitted in August, with the first administrations being conducted in December	**BK virus infection following kidney transplantation** SymBio expects to conduct development in Japan, Australia, and one other country. On June 14, 2022, plans for an international joint Phase 2 clinical trial of BCV targeting BK virus were submitted to the PMDA. In addition, on August 22, 2022, a clinical trial plan notification was submitted to the Australian Department of Health, Therapeutic Goods Administration (TGA). This international joint effort will first conduct a dose-evaluation study using 12 patients in each of three groups. First administrations were carried out in Australia on December 13, 2022. Cohort 1 BCV 0.3mg/1kg body weight, twice weekly for 8-14 weeks Cohort 2 BCV 0.4mg/1kg body weight, twice weekly for 8-14 weeks Cohort 3（expanded cohort） BCV recommended dose twice weekly for 8-14 weeks
Delays occurred due to time required for case accumulation. Suspended due to protocol review	Initially, the company planned to complete Phase 2 in 2025, but due to delays in canvassing cases, decided to review the study protocol again in August 2023, giving priority to other diseases (CMV infections after organ transplants and brain tumors for which there is no effective treatment). The company is currently reviewing the study design, including patient selection criteria, and is preparing to resume the study with a plan to restructure its development strategy by 2024.
In March 2024, SymBio received orphan drug designation in Europe for the prevention of AdV and CMV infections in immunocompromised patients	In March 2024, SymBio received orphan drug designation (for rare diseases) in Europe for the prevention of AdV and CMV infections in immunocompromised patients, and was granted exclusive first-mover sales rights in the EU for 10 years after launch.

The EB virus is associated with hematological tumors

④ Blood cancer (NK/T cell lymphoma, peripheral T cell lymphoma, DLBCL, etc.)

The EB virus is a tumor virus isolated from Burkitt's lymphoma, a type of hematological tumor, as the first human cancer virus (in 1964), and is known to be associated with various cancers, such as nasopharyngeal cancer, Hodgkin lymphoma, NK/T cell lymphoma. However, infection does not necessarily mean carcinogenesis, as genetic changes in infected cells are thought to be involved.

In April 2023, SymBio signed a Collaborative Research and Development Agreement (CRADA) with the U.S. National Institute of Allergies and Infectious Diseases (NIAID) to conduct preclinical trials to evaluate the efficacy of BCV for EBV-associated lymphoproliferative disorders.

NK/T lymphoma is prevalent in Asia and no standard treatment exists

Note: NK/T-cell lymphoma and peripheral T-cell lymphoma (PTCL)

NK/T cell lymphoma is a type of malignant lymphoma derived from NK cells or T cells. It mainly occurs as extranodal NK/T cell lymphoma around the nasal cavity or on the skin. This disease is more prevalent in East Asia and South America than in Europe and the United States, and accounts for less than 1% of non-Hodgkin's lymphomas in Europe and the United States, but about 10% in East Asia (China). Most NK/T cell lymphomas are positive for EB virus. As no standard treatment has been established, the need to development new therapies is urgent.

Dispersion of NK/T cell 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

Peripheral T-cell lymphoma (PTCL) does not respond well to first-line therapy

No standard treatment has been established for refractory or recurrent PTCL

Peripheral T-cell lymphoma (PTCL) is a rare type of malignant lymphoma that accounts for approximately 7% of non-Hodgkin's lymphomas. PTCL is a general term for lymphomas derived from T cells that have migrated to peripheral tissues after differentiation and maturation in the thymus, and includes various disease types, with the main types being peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), adult T-cell leukemia/lymphoma (ATL/L), angioimmunoblastic T-cell lymphoma (AITL), and anaplastic large cell lymphoma (ALCL). Except for some disease types (ATL/L, ALK-positive ALCL), first-line treatment involves multi-drug chemotherapy and radiation therapy, but these are not always sufficiently effective. For recurrent/refractory PTCL (r/rPTCL), various therapeutic drugs (Remitoro, Darvias, Ezharmia, etc.) are used, but a standard treatment has not been established, so the development of new therapeutic drugs is needed.

Major types of NK/T-cell lymphoma and peripheral T-cell lymphoma

Slow progression type	Aggressive type	Very aggressive type
T-cell large granular lymphocytic leukemia	Peripheral T-cell lymphoma not otherwise specified (PTCL-NOS)	Aggressive NK-cell leukemia (ANKL)
Adult T-cell leukemia/lymphoma	Adult T-cell leukemia/lymphoma (ATL/L)	
Cataneous T-cell lymphoma (mycosis fungicides/Sazary syndrome) (CTCL)	Angioimmunoplastic T-cell lymphoma (AITL)	
Primary cutaneous anaplastic large cell syndrome	Extranodal NK/T-cell lymphoma nasal type (ENTKL)	
	Anaplastic large cell lymphoma (ALCL)	

Major NT/K-cell subtypes
Major types of peripheral T-cell lymphoma

Source: Fair Research Inc. using various materials

The EB virus is involved in cancer through various pathways

The mechanism of carcinogenesis by EBV has not been fully elucidated, but the following mechanism is generally recognised: In blood tumor cells such as NK/T cell lymphoma, EBV is in a state of latent infection and expresses various EBV genes. Examples include EBNA-1, EBNA-2, LMP-1, and LMP-2. When EBNA-1 is expressed, it suppresses p53, suppressing apoptosis in tumor cells. LMP-1 activates NF-κB, which also suppresses apoptosis. LMP-2 is thought to be involved in carcinogenesis through the PI3K pathway and the MAPK pathway.

Genes that promote tumor malignancy by EBV

EBNA-1＝＞P53 destabilisation＝＞apoptosis suppression

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

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

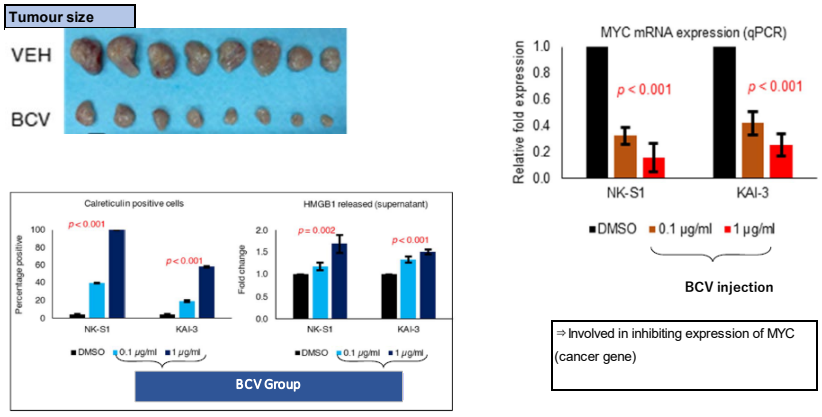
LMP-2 ＝ PI3K pathway /MAPK pathway activation=> carcinogenic involvement, etc.

(a) NK/T cell lymphoma

The therapeutic effect of BCV on NK/T cell lymphoma was descriibed at ASH in 2022

In December 2022, at the ASH (American Society of Hematology) conference, the therapeutic effect of BCV on rapidly progressing NK/T cell lymphoma, for which no effective treatment had yet been established, was announced as a result of joint non-clinical research between SymBio and the National Cancer Center of Singapore. As shown below, the tumour burden in the BCV-administered group was significantly less than the control group, indicating that it is also involved in suppressing the expression of MYC, a cancer gene.

Therapeutic effect of BCV



Source: SymBio company briefing, February 2023

BCV suppresses the expression of MYC, the oncogene involved in tumour malignancy

The oncogene MYC has long been known to be deeply involved in tumorigenesis and is thought to be involved in the malignant transformation of various tumors, as described below.

The involvement of MYC:

〇Unregulated cell proliferation, suppression of cell differentiation, destabilization of the genome

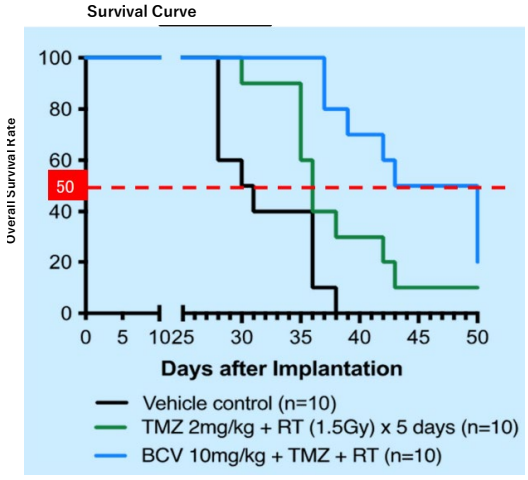
〇Promotion of anaerobic metabolism, promotion of cancer metastasis, angiogenesis

Source: Derived from Experimental Medicine, March 2018: Multifunctionality of MYC

Combined use with immune checkpoint inhibitors offers promise	In addition, this collaborative research confirmed that BCV not only suppresses the expression of a group of genes (MYC) that promotes tumor malignancy caused by EBV, but also activates immune-related signals via the STING pathway (expression of type-I interferon and the resulting increase in anti-tumor immune responses). Hence the possible effectiveness of combined use with immunotherapies, such as anti-PD-1 inhibitors. **Effect of type I interferon (IFN-α, IFN-β, etc.) on the cancer microenvironment** ・Promoting maturation of dendritic cells (antigen-presenting cells) ・Activation of cancer antigen-specific T cells ・Suppressing the immunosuppressive power of regulatory T cells, etc. Source: Fair Research using various materials
Possible partnership with a major pharmaceutical company that has its own immune checkpoint inhibitors	SymBio is currently investigating its use in combination with different immune checkpoint inhibitors and plans to collect data from mid-2024 to fall. If the combination effect is confirmed in animal models, it is possible that negotiations for a partnership with a major pharmaceutical company that has its own immune checkpoint inhibitors may emerge. In addition, the following results from a joint research project between SymBio and the National Cancer Centre Singapore were announced at the International Lymphoma Conference in June 2023: ・High susceptibility to BCV is highly correlated with low expression of TLE1 (tumor suppressor) ・Low expression of TLE1 is highly correlated with poor prognosis (PFS: progression-free survival) in patients with NK/T-cell lymphoma ・Low expression of TLE1 is highly correlated with increased expression of oncogenes such as MYC SymBio plans to analyse the correlation between responses to not only TLE1 but also other biomarkers, and use this correlation as a means to develop clinical trial designs, such as narrowing down patients in future trials.
BCV is effective against peripheral T-cell lymphoma (PTCL) as well as NK/T-cell lymphoma	**(b)Peripheral T-cell lymphoma (PTCL)** In June 2024, at the European Hematology Association Congress (EHA2024), the antitumor effect (preclinical) of BCV against PTCL was announced as the result of joint research between SymBio and the National Cancer Centre Singapore. The following findings were announced: ・BCVshowed high cytotoxicity in a concentration-dependent manner in all T-cell lymphoma cell lines ・Intraperitoneally administered BCV significantly suppressed tumor growth in xenografted mice compared to the control group ・In BCV-treated PTCL cells, changes in gene expression were observed that were similar to those observed in NK/T cell lymphoma models (in particular, decreased expression of MYC-related genes, which show antitumor effects, and induced expression of immune-regulating genes, such as increased IFNγ).

	(c)Diffuse large B-cell lymphoma (DLBCL)
Possibility of also treating DLBCL	In April 2024, at the American Association for Cancer Research (AACR2024), the antitumor effect (preclinical) of BCV against DLBCL was also announced as the result of joint research between SymBio and the National Cancer Center Singapore. **・The antitumor effect of BCV was evaluated using 19 types of B-cell lymphoma cell lines (DLBCL, Hodgkin's lymphoma, Burkitt's lymphoma, etc.). The in vivo effect was also evaluated in mice** **・BCV inhibits all B cell lymphoma cell lines in a concentration-dependent manner** **・Nine of the cell lines showed significant sensitivity, including a refractory double-hit DLBCL cell line** **・High expression of TLE1 was associated with poorer overall survival in DLCBL mice** (In contrast to TLE1 in NK/T-cell lymphoma)
Confirmed the antitumor effect of BCV against various blood tumors, based on which the company will move on to clinical trials (Phase 1b) in August 2024	As described above, the joint research (non-clinical trials) between SymBio and the National Cancer Centre, Singapore confirmed the antitumor effects of BCV against malignant lymphomas such as NK/T cell lymphoma and PTCL. Based on these results, SymBio submitted a clinical trial plan to the PMDA for an international Phase Ib/II clinical trial of BCV (injection) targeting patients with relapsed or refractory lymphoma (NK/T cell lymphoma, PTCL, etc.) in August 2024, and began clinical trials. Hematological tumors have been selected as the next development area for infectious diseases after hematopoietic stem cell transplantation.
	⑤ Solid cancer（GBM）
Half of those patients who contract GBM, a malignant brain tumour, are CMV positive	Glioblastoma is the most common malignant brain tumour, and is a disease with extremely high unmet medical needs, with a survival period of only 15-20 months and a 5-year survival rate of only 5%. Approximately 50% of patients are known to be CMV (cytomegalovirus) positive. Currently, various therapeutic drugs are under development, but there are no antiviral candidates. In addition, in the development of drugs for malignant tumors, the ability to penetrate the blood-brain barrier (BBB) is an issue, but BCV has a high BBB penetration.
Research from Brown University in the US demonstrates the mechanism by which CMV infection promotes the growth of GBM cancer cells	Although the mechanism of CMV and brain tumors is not completely understood, research at Brown University in the US suggests that CMV infection enhances NF-κB signaling, leading to increased expression of the angiogenic factor PDGF-D. A mechanism that promotes the growth of GBM cancer cells has been demonstrated in a mouse model. It has also been found that the antiviral drug cidofovir (CDV) inhibits CMV reactivation and improves survival rates in CMV-infected mice. (The Journal of Clinical Investigation 2019, Sean E Lawler et al.)
BCV may have antitumor effects and malignant progression suppressive effects	The mechanism of action of BCV in GBM is that BCV changes into CDV-PP within cells, inhibiting the replication cycle of tumor cells and inducing apoptosis, which has an antitumor effect and inhibits the reactivation of CMV. It is thought to have an inhibitory effect on malignant progression by suppressing tumor growth.
Combination of BCV with standard therapy confirmed to be effective in animal models	A joint study (animal experiments) between SymBio and the University of California, San Francisco has already demonstrated that a combination of standard therapy (temozolomide (TMZ: an alkylating agent) + radiation) with BCV significantly extends survival compared to the standard therapy. In the following figure, the light blue line is the survival curve for the BCV and standard therapy

group, the green line is the standard therapy group, and the black line is the control group. It is clear that the BCV and standard therapy group has a significantly longer survival period than the standard therapy group. It has also been reported that temozolomide may be effective against unmethylated MGMT groups, for which the efficacy is low. (Alkylating agents methylate DNA to suppress gene expression, but MGMT becomes unmethylated.)



Glioblastoma（GBM）and CMV Infection

●GBM

Survival period is 15 ～20 months

5-year surval rate is below 5%

* Around 50%of GBM patients are infected by CMV
* Although there are many medicines for GBM unde development, there are no medicines targeting bo GBM and CMV

Source: SymBio company briefing, August 2023

SymBio is also currently conducting joint research with Brown University to evaluate the antitumor effects and suppressive effects of BCV on tumor malignancy.

Currently in non-clinical trials and scheduled to start Phase 1 in 2025

Based on an exchange of opinion with the company's Scientific Advisory Board, SymBio has now decided to increase the number of species of animal models for evaluation, and human clinical trials (Phase-1) are scheduled to begin in early 2025.

⑥ Expanding into neurodegenerative diseases

Some neurodegenerative diseases are thought to be caused by inflammation due to viral infection

Some neurodegenerative diseases are thought to be caused by inflammation due to viral infection. SymBio is currently conducting non-clinical trials targeting multiple sclerosis and Alzheimer's dementia.

Currently conducting non-clinical trials for multiple sclerosis (MS) and Alzheimer's dementia

Development plan for neurodegenerative diseases

Multiple sclerosis

Trial type	Tester	Protocol
Basic	NIH/Symbio	Q3/2022（underway）
Animal model	NIH/SymBio	2024～
Clinical (human)	NIH/SymBio	2026/1H～

Alzheimer's dementia

Trial type	Tester	Protocol
3D brain model	Tufts Univ.	2022/Q4（underway）
Animal model	SymBio	2024～
Clinical (human)	Jointly with partner	undecided

Source: Fair Research Inc. using interviews with SymBio

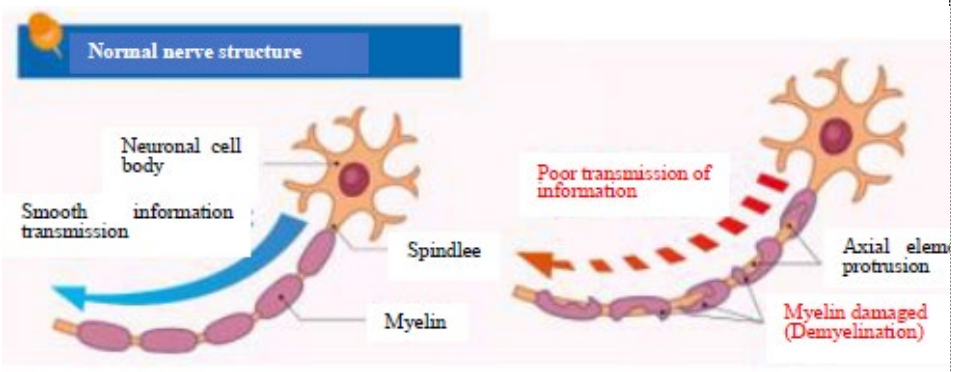
(a) Multiple sclerosis

In February 2022 the company began considering multiple sclerosis as a new target for BCV

In February 2022, SymBio announced that it was considering multiple sclerosis (MS), a type of autoimmune disease, as a new target for BCV. In August 2022, the company entered into a joint research sample provision agreement with the National Institute of Neurological Disorders and Stroke (NINDS), which belongs to the U.S. National Institutes of Health (NIH), to evaluate the antiviral effect of BCV against the EB virus. SymBio has agreed to provide BCV to NINDS for non-clinical studies to evaluate the potential efficacy of BCV for diseases caused by the EB virus. Furthermore, in March 2023, SymBio and NINDS concluded an agreement (CRADA) to conduct joint research and development to verify the effects of BCV in-vitro and in animal models using cells derived from patients with multiple sclerosis associated with EB virus infection. The plan was to step up from basic

A CRADA concluded with NINDS in 2023

Advancing to animal models from early 2024 and human

clinical trials Phase-1 from the first half of 2026. Expect global partnering at this point	experiments to animal models (using marmosets) in the second half of 2023, but as compliance regarding animal experiments grew stricter the review took longer than expected. Therefore, clinical trials (Phase1) are expected to begin in the first half of 2026. As this proceeds, there is the possibility that major pharmaceutical companies will take notice. **Reference: Multiple sclerosis** Multiple sclerosis is an autoimmune disorder which occurs when lymphocytes attack the myelin that covers the axons of nerve cells, causing them to demyelinate, and information cannot be transmitted smoothly in the demyelinated nerves, resulting in various neurological symptoms (movement disorders, visual impairment, sensory disorders, urinary disorders, etc., with repeated relapses and remissions). Lesions occur in various parts of the brain, spinal cord, and optic nerve, and recur at intervals of one month or more. The number of patients in Japan, including neuromyelitis optica, is approximately 18,000, but it is thought that there are approximately 3 million patients worldwide, mainly in Europe and America. There is no fundamental treatment, but steroid pulse therapy, which uses steroids to suppress inflammation, and immunomodulators, which suppress lymphocyte activity, are used.  Source: Multiple Sclerosis.jp Although the mechanism by which multiple sclerosis (MS) is caused by the EB virus is not completely understood, epidemiological studies have supported an association. A Harvard University research team analyzed a sample of more than 10 million U.S. military service adults and found that 955 cases were diagnosed with MS during military service. The risk of developing MS is reported to be 32 times greater than infection (Science magazine Jan. 13, 2022 “Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis”). Recently, a research team at Stanford University proposed a new and powerful hypothesis as a mechanism of MS onset caused by EB virus (Nature, Jan 24, 2022 : "Clonally Expanded B Cells in Multiple Sclerosis Bind EBV EBNA1 And GlialCAM"). This hypothesis is based on the structural similarity between the EB virus transcription factor EBNA1 and the brain's glial cell adhesion molecule GlialCAM, so lymphocytes that produce autoantibodies that recognize both migrate to the central nervous system and mistakenly copy their own myelin. The mechanism by which this disorder leads to the development of multiple sclerosis (MS) involves the targeting of B cells by inhibiting the migration of lymphocytes into the central nervous system (sphingosine 1 (SP1) phosphate receptor agonists) or the migration of lymphocytes from lymph nodes (anti-α4 integrin antibodies) The effectiveness of molecular targeting drugs such as the CD20 antibody (Ocrevus) also suggests that this mechanism is correct. SymBio believes that if this mechanism is so, the progression of MS can be inhibited by promptly eradicating the EB virus using BCV after the onset of MS. Currently, the market size for drugs for multiple

sclerosis is approximately JPY1.5 trillion, or JPY2 trillion if steroids are included. SymBio hopes that BCV will be added as a combination drug offering a new mechanism.

TOP 5 Sales of MS 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 company briefing, August 2024

Many of the recently developed drugs targeting multiple sclerosis are BTK inhibitors, but they are struggling

Looking at the recent drug developments for multiple sclerosis, there are many BTK inhibitors. However, there appears to be a greater likelihood of causing liver damage, and this makes development difficult. CD20 antibodies (such as rituximab and ocrelizumab) have been confirmed as clinically useful, and they differ from other antibody drugs that suppress the proliferation of B cells in that they reduce EB virus-positive B cells. It is unknown whether BTK inhibitors have such an effect.

Drugs that reduce EB virus-positive B cells are effective

(b)Alzheimer's disease

Chickenpox/varicella-zoster virus activates herpes simplex virus type 1, causing amyloid beta accumulation

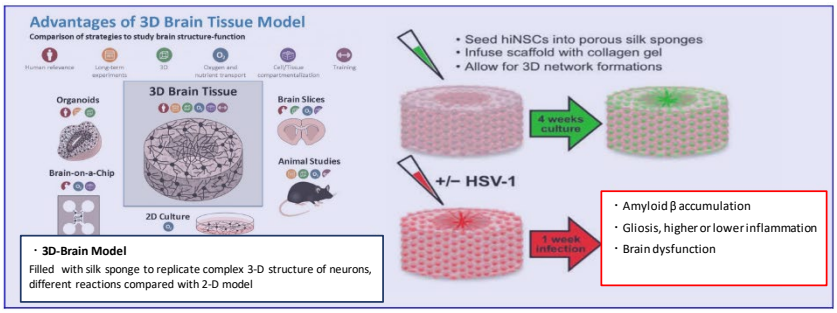
Recently, evidence has been accumulating that herpes simplex virus type-1 (HSV-1) is involved in the onset of Alzheimer's disease (Nikkei-FT Infectious Disease Conference: October 24, 2022: Nikkei Shimbun). Research from Tufts University in the United States has shown that when VSV (varicella-zoster virus) activates HSV-1, it can lead to the accumulation of tau protein and amyloid beta, which can reduce the function of nerve cells. It has been pointed out that people with the APOE4 gene are particularly susceptible to the effects. Oxford University research has also revealed that when HSV-1 is present in the brain, it increases the likelihood of developing Alzheimer's disease in combination with APOE4 (APOE4 is known to facilitate amyloid beta accumulation).

A non-clinical study is underway to verify the effects of BCV using a 3-D brain model owned by Tufts University in the United State

On December 19, 2022, SymBio signed a research agreement with Tufts University and began a preclinical study to test the efficacy of BCV against the Tufts University 3-D brain model of herpes simplex virus (HSV) infection. Promising data are now emerging, and the plan is to move to development in animal models by the end of 2024. The timing of the start of clinical trials in humans has not yet been determined.

Note: HSV infection model using 3-D brain model

An experimental system in which human neural stem cells are cultured on a collagen-filled porous silk protein sponge as a substrate for growth and differentiation into a functional network of neurons and glial cells that are also susceptible to viral infection. In this experimental system, electrophysiological functions, HSV infection-induced amyloid beta fiber formation, and neuro-inflammation can be evaluated under conditions that exclude other factors.



Source: SymBio company briefing, February 2023

BCV marlet potential

The targeted patient population includes 2,000 patients with disseminated AdV infection, 8,000 patients with BKV infection, 15,000 patients with first-line treatment after HSC transplantation, and 10,000 patients with resistant/refractory CMV infection.

However, the number of patients with resistant or intractable CMV infection limited to 5,000 patients who are resistant to Maribavir

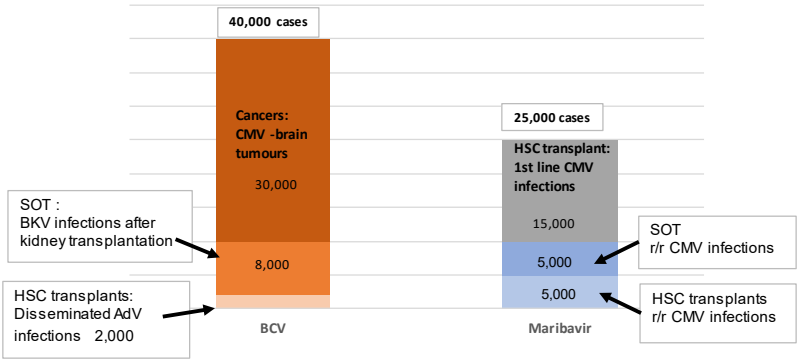
(3) Estimated size of the market for brincidofovir (BCV)

Below we consider the market size for (a) disseminated adenovirus infection after hematopoietic stem cell transplantation, for which POC has been established, as well as (b) BK virus infection after kidney transplantation, which is in Phase 2, (c) 1st - Line CMV infection after hematopoietic stem cell transplantation and (d) resistant/refractory CMV infection after hematopoietic stem cell transplantation or organ transplantation. As blood cancers such as NK/T cell lymphoma have only just begun Phase 1b, we exclude these from the market size calculation.

Neurodegenerative diseases (multiple sclerosis and Alzheimer's disease) are outside of SymBio's current area of expertise and are a field in which collaboration with leading external pharmaceutical companies is essential, so they are not included in the calculation at this stage.

The number of patients in the areas covered by BCV is estimated to be approximately: ①2,000 for disseminated adenovirus infection after hematopoietic stem cell transplantation, ②approximately 8,000 for BK virus infection after kidney transplantation(HSCT), ③approximately 15,000 for 1st Line CMV infection after HSCT and ④approximately 5,000 for each of resistant/refractory CMV infection after hematopoietic stem cell transplantation and resistant/refractory CMV infection after organ transplantation.

Comparison of patient numbers for 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

Note: At present, Maribavir has no indication for 1st-Line CMV infection （HSCT）

However, in the field of ③ first-line CMV infection after hematopoietic stem cell transplantation, it is necessary to take into consideration how much BCV（Injection） will penetrate the existing drug market. Also, ④ about half of the patients with resistant/refractory CMV infection after hematopoietic stem cell transplantation or organ transplantation (a total of about 10,000 people) show resistance to Maribavir, so if we assume that the number of patients eligible for BCV is half of this number, the total number would be about 5,000 people.

Assuming that the drug cost per case is JPY8.4 million yen, the total sales for ①, ②, and ③ and ④ would be a maximum of JPY252 billion	Assuming from a comparison with Maribavir that one course costs JPY8.4 million, then: ① Disseminated adenovirus infection after hematopoietic stem cell (HSC) transplantation: 2,000 cases × JPY8.4 million ＝ JPY16.8 billion ② BK virus infection following kidney transplantation: 8,000 cases × JPY8.4 million ＝ JPY67.2 billion ③ First-line CMV infection following HSC transplantation: 15,000cases× JPY8.4 million ＝JPY126 billion (However, competition in this market with other anti-virus drugs likely) ④ Resistant/refractory CMV infection after HSC transplantation or organ transplantation: 5,000 cases × JPY8.4 million ＝ JPY42 billion
The fields of cancer and neurodegenerative diseases caused by viral infections are expected to be major markets	As mentioned above, the total value for ①, ② and ④ is estimated at JPY126 billion, and assuming a 100% share of ③, our total estimate rises to JPY252 billion. It should further be noted that there is ample room for expansion to other areas.

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

Rigosertib was initially being developed for MDS but it failed to meet Phase 3 endpoint

Rigosertib was initially developed for MDS (myelodysplastic syndrome) but failed to meet its primary endpoint in a global Phase-3 study (INSPIRE study) in August 2020.

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 home page

Onconova, the original licensor, was acquired by Traws Pharma, and rigoserb is now available for licensing out

Meanwhile, Onconova, the company that licensed rigosertib, had been promoting its development as an anticancer drug until 2023, focusing on its function as a RAS inhibitor. However, in April 2024, the company changed its name to Traws Pharma Inc. through a merger, and the business is now run by a new management team. Currently, investigator-initiated clinical trials for rare diseases are being conducted for rigosertib, and Traws Pharma is targeting rigosertib for licensing out.

SymBio continues to explore new uses

SymBio is continuing to explore new uses and new indications for rigosertib.

Treakisym® is a drug that was first developed by SymBio in Japan for the treatment of malignant lymphoma, and modified formulations have since been approved

3.Treakisym® (SyB L-0501 (lyophilized injection) / SyB L-1701 (RTD liquid) / SyB L-1702 (RI liquid))

Treakisym® (generic name: bendamustine) was first developed in Japan by SymBio for the treatment of malignant lymphoma, and has since developed and received approval for modified formulations. Currently, treatment using Treakisym® is one of the standard therapies for malignant lymphoma.

Pipeline	Indication(s)	Clinical Trial Phase 1	Phase 2	Phase 3	NDA※1	MA※2
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 acquired the license rights for bendamustine liquid formulation (RTD formulation, RI administration) from Eagle Pharmaceuticals, Inc. (New Jersey, USA). SymBio will start selling RTD formulations in January 2021, and will gradually introduce RI administration to the market.

RTD: Ready To Dilute, RI: Rapid Infusion

Source: SymBio web site

Treakisym® is indicated for the following four types of malignant lymphoma:

- ○Relapsed/refractory indolent B-NHL and MCL (approved in October 2010)
- ○Untreated indolent B-NHL and MCL (approved in December 2016)
- ○Chronic lymphocytic leukemia (CLL) (approved in August 2016)
- ○Relapsed/refractory DLBCL (approved in March 2021)

Note: Untreated DLBCL is not a formal indication but is Off-Label)

Reference: Types of malignant lymphoma
Lymphoma is a blood disease caused by the cancerisation of immunity cells called lymphocytes (a type of leukocyte). Its rising incidence reflects the ageing of society There are two major types: Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL). Most Japanese cases (94%) of malignant lymphoma are NHL, which can be classified into the following three types depending on speed of disease progression.

- ○ Indolent-B-NHL: Disease progresses annually (MALT or FL (up to grade 3a), etc.)

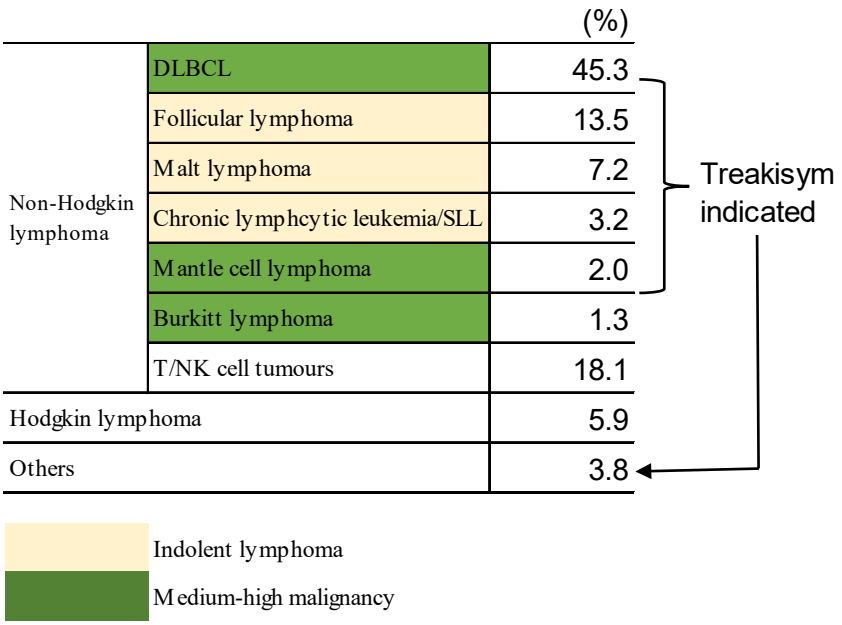
  FL: Follicular lymphoma, MALT: MALT lymphoma

  Follicular lymphoma is a type of low-grade B-cell non-Hodgkin's lymphoma that accounts for approximately 80% of cases.
- ○ Medium malignancy: disease progresses monthly (MCL, DLBCL, etc.)

  MCL: Mantle cell lymphoma, DLBCL: Diffuse large B-cell lymphoma
- ○ Very aggressive: Burkitt lymphoma, etc.

Among NHL cancers the most prevalent type is DLBCL (diffuse large B-cell lymphoma). A poor prognosis is often associated with relapsed/refractory DLBCL

Distribution of malignant lymphomas by type (Japan)



Note: Treakisym indicated for r/r DLBCL, but not for 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 et al., "Difference in incidence and trends of haematological malignancies in Japan and the United States", British Journal of Haematology, 2014

(1) Development timeline

Treatisym® was introduced to Japan by SymBio in December 2005

First indication approved five years after licensing-in

Became a standard therapy in 2018

In 2021, approval for r/r DLBCL was announced, and sales expanded

Treakisym® was first developed in Germany in 1971. In December 2005 SymBio acquired sole development and merchandising rights in Japan from the Astellas European subsidiary, Astellas Pharma (now known as Astellas Deutschland GmbH) and underwent clinical trial development. In October 2010, a mere 5 years after licensing-in, Treakisym® was approved for the treatment of r/r indolent-B-NHL and MCL and sales began in December. Further, in August 2016 chronic lymphatic leukemia (CLL), and in December untreated indolent-B-NHL and MCL received approval. In July 2018, with respect to indolent-B-NHL, MCL and CLL, Treakisym® was for the first time listed as a standard therapy option in the Hematopoietic Tumor Clinical Practice Guidelines 2018 Edition (edited by: Japan Society of Hematology). It thus became a standard treatment both in name and practice. As a result of its new status, the market penetration of Treakisym® rose, completely surpassing R-CHOP, which had been the standard treatment, and in 2018, from the market launch in August, achieved sales in Japan of JPY8.5 billion (approved drug price basis). After that, sales temporarily stagnated due to quality issues with the manufacturer and inventory fluctuations accompanying the switch to an in-house sales system (domestic sales in 2020 were JPY8.1 billion yen; approved drug price basis) In March 2021, however, the company received approval for B-R therapy and P-BR therapy (Polivy® + B-R therapy) for relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL), and entered a phase of renewed sales growth.

SymBio has been

SymBio has also been developing formulations that are easier to use. Until December 2020, Treakisym® was sold as a freeze-dried formulation (FD

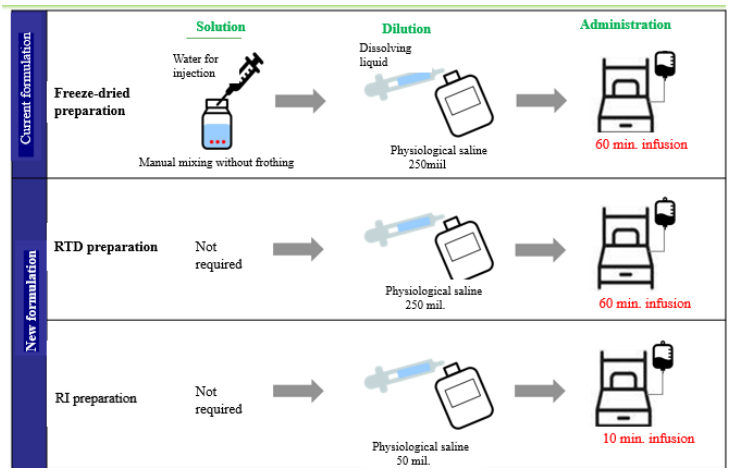
developing easy to use dosage formulations

RTD formulation approved in September 2020.
Potential significant cost savings by switching to RTD formulation

The manufacture and sale of a generic RI administration was approved in February 2022

formulation) manufactured by Astellas Deutschland GmbH, but in September 2017, SymBio announced the introduction of a liquid Treakisym (RTD (Ready-to-Dilute) formulation) from Eagle Pharmaceuticals Inc. in the United States. Although the conventional FD formulation has the advantage of storage at room temperature, it requires dissolving in a solvent and dilution with saline before administration, which is time-consuming. On the other hand, while liquid drugs must be stored in refrigerated conditions, they have the advantage of a shorter dispensing process by simple dilution with saline, thus reducing the work of medical staff. In addition, by switching to a liquid formulation, it is expected that costs can be significantly reduced. As the efficacy and method of administration of the RTD formulation are the same as those of the FD formulation, no additional clinical trials are required, and an application was submitted in September 2019 based only on data on the stability of the drug, and approval was obtained in September 2020 for existing indications, with sales commencing on January 12, 2021. In April 2021, the RTD formulation was also approved for use in r/r DLBCL. Furthermore, for RI administration, which can be administered in 10-minutes (brand name BENDEKA: licensed-in from Eagle Pharmaceuticals), clinical trials were conducted to confirm safety and to examine pharmacokinetics, etc., as the concentration and administration time differ. An application was filed in May 2021, and approval was obtained for all indications in February 2022. As the administration time has been shortened to 10 minutes and the salt content is low, the formulation is positioned as suitable for malignant lymphoma patients, many of whom are elderly.

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



Source: SymBio results briefing

(2) SymBio's response to generic products

① Background to generics

In February 2022, generic versions (RTD) were approved

In February 2022, generic versions of Treakisym® began to enter the market. On February 15, four companies, Pfizer, Meiji Seika Pharma, Koaisei, and Towa Pharmaceutical, obtained manufacturing and sales approval for generic Treakisym® (an intravenous RTD formulation). Under the policy of promoting the wider use of generics, it seems that generics are more likely to be approved as product improvements by incorporating ingredients different from the original drug in terms of formulation and administration method, but there are problems with patent infringement.

On February 25, 2022, SymBio released a document titled "Our Response to Generic Drug Manufacturing and Sales Approval," informing the four companies of

One of the four generic companies decided to postpone sales, but Towa Pharmaceutical went ahead	concerns about patent infringement. The patent in question is owned by Eagle Pharmaceuticals Inc., the US company that licensed the RTD formulation and RI administration, and this has also been recognized in Japan. A legal action for patent infringement of Treakisym's RI administration, BENDEKA®, was lodged in the United States, and generic drug companies have become unable to launch the product for a certain period of time due to Eagle Pharmaceuticals (and Teva, the licensee), winning the case. SymBio also obtained approval for RI administration, which is more convenient than RTD formulations, on February 28, 2022, and has been moving forward with the switch to RI administration. Under these circumstances, Meiji Seika Pharma announced on May 11 that it would postpone the drug price listing scheduled for June, and one of the four generic companies decided to postpone sales, somewhat reducing the risk of generic drugs. Initially, only Towa Pharmaceutical started sales.
In June 2022, generic indications were expanded to include r/r DLBCL.	At the time of approval in February, the indications for the generic drugs from the four companies were indolent-B-NHL and MCL, and did not include r/r DLBCL, but in June Towa Pharmaceutical was given approved to add r/r DLBCL as an indication. CLL has exclusive protection during the reexamination period (until 2026), and is not included in the indications for generic drugs. At this point, use in P-BR therapy for r/r DLBCL was not approved.
In November 2022, Towa Pharmaceutical and Pfizer received approval for generic RI administration. Use in P-BR therapy was also approved	However, on November 9, 2022, Towa Pharmaceutical and Pfizer also obtained approval for RI-administered generic products, with Pfizer beginning sales on December 16. Pfizer's indications include the P-BR therapy for r/r DLBCL (in February 2023, Towa Pharmaceutical also sought authorisation to use it in P-BR therapy). In response, SymBio filed a lawsuit against Towa Pharmaceutical on December 16, 2022, seeking an injunction against the manufacture and sale of generic products and damages for patent infringement, alleging that RI administration may also be a patent infringement. In addition, on December 26, a similar lawsuit was filed against Pfizer. In addition to Towa Pharmaceutical and Pfizer, Takada Pharmaceutical began selling generic versions (manufactured by Koa Isei) in June 2024.
In December 2022, SymBio filed a lawsuit against Towa Pharmaceutical and Pfizer for patent infringement	**② Impact on sales**
As of 2022, the impact of generics on sales was approximately JPY 200 million	The impact of generics on sales appears to have been limited to around JPY200 million for 2022 alone. In August 2022, SymBio lowered its 2022 sales forecast by about JPY990 million from an initial estimate of JPY10,992 million to JPY10,030 million, but estimated the impact of generics to be around JPY200 million. As of mid-October, around 20 facilities had confirmed deliveries of generics, suggesting a cautious attitude toward their adoption. Actual sales for 2022 came in roughly as expected at JPY10,080 million, proving the accuracy of the estimate.
In 2023, generic penetration increased to 50% due to the entry of the powerful brand, Pfizer, and approval for use in P-BR therapy, which has become mainstream for r/r DLBCL. In addition, the overall market shrank due to the spread of infectious diseases, so sales shrank in 2023 by 44.1% compared to the previous year.	However, in December 2022, Pfizer, which has a strong brand power, also entered the market, and generic indications for RI administration and the P-BR therapy, which has become the mainstream in the treatment of r/r DLBCL, were also approved. This has led to a more cautious view of Treakisym® sales. SymBio's initial projected sales in 2023 was around JPY7 billion, a 30% decrease from the previous year, but this was revised downward to JPY6,477 million in August and further to JPY5,603 million in November. The penetration rate of generics was expected to be about 45% as of December 2023, but it was in fact about 50%, slightly higher than expected. In addition, as the impact of COVID-19 continued, the spread of infectious diseases, such as seasonal influenza, has also emerged even in the summer, and doctors have tended to refrain from using bendamustine, which has an immunosuppressive effect. There has thus been shrinkage in the overall market, such that sales in 2023 stood at JPY5,589 million, down 44.1% compared to the previous year.

Sales in 2024 are expected to decline 53.1% year-on-year due to restrained purchases ahead of major drug price revisions and greater-than-expected penetration of generics

In 2024, the company had initially forecast sales of JPY3,641 million (down 34.9% year-on-year), anticipating a major drug price revision (-18.6%) from April and an average annual generic penetration rate of 50%. However, there was a reluctance to purchase in the January-March period, just prior to the price revision, and furthermore generic penetration rates were higher than expected. As a result, the company revised its forecast downward to JPY2,623 million (-53.1% year-on-year) in May (the penetration rate of generics has risen to about 60% as of May). Note that the impact of "selected medical treatment" that will be implemented and applied from October 2024 is not taken into account, as it is not known whether or not the product will be subject to "selected medical treatment". If the current trend continues, the share of generics in 2025 is expected to rise to an average annual rate of about 65%.

Treakisym® sales trend

	2022 (actual)	2023 (actual)	2024 (forecast)
Treakisym Sales （JYP-mil）	10,008	5,589	2,623
No. of vials ('000's)			
Bendumstine market	128	117	114
of which, Treakisym	126	77	45

Source: Compiled by Fair Research Inc. after interviews

＜Pipeline value＞

Our pipeline value calculation is based on various assumptions, and the discount rate is set at 10%

Treakisym® sales estimate takes into account entry of generics into the market

We assume annual sales costs of JPY1 billion

There are a lot of uncertainties affecting calculation of the BCV pipeline value

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

It is expected that BCV targeting AdV infections after hematopoietic stem cell transplantation will be launched in 2028, followed by other launches thereafter

USD175 million milestone payment to Chimerix still outstanding

＜Estimated pipeline value＞

Below we estimate the pipeline value of Treakisym® and Brincidofovir (DCF method). The discount rate is set at 10%, since the emergence of generic versions of Treakisym® will reduce profitability for the time being.

(a)Treakisym® assumptions

The market size is expected to remain as described in the previous section, and to decline to JPY2.6 billion in 2024, JPY2.5 billion in 2025, and JPY2.4 billion in 2026 due to the emergence of generic drugs. It will then continue to decline at a reduced pace thereafter, but is expected to shrink rapidly (10% per year) from 2031 onwards.

The cost rate is assumed to be about 22%, including royalty payments to Eagle. Milestone payments to Eagle have already been made. Sales costs are assumed to be about JPY1 billion per year due to the streamlining of the sales system.

(b)Brincidofovir assumptions

Estimation of the value of BCV is difficult due to many uncertainties. For reference purposes only, the estimates are for: ① disseminated adenovirus infection after hematopoietic stem cell transplantation; ② BK virus infection after kidney transplantation; and ③First-line CMV infection after hematopoietic stem cell transplantation (for the purposes of this estimate, considering the competition with the existing anti-virus drugs, it is assumed that this will occur in one-third of the 15,000 target patients), and ④ resistant/refractory CMV infection after hematopoietic stem cell transplantation or organ transplantation.

Market value assumptions for each of the three indications above:
Based on the above, we will assume that the amounts are ① 16.8 billion yen, ② 67.2 billion yen, ③42 billion yen, which is one-third of 126 billion yen, and ④ 42 billion yen

Development schedule and costs

Since SymBio has not disclosed specific figures regarding development costs or the timing of approval and launch, Fair Research has independently made a number of challenging assumptions, as shown in the table below, for the purpose of making estimates. Please note that in reality, these figures may fluctuate significantly.

Schedule and costs related to BCV

(100mil Yen)

		2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035
HSCT-Adv		Ph2	Ph3	Ph3	Ph3 /File	App/Launch							
HSCT-r/rCMV		Ph2a	Ph2a-b	Ph2b-Ph3	Ph3	Ph3	File/approved	Launch					
HSCT-1stLineCMV				Ph2	Ph2	Ph3	Ph3	Ph3	File/approved	Launch			
Kidney transplant -BKV		Ph2	Ph2	Ph2-Ph3	Ph3	Ph3	Ph3	File/approved	Launch				
Organ transplant -r/rCMV			Ph2	Ph2	Ph2	Ph2-Ph3	Ph3	Ph3	File/approved	Launch			
Milestone													
to Chimerix	180 (mil USD)					10		20	50	50			50
150yen/USD	JYP (100 mil)					15		30	75	75			75
Dev. Costs	HSCT-Adv	5	10	10	3								
（JPYY100 mil）	HSCT-r/rCMV	5	5	15	15	15	3						
	HSCT-1stLineCMV			15	15	45	45	45	3				
	Kidney transplant-BKV	10	10	20	30	30	30	3					
	Organ transplant -r/rCMV		5	5	5	15	15	15	3				

Source: Fair Research Inc.

Milestones

Under the licensing-in contract with Chimerix Inc., SymBio is to pay Chimerix milestones of USD180 million (including a USD5 million contractual lump sum) and royalties. The timing of the milestone payments and details on amounts have

not been released but for the purposes of this calculation, it is assumed that payments will be made when each indication is launched or when a certain sales level is reached.

Chimerix royaties rate posited at 12%

Royalties and manufacturing costs

The royalties rate on sales has been announced as a double-digit percentage, but is thought to be in the low teens, and for the purposes of this calculation, we have assumed it to be 12%. The manufacturing cost rate has also not been announced, but for the purposes of this calculation, we have conservatively set it at 20%.

Assuming an in-house sales structure also for Europe and the US

Sales costs

There is the possibility of joint development or out-licensing with major pharmaceutical companies, but for this calculation we assume that the company will develop the drug in-house until it is marketed, and then build a sales system to establish itself as a specialty pharmaceutical company in Europe and the United States, rather than out-licensing sales rights. This is because the number of transplant centers to be covered is approximately 35 in Japan, compared with approximately 75 in the United States and 90 in Europe, so it makes sense to establish an in-house sales system. In order to build and maintain sales structures in Europe and the US, selling expenses of approximately JPY1 billion per year are expected in both Europe and the US. We assume that sales costs in Japan will be approximately JPY500 million added to the current Treakisym® sales costs of JPY1 billion. Finally, we assume that the probability of success is 60% to 80%, since the effectiveness of BCV has already been confirmed in humans.

Sales costs in Europe and the US will be JPY1 billion each per year, while an additional JPY500 million will be added in Japan

(c)Results of the calculation

The discounted present value results under the above assumptions are as shown in the table below. The value of Treakisym® (before tax) has fallen significantly compared to the previous estimate (due to the growing impact of generics), and is estimated at JPY5.7 billion. The value of BCV, assuming in-house development and sales, is estimated at JPY124.1 billion with a 60% probability of success. (For reference, if the target indications of BCV are limited to infections after hematopoietic stem cell transplants, the estimated value is JPY101.4 billion with a 60% probability of success.) The combined value of Treakisym® and BCV therefore comes to JPY129.8 billion. Assuming an 80% success probability, the value of BCV is estimated at JPY176.1 billion making Treakisym® + BCV = JPY181.8 billion. Although not included in the calculations this time, the pipeline value will increase even further if the scope of BCV indications is expanded (hematological tumors, multiple sclerosis, etc.) and other solid cancers are considered.

Treakisym's pipeline value comes in at JPY5.7 billion (before tax)

The pipeline value of BCV for infections after HSC transplantation and infections after organ transplantation, taking into account the probability of success, comes to JPY124.1 to JPY176.1 billion

Estimate of pipeline value (before tax)

(JPY-100 mil)

	Prob. of success 100%	Prob of succss 80%	Prob. of success 60%
Treakisym®	**57**	---	---
BCV	2,282	**1,761**	**1,241**
(excl. infections post organ transplant)	(1,737)	**(1,375)**	**(1,014)**
Treakisym® + BCV	2,339	**1,818**	**1,298**
(excl. infections post organ transplant)	(1,794)	(1,432)	(1,071)

10% discount rate assumed

Source: Calculations by Fair Research Inc.

Note: No direct comparison can be made between pipeline value and market value

Value will further increase when considering applications in the fields of first-line infectious diseases after HSC transplantation, hematological tumors, malignant brain tumors, and neuroscience

＜First half 2024 results and full year outlook＞

Sales in 2024 are expected to decrease by 53.1% compared to the previous year, mainly due to drug price revisions and the penetration of generic drugs

On the other hand, with the full-scale development of BCV, SG&A expenses in 2024 will increase by JPY563 million from the previous year

As a result, the full-year operating loss is expected to come in at JPY3,702 million

Sales for the first half of 2024 were JPY1,284 million, a significant decrease of 59.6% compared to the previous year due to the penetration of generics, the drug price revision in April, and buyers refraining from purchasing prior to the revision. Sales forecasts for 2024 were revised downwards in May to JPY2,623 million (-53.1% compared to the previous year) due to the decline in the first half and greater-than-expected penetration of generics. The cost ratio for the first half of the year deteriorated to 22.4% due to the weaker yen and the drug price revision, but is expected to improve in the second half due to a possible currency correction, and is expected to be 20.6% for the full year. SG&A expenses in the first half of the year increased 7.6% year-on-year to JPY2,715 million, mainly due to an increase in R&D expenses, especially BCV development expenses. SG&A outlays for the full year are expected to be JPY5,785 million, up JPY563 million year-on-year. R&D expenses are expected to increase to JPY3,409 million due to the start of clinical development targeting blood tumors such as NK/T lymphoma. As a result, operating income for the first half of the year is expected to show a loss of JPY1,719 million, and operating income for the full year is expected to show a loss of JPY3,702 million.

2023-2024 profit and loss

(JPY-mil)

	2023	2024	2024	2023				2024			
	(actual)	(forecast)	(initial forecast)	Jan-Mar (actual)	Apr-Jun (actual)	Jan-Jun (actual)	Jul-Dec (actual)	Jan-Mar (actual)	Apr-Jun (actual)	Jan-Jun (actual)	Jul-Dec (foreast)
Sales	5,589	2,623	3,641	1,544	1,634	3,178	2,411	597	687	1,284	1,339
（YoY）	-44.1%	-53.1%	-34.9%	-33.3%	-36.1%	-34.8%	-53.0%	-61.3%	-58.0%	-59.6%	-44.5%
								Restrained buying before drug price down			
Cost of sales	1,178	541	855	301	404	705	473	126	162	288	253
（cost rate）	21.1%	20.6%	23.5%	19.5%	24.7%	22.2%	19.6%	21.1%	23.6%	22.4%	18.9%
					Defective virals	Defective virals		Yen deprec.	Yen deprec + drug price rev.		
SG&A	5,222	5,785	5,624	1,192	1,330	2,522	2,700	1,277	1,438	2,715	3,070
of which, R&D	2,628	3,409	3,208	549	654	1,203	1,425	691	840	1,531	1,878
		Start of NK/T lymphoma clinicals									
Operating revenue	-811	-3,702	-2,837	51	-100	-49	-762	-806	-913	-1,719	-1,983
Recurring profit	-736	-3,524	-2,867	48	18	66	-802	-727	-754	-1,481	-2,043
Net profit	-1,962	-3,628	-2,870	4	-83	-79	-1,883	-777	-764	-1,541	-2,087
							Impairment and write-off of deferred tax assets		-18% rev to drug prices from April		

Source: Compiled by Fair Research Inc. from company financial results filings

Has enough cash on the balance sheet for next 2-3 years

As a result of the share issuance announced in October 2023 and the execution of a third-party allotment (total amount raised: JPY1,418 million), cash and deposits on the balance sheet as of June 2024 totaled JPY6,358 million, this being sufficient funds for the next 2-3 years. In addition, if a global partnership with a megapharma emerges regarding the development of BCV during this period, there is the possibility of receiving income from a contract lump sums and milestones.

	＜Summary＞
2023: Establishd human POC for BCV for AdV infection after HSC transplantation. Currently considering Phase 3 design. Phase 2 for CMV infection after HSC transplantation also started	SymBio is currently at a major turning point. The Treakisym® market, which SymBio has nurtured as a cash cow for many years, is being seriously eroded by generics. Meanwhile, for brincidofovir (BCV), which SymBio sees as a pillar of its future global expansion, human proof of concept was established in May 2023 for the first indication (disseminated adenovirus (AdV) infection) after hematopoietic stem cell transplantation), and promising data for Phase 2 was published at the American Society of Hematology (ASH) in December 2023. The design of Phase 3 is currently being considered. Following this, a clinical trial (Phase 2) targeting cytomegalovirus (CMV) infection after hematopoietic stem cell transplantation was launched in May 2024, with the first patient enrolled in June. Consideration is also being given to resuming Phase 2 for BK virus infection after kidney transplantation.
The company has begun development in the fields of hematopoietic stem cell and post-organ transplant infectious diseases as well as hematological malignancies	Hence, on its own the company has, on its own, been developing BCV to treat infections following hematopoietic stem cell transplants or organ transplants. As the next step, in August 2024, the company began clinical development (Ph1b/2) targeting malignant lymphomas (NT/T-cell lymphoma, PTCL, etc.).
Beyond that lies development in the field of neurodegenerative diseases	Beyond that, development in the field of neurodegenerative diseases caused by viral infections is also on the horizon. This field of is also one where partnerships with mega-pharmas are expected. If successful, there is no doubt that a very large market awaits, but it is not easy to advance all of these projects simultaneously.
The schedule in 2025 Progress in BCV development	In 2025, two programs, that for adenovirus (AdV) and that for cytomegalovirus (CMV), are scheduled to move into late-stage development. Clinical trials for hematological malignancies are also expected to progress, and clinical trials (Phase 1) for solid tumors are expected to begin.
Concluding a global partnership	SymBio has revealed that it is currently in negotiations with a number of companies regarding global partnerships, and we hope that in 2025 the good news will emerge that a partnership has been concluded with one of these companies.

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