SymBio Pharmaceuticals Ltd.

(4582 GROWTH) Issued: April 11 2025

BCV being developed as a major product to replace Treakisym

BCV: Collaborating on combination therapy with immune checkpoint inhibitors

Since 2022, in a joint research project (non-clinical trials) between SymBio and the National Cancer Center of Singapore, the antitumor effect of the company's next flagship candidate, brincidofovir (BCV), against blood tumors (NK/T-cell lymphoma, peripheral T-cell lymphoma (PTCL), etc.) has been confirmed. Additionally, in December 2024 at the American Society of Hematology annual conference, the effect of a joint administration of BCV and an immunity checkpoint inhibitor antibody (anti-PD1inhibitor) was announced. It was confirmed that: ① BCV inhibits the replication of tumour cell DNA and induces immunogenic cell death;② BCV induces the secretion of interferon and cytokines and the expression of PD-L1, resulting in immune activation; ③ there occurred actual tumor growth suppression and immune cell infiltration. There are mega-pharma companies with immune checkpoint inhibitors whose patents are about to expire and which are planning lifecycle management of the same with new applications, and are therefore looking for partners with promising applications. This could be the start of global partnering for SymBio.

The establishment of POC for CMV infection is close

The plan in 2025 is for two programs targeting adenovirus (AdV) infection and cytomegalovirus (CMV) infection after HSC transplantation to be moved to a later stage of development. The AdV infection program has already produced promising Phase II data, and in mid-2025 the plan is to release details (such as trial design) for Phase III. In the Phase II trial targeting CMV infection, patient enrollment has progressed to about half of the three groups in the second cohort, and the trial is scheduled to be completed by September 2025. What is worth bearing in mind here is that maribavir is targeting only at relapsed/refractory CMV infection and approximately 44% of patients are refractory or resistant to maribavir, whereas BCV is less likely to develop resistance and is being developed to target treatment-naive patients as well. The number of such patients is estimated at 15,000, meaning this could become a major product worth over JPY100 billion.

Tackling Alzheimer's disease

In recent years, it has become clear that viral infections are a cause of neurodegenerative diseases such as multiple sclerosis (MS) and Alzheimer's disease (AD). In AD, it is believed that the herpes virus (HSV-1) latent in nerve cells is reactivated by the varicella virus (VZV), promoting the aggregation of amyloid beta, which leads to abnormal phosphorylation of tau, causing neurodegeneration. If BCV can suppress the aggregation of amyloid beta caused by HSV-1 infection, it will revive enthusiasm for the development of drugs targeting amyloid beta. SymBio has already obtained data in collaboration with Tufts University in the United States that shows that AD-related indicators are suppressed by administering BCV to brain tissue infected with HSV-1 using a 3D brain model, and a patent has been applied for. Global development is not expected to begin in earnest until after 2030, but since the number of patients with neurodegenerative diseases far exceeds the number of patients with post-transplant infections, blood tumors, etc., future development progress is anticipated.

Follow-Up Report

Fair Research Inc.

Tsuyoshi Suzuki

Company Outline	
Location	Tokyo
CEO	Fuminori Yoshida
Established	March 2005
Capital	JPY18,336 mil
Listed	October 2011
URL	www.symbiopharma.com
Industry	Pharma
Employees	108 (consol.)
Key Indicators (Apr. 10, 2025)	
Share Price	144
52-week High	450
52-week Low	126
Shares outstanding	47,921,313
Trading Unit	100 shares
Market Cap	JPY6,901 mil
Dividend Forecast	0.0
EPS Forecast	-80.5
Forecast PER	NM
Actual BPS	JPY84.66
Actual PBR	1.07X

(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 YPY mil	YoY %	Net Income JPY mil	YoY %	EPS JPY	Stock Price JPY	
										High	Low
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	NA	1,999	NA	1.179	NA	30.2	1,284	610
2023/12 Actual	5,589	-44.1	-811	NM	-736	NM	-1,962	NM	-49.1	651	229
2024/12 Actual	2,452	-56.1	-3,876	NA	-3,689	NM	-3,833	NM	-85.0	450	149
2025/12 Forecast	1,858	-24.3	-4,263	NA	-4,347	NA	-4,468	NA	-80.5		

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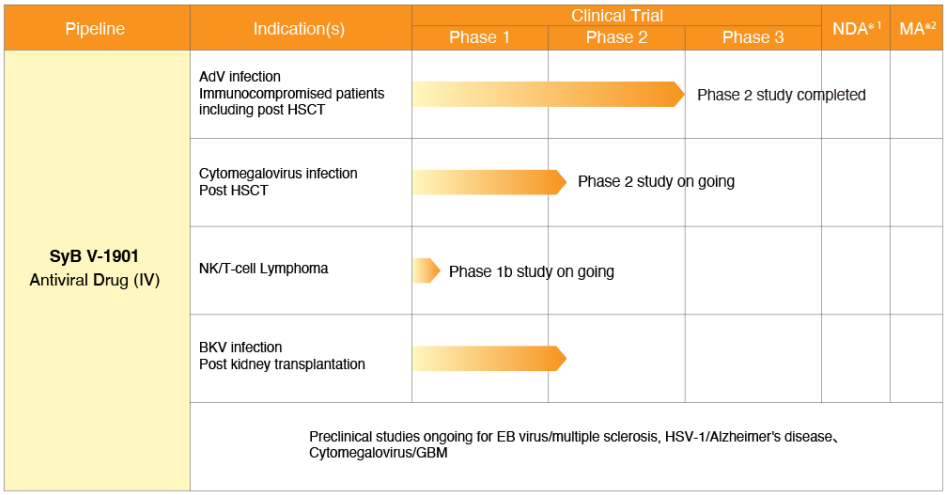
1. Progress in the development of brincidofovir （BCV）(SyB V-1901)

Next flagship candidate, brincidofovir (BCV), is a platform targeting various diseases

SymBio's next major product, brincidofovir（BCV）, is an anti-viral agent now under development for the treatment of a variety of diseases. The diseases SymBio is targeting are, firstly, infectious diseases in immuno-compromised patients after transplantation (such as adenovirus, cytomegalovirus and BK virus), secondly, cancers caused by viral infection (NK/T-cell lymphoma, glioblastoma, etc.) and thirdly, a range of neurodegenerative diseases caused by viral infections, including Epstein-Barr (EB) virus-associated multiple sclerosis, and Alzheimer's disease caused by the herpes simplex virus type-1 (HSV-1).



Source: SymBio Pharmaceuticals website

(1) DNA viral infections after HSC and organ transplantation

Product development for infections after HSC transplantation has progressed to Phase II

Development targeting infections after hematopoietic stem cell transplantation (adenovirus and cytomegalovirus) has already progressed to Phase II (ATHENA trial). Trial results targeting adenovirus (AdV) infections have already been released showing a significant reduction in viral load, and the adenovirus group has already been completed, with plans for Phase III currently being drawn up. Development targeting cytomegalovirus (CMV) (Phase II) is currently underway with the addition of a CMV group to the ATHENA trial.

① Development targeting AdV infections

Phase II trial targeting AdV infection completed with encouraging results

At ASH in December 2023, positive efficacy was reported and there were no serious safety concerns based on data up to cohort 3 of Phase II (ATHENA trials). In October 2024, the results of all cases up to cohort 4 were announced in ID Week 2024 (US International Society of Infectious Diseases Week).

Regarding efficacy, in 20 out of 31 cases AdV was removed from the blood, and 19 of those cases reported the disappearance of, or improvement in, clinical symptoms. In particular, in cohort 3 (0.4 mg/kg administered twice weekly), removal of the virus and improvement in, or disappearance of, infection symptoms was observed in all 9 cases. Furthermore, in cohort 3, viral clearance was achieved in 88.9% of cases within 4 weeks.

Safety and tolerability were also reconfirmed, and the severe gastrointestinal and hepatotoxicity seen with orally administered BCV was not observed with injectable BCV.

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Phase IIa trials targeting adenovirus infections following HSC transplants

	Cohort 1 n=8	Cohort 2 n=9	Cohort 3 n=10	Cohort 4 n=7	Total
Patients with AdV disease, n	8	8	9	6	31
Viremia clearance by WSD1, n (%)	1 (12.5)	1(12.5)	8 (88.9)	3 (50.0)	13 (41.9)
Viremia clearance by end of study, n (%)	2 (25.0)	5(62.5)	9 (100.0)	4 (66.7)	20 (64.5)
Resolved/improved disease, n (%)	2(100.0)	4(80.0)	9 (100.0)	4 (100.0)	19 (95.0)
Resolved disease, n	2	3	6	4	15
Improved disease, n	0	1	3	0	4
No viremia clearance byend of study, n (%)	6 (75.0)	3(37.5)	0(0.0)	2 (33.3)	11 (35.4)
Resolved/improved disease, n (%)	2 (33.3)	0	0	0	2(6.4%)
Resolved disease, n	1	0*	0	0*	1
Improved disease, n	1	0	0	0	1

Dosing of IV BCV
Cohort 1: 0.2 mg/kg or 10 mg/dose BIW
Cohort 2: 0.3 mg/kg or 15 mg/dose BIW
Cohort 3: 0.4 mg/kg or 20 mg/dose BIW
Cohort 4:.0.4 mg/kg or 20 mg/dose QW

Source: SymBio IR materials, October 23, 2024

Reference: Difficulty of developing drugs for infectious diseases
Even if it is proven that a drug reduces or eliminates the viral load in a dose-dependent manner, unless it is linked to an improvement in symptoms, it is often difficult to get approval for the drug. In Japan, the twists and turns surrounding the evaluation of symptom improvement in the emergency approval of Zocova for COVID-19 infection, are still fresh in the memory. Currently, among double-stranded DNA viruses, the only one for which a correlation between viral load and treatment effect (symptoms) has been proven is cytomegalovirus. Proving a correlation requires research using a large number of cases, but it is difficult to accumulate the required number of cases because of the relative rarity of such diseases (with the exception of cytomegalovirus).

Now planning to move ahead to Phase III, but considering how to set the endpoint

Decision on direction by mid-2025 with a start in the 4th quarter

Currently, with a view to moving to Phase III trials the company is in discussions with the authorities in several countries. The trials are expected to target AdV-infected patients after HTC transplants, including adults, and will be conducted in two cohorts (the control cohorts receiving standard therapy, mostly cidofovir). However, there is a difference of opinion between the US FDA and the European EMA regarding the trial's endpoints. It is possible that development may be accelerated in Europe, where there is generally a consensus on trial design. The direction will be decided in mid-2025, and Phase III is scheduled to begin in the fourth quarter of 2025.

② Phase II (ATHENA trials) targeting CMV

The design of the Phase II study targeting CMV has not been disclosed, but it is expected to be a three-cohort dose-escalation study.
Patient enrollment has been completed up to the middle of the second cohort, and is scheduled to end in September 2025

Unlike its predecessor, maribavir, if it can be used on untreated patients, it could become a blockbuster product.

While details of the trials have not yet been released they will probably be along the lines of the AdV trials.

3 cohorts each with around 6 cases – dose escalation study

Starting in February 2024 with first administrations (FPI) in June

Currently: partial completion of second cohort registrations
Completion scheduled for September 2025, followed by announcement of results at an international conference

Patients include not only those with second-line or later refractory CMV infection but also those with first-line CMV infection.

The number of untreated CMV infected patients after HSC transplantation is estimated at 15,000, and the number of patients with refractory CMV infection after second line is estimated at 5,000, with the overwhelming majority of patients being untreated (first line). Depending on the results of future trials, if SymBio can target untreated CMV patients as well, the addressable market size would be blockbuster-level.

1st Line market: 15,000 patients x JPY8,400,000 (same price as maribavir) = JPY126 billion
2nd line + market: 5,000 patients x JPY8,400,000 (same price as maribavir) = JPY42 billion

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Note: Actual sales will also depend on market share as there is competition with existing antiviral drugs

BCV may also be less susceptible to resistance

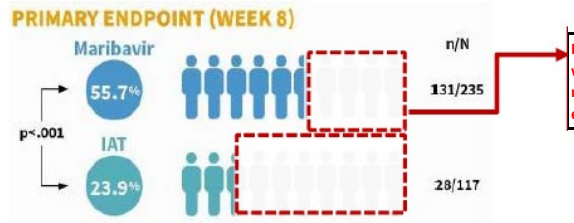
We know that around 44% of patients are refractory or resistant to maribavir, which is therefore ineffective in such patients. While maribavir can give rise to resistance mutations there is little likelihood of that happening with BCV. Maribavir's target molecule is a protein kinase called U97, which is prone to resistance mutations, whereas the target molecule of BCV and CDV is a viral DNA polymerase called UL54, which is essential for viral replication and is therefore unlikely to develop resistance mutations. In point of fact, clinical studies of BCV have not detected any resistance mutations.

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. SOLSTICE 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

Reference: indications for maribavir
Approval for maribavir in 2nd Line+ instances of relapsed/refractory CMV infection was given by the FDA in November 2021. However, in December 2022, in AURORA trials (Phase III) for untreated CMV infection, the maribavir group was unable to demonstrate non-inferiority relative to the control group (valganciclovir group) in terms of achieving the CMV eradication endpoint. Currently, the target indication remains 2nd Line+ relapsed and refractory CMV infection.

③ Product development targeting BK virus infection after kidney transplantation

Development targeting BK virus infection after kidney transplantation will involve a basket trial targeting not only BK virus but multiple viruses

In June 2022, SymBio submitted to the PMDA a clinical trial plan for an international Phase II clinical trial of BCV targeting BK virus infection after kidney transplantation, and in August of the same year, submitted a clinical trial plan to the Australian Therapeutic Goods Administration (TGA). Initially, Phase II was scheduled to be completed in 2025, but due to delays in case accumulation the trial protocol was revised again in August 2023, and the development strategy is currently being restructured.

A development partner is considered necessary

Since cases of CMV infection after kidney transplantation are more numerous than BKV infection the company is now exploring the option of basket trials targeting multiple viral infections and not just BKV. Here again, the issue is whether the authorities will recognize the appropriateness or otherwise of making a reduction or disappearance of viral load an endpoint (evaluation item). In the case of multivirus developments, it is probable that trials and tests would be larger in scale and would require a development partner. Finding such a partner would also be a challenge.

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Clinical development has also begun in the field of hematological cancers

From 2022 onwards, a joint research project between SymBio and the National Cancer Centre of Singapore seeks to confirm the antitumor effects of BCV in the field of hematological cancer

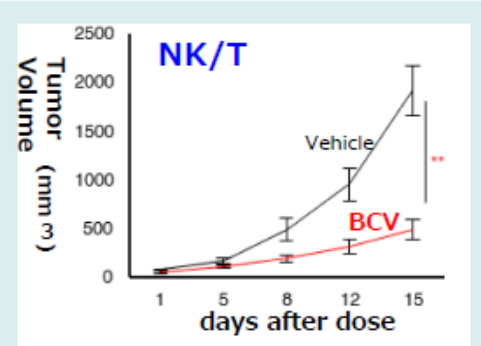
(2) Hematological cancers and solid cancers

① Hematological cancers (NK/T-cell lymphomas and PTCL)

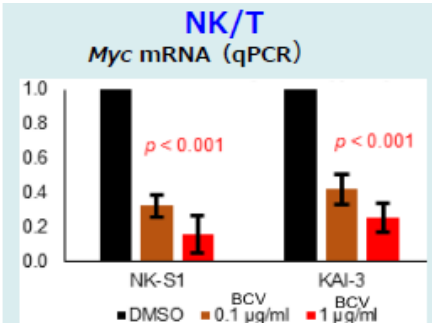
In joint non-clinical research with the University of Singapore National Cancer Center carried out since 2022 it was confirmed that BCV has an antitumor effect against malignant lymphomas such as NK/T cell lymphomas and PTCL.

(a) At the American Society of Hematology (ASH) in December 2022, it was announced that in addition to the tumor-shrinking effect of BCV, BCV not only suppresses the expression of a group of genes (MYC) that promotes tumor malignancy, but also activates immune-related signals via the STING pathway (increased cellular responses associated with the expression of type-I interferon).

Tumour shrinkage effect (NK/T)



Suppressed expression of MYC



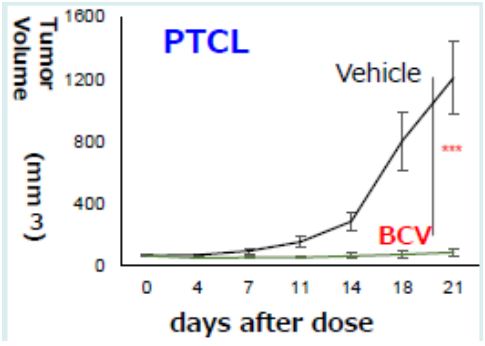
Source: SymBio company briefing, February 2025

(b) In June 2023, the International Congress on Malignant Lymphoma (ICML) announced the results of a study on a biomarker (TLE1) that predicts the antitumor effect of BCV.

(c) In April 2024, the American Association for Cancer Research (AACR2024) also announced the antitumor effect (non-clinical) of BCV against diffuse large B-cell lymphoma (DLBCL).

(d) In June 2024, the European Hematology Association (EHA2024) announced the antitumor effect (non-clinical) of BCV against PTCL.

Tumour shrinkage effectiveness (PTCL)



Source: SymBio company briefing, February 2025

Of the above research studies, in study (a), activation of immune-related signals had already been confirmed, and the effect of combining BCV with immune checkpoint inhibitor antibodies such as anti-PD-1 inhibitors was theoretically expected.

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Previous research has predicted the effectiveness of combining BCV with immune checkpoint inhibitors, and this combination has now been confirmed

(e) At ASH in December 2024, the actual combined effects of BCV with immune checkpoint (PD-1) inhibitor antibodies was announced.

- During the S phase of the cell cycle (DNA repair phase), BCV inhibits DNA replication in tumor cells (causing DNA damage), leading to cell death. In parallel, DNA damage induces immunogenic cell death via the STING pathway.

BCV induces immunogenic cell death

Note: Immunogenic cell death

When cancer cells die and are destroyed, their contents are released, and a signal that the cancer cells have been destroyed is sent to dendritic cells, a type of immune cell, which then teaches effector memory T cells how to distinguish cancer cells, triggering the immune system to act. This type of cell death is called "immunogenic cell death."

In addition to secreting interferon and cytokines, it also induces expression of PD-1 = immune activation

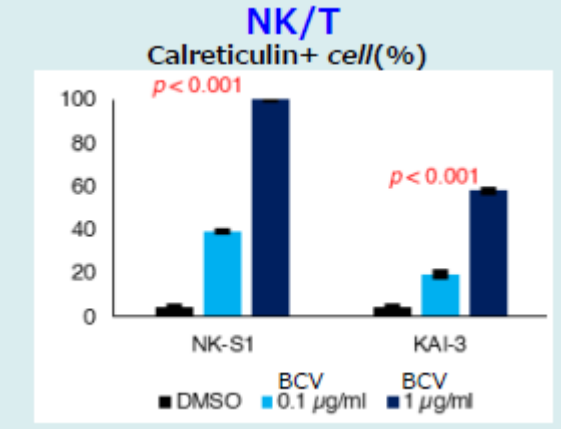
- It induces the secretion of interferon and cytokines and expression of PD-L1, resulting in a state that can activate the immune system. It has also been confirmed that PD-L1 expression is dose-dependent.

- Single agent BCV or combination BCV + PD-1 antibody agents were more effective in suppressing tumour growth than the PD-1 antibody alone.

In fact, tumor growth suppression effect was confirmed

- The gene expression of chemokines (CCL2, CCL12, CXCL9, CTLA4, etc.) that induce T cells and dendritic cells was also higher in the combination group.

Induction of immunogenic cell death (ICD) and dose dependency



Source: SymBio company briefing, February 2025

Note: Calreticulin is a calcium-binding molecular chaperone present in the endoplasmic reticulum within cells. When immunogenic cell death occurs, it becomes exposed on the membrane surface, making it a marker for immunogenic cell death.

(f) Publication of the outline version of the international Phase Ib/II study of BCV (injection mode) for relapsed/refractory lymphoma (NK/T cell lymphoma, PTCL, etc.)

The design of an international collaborative study targeting relapsed/refractory lymphoma (NK/T cell lymphoma and PTCL) has been released

(a) to (e) above suggest that BCV is effective against hematological cancers, although it is still in the preclinical stage. The next step is human clinical trials. In August 2024, SymBio announced the start of clinical trials (Phase Ib/II) targeting hematological cancers, and an outline has been published (December 24, 2024: jRCT2061240096, January 7, 2025: NCT06761677).

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Phase Ib registration is expected to be completed in 2025

Phase Ib: 3 cohorts x 3 cases per group, 18 cases maximum
Indications: relapsed/refractory lymphomas
Administration period: twice per week for a 28-day cycle
Dose escalation study to find the recommended dose in Phase II
(Phase Ib/II is scheduled to end in July 2029)
Patient registration for Phase Ib is expected to complete in 2025.

As there are not so many cases of NK/T cell lymphoma in Europe and the US, an approval application is planned for the Japanese portion of the Phase II trial

Phase II trials are expected to proceed as follows:
Indications: relapsed/refractory lymphomas
No. of cases: 25 (including drop-outs)
Twice weekly single-agent administration at recommended dose
Expected completion: 2027
(assuming Phase Ib patient registration completion in 2025)
As these are open trials, we expect the results of the Japanese portion to be available at year-end 2025. The plan is to move PTCL to global trials depending on the results. There are not many cases of NK/T cell lymphoma in Europe and the US, and it is considered a rare disease in Japan, so it is expected that an approval application will be submitted to the PMDA for the Japanese portion of the Phase II trial.
Administration/observation period: 7 months
End point: Best overall response

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 common 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). Furthermore, most NK/T cell lymphomas are positive for the EB virus. As no standard treatment in and after 2nd-Line has been established, the development of new therapies is much sought after.

Distribution 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	

1) 日本血液学会 2019 年血液疾患症例登録 (補捉率60%として概算) 2) Ito Y et al., Clin. Cancer Res. 2012; 18: 4183-4190, 3) Tisi MC et al., Blood. 2011; 118: 6018-6022, 4)) Bradley M. H et al, C Hematol Malig Rep. 2016 Dec; 11(6): 514–527, 5) Treatment Architecture NHL US, 6) Treatment Architecture NHL EU, 7) Journal of Hematology & Oncology (2019) 12:115, 8) Am J Clin Pathol 2012;138:429-434, 9) 19406007 科学研究費補助金研究成果報告書 10) Diagnostic Pathology volume 13, Article number: 17 (2018), 11) CancerMPad Patient Metrics JP 2020

Source: ASH, December2022

Peripheral T-cell lymphoma (PTCL) is a rare disease that accounts for about 7-10% of non-Hodgkin's lymphomas. In terms of the number of patients, it is estimated that 8,000 to 12,000 people are diagnosed with PTCL each year in the United States, and about 2,000 people in Japan. PTCL is a general term for lymphomas derived from T cells that have migrated to peripheral tissues after differentiation and maturation in the thymus. It includes a variety of disease types, with the main types being peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), and anaplastic large cell lymphoma (ALCL). First-line treatment involves multi-drug chemotherapy and radiation therapy, but these are not always effective. Various therapeutic drugs (Adcetris, Poteligio, Remitro, Darvias, Ezharmia, etc.) are used clinically for

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relapsed/refractory PTCL (r/rPTCL), but a standard treatment has not been established, so the development of new therapeutic drugs is much sought after.

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)	

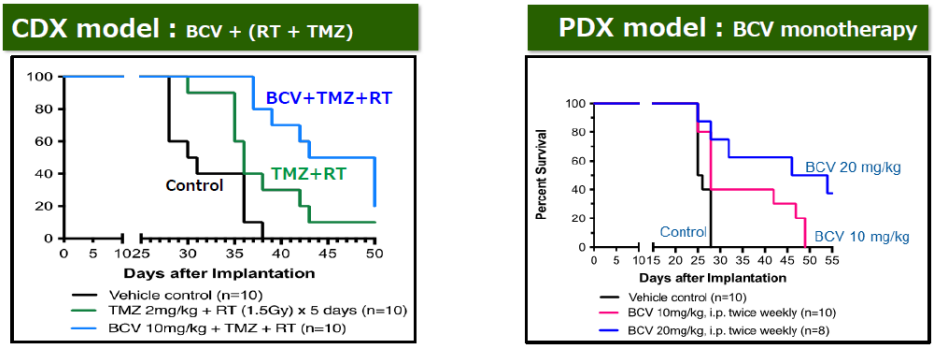
Major NT/K-cell subtypes
Major types of peripheral T-cell lymphoma

Source： Fair Research using various materials

② **Solid tumors: malignant brain tumors, glioblastoma**

Animal experiments have already verified the effects of a combination of BCV with standard therapy (RT (radiation) + TMZ (Temodar)), as well as BCV monotherapy (extension of survival time).

BCV significantly extends survival (both combination therapy and monotherapy)



Source: SymBio company briefing, February 2025

Results of animal experiments on GBM are expected to be published in 2025, and Phase Ib is scheduled to begin in Japan by the end of 2025

Currently, an evaluation is being carried out using more types of model mice, with the results scheduled for publication at an international conference in 2025. Clinical trials (Phase Ib) are due to begin in the fourth quarter of 2025 after consultation with authorities through mid-2025. GBM is a rare disease and is subject to frequent relapses, making it difficult to treat. Development is being considered with the possibility of obtaining *sakigake* designation in Japan.

Reference: Tightening *sakigake* comprehensive evaluation
In 2024, there were cases where drugs received conditional approval under the *sakigake* designation but did not receive full approval (Anges' Collategene and Terumo's HeartSheet) As a result, the "Sakigake comprehensive evaluation" before application appears to have been made stricter. In this evaluation, not only the numerous clinical trials that have been conducted to date but also the detailed contents of the post-marketing clinical trial plan are reviewed.

Search for biomarkers to narrow down patients likely to respond to BCV in order to reduce development costs and shorten development times

Considering the need to reduce development costs and shorten trial periods, and given recent changes in the regulatory environment, it is becoming increasingly important to come up with ways to improve effectiveness and usefulness in preparation for clinical trial applications. In order to further increase efficiency, SymBio is considering narrowing down the number of patients who are susceptible to BCV in advance. They have already discovered candidate biomarkers for this narrowing down, and have filed a patent application. Narrowing down BCV responders will not only improve the efficacy of BCV and the probability of trial success, but is also expected to reduce trial periods and development costs.

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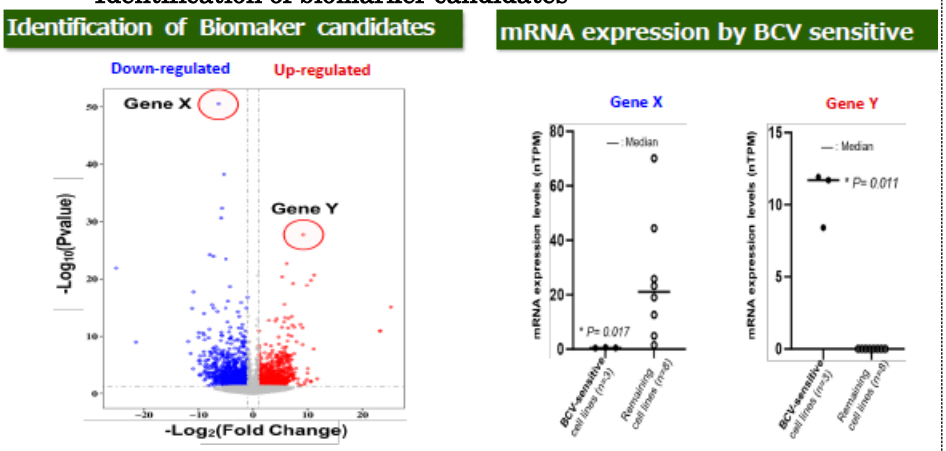
Identification of biomarker candidates



Source: SymBio company briefing, February 2025

Note: Left: Valcano graph. The horizontal axis is the difference in response to BCV between the treatment group and the control group (the greater the deviation from the center), and the vertical axis is significance. The higher the axis, the greater the significance. Genes X and Y are identified, which have a large difference in response and are significant.
The right figure shows the mRNA expression levels of genes X and Y in the BCV-treated group and the control group.

③ Solid cancers: head and neck cancer (HNSCC)

Response rates of immune checkpoint inhibitors in head and neck cancer are low

Combination with BCV is expected to induce immunogenic cell death and improve response rates

Head and neck cancer is a malignant tumor in which the immune surveillance mechanism is suppressed, and because persistent infection with HPV and EBV is involved, the PD-L1 expression rate is elevated. It has therefore been thought of as relatively suitable for treatment with immune checkpoint inhibitors. However, the response rate of such inhibitors (plus radiation) has not been of a satisfactory level. It is hoped that combining it with BCV will induce immunogenic cell death, improving the response rate. The development of BCV for head and neck cancer is likely to become a pillar of anticancer drugs, following hematological cancers and brain tumors.

Reference: Effect of immune checkpoint inhibitors on head and neck cancer

(a) Nivolumab (Opdivo®) Checkmate141 study Phase 2
Overall response rate: 13.3% vs. 5.8% overall response rate for investigator-selected treatment
(Source) Oral Tumor, Vol. 30, No. 4, pp. 144-149, 2018
(b) Atezolizumab (Tecentriq®)
Overall response rate: 22%
Disease stabilization rate: 19% (Phase 1 results, 32 cases)

Source: Annals of Oncology 29, September 2018

④ BCV in hematological cancers and solid cancers – overview

In terms of safety profile and efficacy, BCV is expected to be different from other therapies for blood cancer (PTCL). The combination of standard therapy and BCV is also more effective than standard therapy (RT+TMZ) in the field of brain tumors, and may be an effective option for TMZ-resistant or recurrent/refractory patients. In addition, in head and neck cancer, combination therapy of BCV and immune checkpoint inhibitors may show efficacy exceeding that of immune checkpoint inhibitors alone, and is expected to have significantly improved safety compared to existing chemotherapy (platinum preparations).

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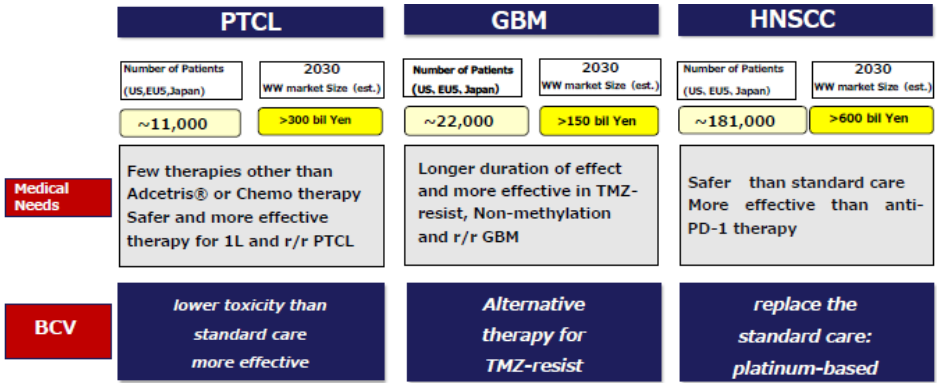
Values of BCV (hematologic and solid cancer fields)



Source: SymBio company briefing, February 2025

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(3) **Neurodegenerative diseases**

Some degenerative brain diseases are thought to be caused by inflammation due to viral infections. SymBio is currently developing drugs targeting multiple sclerosis and Alzheimer's dementia.

① **Multiple sclerosis**

Development for multiple sclerosis begins in vitro and animal testing

In February 2022, SymBio announced that multiple sclerosis (MS), a type of autoimmune disease, was a new target for BCV. In March 2023, the company signed a Collaborative Research and Development Agreement (CRADA) with the National Institute of Neurological Disorders and Stroke (NINDS), part of the National Institutes of Health (NIH), to conduct in vitro and animal model studies to verify the effectiveness of BCV using cells derived from patients with multiple sclerosis infected with EB virus.

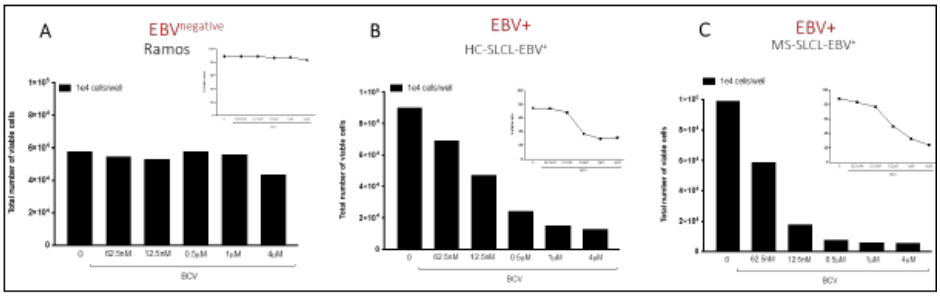
The first report revealed that BCV suppresses viral replication in B cells infected with the causative EB virus

In October 2023, the first results of the study were presented at the 9th ECTRIMS-ACTRIMS Joint Conference by a research group under Dr. Steve Jacobson of NINDS.

・In EBV-positive B cell lines infected with EBV derived from multiple sclerosis patients and healthy individuals, viral replication was suppressed in a concentration-dependent manner by BCV treatment (Figure B (derived from healthy individuals) and C (derived from multiple sclerosis patients) in the figure below).

・In EBV-negative (not infected with EBV) B cells, no effect of BCV was observed, including inhibition of proliferation (Figure A below).

Reduction of EBV-positive B cells by BCV



Source: SymBio company briefing, February 2025
Note: BCV reduces the number of EBV-positive SLCLs (B and C) but not EBV-negative B cell lines (A)

The results of animal testing are expected to be collated in June-July 2025, with clinical trials likely to begin in 2026

The plan was to move from basic experiments to animal testing (using marmosets) in the second half of 2023, but as compliance regarding animal testing became stricter, the review was prolonged, and animal testing finally began in 2024. It is still ongoing. The results will be compiled in June-July 2025, and if the results are supportive, clinical trials (Phase 1) will be considered for initiation in 2026. Based on the results of joint research with the NIH, SymBio has also applied for a patent for BCV therapy for multiple sclerosis. It is also thought that major pharmaceutical companies may take notice as the study progresses to clinical trials.

Reference: Multiple sclerosis

This is an autoimmune disease in which lymphocytes attack and demyelinate the myelin that covers the axons of nerve cells for some reason, reducing the smooth transition of information through the demyelinated nerves, resulting in various neurological symptoms (movement disorders, visual impairment, sensory impairment, urinary problems, etc.), with the disease going into repeated remission and recurrence. Lesions occur in various parts of the brain, spinal cord, and optic

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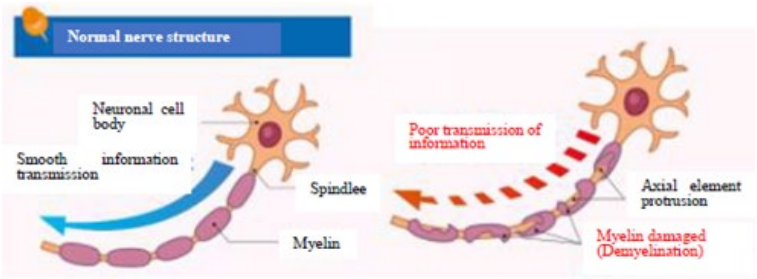
nerve, and recurrences occur at intervals of more than one month. There are approximately 18,000 patients in Japan, including those with neuromyelitis optica, and it is estimated that there are approximately 3 million patients worldwide, mainly in Europe and the United States. There is no fundamental treatment, and steroid pulse therapy, which uses steroids to suppress inflammation, and immunomodulators, which suppress the activity of lymphocytes, are used.



Source: Multiple Sclerosis.jp

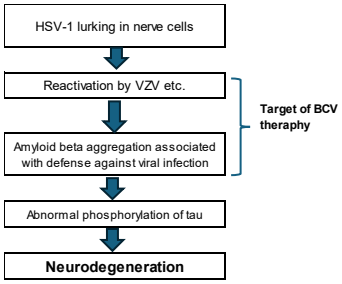
The mechanism by which the EB virus causes multiple sclerosis (MS) has not been fully elucidated, but epidemiological studies have supported its association with the virus. A Harvard University research team analysed a sample of more than 10 million adult US military service personnel, and found that 955 cases were diagnosed with MS during military service. In examining these 955 cases, it was reported that after EB virus infection, the risk of developing MS was 32 times higher than with other viral infections. (Science 2022 Jan.13, "Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis")

Recently, a research team at Stanford University has proposed a promising hypothesis as the mechanism by which the EB virus causes MS (Nature 2022, Jan.24 "Clonally Expanded B Cells in Multiple Sclerosis Bind EBV EBNA1 And GlialCAM"). This hypothesis suggests that because the transcription factor EBNA1 of the EB virus and the glial cell adhesion molecule Glia-CAM in the brain are structurally similar, lymphocytes that produce autoantibodies that recognize both migrate to the central nervous system and mistakenly damage the patient's own myelin, resulting in the onset of multiple sclerosis (MS). The effectiveness of molecular targeted drugs such as sphingosine 1 (SP1) phosphate receptor agonists that inhibit lymphocyte migration into the central nervous system (anti-α4 integrin antibodies), and CD20 antibodies (Ocrevus), which target B cells, also suggests that this mechanism is correct. SymBio believes that if this is so, it is possible to inhibit the progression of MS by quickly eliminating the EB virus using BCV after the onset of MS.

② Alzheimer's dementia

Activation of HSV-1 leads to the aggregation of amyloid beta, which then induces abnormal phosphorylation of tau, resulting in the death of neurons

Recently, there has been growing evidence suggesting that the herpes simplex virus type 1 (HSV-1) is involved in the development of Alzheimer's disease (NIH big data analysis of a total of 500,000 people from Finland and the UK: Neuron magazine, January 2023). A study at Tufts University in the United States has pointed out that when VSV (varicella-zoster virus) activates HSV-1, amyloid beta accumulates, and the deposited amyloid beta causes abnormal phosphorylation of tau, which may lead to the progression of neurofibrillary degeneration and the death of neurons. In particular, it has been pointed out that people who carry the APOE4 gene are more susceptible. Oxford University has also revealed that when HSV-1 is present in the brain, in combination with APOE4, the likelihood of developing Alzheimer's disease increases (APOE4 is known to facilitate the accumulation of amyloid beta).



Source：Fair Research Inc based on SymBio company briefing

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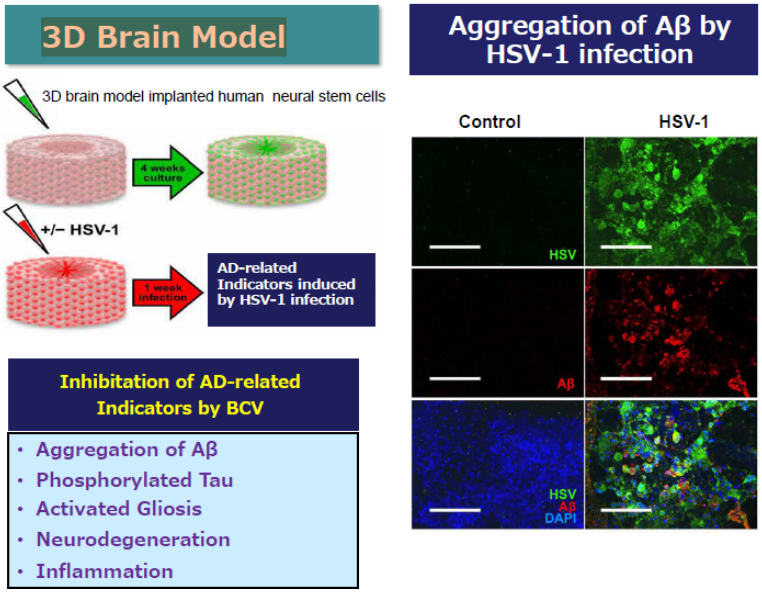
The mechanism by which HSV-1 activation leads to the deposition of amyloid beta remains unclear	It is believed that the defense response to HSV-1 infection leads to Aβ aggregation, but it is not clear by what mechanism HSV-1 activation leads to the deposition of amyloid beta. It is hypothesised that HSV-1 infection activates NLRP3 to promote the deposition of amyloid beta, or that microglial cells, which are immune cells, decrease around amyloid beta and increase around HSV-1, reducing the amyloid beta removal ability of microglial cells. (Reference: "Herpes Simplex virus 1 accelerates the progression of Alzheimer's disease by modulating microglial phagocytosis and activating NLRP3 pathway", Wang et al., Journal of Neuroinflammation 2024).
BCV may be a potential treatment for Alzheimer's disease	BCV, an antiviral drug, may become one of the treatments for Alzheimer's disease. To date, BACE inhibitors and anti-Aβ antibodies have been developed targeting Aβ, but it is difficult to remove aggregated Aβ, and only some anti-Aβ antibodies (such as lecanemab) have been approved for mild cognitive impairment (MCI). BCV is expected to suppress VZV infection so that latent HSV-1 in nerve cells is not reactivated by VZV, etc., or to suppress infection by activated HSV-1 and prevent the aggregation of Aβ caused by HSV-1. It is also thought that BCV may suppress the decrease in the Aβ removal function of microglial cells caused by HSV-1 infection.
Preclinical studies using a 3-D brain model of Alzheimer's confirmed that BCV suppresses Alzheimer's disease-related indicators Considering moving to an animal model	SymBio has signed a research agreement with Tufts University and conducted non-clinical trials to verify the effect of BCV on the herpes simplex virus (HSV) infection model using Tufts' 3-D brain model. As shown in the figure below, SymBio confirmed that amyloid beta aggregates due to HSV-1. Furthermore, SymBio has obtained data showing that BCV suppresses Alzheimer's disease-related indicators (amyloid beta aggregation, phosphorylated tau, activated gliosis, inflammation.). Based on this data, SymBio has applied for a patent for the inhibition of HSV-1-induced amyloid aggregation by BCV. Currently, SymBio is considering moving to an animal model. **Amyloid beta aggregation due to HSV-1 infection (3D brain model)**  Source: SymBio company briefing, February 2025 Reference: **Antiviral drugs and Alzheimer's disease:** Valacyclovir has already undergone Phase II clinical trials (NCT03282916, NCT02997982) to determine whether it can slow the progression of HSV-positive Alzheimer's disease. These trials were expected to be completed by 2024, but the results have not yet been released.

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<BCV Recap>

Next flagship candidate: Brincidofovir (BCV) is a platform targeting various diseases

BCV is a highly active, broad-spectrum antiviral agent

BCV is a safe drug

It can easily pass through the blood-brain barrier

<Reference: BCV recap>

Background to introduction of BCV

BCV was originally a highly active multi-viral infection drug developed by Chimerix Inc. of the United States. On October 1, 2019, SymBio announced that it had acquired exclusive global rights (development, manufacturing, and sales) for BCV for all diseases except Orthopox (smallpox and Empox (monkeypox)), from Chimerix as a strategic product to take over from Treakisym®. Until then, SymBio had licensed BCV from overseas and developed it mainly for the Japanese market, but with this agreement, it has acquired the ability to license out its products globally. (Note that in September 2022, Chimerix transferred the license for BCV to Emergent BioSolutions Inc., but this does not affect the rights that SymBio has acquired.)

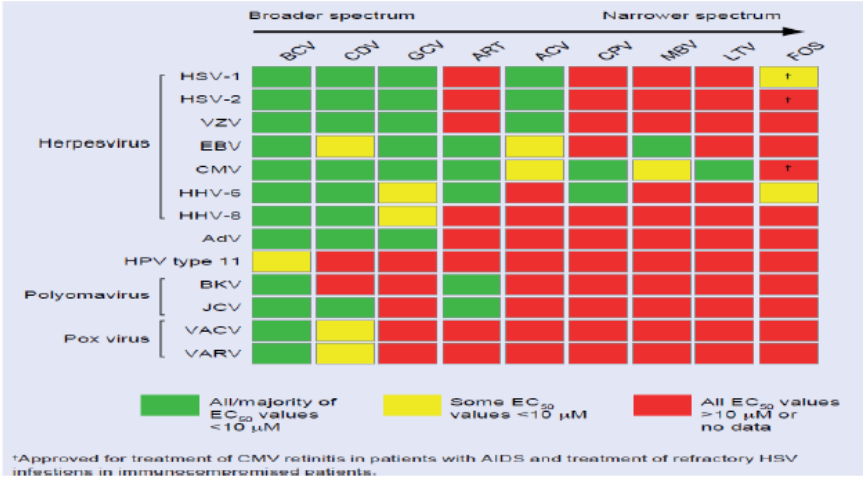
(1) Characteristics of brincidofovir

Brincidofovir (BCV) is a more active multi-viral infection drug than other antiviral drugs such as cidofovir (CDV) and foscarnet (FOS). CDV has a broad spectrum similar to BCV but is nephrotoxic and difficult to handle. On the other hand, BCV has low toxicity and is safer despite its high level of activity.

Three characteristics of BCV:

◎ High antiviral effect against a wide range of double-stranded DNA viruses
◎ No nephrotoxicity or bone marrow suppression, which are serious side effects of other antiviral drugs.
◎ High blood-brain barrier (BBB) permeability.

Brincidofovir is highly active across a broad spectrum



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

Source: Chimerix data
Note: The lower the EC50 (the concentration at which a drug or antibody shows 50% of its maximum response above the minimum), the higher the activity. The above figure is color-coded according to the EC50, with green indicating high activity and red indicating low activity. BCV, on the far left, is green for various viruses, meaning it has a broad spectrum.

Reference: Brincidofovir mechanism of action
Brincidofovir 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 prolonged period, resulting in a compound with dramatically

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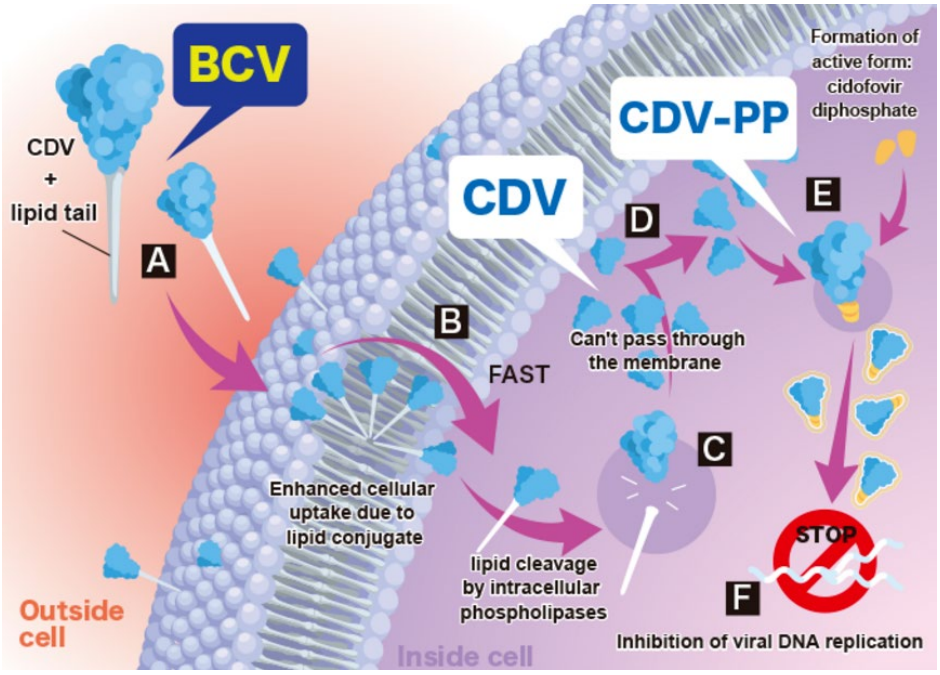
improved antiviral activity. In addition, the HDP binding prevents accumulation in renal tubular epithelial cells by the OAT-1 transporter, and the level of CDV released into the blood is low, avoiding the fundamental problem of CDV, nephrotoxicity. (CDV does not have a fatty chain, so it becomes a substrate for OAT-1 and accumulates in renal tubular epithelial cells, which makes it prone to causing nephrotoxicity.)



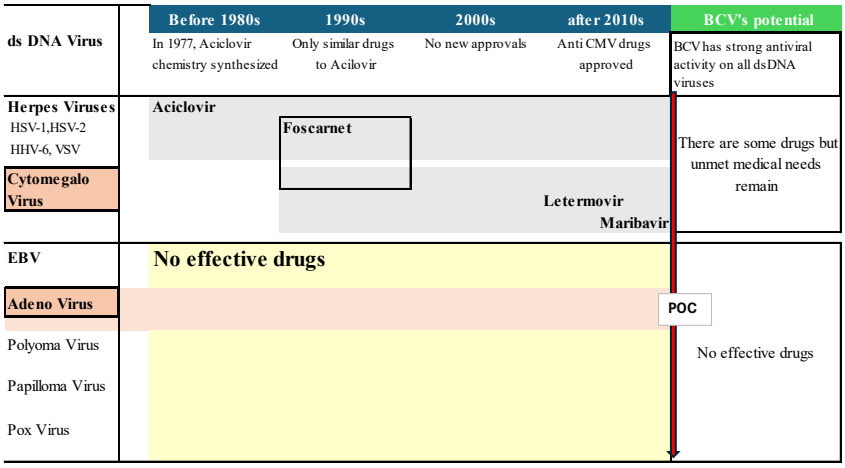
Source: SymBio IR material

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

(2) Areas where brincidofovir (BCV) is expected to be effective

The first dsDNA virus drug to appear was acyclovir (ACV) in 1977. In the 1990s, similar drugs such as foscarnet (FOS) and ganciclovir (GCV) were developed. No new drugs appeared in the 2000s, but in 2017, Merck introduced letermovir (LTV) from AiCuris and it was approved and released. Then, maribavir, which Takeda Pharmaceutical acquired when it bought Shire Pharmaceuticals, was approved. There are, therefore, not many antiviral drugs for dsDNA viruses. Furthermore, the targets for which the existing antiviral drugs are active are herpes viruses and cytomegalovirus (CMV). Needs are as yet unmet for the Epstein-Barr virus (EBV), adenovirus (AdV), polyoma virus, human papilloma virus (HPV), etc., so much is expected from BCV, which has a high level of activity and a wide spectrum.

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



Source: SymBio company briefing, August 21, 2024

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BCV is also expected to be effective in areas where there are concerns about side effects and resistance to existing antiviral drugs Diseases that could be targeted include post-transplant infections, hematological tumors, solid cancers, and neurological disorders	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. 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, immuno-suppressants are administered to suppress rejection during HSC transplants and organ transplants, and the reactivation of these viruses can cause serious infections during such immuno-suppressed states. In addition, the EB virus has been linked to blood tumors such as NK/T-cell lymphoma, and a 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.

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2. 2024 results and 2025 outlook

Generics are penetrating at a pace slightly faster than expected

Lawsuits with two generic manufacturers settled; impact on current and future performance is minor

Sales for 2024 are expected to be JPY2,452 million from Treakisym, down 56.1% from the previous year due to the penetration of Treakisym generics and the drug price revision in April. Generics' share was previously expected to grow from approximately 60% in June 2024 to 65% in 2025, but it appears that in reality it is on track to reach 70%, slightly above the expected rate. Elsewhere, settlements have already been reached with two generics makers (Towa Pharmaceutical and Pfizer (Japan)) regarding lawsuits seeking injunctions against manufacturing and sales, and damages. It has been announced that the impact of these settlements on the company's performance for the current fiscal year will be minor, and the impact on future performance is thought to be negligible.

Cost ratio to worsen in 2024 due to the effects of the weak yen and drug price revisions, as well as other temporary factors

Rising R&D costs lead to larger deficit

The cost ratio for 2024 was 23.8%, a deterioration of 2.5 percentage points from the previous year. In the April-June period, it worsened to 23.6% due to the weakening of the yen and drug price revisions. The cost ratio for the July-September period worsened to 27.0%, worse than the April-June period, but this was due to a transient factor - inventories for which inspection costs had increased due to a defective product issue last year were shipped in July and August. The cost ratio for the October-December period returned to the 22% range. SG&A costs for 2024 were JPY5.75 billion, which was mainly due to an increase in research and development expenses, especially BCV development expenses. As a result, operating profit for 2024 registered a loss of JPY3.876 billion.

Profit and loss 2024-2025

(JPY-mil)

	2023 (Actual)	2024 (Actual)	2025 (Forecast)	2023 Jan-Mar (Actual)	2023 Apr-Jun (Actual)	2023 Jly-Sep (Actual)	2023 Oct-Dec (Actual)	2024 Jan-Mar (Actual)	2024 Apr-Jun (Actual)	2024 Jly-Sep (Actual)	2024 Oct-Dec (Actual)
Sales	5,589	2,452	1,858	1,544	1,634	1,243	1,168	597	687	614	554
(YoY)	-44.1%	-56.1%	-24.2%	-33.3%	-36.1%	-49.9%	-56.0%	-61.3%	-58.0%	-50.6%	-52.6%
								Slow sales in advance of price rev.			
Cost of sales	1,178	579	503	301	404	239	234	126	162	166	125
(Cost ratio)	21.1%	23.6%	27.1%	19.5%	24.7%	19.2%	20.0%	21.1%	23.6%	27.0%	22.6%
		Price rev.	Price rev.		Defective product			Yen weakens	Yen weakens+price	Dispeal of def. invent.	Retune to 22% level
SG&A	5,222	5,750	5,620	1,192	1,330	1,237	1,463	1,277	1,438	1,520	1,515
of which, R&D	2,628	3,379	3,661	549	654	620	805	691	840	961	887
		Start of clinical trials for NK/T lymphoma	BCV dev. revs up								
Operating profit	-811	-3,876	-4,263	51	-100	-234	-528	-806	-913	-1,072	-1,085
Recurring profit	-736	-3,689	-4,347	48	18	-222	-580	-727	-754	-1,278	-930
Net profit	-1,962	-3,833	-4,468	4	-83	-709	-1,174	-777	-764	-1,304	-783
									Drug prices reduced by 18% from April		

Source: Fair Research Inc. using company results filings

Sales will continue to decline in 2025 due to the penetration of generics and drug price cuts

Although there will be savings on administrative expenses and elsewhere, R&D expenses will increase and overall SG&A expenses will remain flat, so the deficit will increase

As of December, the cash and deposits level was JPY3,963 million, and funds

The company's forecast for 2025 is that Treakisym® sales will fall 24.3% year-on-year to JPY1,858 million, taking into account the impact of generics (generics' share will rise to an average of 72.5% annually) and drug price cuts (a 5.5% cut from April). Meanwhile, research and development expenses are expected to increase to JPY3,661 million as the development of BCV gets underway in earnest, but overall SG&A expenses are expected to remain roughly flat at JPY5,620 million due to cuts in other SG&A expenses. As a result, the operating loss will expand to JPY4,263 million and the net loss for the period will be JPY4,468 million. However, this does not include the costs associated with the acquisition of a new licenses scheduled for the third quarter.

As of December 2024, the cash and deposits level stood at JPY3,963 million, and funds for the next year or so have been secured. However, while Treakisym sales are gradually being eroded by generics, various developments related to BCV are gaining momentum, so SymBio needs to continue raising funds to avoid stagnation of development.

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for the next year or so have been secured

The company will continue to raise funds to avoid stalling BCV development

An overview of fundraising related to the development of BCV to date is as follows. Although the fundraising planned for June 2022 was completed by raising JPY622 million through the issuance of new shares via a third-party allotment, the 58th stock acquisition rights remain unexercised, and the JPY1,569 million expected from such exercise has not yet been raised. In addition, due to the sluggish share price, the fundraising through the comprehensive equity issuance program (STEP) planned for October 2023 (issuance of stock acquisition rights in five installments) actually raised JPY1,238 million, compared to the initially planned JPY2,183 million.

Funding for BCV over the past three years

I. New share issue via 3rd party allotment (June 2022) (JPY-mil)

	Use of Funds (initial plan)	Spending Period (initial plan)	Amount Raised and alloc. Status
①Funds for BCV development （direct costs）	432	July-Oct 2022	432
②Funds for BCV development （indirect costs）	190	July-Oct 2022	190
Total	622		622

II .Issue of 58th new share options (issued June 2022) =>unexercised (JPY-mil)

	Use of Funds (initial plan)	Spending Period (initial plan)	Amount Raised and alloc. Status
①Funds for BCV development （direct costs）	787	Oct 2022-Mar 2023	0
②Funds for BCV development （indirect costs）	386	Oct 2022-Mar 2023	0
③New licensing-in/M&A	396	July 2022-Mar 2023	0
Total	1,569		0

Note: The exercise price will be revised to the same amount as the conversion price of IV.CB below.

III. Previous （Oct. 2023) financing (STEP program) (JPY-mil)

	Use of Funds (initial plan)	Spending Period (initial plan)	Amount Raised and alloc. Status
①Funds for BCV development （direct costs）	658	Oct.2023-June 2024	633
②Funds for BCV development （indirect costs）	742	Oct 2023-June 2024	584
③New licensing-in/M&A	783	Oct 2023-June 2024	21
Total	2,183		1,238

Source: Fair Research using SymBio IR data

December 2024: Four CBs to raise JPY2.4 billion

It was in this context that SymBio on December 25, 2024 announced a convertible bond issuance program with Cantor Fitzgerald Europe as the allottee. Cantor Fitzgerald Europe is the European arm of the Cantor Fitzgerald group, conducting global investment banking operations among a broad network of institutional investors. The group has a professional team specializing in bio-healthcare, including many analysts covering bio-health companies. It sponsors an annual global healthcare conference in New York.

Due to sluggish stock prices the amount to be raised was reduced to JPY1.8 billion

Initially, the plan was to issue CBs to the allottee every month from January to April 2025, raising a maximum total of JPY2.4 billion. The total amount after deducting

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issuance costs was expected to be a maximum of JPY2.3 billion. However, as the increase in the number of potential shares reached approximately 6.8 million shares, and in light of the upper limit of potential shares for this entire procurement program being 11.3 million shares, the company decided to cancel the 6th CB and end procurement with the 7th CB. As a result, the total amount procured will be JPY1.8 billion, and the total amount obtained after deducting issuance expenses will be JPY1.7 billion. The total number of potential shares will be approximately 10.6 million shares, and the dilution rate will be 23.09%.

Convertible bond program (Jan-April 2025)

	Amount (JPY-mil)	Conversion price (JPY)	Yield	Maturity
No 4 CB	600	182.7	Jan 10, 2025 to Jan 11 2026 : 3.5% After Jan 11: 6%	2027/1/10
No. 5 CB	600	171.0	Feb 6, 2025- Feb 6, 2026: 3.5 % After Feb.6 : 6%	2027/2/5
No 6 CB (suspended)	0	90% of the share price on the day before issue terms fixed (Feb 20,2025)	March 11, 2025-March 10, 2026: 3.5% After March 10: 6%	2027/3/10
No 7 CB	600	157.5	April 11, 2025-April 10, 2026: 3.5% After April 10: 6%	2027/4/10
Total	1,800 (after No.6 CB cancelled)			

(Note)The sixth round was canceled because "if the total number of shares to be issued upon conversion of the CBs exceeds 11.3 million shares, the amount of subsequent CBs to be issued will be reduced or suspended."

Estimated amount after deducting issuance expenses	1,700 (after No.6 CB cancelled)

Use of funds raised through No.4～No.7 CBs (January to April 2025) (JPY-mil)

	Uses of funds (initial plan)	(after changed)	Spending period
①Funds for BCV devepopment (direct costs)	1,300	960 (75)	Jan 2025-Oct. 2025
②Funds for BCV development (indirect costs)	1,000	740 (23)	Jan 2025-Oct. 2025
Total	2,300	1,700	

(note) the figures in the parenthesis is the amount which have been already spent by January 2025

Source: Compiled by Fair Research Inc. using SymBio IR materials

The scheme ensures the acquisition of funds through CB's while also taking into consideration existing shareholders

The main point to bear in mind here is that the issue of CB's gives a level of reliability to raising finance. At the same time, the program factors in the interests of existing shareholders. First, to prevent dilution, the amount to be raised is restrained so that the total number of shares to be issued through CB conversion does not exceed approximately 25% of the total number of shares issued (11.3 million shares). In fact, the issuance of the 6th CB was canceled. Furthermore, even if the allottee converts the CB's to shares, due to factors such as the rise in share prices accompanying progress in product development, in principle they are not allowed to sell the shares on the market, and the plan is for them to be sold off-market to overseas investors. (However, it is possible that the overseas investors who acquire the shares being sold may sell them on the market).

The maturity is two years, but during that time, the development of BCVs may progress and CBs may be converted

Each CB has a maturity of two years and will mature by April 2027. The interest rate on the CB is 3.5% in the first year and 6% in the second year. However, this need not be financially burdensome for the company: as alluded to in the previous paragraph, events related to product development could occur within the next two years, such as a rise in the share price due to renewed optimism about development or expectations of a mega-pharma tie-up.

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	Mid-2025 ◎ Outline of Phase III, targeting AdV infection following HSC transplantation ◎ Announcement of Phase II results for CMV infection after HSC transplantation, which has the potential to become a major product, plus perhaps a partnership based on the Phase II results? ◎ Domestic: Emergence of new products ◎ Establishment of animal proof-of-concept for multiple sclerosis (MS) **Late 2025** ◎ AdV infection after HSC transplantation: Phase III starts ◎ NK/T cell lymphoma: Establishment of POC through results of Phase Ib ◎ Brain tumor (GBM) Phase Ⅰb starts ◎ Emergence of global partnership for BCV (combination therapy with immune checkpoint inhibitors for hematological malignancies and head and neck cancer) **2026-2027** ◎ Start of clinical trials (Phase I) targeting multiple sclerosis ◎ Moving toward POC confirmation in the area of neurodegenerative disorders ◎ Progress in Phase II targeting hematological tumours. For NK/T-cell lymphoma, it is possible that an application will be submitted to the PMDA based only on Japanese data.
Demonstrates SymBio's confidence in the success of BCV development	In other words, it can be inferred that SymBio has great confidence in the progress of BCV's development, which is why it has set the CB maturity at two years and has a mechanism for stepping up interest rates.

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3. Summary: growth scenario

<Expectations in 2025>
Newly licensed products will cover the decline in Treakisym® sales

SymBio is currently approaching a major turning point. The Treakisym® market, which has been nurtured as a cash cow for many years, is now being seriously eroded by generics. Meanwhile, brincidofovir (BCV), which SymBio sees as a pillar of its future global expansion, is set to establish human proof-of-concept (POC) for its first indication (disseminated adenovirus (AdV) infection after hematopoietic stem cell transplant) in May 2023, with Phase III trials set to begin in the fourth quarter of 2025. Until BCV is launched, SymBio plans to introduce new products (new license acquisitions) by the third quarter of 2025 in the hematology and oncology field, SymBio's specialty, in order to make up for declining sales of Treakisym®.

Phase III targeting AdV infections after HSC transplants is scheduled to begin in the 4th quarter

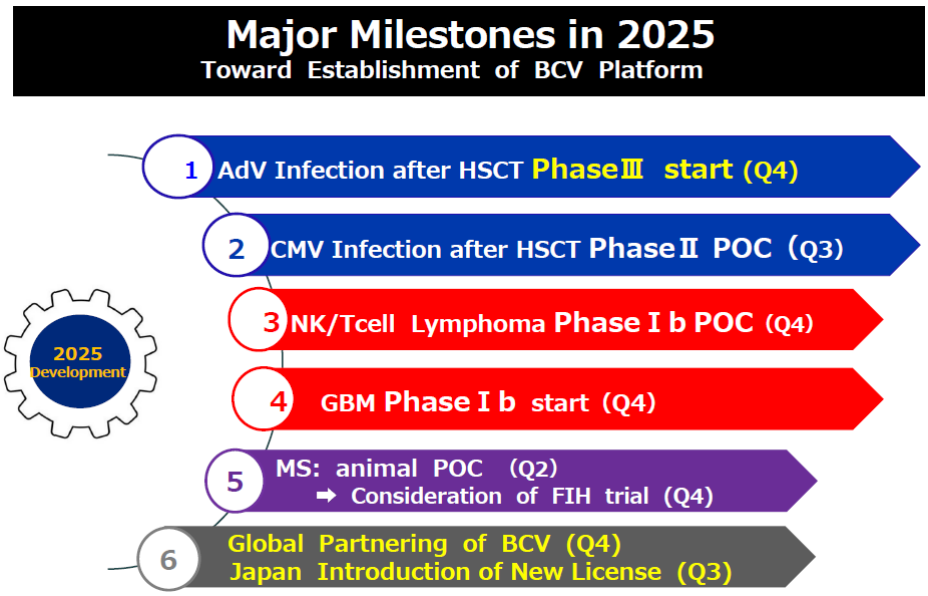
Development targeting CMV infections after HSC transplants is scheduled to establish POC in 3Q

Potential to become a major product

Following the first indication for BCV, clinical trials (Phase II) targeting cytomegalovirus (CMV) infection after hematopoietic stem cell transplantation are also progressing with patient enrollment, and Phase II trials are expected to be completed in the third quarter of 2025, with human POC established. It is important to note that the earlier drug, maribavir, is targeted only at relapsed and refractory CMV infections, and approximately 44% of patients are refractory or resistant to maribavir, whereas BCV is less likely to develop resistance and is being developed for use in treatment-naive patients as well. The number of such patients is estimated at 15,000, making this a potentially major product.

In the field of hematological oncology, the aim is to establish POC in the fourth quarter 2025

In addition, in August 2024, a start was made on clinical development (international collaborative Phase Ib/II) targeting malignant lymphomas (NK/T-cell lymphoma, PTCL, etc.) Patient registration is scheduled for completion in the course of 2025 and human POC would be established based on the PhaseIb data of Japanese part in the fourth quarter 2025. Then, human POC should be established in two therapeutic areas: post-transplant infectious diseases and hematological cancer.



Source: SymBio company briefing, February 2025

Non-clinical trials suggest efficacy in combination with immune checkpoint inhibitors. Expectations for global partnering to emerge within the year

In addition, non-clinical trials have suggested the efficacy of BCV and immune checkpoint inhibitors combined. Mega-pharma companies with immune checkpoint inhibitors whose patents are about to expire are planning lifecycle management of their inhibitors for new applications and are looking for partners who can provide promising applications. Global partnership opportunities could emerge within the year.

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<Expectations from 2026 onwards>

Human POC to be established in three areas by 2027

First NDA slated for 2028

By 2030: Approvals expected for new drugs in two areas

After 2030: Global development in the field of neurodegeneration

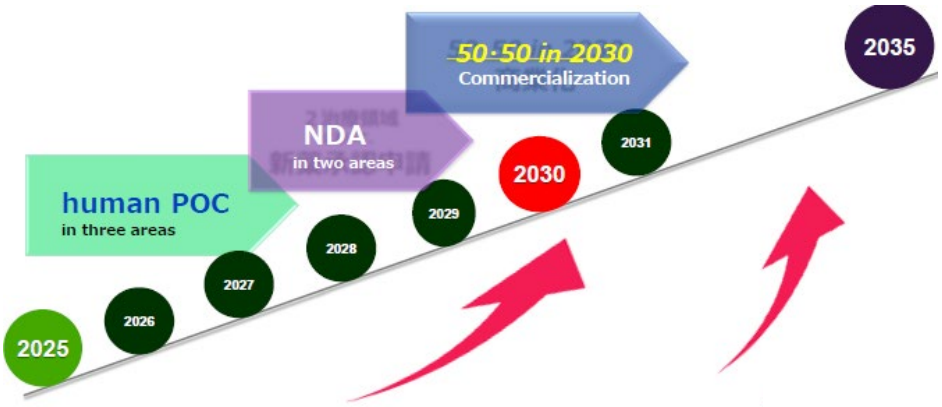
Between 2026 and 2027, human POC will be established in the field of neurodegeneration, and human POC for BCV is expected to be achieved in three fields.

Regarding commercialization, the plan is for a new drug approval application for BCV targeting adenovirus infections after HSC transplantation, which is the most advanced, to be submitted by 2028. Thereafter, multiple new drug approvals are planned for the two fields of post-transplant infections and cancer (hematological cancers and solid cancers) by 2030. As a result, the size of domestic sales and overseas sales are expected to be approximately level around 2030.

Global development in the field of neurodegeneration, one of the three fields mentioned, will not begin until after 2030. The number of patients affected annually is expected to be more than 9.9 million, far exceeding the numbers for post-transplant infections (>40,000) and oncology (>200,000).

Note: Patient numbers sourced from SymBio company briefing, February 2025.

Growth strategy scenario heading to 2030



Source: SymBio company briefing, February 2025

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