SymBio Pharmaceuticals Ltd.

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New Business Development: Advances Made in BCV

Still room for Treakisym® to grow despite emergence of generics

SymBio Pharmaceuticals was the first company to receive approval in Japan for Treakisym® as a treatment for malignant lymphomas and subsequent formulations. Generics began to appear in February 2022. In that month four companies received approval to manufacture and sell generic RTD Treakisym®. After SymBio notified these companies of possible patent infringement, Towa Pharmaceutical initiated sales (the other three put off commencing sales). In addition, the generic versions were initially indicated only for indolent B-NHL and MCL, but in June approval was given for the additional indication of r/r DLBCL (B-R therapy). The CLL and r/r DLBCL P-BR therapy remained un-indicated. Given this situation, SymBio accelerated a switch to RI administrations. According to SymBio, some 20 institutions were receiving deliveries of the generic formulation by mid-October, indicating a cautious stance on the part of medical facilities. As a result, the company's July-September sales were trending around the level SymBio had forecast in August. However, in November 2022, the RI-type generic from Towa and Pfizer (Japan) received approval. SymBio believes that there is a possibility of patent infringement regarding RI administration On December 16, it filed a patent infringement lawsuit against Towa Pharmaceuticals, and on December 26, filed a similar lawsuit against Pfizer. In the fields of hematology and oncology, a relatively cautious attitude toward generic products with slight differences from Treakisym® in terms of constituents still persists. Further, since the use of the B-R therapy and the P-BR therapy in the treatment of r/r DLBCL is less than 50%, it is believed that there is still room for Treakisym® to penetrate.

Despite the emergence of BiTEs, the position of Treakisym® remains solid

SymBio's mainstay product, Treakisym®, is mainly aimed at malignant lymphomas, particularly r/r DLBCL, an area in which work on antibody therapy and immunotherapy development is very active. Hence the appearance of ADC's (antibody drug conjugates) such as Polivy and a number of highly effective CAR-T therapies. There is also much hope placed in the development of BiTEs (bispecific T cell inducer antibodies). Polivy® has achieved significant market penetration in a combination therapy with Treakisym®. The CAR-T therapy is currently restricted to third-line treatment and also faces major barriers in terms of cost and availability. BiTEs is making progress and there have been several examples of overseas approvals, but these have been more late-line therapy approvals. The sort of indications for which BiTEs will be approved is still unclear. Unless a therapy clearly more effective than the familiar B-R therapy is developed there is for the time being no threat to Treakisym's position.

Progress in development of brincidofovir (BCV)

SymBio first developed BCV in the area of haematology: ① to treat viral infections following stem cell transplants; and further, ② expanded development to viral infections at the time of organ transplant. As for ①, Phase-2 international collaborative clinical trials are currently underway and are due for completion in the first half of 2023. As for ②, Phase-2 international collaborative clinical trials just started and, following establishment of POC, the plan is to launch corporate tie-up activities. Further, SymBio is considering developing BCV for "therapeutic voids" where no existing antiviral agents have been approved. Actual developments under consideration include ③ glioblastoma (GBM), a malignant brain tumour, and ④ multiple sclerosis (MS). SymBio is undertaking a variety of joint research projects with multiple US universities. In addition, it is also promoting a joint research provision agreement with the National Institute of Neurological Disorders and Stroke, which belongs to the National Institutes of Health, to evaluate the antiviral effect of BCV against the EB virus. The first results of collaboration are already apparent, and the expectation is that major pharmas will show an interest.

Follow-Up Report

Fair Research

Tsuyoshi Suzuki

Company Outline	
Location	Tokyo
President	Fuminori Yoshida
Established	March 2005
Capital	JPY17,152 mil.
Listed	October 2011
URL	www.symbiopharma.com
Industry	Pharma
Employees	125 (consol.)
Key Indicators (Jan. 12, 2023)	
Share Price	640
52-week high	1,284
52-week low	610
Shares Outstanding	39,585,406
Trading Unit	100 shares
Market Cap	JPY25,335 mil.
Dividend (est.)	0.0
Forecast EPS	JPY42.4
Forecast PER	15. 09X
Actual BPS	JPY213.9
Actual PBR	2.99X

(Note: EPS、PER、BPS、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 High	Stock Price 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
2021/1Q-3Q Actual	5,553	138.1	424	NA	414	NA	324	NA	8.4	2,423	387
2022/1Q-3Q Actual	7,355	NM	1,588	NA	1,843	NA	1,555	NA	40.0	1,284	610
2022/12 Forecast	10,003	NM	2,000	NA	2,300	NA	1,650	NA	42.4		

Company overview and management philosophy

＜BUSINESS MODEL＞

The company is a pharmaceuticals venture business aiming for high returns using a niche strategy, operating without laboratories or manufacturing facilities to reduce much of the risk inherent in new drug discovery

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

① Post-POC strategy

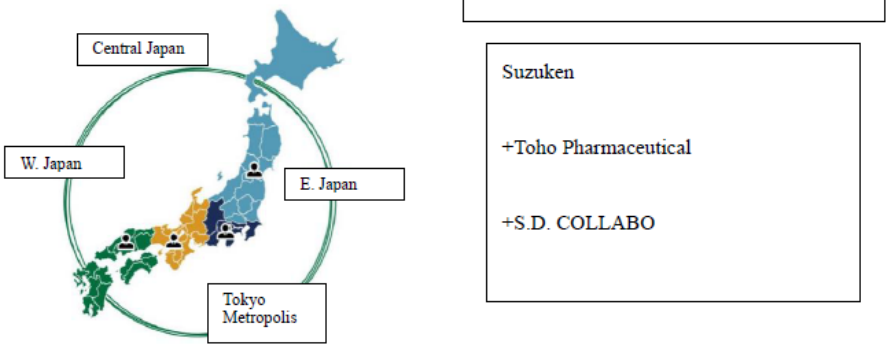
The company does not itself undertake drug discovery research but investigates new drug candidates developed by drug discovery ventures and pharmaceuticals companies around the world. Usually, proof of concept has already been established. By insisting on prior evidence of efficacy and safety in human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

② 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 haematology, 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 haematology.

The company's sales sysem

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



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

③ Global licensor

Further, in September 2019, SymBio acquired exclusive rights (development, production and sales) to brincidofovir (BCV), a product with global

applications. SymBio has thus evolved from a company seeking licenses in Japan to one providing licenses around the world, firstly in Asia, including China, and also the US and Europe.

The key to performance 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® (generic name: bendamustine), 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

Members of the SAB （Scientific Advisory Board）

Source: SymBio Pharmaceuticals

This product was selected in 2018 as the standard therapy

The company has also succeeded in expanding indications

Current SymBio sales come from the company's first product, Treakisym® (generic name: bendamustine). Treakisym® took only around five years to go from licensing-in in 2005 to receiving manufacturing and sales approval in 2010 (the first approved indications were relapsed/refractory low-grade non-Hodgkin's lymphoma and mantle cell lymphoma). This was followed by a series of additional approvals: for chronic lymphocytic leukemia (CLL) in August 2016, and untreated low-grade NHL/MCL in December of the same year. Further, in July 2018 Treakisym® for all approved indications 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), and the B-R therapy combining Treakisym® (bendamustine) with Rituxan® (rituximab) became the standard therapy. Then, in March 2021, there was success in acquiring approval for a further indication, relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL). At the same time, the P-BR therapy combining Roche's Polivy® and Treakisym® (bendamustine) and Rituxan® (rituximab) received approval for all previously authorised indications.

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

Reference: Types of malignant lymphoma

Lymphoma is a blood disease caused by the cancerization of lymphocytes (a type of white blood cell) that act as immunity cells. There are two major types: Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL), with Japanese patients mostly of the NHL type. NHL, which is the target of Treakisym®, can be divided into three types depending on speed of disease progression. Further, the most common form of medium-grade NHL in Japan is diffuse large B-cell lymphoma (DLBCL).

Distribution of malignant lymphoma by type (Japan)

(%)

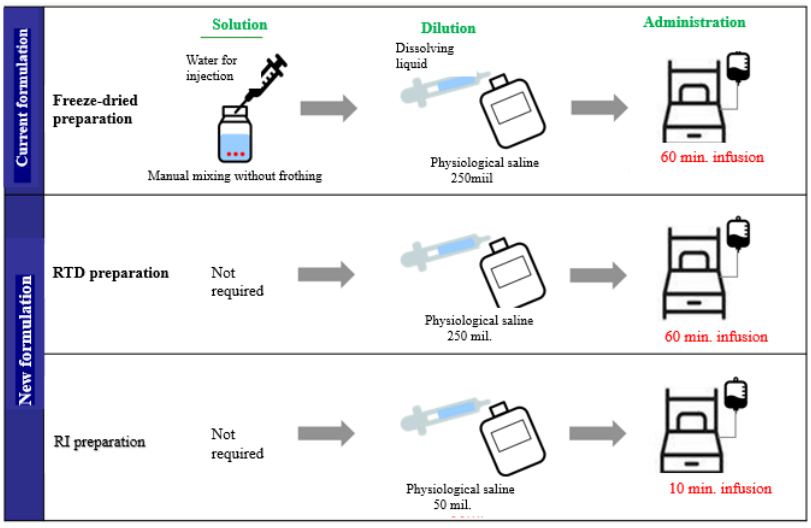
Non-Hodgkin Lymphoma	**DLBCL**	**45.3**
	Focular Lymphoma	13.5
	MZBCL	7.2
	CLL/SLL	3.2
	MCL	2.0
	Burkitt Lymphoma	1.3
	T/NK Cell Lymphoma	18.1
Hodgkin Lymphoma		5.9
Others		3.8

Low grade lymphoma
Medium-High grade lymphoma

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

The company has also developed new formulations and administration modes. Hence, in addition to the existing freeze-dried formulation it is also promoting a very convenient liquid formulation, and in September 2020 received approval for an RTD formulation, which has now been supplied to most medical facilities in Japan. Additionally, approval was given for the highly convenient (10-minute administration) RI formulation in February 2022. As of September 2022, more than 94% of medical facilities have confirmed their intention to use RI administrations, demonstrating a smooth crossover.

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



Source: SymBio Pharmaceuticals results meeting

	1.The impact of generics
In 2022 RTD generics entered the market	SymBio was the first company in Japan to develop and receive approval for Treakisym® and a number of new formulations, for the treatment of malignant lymphomas. From February 2022, however, generics began entering the market. In 2022, Pfizer (Japan), Meiji Seika Pharma, Koaisei, and Towa Pharmaceutical received approval for the manufacture and sale of generic versions of Treakisym® intravenous infusion (RTD formulation). In Japan, under the government's policy of promoting the use of generics, it seems that a generic is likely to be approved as an improved product if it includes constituents different from the original product, but there remains the problem of patent infringement.
One of the companies SymBio notified of patent infringement concerns started sales	On February 25 2022, SymBio notified the four companies of concerns about patent infringement. The patent in question, which has also been recognized in Japan, is the property of Eagle Pharmaceuticals Inc., a US company, which is the original licensor of the RTD formulation and RI administration. There was a previous instance in the US of patent infringement involving the Treakisym Bendeka® RI administration. The court in that case found for Eagle Pharmaceuticals (the licensor was Teva) and enjoined the generics makers from selling the product for a prescribed period. On February 28 2022 approval was given for the RI formulation, which is even more convenient to administer than the RTD formulation, and SymBio began encouraging a switch. On May 11, Meiji Seika Pharma announced it was putting off the posting of drug prices scheduled for June. With this the risk posed by generics receded somewhat and, in fact only one company, Towa, got as far as posting prices and starting sales.
CLL and P-BR therapy are not indicated for generics	The indications approved for the four generics makers in February covered indolent B-NHL and MCL, but not r/r DLBCL. In June, Towa received approval for the additional indication of r/r DLBCL. Meanwhile, CLL is covered by exclusive protection during the reexamination period (until 2026) and cannot be included in the indications for generic products. Additionally, not approved for the P-BR therapy to treat r/r DLBCL.
In November 2022, two companies received approval for their RI generics	However, on November 9 2022 Towa Pharmaceuticals and Pfizer (Japan) received regulatory approval for an RI generic, and Pfizer (Japan) began sales on December 16. The indications approved for Pfizer included P-BR for r/r DLBCL. SymBio also believes this RI generic could be in breach of its patent. On December 16 2022, SymBio filed a lawsuit against Towa Pharmaceuticals seeking an injunction against the manufacture and sale of generic products and compensation for damages on the grounds of patent infringement. Then, on December 26, SymBio also initiated a similar legal action against Pfizer (Japan).
Lawsuit filed for patent infringement	
In August the impact of generics was estimated at JPY200 million (second half of 2022)	In August 2022 SymBio reduced its forecast for sales by around JPY992 million from an initial JPY10,992 million to JPY10,003 million. The reasons given for the downward revision were the continued effects of COVID-19 and the entry of generics, with the latter accounting for an estimated JPY200 million. The estimate was arrived at by a quantified consideration of the proportion of generics adopted by each facility, the recent status of anti-cancer drug use by each facility, the proportion of in-patients to out-patients, the ownership of each facility (public hospitals are under pressure to use generics), and whether or not the facility has received guidance on the freeze-dried formulation. Precise predictions are obtained by distributors/agents drug expertise, familiarity of MR's (Treakisym Managers – TM's) with medical facilities, the status of RI use and the timing of any switch to RTD. The forecast third quarter sales was JPY2,476 million and for the fourth quarter JPY2,654 million. Since actual third quarter sales came in at a close JPY2,481 million the accuracy of the estimation is evident. There were 20 facilities
Sales in the July-September period approximately in line with expectations	

As of mid-October, it was confirmed that 20 facilities had received delivery of generics

The impact of the RI generics will now be closely scrutinised

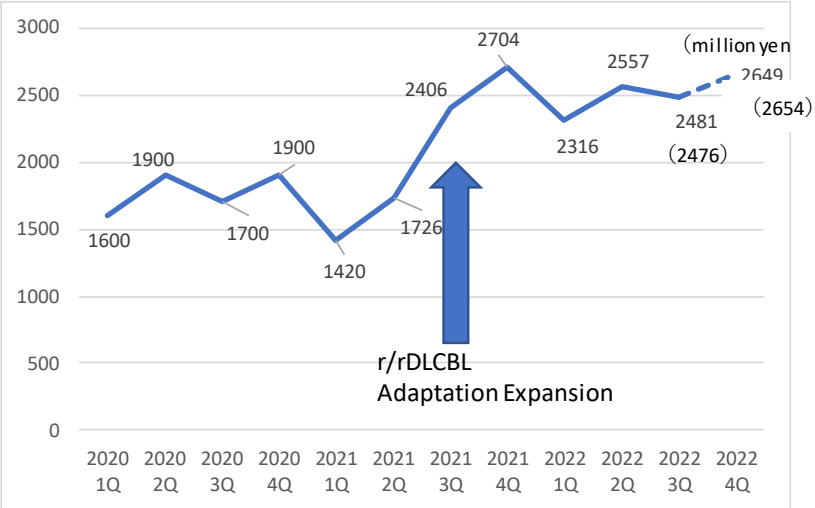
Medical facilities relatively cautious about generics

Still room for the BR and P-BR therapies to increase market penetration

receiving deliveries of generics in mid-October, so the concern about generic use is well founded.

SymBio plans to announce new forecasts, including the impact of the emergence of generics for RI administration, at a briefing in February 2023. However, a major consideration is that haematological oncology departments are relatively cautious about generics since they differ slightly from Treakisym® in terms of constituents. In addition, prescriptions are still expected to increase due to market share expansion because the share of the B-R and P-BR therapies in treating r/r DLBCL is still less than 50%. Put more accurately, the B-R and P-BR therapies in the treatment of r/r DLBCL started as late-line intervention (third-line or fourth-line) but interventions at earlier stages have increased. This could significantly boost sales and explains the efforts being put by the sales department into expanding use in the area of r/r DLBCL.

Treakisym® sales trend



Note: Values in parentheses are forecasts as of August

Source: SymBio Pharmaceuticals

Reference: 3rd quarter (July-Sept) 2022 results and full-year 2022 revised forecast

Sales in the July-September quarter came in at JPY2,482 million, below the level of the previous period, mainly because of the continued effects of COVID-19, but this was still in line with the predicted JPY2,476 million. There was not much of an impact from generics since, as noted above, generic RI administration had not yet been approved, and the scope of indications was limited.

Gross profit from sales came in at JPY146 million, making it look as though the gross profit rate had fallen sharply, but this was in fact due to the payment of a JPY550 million sales milestone to Eagle Pharmaceuticals. This needs to be excluded, leaving a gross profit margin of 80.8%. In the October-December quarter a gross profit of 79.3% is expected but yen depreciation means the trend is slightly more sluggish than in the first half.

R&D outlays in the July-September quarter totaled JPY554 million but are likely to rise to JPY920 million as BCV-related R&D accelerates in the October-December quarter. As a result, the plan is for total SG&A to go from JPY1,204 million in the July-September quarter to JPY1,689 million in the October-December quarter.

However, compared with the revised management plan in August, because of downward pressure on SG&A, operating revenues for the full 2022 year have been revised up by JPY230 million to JPY2 billion. In addition, full-year recurring profit in 2022 has been revised up by JPY550 million to JPY2.3 billion due to currency gains on foreign currency assets, and net earnings has been revised up by JPY170 million to JPY1.65 billion.

Results – quarterly trend and 2022 full year

（JPY-mil）

	Jan-March	April-June	Jly-Sept	Oct-Dec (Est)	2022 (Rev. plan)	2022 (Aug plan)
Sales	2,315	2,558	2,482	2,648	10,003	10,003
（forecast as at August）			(2,476)	(2,654)		
Gross Profits	1,898	2,112	1,456	2,101	7,567	8,106
	82.0%	82.6%	**58.7%**	**79.3%**		
SG&A	1,388	1,285	1,204	1,689	5,566	6,336
R&D	469	540	554	920	2,483	2,524
Op. income	509	863	216	412	2,000	1,770
Rec. profit	478	969	396	457	2,300	1,750
Net profit	163	945	447	95	1,650	1,480

Source: Compiled by Fair Research Inc, using short-form earnings reports

2. Trends in DLBCL therapy development and Treakisym®

The B-R therapy has become the standard treatment for DLBCL, the prevalent type of malignant lymphoma

Looking back briefly at the history of DLBCL therapies, this condition, particularly r/r DLBCL, had no effective treatment until the development of multi-drug chemotherapy (such as the CHOP therapy). While CHOP was developed in the 1970's and DLBCL ceased to be incurable, its effectiveness left much to be desired. In 1997, the R-CHOP therapy using Rituxan® (generic name: rituximab) was approved, providing a much better OS than CHOP. Nevertheless, one-third of patients failed to recover or suffered a relapse, making this an area of high unmet medical need. Additionally, malignant lymphomas are particularly prevalent in the elderly, who are susceptible to the side-effects of the multi-drug chemotherapy used in R-CHOP. In contrast, the B-R therapy (P-BR therapy) has fewer side-effects and a high response rate, thus allowing it to make rapid inroads in the area of r/r DLBCL. Despite being launched only in the second half of 2021 it has already captured around 45% of the market and looks set for 60%.

Reference

Results of the Phase-3 trials of the B-R therapy targeting r/r DLBCL were announced at the European Hematology Association conference (EHA) in June 2020. The overall response rate (ORR) reported was a high 76.3%, and the complete response rate (CR) was 47.4%. An important finding was the efficacy in elderly patients (age 65 and over) for whom HSC transplantation was not the standard therapy. In addition, it was reported that the complete response rate for non-GCB DLBCL's, which have a poor prognosis, was 39%.

Results of Phase-3 trials of the B-R therapy targeting r/r DLBCL

Complete response rate: 47.4%, overall response rate: 76.3%

	(n)	ORR(%)	CR(%)	PR(%)
All patients	38	76.3	47.4	28.9
Response rate by age				
～64 years old	7	85.7	71.4	14.3
65～74 years old	20	75.0	45.0	30.00
75～ years old	11	72.7	36.4	36.3

Source: SymBio company briefing

As noted above, Treakisym® has secured its position as a core therapy in the treatment of blood cancers. However, in recent years a number of new therapies in the blood cancer area targeted by Treakisym® have emerged, requiring a re-examination of the competitive landscape.

① Indolent-B-NHL (low grade B-cell non-Hodgkin's lymphoma)

In recent years, in the area of malignant lymphoma treatment there has been a lot of development work being done on new modalities using antibody therapy and immunotherapy

For indolent-B-NHL, the combination therapies (BR therapy and B-G therapy) of Treakisym® and an anti-CD20 antibody (rituximab, trade name Rituxan) or obinutuzumab (trade name: Gazyva) are the standard and recommended treatment options in the main clinical practice guidelines for hematopoiesis. In January 2020, a therapy combining lenalidomide (trade name: Revlimid®) and rituximab (R-R therapy) was approved for relapsed /refractory indolent-B-NHL. Revlimid® is a thalidomide derivative and may be teratogenic, so appropriate control procedures have been established. Treatment should be selected based on the individual patient's condition and the drug's characteristics, but the B-R therapy is still considered one of the standard therapies.

While an R-R therapy to treat relapsed/refractory indolent B-NHL has been approved, there has been no change in the standard therapy status of the B-R therapy

Reference: In the AUGMENT study, which underpinned approval of the R-R therapy, the median progression-free survival (PFS) for R-R was 39.4 months, well above the 14.1 months of rituximab alone. While no direct comparison can be made, in the comparative tests of the CHOP-R therapy and B-R therapy mentioned earlier, the B-R therapy registered a median PFS of 69.5 months.

② Relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL)

＜P-BR therapy and B-R therapy＞

In June 2019 the FDA announced the expedited approval of a three-drug therapy (P-BR) for the treatment of transplant-ineligible relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL). This therapy consists of the B-R therapy of bendamustine (Treakisym®) + rituximab (Rituxan®) together with the anti-CD79b antibody drug-conjugate polatuzumab vedotin (product name: Polivy®, developed by Genentech and Roche). In Japan, an application for approval of the combined B-R and Polivy® therapy was submitted by Chugai in July 2020, and approved in March 2021. While the amount of Treakisym® required for the B-R therapy alone is 120mg per dose, for the three-drug therapy it is 90mg.

Polivy® was the first antibody drug conjugate (ADC) worldwide to receive approval

Polivy® is not used alone but in combination with Treakisym® and Rituxan® (Pola+BR therapy)

Reference: P-BR therapy vs B-R therapy (r/r DLBCL)

Data shows that the complete response (CR) rate for P-BR is 40% (GO29365 study; Phase-1b/2. Source: Sehn LH e al., J Clin Oncol, 2019). In addition, Phase-2 trials in Japan (P-DRIVE trials) produced a CR rate of 34.3%. The CR rate for the B-R therapy, whose cohort was included in the GO29365 study, was 17.5%. Elsewhere, the Phase-3 results for the B-R therapy on r/rDLBCL and released by SymBio, produced a 47.4% CR rate, a 76.3% overall response rate (ORR), and a median overall survival rate (mOS) of 29.2 months. (Note: 70% of the patients on whom genetic analysis was conducted were of the non-GCB type; 57.5% of the patients in the B-R therapy GO29365 study cohort were non-GCB).

	GO29365 Trial		Symbio
	Pola-BR (90mg/㎡)	B-R	B-R (120mg/㎡)
ORR(%)	70.0	32.5	76.3
CR(%)	57.5	20.0	47.4
mOS (month)	12.4	4.7	29.2

( ) dose of Treakisym

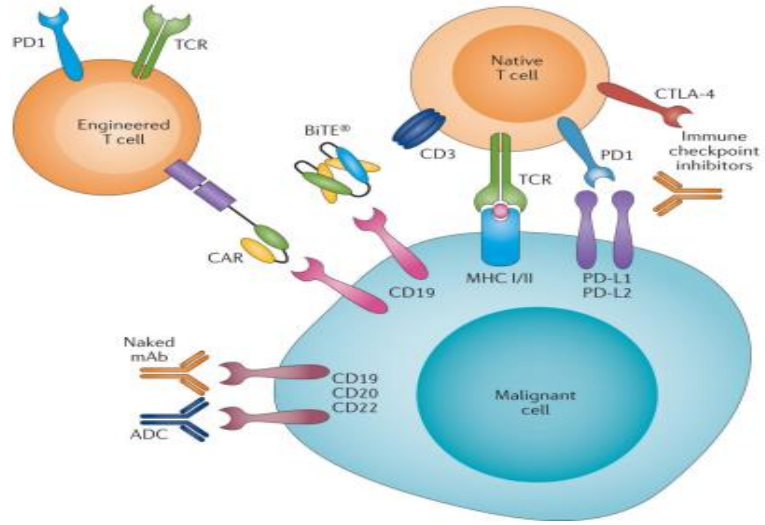
Source:Compiled from Sehn LH et. al, J Clin Oncol 2019, and SymBio IR materials

Since the two patient cohorts have different backgrounds we cannot make a simple comparison. Also, in the GO29365 B-R trials the Treakisym® dose administered was 90mg/m^2, while the Treakisym® dose administered in the Phase-3 B-R trials released by SymBio was 120mg/m^2. This means that the difference in response, for the same B-R therapy, could be due to the difference in dosage. It is not at present possible to say one is superior to the other.

In any event, P-BR and B-R will remain the main therapies for r/r DLBCL.

Pola-BR and B-R are both becoming mainstream in the treatment of r/r DLBCL

In December 2021, Chugai Pharmaceutical submitted an application for the P-RCHP therapy targeting first-line DLBCL (Treakisym® non-indicative). However, clinicians are divided on how to evaluate the clinical test results since there was only a small difference from R-CHOP in OS terms. It is unclear at the present time whether or not disease recurrence is reduced using P-RCHP. If recurrence is lower, then the r/r DLBCL market could shrink and the proportion of refractory patients resistant to treatment would rise. In addition, if P-RCHP therapy is selected for the

	1st-line, it is currently unknown whether P-BR therapy will be effective in refractory cases and recurrent cases from the 2nd-line onwards. **＜The CAR-T therapy＞** In the area of r/r DLBCL treatment CAR-T therapies are becoming more widely accepted, with such CAR-T therapies as Kymriah®, Yescarta® and Breyanzi® having already received approval. CAR-T is a T cell with a CAR (chimeric antigen receptor) that specifically binds to the cancer antigen CD19 on the surface of tumorised B cells. T cells specifically attack cancerous B cells, and the response rate is thought to be in the area of 70-90%. Previously, it was thought that bendamustine (Treakisym®) could be used as a pretreatment for the CAR-T therapy. Today, however, various guidelines and reviews have recommended that the use of Treakisym® be avoided in pre-treatment, such that there are now almost no cases of the P-BR and BR therapies being used prior to CAR-T.
The CAR-T therapy faces many challenges before it can be widely adopted	However, the target patients for CAR-T therapy are currently limited mostly to those who are not indicated for transplantation (mainly third-line). In addition, the use of autologous cells in CAR-T therapy requires sophisticated technology and equipment, and is time-consuming. It is also extremely costly (said to be in excess of JPY30 million per procedure) and can only be carried out at facilities that can handle adverse events, such as cytokine release syndrome. The use of CAR-T therapy is thus, in any case, likely to be extremely limited.
Development of γ δ CAR-T therapy is still in progress	Recently, a lot of interest has been shown in the development of γ δ CAR-T therapies that can be used off the shelf without autologous cells. However, there is as always a number of problems about safety, and in the case of research on the more advanced AD-001 there is a problem with sustaining effectiveness (after 6 months following the start the response rate falls to 20%). It therefore seems that it will not be competitive for some time. **CAR-T and BiTEs - image**  Source: Batlevi CL et al.「Novel immunotherapies in lymphoid malignancies」 Nat Rev Clin Oncol 2016

A lot of interest is now being shown in the development of BiTEs（ bispecific T cell engagers）

＜BiTEs（Bispecific T cell engagers)＞

A promising therapy now being developed which has fewer barriers to overcome than CAR-T is bispecific T-cell engagers (BiTEs). This involves a cancer immunotherapy that induces a complex containing a portion that binds to CD19 and CD20 appearing on the surface of tumorigenic B cells and a portion that binds to CD3 appearing on the surface of T cells, and transforms T cells, which are immune cells, into tumors.

A number of late-line therapies have been approved

In October 2022, AbbVie Inc. applied for approval of Epcortimab for the third-line treatment of NHL. Of particular note is that, even cases which were non-responsive to CAR-T have evidenced a 54% ORR.

Roche is developing two bispecific T cell engagers. Glofitamab is one, which has undergone Phase-2 trials and for which interim results show a 52% ORR and a 39% CR . The other is Mosunetuzumab, which has already been approved in Europe and theUS for the treatment of relapsed/refractory follicular lymphoma. Its brand name is Lunsumio and Phase-2 SUNMO trials in combination with Glofitamab to treat r/r DLBCL are now being undertaken.

At present, it is unclear what indications bispecific T cell inducer antibodies will be approved for. In addition to which, the response rate of the familiar B-R therapy is by no means low (while a simple comparison cannot be made, it has an ORR of 76% and a CR of 47% against r/r DLBCL.) Unless a therapy emerges which is clearly superior to the B-R therapy in terms of responsiveness, it is likely that the position of Treakisym® is assured for the time being. One long term side effect of Treakisym® is that it inhibits the activity of T cells and since the bispecific antibody exerts its effect by engaging T cells, the possibility of combined use is thought to be low.

In the absence of a treatment which clearly exceeds the response rate of the more familiar B-R therapy the position of Treakisym is assured

BiTEs and relapsed/refractory B-cell non-Hodgkin lymphoma

	Type	Targeting	Cases	Phase	ORR	CR	CRS	Notes	Developer
Blinatumomab	CD19/CD3	r/r aNHL	25	Ph2	43%	19%	13% > G3	FDA in Sept. 2016 and PMDA in Aug. 2018 approved all	Amgen/Astellas
									Product name: BLINCYTO
Glofitamab	CD20 × 2/CD3	r/r DLBCL(2L+)	155	Ph2 (NP30179)	52%	39%	3.9%>G3	Now at Phase2 for r/r DLBCL (2L+) (STARGLO studies, SUNMO trials)	Roche GROUP
								Now at Phase2 for FL (2L+) (CELESTIMO study)	Roche GROUP
Mosunetuzumab	CD20/CD3	r/r aNHL	129	Ph1 NCT02500407	35%	19%	% of NHL total	Now at Phase2 for DLBCL (2L+) (SUNMO trial of Glofitamab combination)	Roche GROUP
		of which, pre-CAR treatment	19		37%	26%	> G3		
		r/r iNHL	68		66%	49%			
		r/r FL	90	Ph2 GO29781	80%	60%		Approved in Europe and US for r/r FL Trade name: Lunsumio	
Odronextamab	CD20/CD3	r/r NHL	136	Ph1 (ELM-1)	33%	24%	7%>G3	Now re-dosing Phase2 (NCT03888105) Suspended due to treatment-related deaths	Regeneron
		of which, DLBCL(>80mg)	21						
Epcoritmab	CD20/CD3	r/r DLBCL (3L+)	157	Ph2 (EPCORE NHL-1)	63%	39%	2.5%>G3	Phase3 targeting DLBCL (NCT04628494) 2022Oct 3rL NHL application	AbbVie/Genmab
		of which, pre-CAR treatment			54%	34%			
REGN5837	CD22/CD28	r/DLBCL		Ph1 ATHENA-1				Odronextamab combination	Regeneron
Imvotamab	CD20/CD3	NHL,CLL	260	Ph1/2 (IGM-2323)				In 2021 ASH reported unsurprising results	IGM
Plamotamab	CD20/CD3	r/NHL	240	Ph2	47% (Ph1)	18% (Ph1)		Phase2 trails on r/NHL with tafasitamab and lenalidomide	Xencor
AFM13	CD30/NK	r/NHL		Ph1/2	97%	71%		ASH reports ORR and CR for 24 2022.cas	Affimed
Others									
ADI-001	γ δ CAR-T(CD20)	NHL	9	Ph1	22%			Recurrence 6 months later	Adicet

Source: Fair Research Inc. using various resources

By acquiring BCV SymBio has become a global pharma specialising in haematology and is expanding into oncology and cranial nerve diseases

AdV infection after hematopoietic stem cell transplantation in hematological cancer is the first target

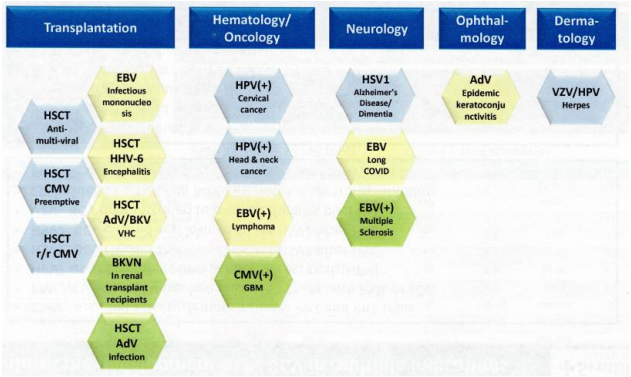
3. Brincidofovir (BCV) development

SymBio is now a global pharmaceuticals company specializing in haematology, and is beginning to expand its foothold in the oncology and neurological disease fields.

On October 1 2019 SymBio announced that, as a strategic product successor to Treakisym®, it had acquired from Chimerix Inc. exclusive global license rights (development, manufacturing and sales) to brincidofovir (BCV) for all diseases except smallpox. Developed by Chimerix, BCV is highly active and effective against multiple infectious diseases.

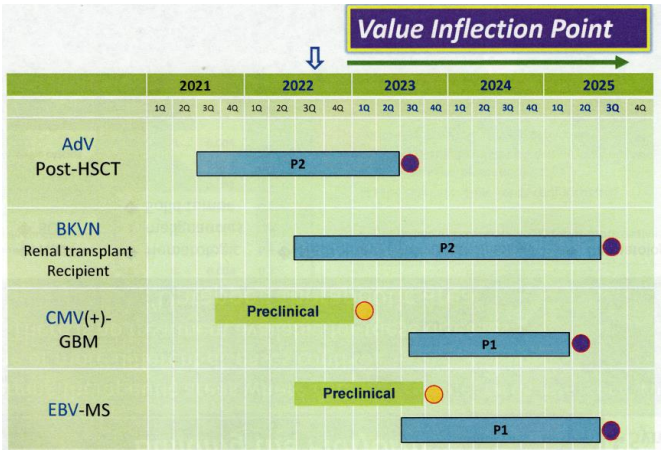
Heretofore, SymBio has acquired licenses overseas and developed them in the Japanese market, but with this agreement it has evolved into a licensor of developed products which it licenses out globally (parenthetically, in September 2022 Chimerix announced it had transferred the BCV license to Emergent BioSolutions Inc., but this has no effect on the rights acquired by SymBio).

SymBio first started development of BCV in haematology targeting viral infections after hematopoietic stem cell transplantation. It then expanded development to viral infections during organ transplantation. The strategy now is to develop BCV to target "therapeutic voids" for which existing antiviral agents have not been approved. As noted below, in addition to transplantation-related fields, the company is also looking at a wide range of fields related to viral infections, cancer, nervous system diseases, ophthalmology, and dermatology.



Source: SymBio Pharmaceuticals company briefing

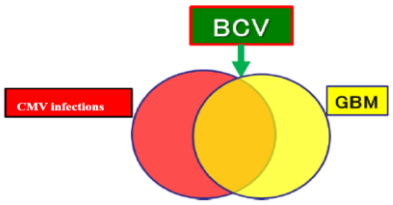
After development of the transplantation-related area the company plans to work on GBM (glioblastoma, a malignant brain tumor) and MS (multiple sclerosis).

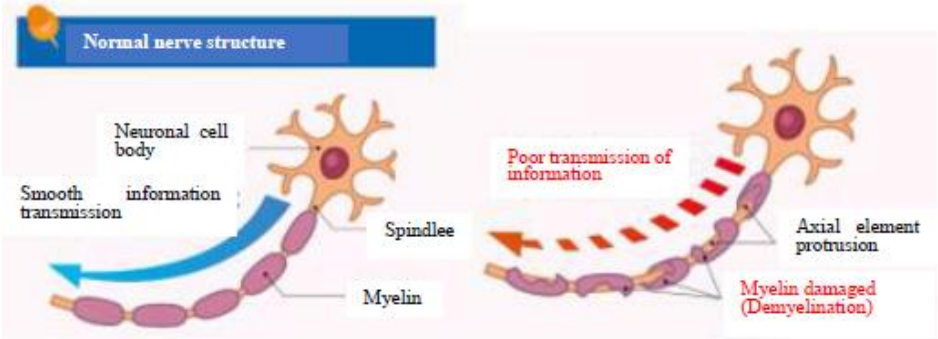


Source: SymBio Pharmaceuticals company briefing

International joint Phase-2 trials on AdV virus infections in children – FPI achieved in August 2021	**① Disseminated adenoviral infections after hematopoietic stem cell transplantation** In general, in the case of hematopoietic stem cell (HSC) transplantations and organ transplantations (SOT), irradiation and immuno-suppressants are used to suppress rejection, thus rendering the patient vulnerable to infection. It used to be that CDV, FOS or some other anti-viral drug was used to offset this, but with the attendant risk of nephrotoxic side-effects. Hence, the importance of BCV, which has low risk of nephrotoxicity, to SymBio's goal of becoming a specialty pharmaceuticals company in the field of haematology. SymBio originally planned to develop BCV to target viral infections after HSC transplantations, an area with poor prognosis, high lethality, and of strong unmet medical needs. After a meeting of the company's Global Advisory Board in February 2020 it was decided that the first development target would be adenovirus infections contracted after HSC transplantation, and that tests on children would be given particular priority. Since Chimerix data had already confirmed safety, the first step would be Phase-2 dosing tests, after which, when POC was confirmed in trials on children, development directed at adults would start.
Development moving ahead to global Pivotal trials when joint international trials are completed in the first half of 2023	SymBio submitted an application to conduct Phase-2 joint international trials of BCV for adenovirus infections in children on March 10, 2021 (registration number NCT04706923). On April 26, the FDA gave fast track examination status to development programs for pediatric adenovirus infections. On August 16, 2021, SymBio registered its first patient (FPI). In January 2022, an application to conduct clinical trials was submitted in the UK. Firstly, in Phase-2a ATHENA trials, four groups of six patients each are to receive stepped increases in doses to test safety and tolerance. At the present time, registrations have been completed up to and including two cases in the third group (depending on the results of the third group the FDA may permit registration to close early). Phase-2 is scheduled for completion in the first half of 2023. First cohort: BCV 0.2mg per1kg body weight. Two administrations per week for more than 4 weeks Second cohort: BCV 0.3mg per 1kg body weight. Two administrations per week for more than 4 weeks Third cohort: BCV 0.4mg per 1kg body weight. Two administrations per week for more than 4 weeks Fourth cohort: BCV 0.4mg per1kg body weight. two administrations per week for more than 4 weeks
Development work to treat viral infections after kidney transplantations is viewed with promise	If all goes according to plan, Phase-3 (several hundred cases) will start in the first half of 2024 and an NDA to the FDA will be submitted in 2026-2027 prior to a market launch in 2027-2028. Phase-2 trials for adult cases are expected to begin in around 2027, when approval for children is scheduled.

Start of patient administrations for international joint tests (Phase-2) Phase-2 completion set for first half of 2025 POC could be the trigger for a corporate tie-up The company plans to move also into the area of oncology	**② Kidney transplantations – BK virus infections** SymBio plans to move development beyond viral infections following haematopoietic stem cell transplantation to viral infections at the time of organ transplantations. Organ transplants are more common in the West than in Japan. For example, while some 1,600 kidney transplantations are carried out annually in Japan, 20,000 are carried out in the US and around the same number in the five major European countries. Of these, an estimated one-third contract the BK virus and the CMV (cytomegalovirus). While the number of infections is a quite low 560 in Japan, in the US + 5 main countries of Europe the total is around 15,000 cases annually. SymBio is scheduled to begin development in Australia, Japan and one other country and on June 14 2022 submitted to the PMDA an application to conduct Phase-2 joint international clinical trials of BCV on BK viral infections after kidney transplantations. Additionally, on August 22 2022 the company submitted a clinical trials plan to the Australian Therapeutic Goods Administration (TGA). In these joint international trials, dose-setting tests are first carried out, and the plan is to have 3 groups of 12 cases each. The beginning of administrations in Australia was announced on December 13 2022. Phase-2 is scheduled for completion in the first half of 2025. Cohort 1 BCV 0.3mg per 1kg body weight Two administrations per week for 8-14 weeks Cohort 2 BCV 0.4mg per 1kg body weight Two administrations per week for 8-14 weeks Cohort 3 (expanded cohort) BCV recommended dose Two administrations per week for 8-14 weeks The company plans to undertake its own trials, but the organ transplantations are outside its area of expertise, and there are not enough cases in Japan. For those reasons it is thinking of partnering with a European or US company to promote development and sales in the area of organ transplantations. The same goes for adenovirus development, and the establishment of POC (at Phase-2 completion) could be key to setting up collaborative partnerships. Additionally, the company in November 2022 entered a research sharing agreement with the Pennsylvania State University, and started non-clinical tests evaluating the efficacy of BCV using the polyomavirus infection model. Polyomavirus is a double-stranded DNA virus that causes serious disease and existing antiviral agents have virtually no effect. The BK virus and JC virus are both types of polyomavirus.

There is a connection between the cytomegalovirus and malignant brain tumours	**③ Development targeting glioblastoma (GBM)** Glioblastoma (GBM) is the most common malignant brain tumor and is an area of extremely high unmet needs, with a survival rate of only 15 to 20 months and a 5-year survival rate of 5% or less. It is known that about 50% of GBM patients are CMV (cytomegalovirus) positive. Various drug therapies are these days being developed for various conditions but there is no drug development candidate targeting CMV.  While the CMV-brain tumour mechanism is certainly not fully understood, research using a mouse model conducted at Brown University shows that CMV infection enhances the NF-κB signal, leading to increased expression of PDGF-D, an angiogenetic factor, which promotes the growth of GBM cancer cells. It has also been found that the antiviral agent cidofovir (CDV) inhibits CMV reactivation in CMV-infected mice and improves survival rates. (The Journal of Clinical Investigation, 2019, Sean E Lawler et al.) SymBio is now considering whether or not to develop BCV as a treatment for GBM based on this and other research. The mechanism of action of BCV against GBM consists of BCV converting to CDV-PP in the cell, inhibiting the replication cycle of tumor cells and inducing apoptosis. BCV inhibits reactivation of CMV and is thought to have an inhibitory effect on tumor growth.
When data from the joint research with US universities becomes available a decision will be made on the next step	SymBio is now doing joint research with the University of California on evaluating the anti-tumour potential of BCV. It is also working with Brown University to evaluate BCV's anti-tumour effectiveness and its tumour malignancy suppression effect. As soon as the data from this research is available a decision will be made on what the next stage should be.
Attention focused on antiviral effect of BCV on EB virus	**④ Expansion into the field of neurovirology (multiple sclerosis)** The EC50 value of BCV against the Epstein-Barr virus (EB virus) is significantly lower than that of other antiviral agents, and BCV is known to have extremely high antiviral activity against the EB virus. The EB virus is also known as human herpesvirus 4, and 95% of adults are infected. It is almost entirely symptom free and is inactive in lymphocyte B cells in a latent state. However, in some people it is thought to cause blood cancers and other intractable diseases (such as autoimmune diseases).
Thought is being given to multiple sclerosis as an additional indication	SymBio in February 2022 announced it was considering making multiple sclerosis (MS), one type of autoimmune disease, a new target indication of BCV. In addition, in August 2022, the company concluded a joint research exchange agreement with the National Institute of Neurological Disorders and Stroke (NINDS), within the National Institutes of Health (NIH), to evaluate BCV's antiviral effect on the EB virus. Under this agreement, SymBio provides NINDS with BCV for non-clinical tests to evaluate the potential effect on diseases thought by NINDS to be caused by the EB virus. It is possible that in late 2023 the collaboration will be strengthened. If that comes about the major pharmaceutical companies are bound to take an interest.
Concluded a joint research exchange agreement with	

the National Institute of Neurological Disorders and Stroke (NINDS), within the National Institutes of Health (NIH)	Reference: Multiple sclerosis For reasons which are unclear, lymphocytes attack and demyelinate the myelin that covers the axons of nerve cells, preventing the smooth transmission of information to the nerves where demyelination has occurred. This causes various neurological symptoms (motor disorders, visual disorders, sensory disorders, and dysuria.). It is an autoimmune disease with repetitive recurrence and remission. Lesions occur throughout the brain, spinal cord, and optic nerve, and relapse at intervals of one month or longer. It affects around 18,000 people in Japan (including neuromyelitis optica), but it is estimated there are about 3 million sufferers worldwide, mainly in Europe and the United States. There is no definitive cure, but steroidal pulse therapy to suppress inflammation with steroids, and immunomodulators to suppress lymphocyte activity are used.  Source: Multiple Sclerosis.jp The mechanism by which the EB virus causes MS is not fully understood, but epidemiological surveys have supported the association. A Harvard research team analyzed a sample of around 10 million serving U.S. military personnel, and found that 955 cases were diagnosed with MS during military service. Analysis of these 955 cases found that the risk of contracting MS after being infected with the EB virus was 32 times higher than that from other viral infections.（Science, January13 2022, “Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis”） A research team at Stanford University has recently put forward a powerful new hypothesis explaining the mechanism of MS onset by EB virus (Nature, January 24 2022: “Clonally expanded B cells in multiple sclerosis bind EBV EBNA1 and Glial CAM”) According to this hypothesis, the EB virus transcription factor, EBNA1, and the glial cell adhesion molecule, GlialCAM, in the brain are structurally similar, leading the lymphocytes that produce autoantibodies which recognize both to migrate to the center, accidentally damaging their own myelin, leading to the onset of multiple sclerosis (MS). This hypothesis is supported by the effectiveness of blocking the transfer of lymphocytes into the central nervous system (sphingosin 1-phosphate receptor agonist) or blocking the migration of lymphocytes from the lymph nodes (anti-α4 integrin antibody) and the effectiveness of molecular-targeted drugs such as the anti-CD20 antibody (ocrevus) in targeting B-cells. SymBio believes that if our understanding of this mechanism is correct, the progression of MS can be inhibited by the prompt elimination of the EB virus using BCV after the onset of MS.

Applications of BCV are also being studied in the field of haematological tumours

⑤ Applications in the area of haematological malignancies (NK/T cell lymphoma applications)

The EB virus was the first human cancer virus, an oncovirus isolated from Burkitt's lymphoma, a type of blood tumor (1964), and is known to be associated with various cancers. Involvement in nasopharyngeal cancer, Hodgkin's lymphoma, NK/T cell lymphoma, and others has been clarified. However, infection is not necessarily the same as cancer onset. Rather, genetic changes in infected cells contribute to carcinogenesis by the EB virus.

In December 2022 the American Society of Hematologists (ASH) reported that results of joint research by SymBio and the National Cancer Centre of Singapore, had demonstrated BCV was effective in non-clinical trials on rapid onset NK/T cell lymphoma, for which to date there has been no effective therapy.

Occurrences of NK/T lymphoma are particularly frequent in Asia (most patients are infected with the EB virus)

NK/T cell lymphomas are malignant lymphomas originating in NK cells or T cells, occurring mainly in the perinasal and cutaneous areas, primarily as extranodal NK/T-cell lymphomas. This disease is more common in East Asia and South America than in the US or Europe. While it accounts for less than 1% of non-Hodgkin's lymphoma in Europe and the US, in East Asia (China) it accounts for around 10%. In addition, most patients test positive for the EB virus.

Distribution of NK/T lymphomas

	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

BCV suppresses the expression of genes that promote tumor malignancy, and also induces immunogenic cell death

The causes underlying carcinogenesis are no means well understood but the following mechanism is a possibility. The EB virus exists in a dormant state but expressing various EB virus genes is in the cancer cells within the NK/T lymphoma. For example, EBNA-1, EBNA-2, LMP-1, LMP-2, and so on. When EBNA-1 is expressed, p53 is suppressed and cancer cell apoptosis controlled. In the case of LMP-1, the activation of NF-κB suppresses apoptosis. LMP-2 is thought to promote carcinogenesis via the P13K and MAPK pathways.

Genes promoting EBV tumor malignancy

EBNA-1＝P53 instability＝＞apoptosis suppression

EBNA-2=>MYC, LMP1/2 expedited expression=>immortality

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

LMP-2 ＝PI3K pathway /MAPK pathway activation

=>involvement in carcinogenesis

In the area of cranial nerve diseases, there is also the possibility of application to

This research confirmed that BCV not only suppresses the expression of genes which promote the EB-virus induced tumour malignancy, but destroys tumour cells and induces immunogenic cell death that activates cancer immunity. As a result, it

treat the after effects of COVID-19, and Alzheimer's disease.	is expected to be effective in combination with the immunotherapy provided by, for example, anti-PD-1 inhibitors. Note: Immunogenic cell death When cancer cells die, intracellular matter is expelled from the destroyed cells and dendritic cells, a type of immune cell, receive a signal that cancer cells have been destroyed. Effector memory cells are taught how to recognise cancer cells, bringing the immune system into play. This type of cell death is called immunogenic cell death. **⑥ Possible therapy for Alzheimer's** Furthermore, there is increasing evidence that the herpes simplex type-1 virus (HSV-1) is a contributing factor in the occurrence of Alzheimer's disease (Nikkei-FT Infectious Diseases Conference, October 24, 2022, as reported in the Nikkei newspaper). According to the article, research at Tufts University has raised the possibility that the VSV (varicella-zoster virus) activates HSV-1 and leads the tau protein and amyloid β to accumulate, reducing the functioning of nerve cells. In particular, it has been pointed out that carriers of the APOE4 gene are receptive. Research at Oxford University has also shown that when HSV1 is present in the brain the combination with APOE4 increases susceptibility to Alzheimer's. On December 19 2022 SymBio concluded a Sponsored Research Agreement with Tufts University, using the 3-D brain infection model established by Tufts to conduct non-clinical tests to evaluate the efficacy of BCV in a herpes simplex virus (HSV). Longer term, this may lead to the development of an anti-virus to treat Alzheimer's. Note: HSV infection model using 3-D brain model An experimental system in which human neural stem cells are cultured using collagen-filled porous silk protein sponge as a base material, and then proliferated and differentiated into a functional network of neurons and glial cells that are also susceptible to virus infection. In this experimental system, electrophysiological functions, amyloid-ß fibril formation due to HSV infection, neuroinflammation, etc. can be evaluated under conditions excluding other factors. **⑦ After effects of COVID-19** SymBio is now considering the possibility that the after-effects of COVID-19 (long COVID symptoms: fatigue, brain fog, rash, etc.) may be caused by the reactivation of the EB virus by an inflammatory reaction after COVID-19 infection. In July 2021, Professor Gold of the World Health Organization noted in The Journal of Pathogens that most patients with long COVID symptoms have registered positive for EB virus reactivation, versus only 10% in the control group.

Reference 1: Principal features of brincidofovir

Compared to other anti-viral drugs such as cidofovir (CDV) and Foscarnet (FOS), BCV is highly active and effective against multiple infectious diseases.

Brincidofovir (BCV) is highly active across a broad spectrum

Viral Family	Virus	BCV	Cidofovir	Maribavir	Letermovir	Ganciclovir*	Foscarnet	Acyclovir
Herpes	Cytomegalovirus	0.001	0.4	0.31	0.005	3.8	50-800	>200
	Epstein-Barr Virus	0.03	65.6	0.63	>10	0.9	<500	6.2
	Human Herpesvirus 6	0.003	2.7	Inactive	>10	5.8	16	10
	Human Herpesvirus 8	0.02	2.6	Inactive	—	8.9	177	>100
	Herpes Simplex Virus 1	0.01	3.0	Inactive	>10	0.7	92-95	3.8
	Herpes Simplex Virus 2	0.02	6.5	Inactive	>10	2.5	91-96	4.4
	Varicella Zoster Virus	0.0004	0.5	Inactive	>10	1.3	39.8	3.6
Adenovirus	Adenovirus (AdV-B7)	0.02	1.3	—	>10	4.5-33	Inactive	>100
Polyoma	BK Virus (BKV)	0.13	115	—	—	>200	Inactive	>200
	JC Virus (JCV)	0.045	>0.1	—	—	—	Inactive	—
Papilloma	Human Papillomavirus	17	716	—	—	Inactive	—	Inactive
Pox	Variola	0.1	27	—	—	—	—	—
	Vaccinia	0.8	46	—	—	>392	Inactive	>144

Source: SymBio Pharmaceuticals company briefing

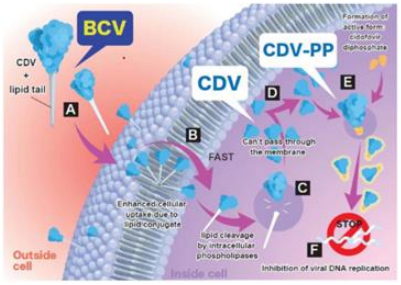
Note1: The figure above shows antiviral IC50 activity data; lower readings indicate higher activity

Note 2: Cidofovir (CDV):

Was approved by the FDA in 1996 for the treatment of cytomegalovirus retinitis in AIDS patients. CDV is a cytosine nucleotide analog which inhibits the replication of DNA viruses such as adenovirus, papillomavirus, and polyomavirus as well as the herpesvirus family. CDV is also effective against ganciclovir (GCV) resistance (UL97 gene mutation) and is thought to be of use when foscarnet (FOS) cannot be administered due to the development of GCV resistance. It is not approved for use in Japan.
As can be discerned from the previous table, cidofovir (CDV) has a similar level of activity across as broad a spectrum as BCV. However, while CDV is nephrotoxic and difficult to handle, BCV has low toxicity and is very safe despite being highly active.

Reference 2: BCV action mechanism

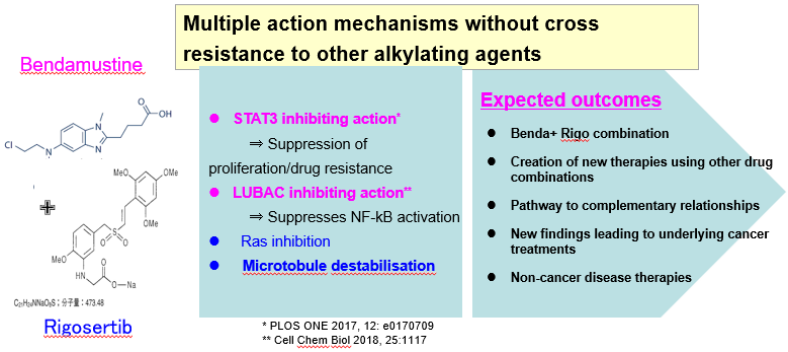
Brincidofovir (BCV) has a structure in which a fatty chain (hexadecyloxypropyl: HDP) is bonded to cidofovir (CDV) and is rapidly taken into a lipid bilayer membrane and efficiently translocated into cells. The compound whose fatty chain is cleaved by metabolism by intracellular phospholipase and the generated activated form (CDV-PP: CDV diphosphate) is retained in the cell for a protracted period, resulting in a dramatic improvement in antiviral activity. In addition, because HDP binding does not cause accumulation of renal tubular epithelial cells by the OAT-1 transporter and the low level of CDV released into the blood, nephrotoxicity, a fundamental problem of CDV, is reduced (because CDV does not have a lipid tail it becomes a substrate of OAT-1 and accumulates in renal urinary duct epithelial cells, with nephrotoxicity the likely outcome).



Source: SymBio Pharmaceuticals IR materials

Reference 3: Possibility of using rigosertib and Treakisym® (bendamustine) in combination

Analysis is now being conducted of joint research undertaken with Kyoto University on how bendamustine (Treakisym®) affects the LUBAC anti-tumour mechanism. By verifying the effects on other pathways involved in this mechanism, the aim is to develop new treatment methods. At the same time, joint research is being undertaken with Tokyo University and Gunma University on the efficacy of combining Treakisym® with other drugs, including rigosertib. The direction of future development could possibly emerge in the middle of next year.



Source: SymBio Pharmaceuticals company briefing

＜Conclusions＞

The effect of generics constrained at the present time

SymBio in 2020 built an in-house sales structure and acquired brincidofovir, thereby laying the groundwork for the company's growth as a haematology-specialised pharma with a global license. Then, in 2021 it expanded the diseases for which its main product, Treakisym®, was indicated to r/r DLBCL, since which time its finances have moved firmly into the black. While Treakisym® generics began emerging in the second half of 2021, the impact is so far limited because of caution on the part of haematology departments towards generics and differences in approved indications. Additionally, SymBio is taking Towa Pharmaceuticals and Pfizer（Japan） to court over patent infringement and is seeking an injunction on the manufacture and sale of generic products and the payment of damages.

Now taking legal action against two generics manufacturers

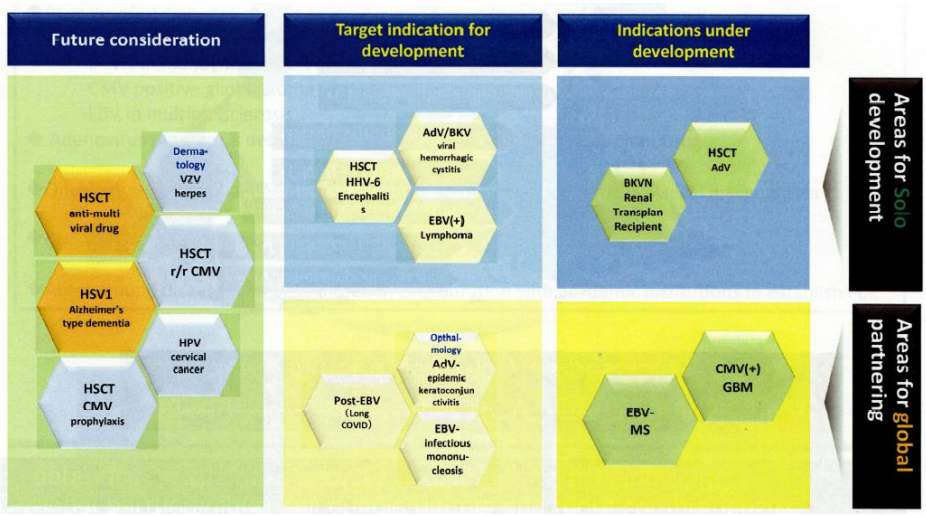
It looks as though SymBio will for the time being seek to maintain sales growth by increasing the use of the B-R therapy and P-BR therapy in the treatment of r/r DLBCL. Given its high marginal profit ratio, earnings growth momentum is probably inherent.

Treakisym® sales could grow if the penetration rate of the B-R and P-BR therapies rises

If Treakisym sales do peak out, new growth drivers will emerge from the expansion of licensed-in products in the company's specialist field of haematology, and from collaboration on developing and launching of brincidofovir (BCV) for viral infections after hematopoietic stem cell transplantation and viral infections after kidney transplantation.

Expansion of indications now in sight for BCV, the next growth driver

SymBio's business development strategy



Source: SymBio Pharmaceuticals company briefing

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