SymBio Pharmaceuticals Ltd.

(4582 Growth) Issued: June08, 2022

Outlook for Business Development Acceleration

Establishing itself as a specialty pharma in the area of haematology

SymBio Pharmaceuticals is entering a new phase of development, having laid the groundwork necessary for a pharmaceutical company with a global license specialising in haematology. This it achieved with its establishment of an in-house marketing structure and its acquisition of the drug, brincidofovir (BCV). There has been some loss of sales momentum in the company's main product, Treakisym®, due to inventory adjustments accompanying the switch to an in-house sales structure, and as a result of the coronavirus pandemic. On the other hand, there has been an increase in approved clinical indications, changes in formulation and the start of in-house sales. SymBio's operating revenues had been in negative territory since the December 2008 period, when it licensed out Treakisym® exclusive sales rights in Japan to Eisai and recorded a lump-sum contract payment. In 2021 the company at last achieved profitability, and in 2022, rising profitability on the back of growth in Treakisym® sales, should help it manage a 74.2% increase in operating revenues, even with higher disbursements on brincidofovir R&D.

Challenging new areas (tumours/cranial nerves)

In 2022, SymBio began to expand from its global haematology specialism to the areas of cancer and the cranial nerve system. BCV is now in Phase-2 trials for disseminated adenovirus infections after hematopoietic stem cell transplantation, and Phase-2 trials are about to start on BK virus infections after kidney transplantations. In addition, it now appears that BCV can be used on malignant brain tumours and development is in the planning stages. The company sees continued earnings growth from Treakisym® for the time being but looking ahead it not only wants to further solidify its position as a specialist in hematology with the introduction of new drugs in this area, but also wants to expand into new areas (infections, cancers and cranial nerves). This it hopes will allow it to evolve a structure for alternative growth areas if earnings expansion flattens out.

Impact of generics

On February15 2022, four companies received approval for the manufacture and sale of the Treakisym® intravenous drip solution (RTD generic). In response, SymBio has notified the four companies of concerns about patent infringement. The patent is considered the property of the US company, Eagle Inc. which is the original licensor of the RTD preparation. There was an earlier case of Treakisym® patent infringement (RTD/RI formulation) in the US, with Eagle (and co-licensee Teva) winning the court case, as a result of which generics makers cannot sell this product for a certain period. Indolent B-cell non-Hodgkin's lymphoma was the indication submitted by the four companies at time of submission in February, and there are moves to extend indications to relapsed/refractory DLBCL. However, one of the four companies decided in May to postpone sales. Chronic lymphocytic leukemia (CLL) also has exclusive protection during the re-examination period (until 2026) and is not included among the indications for generic products. Further, SymBio has received approval for the RI formulation (10-minute infusion), which is even more convenient than the RTD formulation, and is pursuing a switch to RI. At the moment, with the drug price of generics undecided, it is unclear how much of an impact they will have, but we infer it will not immediately be very significant.

Note: This report is the English-language version of the original Japanese-language report issued on June 8th, 2022, to which you should refer for precise details

Revised Basic Report

Fair Research Inc

Tsuyoshi Suzuki

Company Outline	
Location	Tokyo
President	Fuminori Yoshida
Established	March 2005
Capital	JPY17,169 mil
Listed	October 2011
URL	www.symbiopharma.com
Industry	Pharma
Employees	141 (non-consol)
Key Indicators (June 7th, 2022)	
Stock Price	JPY689
52-week high	JPY2,423
52-week low	JPY622
Shares outstanding	39,553,931
Trading Unit	100 shares
Market Cap	JPY27,253mil
Dividend (est)	0.0
Forecast EPS	JPY38.6
Forecast PER	17.87X
Actual BPS	JPY164.6
Actual PBR	4.19X

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

Results	Revenues JPY-mil	YoY %	Op. Income JPY-mil	YoY %	Rec. Profit JPY-mil	YoY %	Net Income JPY-mil	YoY %	EPS JPY	Stock Price High	Stock Price Low
2017/12 Actual	3,444	45.4	-3,947	NA	-3,976	NA	-3,977	NA	-79.7	335	196
2018/12 Actual	3,835	11.4	-2,656	NA	-2,748	NA	-2,752	NA	-165.5	289	115
2019/12 Actual	2,837	-26.0	-4,301	NA	-4,376	NA	-4,376	NA	-189.0	275	150
2020/12 Actual	2,987	5.3	-4,506	NA	-4,615	NA	-4,090	NA	-124.1	653	243
2021/12 Actual	8,256	176.4	1,016	NA	1,001	NA	2,032	NA	53.0	2,423	387
2022/12 Forecast	10,992	33.1	1,770	74.2	1,750	74.8	1,480	-27.2	38.6		

Company overview and management philosophy

＜Business model＞

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

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

① Post-POC strategy

The company does not itself undertake drug discovery 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 hematology, where the need is high, but where the major pharmaceuticals companies are relatively unrepresented. Using this niche strategy, the company seeks high market share and high returns. Until 2020, the company's business model involved entering into licensing agreements covering new drug candidates it had selected, developing them in Japan and then licensing out to other pharmaceuticals companies. Since 2021, however, it has set up its own sales function in Japan and has established itself as a pharma specialising mainly in hematology.

③ Global licensor

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

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

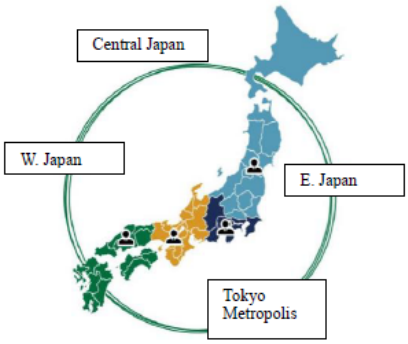
Focus on human capital and company organisation to support networking and expertise

The elements which underpin this track record are the company's human resources and organisation. Hence, one-third of its 141 employees are engaged in research and development, and the company also boasts a Scientific Advisory Board consisting of specialists, including Nobel Prize candidates, to support its drug search and scrutiny activities. Needless to say, the role and professional network of the company founder and current president, Fuminori Yoshida, are pivotal.

Establishment of an in-company sales structure

The company's sales sysem

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



Nationwide distribution network

Suzuken

+Toho Pharmaceutical

+S.D. COLLABO

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

Members of the SAB （Scientific Advisory Board）

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

Senior Advisor

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

Source: SymBio materials

Significant events

2005/3	SymBio established
2005/12	Acquires from Astellas in Germany the exclusive rights in Japan for the development and sale of bendamustine
2008/8	Concludes with Eisai an agreement on the sale in Japan of freeze-dried bendamustine
2010/10	Acquires approval for manufacture and sale of Treakisym® (freeze-dried bendamustine) in Japan
2010/12	Starts sales of Treakisym®
2011/7	Concludes rigosertib licensing agreement with US company Onconova Therapeutics Inc.
2011/10	Listed on JASDAQ
2015/8	Onconova re-designs rigosertib tests and starts joint international Phase 3 (INSPIRE) trials
2015/10	The Medicines Company in the US acquires sole development and sales rights in Japan for IONYS® post operative self-administered pain medicine
2016/5	Treakisym® approved for additional indication in Japan - chronic lymphocytic leukemia
2016/8	Approval given for expanded indications in Japan for low-malignity non-Hodgkin's lymphoma and mantle cell lymphoma
2017/9	Acquires from US company Eagle Pharmaceuticals the sole rights in Japan to develop and sell bendamustine liquid formulation (RTD and RI preparations)
2017/10	Petition seeking arbitration for damages due to non-performance of The Medicines Company's agreement on license for IONSYS®
2017/11	IONSYS® agreement cancelled
2018/7	Approval of Treakisym® and Gazaiba® combined treatment for follicular lymphoma (CD positive)
2018/7	Treakisym® listed for the first time in the Hematopoietic Tumor Clinical Practice Guidelines (2018 Edition) as a first-line treatment for malignant lumphomas
2019/3	Treakisym® approved as pre-treatment for Kymriah CAR-T treatment of r/r acute lymphocytic leukemia
2019/9	Acquires sole global license for development, manufacture and sale of the anti-viral agent BCV from the US company, Chimerix (excludes smallpox)
2020/8	Top-line results of internatonal joint Phase 3 (INSPIRE) trials on rigosertib show no significant difference from physician-chosen treatment
2020/9	Approval given for the Treakisym® RTD formulation on existing indications
2020/9	IONSYS® arbitration handed down: SymBio to receive half the costs of arbitration-related costs
2020/12	SymBio takes over sales of Treakisym®
2021/1	Enters agreement with the Institute of Medical Science, Tokyo University on joint research into discovering new indications for which bendamustine and rigosertib night be indicated
2021/3	Phase 2 trials start in the US to test BCV targeting adenovirus infections following HSC transplants
2021/3	Combined Treakisym® and Rituxan® therapy approved for treatment of r/r DLBCL
2021/3	Combination of Treakisym® Rituxan® and Polivy® approved
2021/4	Treatisym RTD liquid formulation approved for r/r DLBCL treatment
2021/4	Development of BCV targeting adenovirus infections in children given fast track examination status
2021/5	Application submitted for approval of Treakisym® RI formulation
2021/8	Among the adenovirus targets of BSV was that for pediatric cases - Phase-2 FPI administrations
2022/2	Treakisym® RI formulation approved

Treakisym related events
Rigosertib related events
IONSYS® related events
BCV related events

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

＜Product pipeline＞

SymBio's mainstay product is Treakisym® (generic name: bendamustine) for the treatment of malignant lymphomas. Treakisym® has been developed for a series of additional indications, has undergone a number of formulation changes, and is now ready for direct sales by the company. Looking ahead, Treakisym's profitability and market expansion will support the development of the company's next mainstay candidate, the antiviral drug brincidofovir, and will support analysis and applied research (in the area of anti-tumour activity) of new modes of action of Treakisym® and rigosertib. These represent a new stage in corporate value creation.

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

[TREAKISYM®]

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

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

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

NDA：New Drug Application
MA:Marketing Approval

Reference: Types of malignant lymphoma

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

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

FL：Follicular lymphoma, MALT: MALT lymphoma

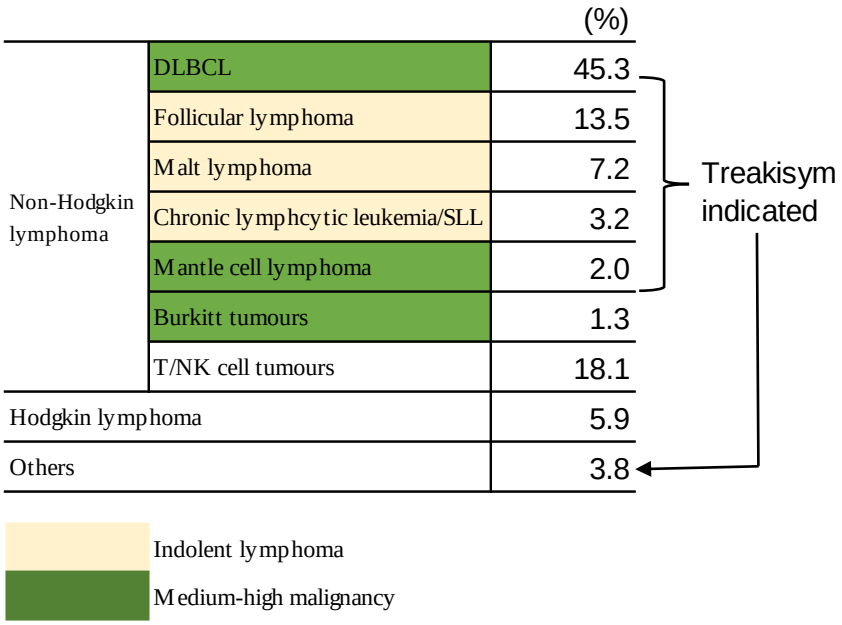
Follicular lymphoma accounts for 80% of indolent non-Hodgkin's lymphoma cases

○Medium malignancy: disease progresses monthly (MCL, DLBCL, etc.)

○High malignancy: Burkitt tumours, etc.

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

Distribution of malignant lymphomas by type (Japan)



Note: Among DLBCL's indicated for r/r DLBCL, 1st-Line DLBCL - off-label

Further, splenic green band B-cell lymphoma, lymph plasma cell lymphoma, and nodal line green band B-cell lymphoma belonging to other categories are also indicated.

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

(1) History of indications and development

Among various malignant lymphomas Treakisym® is indicated for the following four:

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

Note: Not indicated for untreated DLBCL (off-label)

Treakisym® was approved within 5 years of being licensed in, and new clinical indications have been added since then

After its first approval in 2010, Telomelysin® received approval for two further indications in 2016

Treakisym® was first developed in Germany in 1971. In December 2005 SymBio acquired sole development and merchandising rights in Japan from the Astellas European subsidiary, Astellas Pharma (now known as Astellas Deutschland GmbH) and underwent clinical trial development. In October 2010, a mere 5 years after licensing-in, Treakisym® was approved for the treatment of r/r indolent-B-NHL and MCL and sales began in December. Further, in August 2016 chronic lymphatic leukemia (CLL), and in December untreated indolent-B-NHL and MCL received approval. In July 2018, with respect to indolent-B-NHL, MCL and CLL, Treakisym® was for the first time listed as a standard therapy option in the Hematopoietic Tumor Clinical Practice Guidelines 2018 Edition (edited by: Japan Society of Hematology). It thus became a standard treatment both in name and practice. As a result of its new status, the market penetration of Treakisym® rose, completely surpassing R-CHOP, which had been the standard treatment, and in

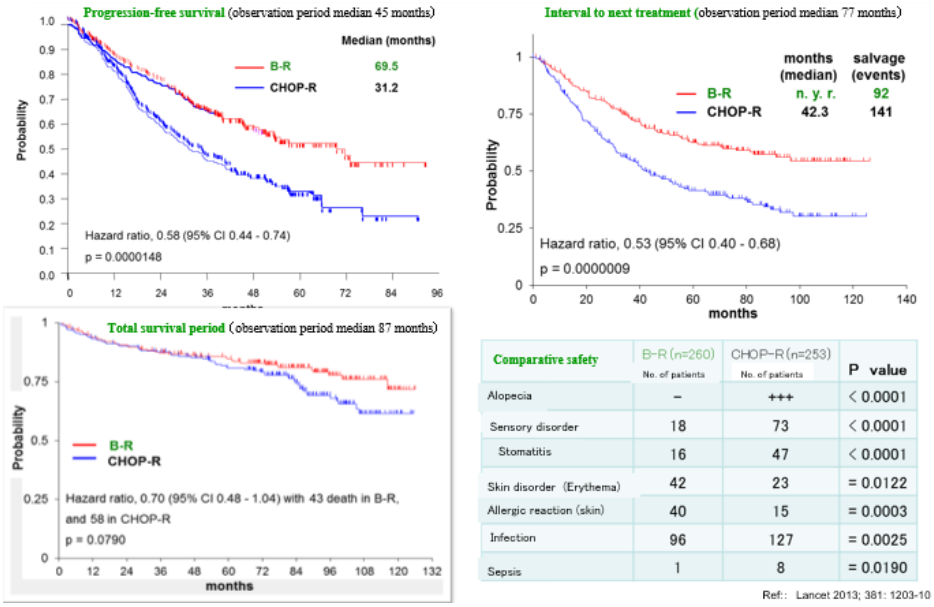
with a consequent increase in level of market penetration

2018, from the market launch in August, achieved sales in Japan of JPY8.5 billion (approved drug price basis).

Became the standard treatment in July 2018

Behind this was the demonstrated superiority of the B-R therapy, combining Treakisym® and rituximab, over what had been the standard therapy, the R-CHOP therapy (see comparative charts below).

Comparative study of the CHOP-R and B-R therapies



Comparative safety	B-R (n=260) No. of patients	CHOP-R (n=253) No. of patients	P value
Alopecia	–	+++	< 0.0001
Sensory disorder	18	73	< 0.0001
Stomatitis	16	47	< 0.0001
Skin disorder (Erythema)	42	23	= 0.0122
Allergic reaction (skin)	40	15	= 0.0003
Infection	96	127	= 0.0025
Sepsis	1	8	= 0.0190

Ref:: Lancet 2013; 381: 1203-10

Source: SymBio company briefing (showing better results for the B-R therapy)

Note: CHOP-R therapy

Chemotherapy that combines the molecular targeted drug rituximab with the anticancer drugs cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and the steroid prednisolone.

Subsequently, there was some stagnation in domestic sales, to JPY8.1 billion in authorised drug price terms in 2020, due to inventory fluctuations caused by product quality problems with the supplier and the switchover to direct selling. However, sales rebounded after the approval in March 2021 of the B-R therapy and the Polivy®+BR therapy for the treatment of r/r DLBCL.

There was then a short-term decline in sales, followed by a recovery due to the expansion of indications to include r/r DLBCL

Until the development of multi-agent chemotherapies (such as the CHOP therapy) there was no effective treatment for DLBCL or especially r/r DLBCL. CHOP was developed in the 1970's but, while DLBCL ceased to be incurable, efficacy fell short.

The B-R therapy has fewer side effects and has a high response rate

In 1997, the R-CHOP therapy using Rituxan (generic name rituximab) was approved, demonstrating a far better survival period than CHOP. However, this is not effective in about one-third of patients who suffer relapses, and is therefore an area of high unmet medical need. In addition, many malignant lymphoma patients are of advanced years and the possible side effects of the multi-agent chemotherapy used in R-CHOP are of great concern. On the other hand, the B-R therapy comes with fewer side effects and greater responsiveness, allowing it to more rapidly make inroads into the r/r DLBCL market. While it was introduced only as recently as the second half of 2021, it has already captured around 30% of the market and is expected to capture 60%.

30% market penetration achieved in a short time after launch

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 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

Review of the competitive environment

(2) Competitive environment

As noted earlier, Treakisym® has established itself as the main treatment in the area of haematological cancers. However, this area has seen the arrival of a variety of new therapies in recent years. In addition, in February 2022, there appeared a new reality in the shape of regulatory approval of Treakisym® generics. This requires a re-evaluation of Treakisym's competitive environment.

While a combination therapy of Revlimid® and Rituxan (R-R theapy) has recently been approved for the treatment of indolent-B-NHL, there has been no change in the standard therapy status of the B-R therapy

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

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.

Reference: In the AUGMENT tests which underpinned approval of the RR therapy, the median progression-free survival (PFS) for RR 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.

Treatments for r/r DLBCL include both the B-R therapy and now the P-BR therapy. The latter uses lower doses of Treakisym®

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

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.

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

There is data showing 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 targeting 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 (90mg/㎡)	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 Treaksym

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

Since there is no superiority of one over the other both could become mainstream

Since the two patient cohorts have different backgrounds we cannot make a simple comparison. Also, in the GO29365 B-R therapy 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, the P-BR therapy and the B-R therapy will probably be mainly indicated for 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 lower 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. It is believed that, after first-line P-RCHP, the P-BR therapy will not be effective in second-line or subsequent refractory or relapsed cases.

③ The CAR-T therapy

The use of Treakisym® prior to CAR-T is now very rare, but this should have only a small impact because the use of CAR-T itself is relatively limited.

In the area of r/r DLBCL treatments 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 very few cases of the P-BR and BR therapies being used prior to CAR-T.

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 expensive (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 likely to be extremely limited.

④ Appearance of generics

Appearance of a generic RTD formulation

Patents protecting the RTD formulation belong to the US company, Eagle

In the United States, sales of generics are not possible for a certain period

In Japan, one of the four generic makers has decided to postpone sales

On February 15 2022, four companies (Pfizer Inc., Meiji Seika Pharma, KOA ISEI Co. Ltd., and Towa Pharmaceutical) were approved to manufacture and market generic versions of the Treakisym® RTD intravenous infusion. At the time of regulatory approval in February, the four companies generics were indicated for indolent-B-NHL and MCL, but not r/r DLBCL. Recently, however, procedures undertaken suggest that a move is underway to add r/r DLBCL as an indication (Towa Pharmaceutical on June 1). CLL has exclusive protection during the re-examination period (until 2026) and cannot be included in the indications for generic products.

In reaction, on February 25, SymBio released a document in which it notified the four companies of concerns about patent infringement. It is thought that the patent in question belongs to the US company, Eagle Pharmaceuticals Inc., which was the original licensor of the RTD formulation. There was a previous instance of patent infringement involving the Bendeka® RT formulation in the US. The court decision in that case enjoined the generics makers from selling the product for a prescribed period of time. In Japan, on May 11, Meiji Seika Pharma announced it was postponing the posting of standard drug prices from the original June date. The risk poised by generic products is receding, with one of the four generic makers deciding to postpone sales.

Switching to the more user-friendly RI administration will provide a protective wall against competition

In February 2022, SymBio obtained approval for the RI formulation, which is even more convenient than the RTD formulation, and is proceeding with the switch from one to the other. As pricing of the generic is at present undecided, any impact is unclear, but it is felt that there is unlikely to be a significant impact in the near term. SymBio has not made any changes to its 2022 management plan.

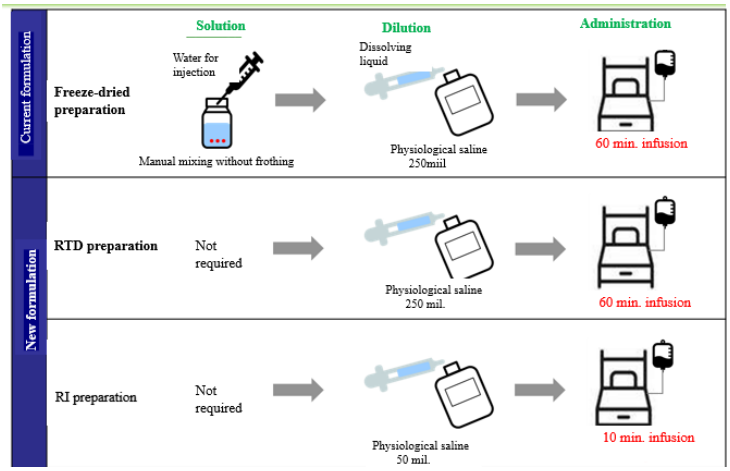
Reference: New formulations

Until December 2020 the Treakisym® on the market was the freeze-dried (FD) formulation manufactured by Astellas Deutschland GmbH. In 2020, 10 years had passed since Treakisym® was approved and from 2021 there was a risk of competition from generics. Preparations have therefore been made to extend the product's life to 2031 by means of new formulations.

As a first step, in September 2017 SymBio announced it was licensing in ready-to-dilute (RTD) and rapid infusion (RI) Treakisym formulations from the US company, Eagle Pharmaceuticals Inc. While the conventional FD formulation has the advantage of room-temperature storage, it is time consuming and troublesome because of the need to dissolve in a solvent and to dilute in physiological saline prior to administration. In the case of a liquid formulation, while refrigerated storage is necessary, the burden on medical staff is reduced because it only requires dilution in physiological saline. The switch to a liquid formulation should also mean an appreciable reduction in costs.

Since the RTD formulation is the same in terms of efficacy and method of administration as the FD formulation, additional tests were deemed unnecessary. A submission was filed with drug stability data in September 2019 and approval was given for the existing indications in September 2020 with sales beginning on January 12, 2021. In April 2021 approval of an additional indication, r/r DLBCL, was received also for the RTD formulation. SymBio expected the RTD liquid formulation to rise from 20% if sales in January-March 2021 to around 80% by year end.

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



Source: SymBio results meeting

Note: Having launched a freeze-dried formulation in the US in 2014, Teva Pharmaceutical Industries, in January 2016 launched an RI preparation (product name: Bendeka® (10-minute infusion), licensed in from Eagle Pharmaceuticals. In only two years, the BENDEKA® replaced 97% of the TREANDA® market.

Since the RI formulation (10 minutes infusion) has a different concentration and administration time, a number of clinical tests to confirm safety and investigate pharmacokinetics was undertaken before submitting an application in May 2021. In February 2022 approval was given for all indications. With its 10-minute administration time and low salt content it is regarded as particularly suitable for the many elderly patients with malignant lymphomas. With the introduction of these liquid formulations, the product's life cycle will be extended until the end of 2031.

The development of oral PI3K inhibitors tareting haemological cancers has stagnated due to problems with safety and effectiveness

Reference: PI3K inhibitors

In the field of hematological cancer, PI3K inhibitors have attracted attention as easy-to-administer oral agents. In the United States, four PI3K inhibitors have been approved in the field of hematological cancer since idelalisib was authorised in 2014.

All of these qualified for accelerated examination based on Phase-2 studies and became subject to revalidation of efficacy and safety in post-marketing validation studies. As a result of this re-verification, approval has been withdrawn for some idelalisib indications, and approvals/ applications have been withdrawn for a number of other drugs. In view of these results, the FDA has changed its stance such that in future randomised control trials are required for PI3K applications. There has thus been a major change in the outlook for zandelisib, for which an application via accelerated examination was planned using Phase-2 data.

Developments currently underway in Japan include pasaraclib (Phase-2), zandelisib (Phase-3), and duvelisib (submission completed). Pasaraclib Phase-2 targets third-line follicular lymphoma, and zandelisib Phase-3 targets second-line follicular lymphoma. Telomelysin® is also indicated for first-line, thus marginally improving sales prospects. The indications for duvelisib are the extremely limited fields of third-line CLL/SLL.

2. Brincidofovir（SyB V-1901）

Brincidofovir (BCV) is a highly active multiviral infection drug developed by the US company, Chimerix Inc.

In 2019 SymBio licensed in from the US company Chimerix rights to the highly active antiviral agent brincidofovir

[Brincidofovir]

Pipeline	Indication(s)	Clinical Trial			NDA※1	MA※2
		Phase 1	Phase 2	Phase 3		
SyB V-1901 Antiviral Drug (IV)	Adenoviral disease of immunocompromised patients including post hematopoietic stem cell transplantation (Global) (US・UK)					
	BKV infection post kidney Transplantation (Global)(JPN・AU)					
	CMV infection GBM (Global)(US)	Preclinical study on going				

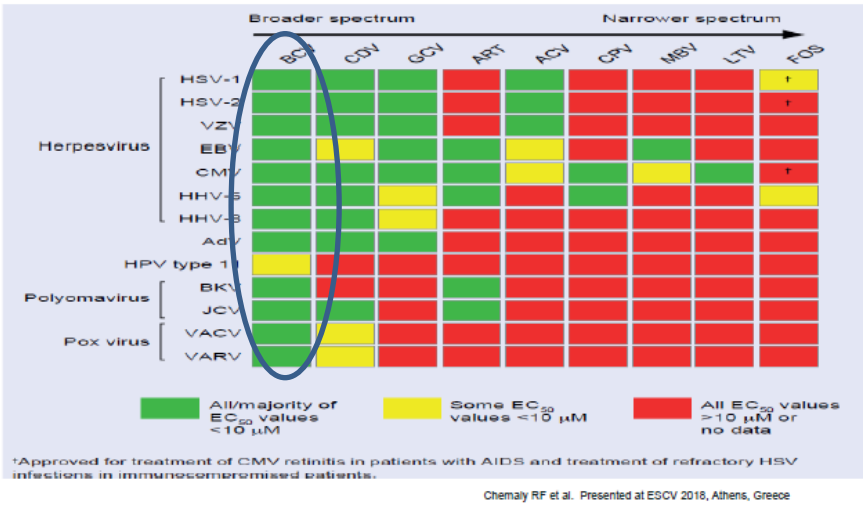
On October 1 2019 SymBio announced it had acquired from Chimerix Inc. exclusive global license rights (development, manufacture and sale) to brincidofovir (BCV) for all indications except smallpox. It is intended as the company's strategic product successor to Treakisym®. Until now SymBio has obtained licenses overseas and developed them in the Japanese market. The contract with Chimerix allows it to license out development products globally. (On May 16, 2022 Chimerix announced it had transferred the BCV license to Emergent BioSolutions Inc., but this has no effect on the rights acquired by SymBio.)

（1） Principal features of brincidofovir

Brincidofovir is highly active against various infections

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



Source: Chimerix documents

Note: **EC50** (the concentration at which a drug or antibody shows a 50% maximum response from the lowest value) indicates that the lower the number, the higher the activity. In the above chart, EC50 is color-coded depending on the level. Green has high activity and red has low activity. The left-most BCV column is green for various viruses = has a broad spectrum.

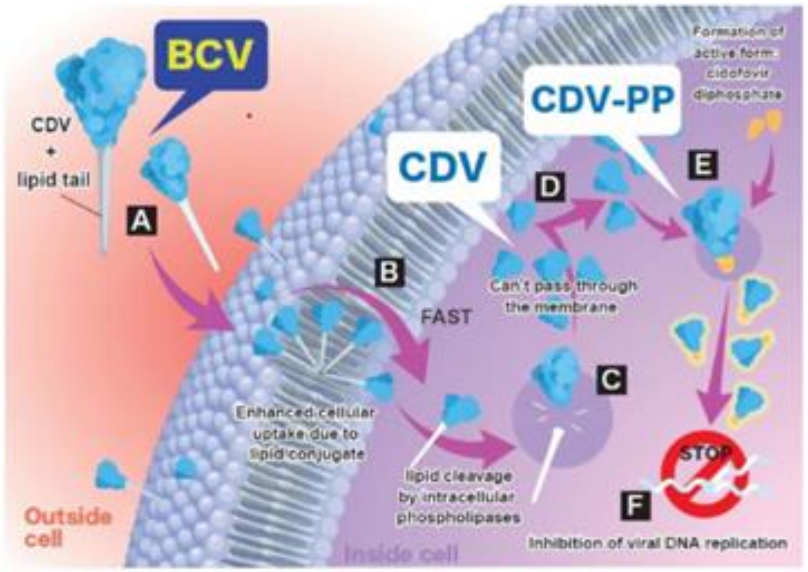
Reference: cidofovir (CDV)
Was approved by the FDA in 1996 for the treatment of cytomegalovirus retinitis in AIDS patients. CDV is a cytosine nucleotide analog which inhibits the replication of DNA viruses such as adenovirus, papillomavirus, and polyomavirus as well as the herpesvirus family. CDV is 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 in Japan.

As can be discerned from the previous figure, 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.

(2) BCV mode of action

Further, nephrotoxicity, which is a common problem in antiviral agents, is low

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 lipid tails it becomes a substrate of OAT-1 and accumulates in renal urinary duct epithelial cells, with nephrotoxicity the likely outcome).



Source: SymBio IR materials

(3) Targeted disease areas

SymBio targets the blank therapy spaces in a “blue ocean strategy”

SymBio’s development strategy for BCV focuses on the “blank therapeutic spaces” for which existing antiviral agents have not been approved. However, although there are many antiviral agents for which CMV (cytomegalovirus) is indicated, anti-CMV agents for glioblastoma (GBM), which is a malignant brain tumor, also constitute a "blank therapeutic spaces". This field is also considered a promising development target.

Many blank therapeutic spaces awaiting drug solutions

	CMV	AdV	BKV	EBV
Brincidofovir		○	○	○
Maribavir	●			
Letermovir	●			
Foscarnet	●			
Cidofovir	●			
Ganciclovir	●			

● : Approved
○ : Development Target

However, CMV-GBM is 「Blank treatment area」

Source: SymBio results meeting, February 2022

The first of these blank spaces is disseminated adenovirus infection after hematopoietic stem cell transplantation

① Disseminated adenovirus infection after HSC transplantation

In general, in the case of hematopoietic stem cell (HSC) transplantations and organ transplantations, 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 a 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 region of hematology.

SymBio originally planned to use 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 trials on children had begun, adult dosing tests would start.

Development from Phase-2 has already begun in the US and UK

SymBio submitted an IND application for the BCV Phase-2 trials for adenovirus infection after HSC transplantation to the US FDA on March 10, 2021 (registration number NCT04706923). In addition, on April 26, the FDA gave fast track examination status to development programs for pediatric adenovirus infections. On August 16, 2021, SymBio succeeded in registering its first patient (FPI) for Phase-2 joint international trials of the anti-viral brincidofovir intravenous preparation (BCV IV) for treatment of child adenovirus infections (AdV infections). In January 2022, an application to conduct clinical trials was submitted in the UK. Firstly, four groups of six patients each will receive stepped increases in doses to test safety and tolerance. The trials are scheduled for completion in the second half of 2022 or early 2023. Phase-2 trials targeting adults will also begin in 2022. If all goes according to plan, Phase-3 with several hundred participants will start in the first half of 2024, an NDA will be submitted in 2026-2027, and product launch will occur in 2027-2028.

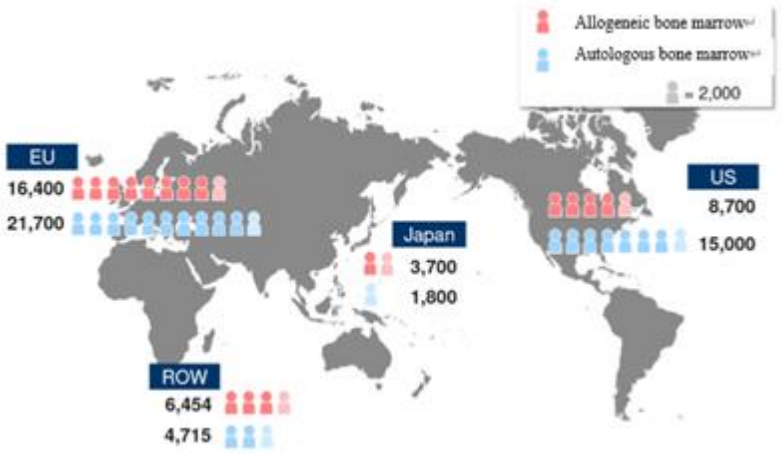
After fast-tracking for children, Phase-2 for adults will commence in 2022

The next phase is scheduled to start in the first half of 2024

Reference: Number of HCT transplantations

It is estimated that worldwide there are some 78,000 HSC transplantations a year, of which around 43,000 are autologous (using the bone marrow of family members) and therefore less subject to rejection. There are some 35,000 allogeneic transplants using the bone marrow of non-family donors with the same white cell type, for whom immunoreactions need to be controlled to suppress rejection, and which are highly vulnerable to viral infection. These are on the rise.

Number of HCT transplantations



Source: SymBio results meeting, February 2020

② BK virus infections after kidney transplants

The second “blank space” is BK viral infections following kidney transplants

In addition to work on infections following hematopoietic stem cell transplants the company is also planning to extend its efforts into viral infections at the time of organ transplants. Organ transplants are more common in the West than in Japan. For example, while some 1,600 kidney transplants 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-one-third contract the BK virus infection and the CMV (cytomegalovirus) infection. 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.

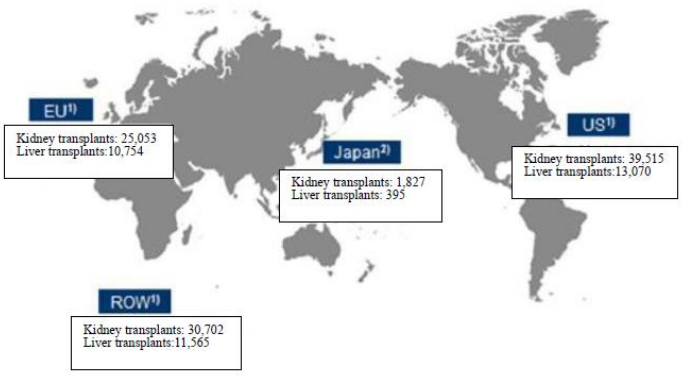
Phase-2 scheduled to commence in Australia and elsewhere in the first half of 2022

SymBio is scheduled to begin development in Australia, Japan and one other country during 2022. Apparently, for the Phase-2 dosage trials they are thinking of a scale similar in size to the adenovirus Phase-2 trials. The company plans to do the early trials itself, but the organ transplants are outside its area of expertise, and there are not enough cases in Japan. For those reasons it is thinking seriously of partnering with a European or US company to promote development and sales in the area of organ transplants.

Development of targets for viral infections after organ transplantation needs to be promoted with western pharmaceutical companies as partners

Potential market for SOT transplantations

US>ROW>EU>Japan； Global business development honing in on regional characteristics



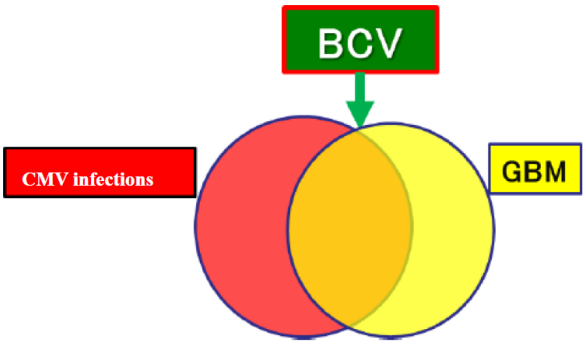
Source: SymBio: Matters concerning business plans and growth potential

The third “blank space” is malignant brain tumours (glioblastoma)

In this area there is currently no prospective drug for CMV (cytomegalovirus)

③ Development directed at malignant brain tumours (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.



We now know that CMV infection promotes the growth of GBM

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 cytomegalovirus (CDV) inhibits CMV reactivation in CMV-infected mice and improves survival rates.（The Journal of Clinical Investigation, 2019, Sean E Lawler et al.)

BCV has an anti-tumour effect and is able to constrain the degree of malignancy

SymBio is now considering whether or not to develop BCV as a treatment for GBM based on this and separate research. The mechanism of action of BCV against GBM consists of BCV converting to CDV-PP in the cell. It has an antitumor effect that inhibits the replication cycle of tumor cells and induces apoptosis, with BCV inhibiting the reactivation of CMV. It is thought to have the effect of suppressing malignancy that suppresses tumor growth. It is inferred that BCV’s malignancy suppression has the effect of controlling tumour growth.

Joint research now being underaken with the University of California and Brown University

SymBio is now doing joint research with California University 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.

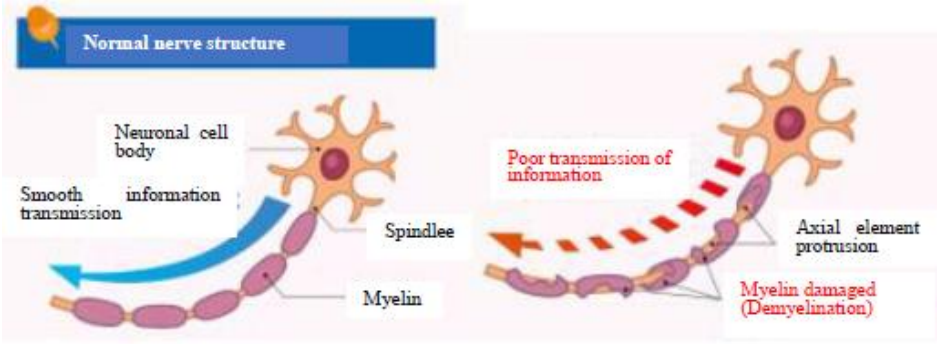
④ Expansion into the field of neurovirology (multiple sclerosis)

The fourth ‘blank space’ involves the search for a therapy for 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 get infected with it. 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). In particular, there is a clinically clear association with some blood and pharyngeal cancers.

The EB virus is a neoplastic virus and is attracting attention as a cause of multiple sclerosis

SymBio in February 2022 announced it was considering making multiple sclerosis (MS), one type of autoimmune disease, a new target indication of BCV.

	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 urinary disorders.). 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, 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
Epidemiological research papers have been published pointing to a strong connection between the EB virus and MS	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 more than 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 was times higher than that of other viral infections.（Science, January13 2022, “Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis”）
Transcription factors of lymphocytes (B cells) infected with the EB virus are analogous in structure to glia cell adhesion factors in the brain	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).
Auto-antibodies that interact with the EB virus inadvertently damage nerve axons BCV eliminates the EB virus, thus stimying progress of the mutliple sclerosis Considering now whether or not to proceed	This hypothesis is supported by the effectiveness of blocking the transfer of lymphocytes into the central nervous system (sphingosin 1 (SP1) phosphate receptor agonist) or blocking the 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 this mechanism is correct, the progression of MS can be inhibited by promptly exterminating the EB virus with BCV after the onset of MS. At present, the value of the market for multiple sclerosis treatments is thought to be JPY1.5 trillion, or JPY2 trillion if steroid treatments are included. SymBio expects that BCV will be added as a concomitant drug with a new mechanism and is considering conducting applied research with overseas experts on BCV in the field of neurological disorders. In the second half of 2022 a decision will be made on business development.
The EB virus may also be a sequela of the coronavirus,	Further, SymBio is focusing on the possibility that the after-effects of the new coronavirus infection (long COVID symptoms: fatigue, brain fog, rash, etc.) may be

suggesting BCV may have a wide range of applications in the field of the cranial nerves

caused by the reactivation of the EB virus by an inflammatory reaction after COVID 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. SymBio has not decided whether or not to make long COVID a target of research, but BCV has the potential to extend its application range beyond MS to the cranial nerve area.

Major Multiple Sclerosis Drugs (2020)

(JPYbillion)

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

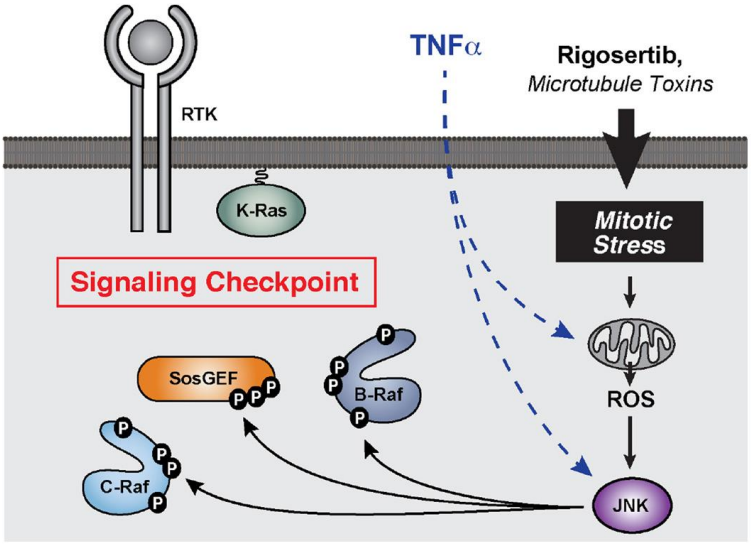
Source: SymBio results meeting, February 2022

Rigosertib was developed for MDS until suspended. Now consideration is being given to developing it with the focus on other modes of action

3. Development of rigosertib (injection and oral formulations)

Rigosertib was first developed to treat myelodysplastic syndrome (MDS) but failed to achieve its primary endpoint at international joint Phase-3 INSPIRE trials (August 2020). Now, however, the focus is on its function as a RAS inhibitor, and its development is being promoted as a cancer drug, particularly by the licensor, Onconova Therapeutics.

Rigosertib mode of action



Source: Daniel A Ritt et al, 「Inhibition of Ras/Raf/MEK/ERK Pathway Signaling by a Stress-induced Phospho-regulatory Circuit」 Mol Cell 2016 Dec

Rigosertib's microtubule-inhibiting action is thought to activate JNK and act on the Ras / Raf / MEK / ERK pathway.

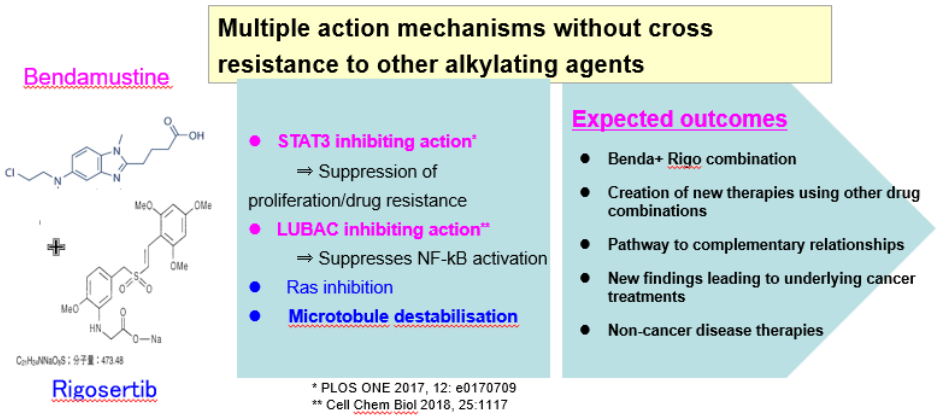
Onconova focusing on the RAS–inhibitory function

In September 2021 Onconova released interim results of the Phase-1 part of trials (Phase1/2a) of a therapy combining oral rigosertib and the anti-PD-1 antibody nivolumab (Opdivo®) for the treatment of non-small cell lung cancer (NSCLC) with KRAS mutation.

The subjects were NSCLC patients with KRAS mutations and all had had at least one experience of treatment with an anti-PD-1 antibody. For NSCLC patients, anti-PD-1 antibodies such as Opdivo® are targeted at patients with a PD-L1 expression ratio of 50% or higher. However, of the patients with a PD-L1 expression rate of 50% or more, only about 45% respond to the anti-PD-1 antibody. In other words, even if selected for treatment with the anti-PD-1 antibody (Opdivo) by genetic testing, it is ineffective as a first-line treatment in 55% of cases. There is clearly an unmet medical need here and an area of great competition between companies.

In terms of test results, of the 12 cases tested 2 had not yet reached the evaluation stage, and 3 were terminated due to side-effects, leaving 7 patients who could be evaluated. Of these, 2 showed a partial response (PR) and 1 showed stability of disease (SD), making for a disease control rate of 43%. Looking at partial response subjects, both KRAS G12C and KRAS G12V mutations were observed. No unexpected serious side effects were observed.

KRAS mutations have been observed in about 20% of NSCLC cases, of which the most common (13%) is G12C mutation. The first KRAS inhibitor recognized anywhere was the G12C mutation inhibitor, LUMAKRAS (generic name Sotorasib

SymBio now cooperating with academia on new modes of action The future direction will become clear in the second half of 2022	from AMGEN, given expedited approval in May 2021). Also in the area of NSCLC, progress is being made by the American company, Mirati Therapeutics, in the development of adagrasib, a KRAS (G12D) inhibitor, and work has begun on the development of a KRAS (G12D) inhibitor targeting pancreatic and other cancers. However, AMGEN and Mirati's medicines both bind with specific KRAS mutations and act exclusively on them. On the other hand, rigosertib probably has multiple action mechanisms, such as RAS signal inhibition and microtubule destabilisation and, as described above, a response can be obtained regardless of the particular KRAS mutation. Rigosertib is therefore considered to have the potential for wider applications. SymBio has been cooperating with academia (Institute of Medical Science of the University of Tokyo, Gunma University) on research into novel modes of action of rigosertib and Treakisym® (bendamustine) and will make a decision on where to go from here in the second half of 2022. **Possibilities offered by therapies combining rigosertib and Treakisym® (bendamustine)**  Source: SymBio company briefing

<Potential market for the company's main products>

For the three indications of relapsed/refractory indolent-B-NHL, CLL and untreated indolent-B-NHL, Treakisym sales in 2021 came in at JPY6.13 billion, and for r/r DLBCL, JPY2.13 billion

If we count in increased market penetration of untreated follicular lymphoma, which accounts for approximately 80% of untreated indolent-B-NHL, and increased market penetration of relapsed / refractory DLBCL, then peak sales should come in at JPY12.3 billion (JPY15 billion on a regulated price basis)

1. Potential market for Treakisym®

Here we look at the market size of SymBio products on the assumption that the effect of patent problems is minor, and that the switch to 10-minute RI administrations will blunt the impact of generics. The market for Treakisym® is expected to grow mainly in those fields where clinical indications were expanded in 2021. Up to 2021 the areas that had been approved and sales begun were: ① Relapsed/refractory indolent-B-cell NHL/MCL; ② Chronic lymphocytic leukemia (CLL); ③untreated indolent-B-cell NHL/MCL. The sales value (net basis) of Treakisym® for indications ① to ③ totaled JPY6.13 billion in 2021. We believe that in the areas ① and ② market penetration by Treakisym® has already been achieved, but market penetration for untreated follicular lymphoma, which accounts for 80% of untreated indolent-NHL, currently has a market penetration of only 50%. Looking ahead, this is likely to rise to 75% in the future. We therefore see peak net sales of JPY7.3 billion (regulated price basis: JPY8.7 billion). Further, sales of Treakisym® for r/r DLBCL, which was approved as recently as March 2021, totaled JPY2.13 billion (net basis) in 2021, and the current market penetration is estimated at about 30%. SymBio is looking to secure a 60% market penetration in this segment and expects it to be a main driver of market growth. Peak net sales could come to JPY5 billion (and around JPY6 billion on a regulated price basis). Overall peak sales should come in at JPY15 billion, or JPY12.3 billion on a net basis.

Number of Treakisym-indicated cases (annual)

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

Source: Fair Research Inc. using SymBio data

The number of potential patients could be 2,000 for disseminated AdV infection, 8,000 for BKV infection, and 30,000 for malignant brain tumors

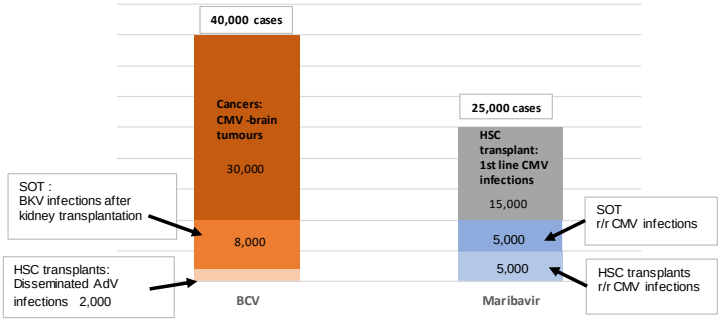
Assuming a cost per case of JPY3 million: JPY300 billion for the two infections alone, and JPY1.2 trillion including malignant brain tumours

2. Potential market size for brincidofovir（BCV）

Here, we consider the market size for disseminated adenovirus infections after hematopoietic stem cell transplantation, BK virus infections after kidney transplantation, and malignant brain tumors (GBM). For these, SymBio has indicated a policy of in-house development.

SymBio has estimated the following patient numbers: 2,000 for disseminated adenovirus infections after hematopoietic stem cell transplantation; 8,000 for BKV virus infections after kidney transplantation; and 30,000 for malignant brain tumours. The total comes to around 40,000 patients.

Comparison of patient numbers for brincidofovir and maribavir



Figures for Maribavir based on IR Material by Takeda Pharm. 2019 Nov 21

Global data for GBM is based on forecast incidence of cases of GBM in US, EU5, China and Japan (2027)

HCT data based on Bone Marrow Transplantation 2016, Bone Marrow Transplantation 2019

SOT data is based on International Report on Organ Donation and Transplantation Activities, executive summary 2019, April 2021 and Transplantation 2012

Source: SymBio IR materials, February 2022

Assuming that the drug cost per case is JPY3 million by comparing with other antiviral drugs, total sales is estimated at about JPY1.2 trillion. However, as of 2022, limiting our estimate to diffused AdV following hematopoietic stem cell transplant, now undergoing Phase-2 clinical trials, sales comes to JPY60 billion. For BKV infections following liver transplants, expected to start Phase-2 clinical trials in the first half of 2022, sales of around JPY240 billion is expected. As of 2022, JPY300 billion of the market is still subject to Phase-2 trials.

In passing, according to Takeda Pharmaceutical, the maribavir market has a value of USD700-800 million (JPY840-960 billon, assuming JPY120/USD).

Reference: modeling value of the product pipeline

Calculation based on a number of suppositions

We here estimate (using the DCF method) the value of the Treakisym® and brincidofovir pipelines. In view of the fact the company is now profitable we set a discount rate of 8%.

The discount rate was set at 8% to reflect the company's emergence into profitability

① Treakisym® assumptions

In line with our earlier comments, we assume that peak sales will occur in the fourth year after market launch and will maintain that level for the next 3-4 years, before shrinking at 5% per year and, from 2031, shrinking rapidly at 10% per year.

We have set the Treakisym® cost ratio at 20%

Annual selling costs assumption JPY2 billion

From 2021 Treakisym® sales channels moved in-house, and should in subsequent years be moved almost entirely to the liquid RTD formulation. Liquid formulations will have, we assume, a cost advantage over the conventional formulations. After switching, we assume the cost ratio, including the payment of royalties to Eagle, should be in the area of 20%. We assume milestones of JPY550 million will be payable in each of 2023 and 2024, and annual sales costs we assume will come to around JPY2 billion

② Brincidofovir assumptions

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

Making estimates concerning brincidofovir (BCV) are complicated by the number of uncertainties. We therefore restrict our calculation to disseminated AdV infections following hematopoietic cell transplants, currently in Phase-2, and BKV infections following liver transplants. As noted earlier we are assuming market sizes of, respectively, JPY60 billion and JPY240 billion. In terms of the development schedule, the disseminated AdV treatment is slightly ahead, with Phase-2 expected to occur by 2023, and Phase-3, embracing 400 people, occurring between 2024 and 2027. We are assuming an NDA submission will be made in 2027 and market launch we anticipate will occur in 2028. For the BKV infections, Phase-2 trials we expect to begin in 2022 for completion in 2024. Phase-3 (1,200 subjects), we anticipate will last from 2025 to 2028 with submission of an NDA in 2029 and market launch in 2030.

Target diseases are limited to the above-mentioned AdV and BKV infections. Launch dates are assumed to be 2028 and 2030, respectively

We assume royalty payments to Chimerix of 12%

Under the licensing-in contract with Chimerix Inc., SymBio is to pay Chimerix milestones of USD180 million (including the USD5 million contractual lump sum) and royalties. It has been revealed that the royalties rate will be a two-digit percentage. In the pipeline calculation we assume 12%. Meanwhile, in the case of disseminated AdV infections, SymBio will go it alone until Phase-3, after which it will license out development and sales rights to a global pharma. With respect to BKV infections, after establishing POC (after completing Phase-2) there will be a licensing-out. It may be that the development costs of Phase-3 will be shared. We assume that SymBio's share of development costs (Phases 2 and 3) will be JPY8 billon for disseminated AdV infections and JPY13 billion for BKV infections. The milestone associated with the licensing-out is assumed to be JPY25 billion, which is a quarter of peak sales, and 50% of sales will be received as gross profit. Since the effectiveness of BCV in humans has already been established we have set probability of success at 60-80%.

We are assuming development of AdV will be done in-house up to Phase-3, and BKV will be developed with a partner from Phase-3. SymBio's share of development costs we assume will be JPY8 billion and JPY13 billion respectively

We assume the milestone receivable from the sales licensee will be one quarter of peak sales

In addition to existing drugs there will be annually recurring basic R&D costs to fund the search for new drug candidates and costs associated with company-wide administration. We assume the former at JPY600 million and the latter at JPY1.6 billion, for a total of JPY2.2 billion.

③ Results of calculation

Treakisym® value JPY55.2 billion (before tax)

The results of our discounted present value calculations using the above suppositions are shown in the table below. Using a discount rate of 8%, we posit a value before tax of JPY55.2 billion for Treakisym®. The value calculation for BCV is

The value of BCV is JPY26.7-42.7 billion after taking probability of success into consideration

Value at the JPY50 billon level after deducting company costs

Expanding into the area of malignant brain tumours and cranial nerves would produce an even higher value

complicated but on the basis of various assumptions and given a 60% probability of success we posit a value of JPY26.7 billion. The combined value of Treakisym® and BCV therefore comes to JPY81.9 billion. Deducting company-wide costs produces a pipeline value (before tax) of JPY54.4 billion.

Pipeline value calculations (before tax)

(100 mil.JPY)

	Prob. of success 100%	Prob. of success 80%	Prob. of success 60%
Treakisym®	**552**	---	---
BCV (AdV+BKV alone)	571	427	**267**
Sub-total	1,123	979	819
Company costs	-275	-275	-275
Total	848	704	**544**

Source: calculations by Fair Research Inc.

Note: Please note that pipeline value and market value are not directly comparable

Although not included in the above calculations, pipeline value would be higher if further indications for brincidofovir (malignant brain tumors, multiple sclerosis, etc.) and rigosertib were included

<Earnings and management plan>

Turned profitable in 2021

Sales revenue in 2021 rose because of in-house sales and expanded clinical indications. However, expectations for the year not met due to the effect of COVID-19 on inventories

Big improvement in the cost ratio. However, due to the switch to the liquid formulation an inventory evaluation loss was made on the FD product, and bcause the switch was later than expected the improvement was narrower than originally projected

Sales of products and income from licenses are the sources of SymBio's earnings. Apart from the period ending December 2008, when it received a lump sum for licensing out Treakisym® sole domestic sales rights to Eisai and went into the black, it had always operated at a loss. However, when it brought the sales function in-house in 2021 it again turned profitable.

1. 2021 results

Revenues in the 12/2021 year came to JPY8,256 million, a big increase on previous years. Until the previous year the company had been wholesaling through Eisai but from 2021 this function came in house. Nevertheless, COVID-19 caused postponements and delays to treatment (around JPY400 million foregone), and because of absorbing the Eisai inventories which had built up in the market (JPY450 million foregone), sales failed to reach the JPY9,151 million originally projected. In addition, the cost ratio improved significantly from the previous year (71.0%) to 29.7% due to self-sale, but the switch from the FD formulation to the RTD formulation caused an inventory valuation loss from the FD formulation of JPY330 million. Also, due to the delayed switch to the RTD formulation, the improvement in the cost ratio was reduced by about 5.7 percentage points from initial expectations.

Revenues and financial structure

(JPY-mil)

	2015	2016	2017	2018	2019	2020	2021 Actual	2021 Initial plan
Sales	1,933	2,368	3,444	3,835	2,838	2,987	8,256	9,151
Sale of goods	1,933	2,137	3,444	3,809	2,811	2,977	8,256	9,151
License income	0	231	0	25	27	10	0	0
Cost of sales	1,483	1,737	2,413	2,662	1,973	2,120	2,456	2,194
Rate	76.7%	73.3%	70.1%	69.4%	69.5%	71.0%	29.7%	24.0%
SG&A	3,135	3,031	4,978	3,828	5,166	5,373	4,784	5,596
of which, R&D	2,035	1,667	3,017	1,832	2,442	2,266	1,736	2,019
<excl. R&D>	1,100	1,364	1,961	1,996	2,724	3,107	3,048	3,577
Op. profit	-2,552	-2,127	-3,947	-2,656	-4,302	-4,565	1,016	1,361
Rec.profit	-2,630	-2,317	-3,976	-2,748	-4,377	-4,615	1,001	1,350
Pre-tax profit	-2,628	-2,309	-3,974	-2,748	-4,372	-4,087		
Net profit	-2,632	-2,313	-3,978	-2,752	-4,376	-4,090	2,302	1,149
Current assets	4,827	6,685	4,037	6,038	4,887	5,815	6,747	
of which, cash etc.	4,261	5,719	2,947	4,821	3,910	3,848	3,860	
Fixed assets	158	193	216	200	386	459	1,705	
Current liabs	551	942	1,011	1,336	872	1,615	1,518	
Fixed liabs	2	451	1	1	1	2	189	
of which, debt	0	450	0	0	0	0	0	
Net assets	4,432	5,485	3,239	4,901	4,400	4,657	6,745	
of which, shareholders equity	4,132	5,054	2,702	4,372	3,779	4,037	6,226	
of which, stock acquisition rights	300	431	537	530	620	620	519	
(Ref)								
Income from issue and exercise of stock acquisition rights	0	687	1,178	4,301	3,771	4,244	0	
Income from issue of CB's	0	3,000	0	0	0	0	0	
Event	Cost of IONSYS licensing in		Cost of liquid Treakisym licensing in		Cost of BCV licensing in In-house sales structure	In-house sales structure RTD milestone Receipt of court award	In-house sales start Formulation change - improved cost of goods Loss on FD inventory Deferred tax capitalised	

Source: Compiled by Fair Research Inc. from securities report filings

Increased efficiency of R&D activities help reduce R&D costs

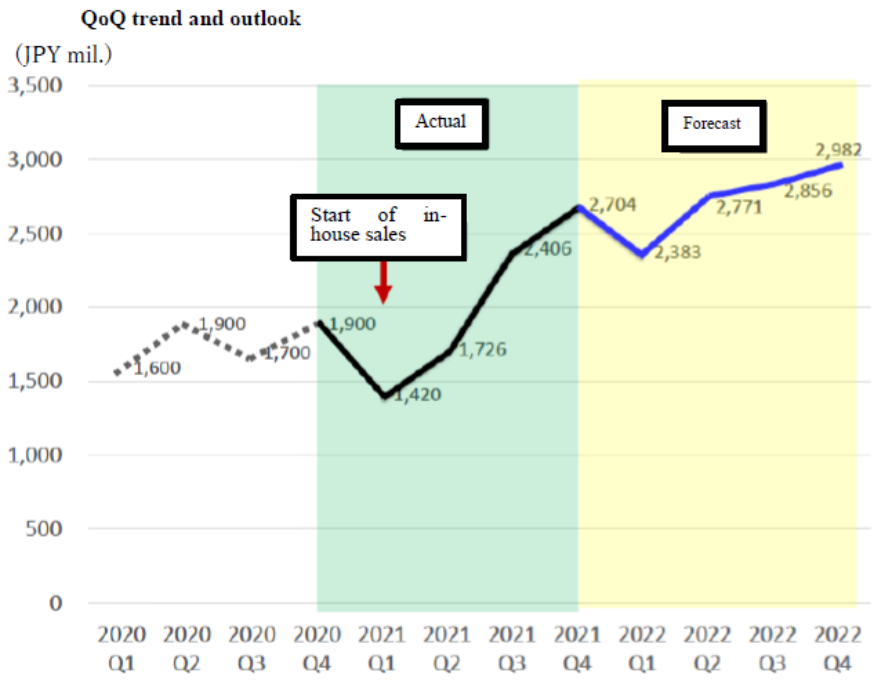
The arrival of profitability means the availabilty of deferred tax assets and a

Research and development spending in 2021 stood at JPY1,736 million, below the 2020 level of JPY2,424 million. 2020 spending includes the milestone payment (around JPY500 million) made in respect of the RTD formulation's approval. Adjusting for this leaves a decrease of about JPY200 million. It is inferred that this is the result of promoting the efficiency of R & D activities due to the increase in expenses associated with the establishment of an in-house sales system. Non-R&D sales and administration expenditure in 2021 came to JPY3,048 million, about the same level as the previous year. As a result, operating income came in at JPY1,016

steep rise in net profits

million. In addition, as the company had made a profit it was able to activate JPY1,270 million in deferred tax assets, boosting net income to JPY2,032 million.

Quarterly sales and outlook



Source: SymBio "Matters concerning the business plan and growth potential"

Note: Actual sales was JPY2,315 million in the first quarter of 2022, in line with expectations

Cash reserves stay at the JPY3.8 billion level

Reflecting the arrival of profitability at the company, net assets at the end of 2021 rose JPY2.08 billion and cash maintained the JPY3.8 billion level.

2. 2022 outlook

In 2022, sales are expected to increase by 33.1%, driven by such factors as continued growth in demand in the DLBCL. segment

We are assuming that sales in 2022 will rise 33.1% on a YoY basis to JPY10.992 billion, driven by the expansion of approved indications in March 2020 to include r/r DLBCL. The cost ratio is expected to fall to 20% in anticipation of the completion of switching to the liquid formulation (RTD/RI), and gross profits will reach 80%. Regulated prices for generics are due to be posted in June 2022 but any effect will not be apparent until late in the second half. SymBio is not changing its forecast for 2022 sales.

With the switch to liquid formulations complete, further improvement in the cost ratio

Any impact from generics will not be felt until the second half

Elsewhere, SG&A expenses are scheduled to come in at JPY7,026 million, an increase of JPY2,241 million on the previous year. Of this, an expected JPY3,056 million is for R&D, an increase of JPY1,319 million. This is mainly due to a ballooning of BCV-related outlays, including the start of BK virus clinical trials in Australia in the second quarter of 2022. All the same, the expectation is for operating revenues to hit JPY1,770 million, an increase of 74.2%. The operating profit margin should come in at 16.1%.

While there will be a significant increase in R&D outlays due to the full-scale

development of BCV, the company can still manage a 74.2% increase in profits

2022 outlook (management plan)

(JPY-mil)

	2021 (Actual)	2022 (Forecast)	2022- 1 Q (Actual)
Sales	8,256	10,992	2,315
Gross sales profits	5,800	8,796	1,898
Margin	70.3%	80.0%	82.0%
SG&A	4,784	7,026	1,388
of which, R&D	1,736	3,056	469
（BCV-related）	408	1,269	NA
Op. profit	1,016	1,770	509
Op. profit margin	12.3%	16.1%	22.0%
Rec. profit	1,016	1,750	478
Net profit	2,032	1,480	163

Source: Compiled by Fair Research Inc using SymBio medium-term management plan and security report filings

Reference: Committed line of credit (upper limit JPY3 billion) extended from December 2020 to March 2022

Company evolves from financing that relies solely on equity finance: working capital to be sourced from bank borrowing

The company has normally relied on equity finance in the form of new share warrant issues to secure corporate funds. In December 2020, however, with the prospect of turning profitable, the company concluded committed line of credit contracts (upper limit JPY3 billion) with two banks. It intends from now on to borrow cash to cover operational requirements. In March 2022, the contracts were rolled over with a new upper limit of JPY3.15 billion.

Reference: First quarter 2022 results

In the Q1/2022 results released on May 12 2022, sales came in at JPY2.315 billion, roughly in line with expectations. The formulation change seems to be proceeding smoothly with the RTD formulation accounting for in excess of 99% of sales as of March end, 2022. As a result of the formulation switch and of the switch to in-house sales the gross profit margin came in at 82%. Then, despite boosting SG&A expenses by 13.8% YoY, operating revenues totaled JPY509 million. It also appears that, as of the end of April, more than 93% of medical institutions were on the way to switching to the RI formulation.

3. New source of capital – Heights Capital Management Inc makes an investment approach

The company received an approach from an investor whose selection strategy involves cultivating investment targets after first developing good relations

On May 16, 2022 SymBio announced a new JPY2.19 billion fund raising. The methodology chosen was the issue of 1 million new shares and the equivalent of 2 million shares in new share subscription rights, both to be placed in a third-party allotment to CVI Investments Inc, managed by Heights Investment Capital Management Inc. Heights is part of the Susquehanna International Group, which has a track record of over a hundred investments in biotech, including in Japan, and whose investment approach involves developing long term relations with potential investment targets.

The company plans to raise a total of JPY2.19 billion for BCV development, the acquisition of new licenses, and M&A

Heights made contact with SymBio around October 2021 and, after subsequent consideration, SymBio judged Heights could be a long-term equity partner well positioned to help accelerate future growth. Judging there would be little risk of a downside effect on the stock price, it accepted an investment proposal. The exercise price for the new share options is set at JPY785 (no adjustment clause) and an exercise period of five years from June 2, 2022 to June 1, 2027. The new shares were priced at JPY662 on issue.

As for uses of funds, a total of JPY1,785 million is allocated to BCV development, with JPY1,219 million going into direct spending, and JPY576 million into indirect. In addition, the company plans to spend around JPY395 million on the acquisition of new licenses, M&A and other investment activities. It is possible these will be directed at new products in the area of SymBio's specialization, haematological cancers.

A financing to put future growth on solid foundations

(JPY-mil)

	Funds raised by new share issue	Expenditure period	Funds raised by issue and exercise of warrants	Expenditure period	Total
Dev. funds for the antiviral drug, BCV - direct expenditures	432.00	2022/7～2022/10	787.00	2022/10～2023/3	1,219.00
Dev. funds for the antiviral drug, BCV - indirect expenditures	190.00	2022/7～2022/10	386.00	2022/10～2023/3	576.00
Funds for new license acquisitions and M&A to secure long-term growth	-		395.76	2022/7～2023/3	395.76
Total	**622.00**		**1,568.76**		**2,190.76**

Source: SymBio notification on May 16, 2022 concerning the third party allotment of new shares and the issue of No.58 new share subscription rights

Conclusions

For the time being the company will retain strong earnings growth momentum

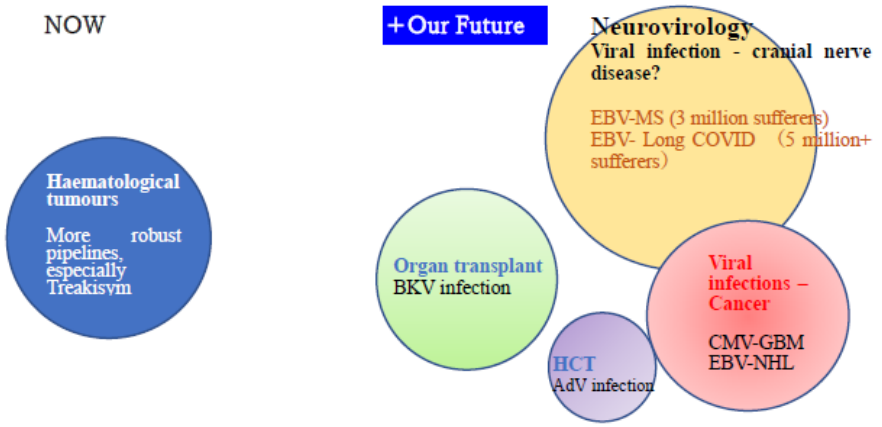
SymBio in 2020 built an in-house sales structure and acquired brincidofovir, thereby laying the groundwork for the company's growth as a haematology-specialised pharma with a global license. Then, in 2021 it expanded the diseases for which its main product, Treakisym®, was indicated to r/r DLBCL, and since 2021 its finances have moved firmly into the black. We believe that until sales peak, Treakisym® will retain strong profit growth momentum, reflecting the product's high profit margin.

Meanwhile, the develoment of brincidofovir will proceed and the company will evolve from a pharma specialising in haematology to one embracing tumours and cranial nerve ailments

Looking ahead, even when Treakisym® reaches peak sales and profit growth flattens out, the company can expand the number of products in its blood field specialism and target viral infections after hematopoietic stem cell transplantation and kidney transplantation. Thus, regulatory approval and the launch of brincidofovir (BCV) will emerge as the next growth driver. Further, even as the RI formulation patent expires in 2031 the development area of brincidofovir will be expanding to areas of oncology, such as malignant brain tumours, and in the neurological disease field, such areas as multiple sclerosis. Thus, further expansion of business value will remain possible.

Brincidofovir development will soon start in earnest and there is a possibility that earnings growth momentum will slow down. However, the receipt of investment funds from Heights Capital Management will not only support the promotion of BCV development but will provide the funds necessary for the company's acquisition of new licenses. That investment, then, further strengthens the foundation for future and more rapid growth.

The business value of the pipelines is about JPY55.2 billion (before tax) for Treakisym® alone, and JPY26.7-42.7 billon for brincidofovir in the field of disseminated AdV infection after hematopoietic stem cell transplantation and BKV infection after kidney transplantation. However, the value is immeasurable if we consider the expansion of indications to malignant brain tumours and multiple sclerosis.



Focus on 4 therapeutic areas
1.Blood tumours
2.Infections following HCT
3.Infections following organ transplants
4.Virus infections - cancers
Virus infections – cranial nerve diseases **(under consideration)**

Source: SymBio company briefing, February 2022

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