SymBio Pharmaceuticals Ltd.

(4582 JASDAQ) Issued June 1, 2021

New Direction for SymBio - Building on Success

From drug discovery venture to global specialty pharma

SymBio Pharmaceuticals Ltd. does not undertake research in new drugs. Rather, it relies on a worldwide network of drug discovery companies and its own expertise to adopt and develop promising new drugs. It occupies a niche, seeking to maximise market share and earnings by focusing on areas of medical need in rare diseases (particularly hematopoietic tumours) unmet by the drug majors. Most of the drug candidates it takes on already have a proven record of efficacy and safety, which makes them a low-risk development proposition. The company's first drug was Treakisym®, which was approved and launched five years after being adopted by the company and was accorded standard treatment status in 2018. With the completion of its switch to in-house sales in 2020 it became a pharmaceuticals company specialising in hematology. In September 2019, the company acquired the sole global license (development, manufacturing and sale) for brincidofovir, its third product, thereby laying the groundwork for its evolution into a licensor with a global reach embracing firstly Asia and extending to the US.

Beginnings of the company's second stage of development

With the approval in March 2021of Treakisym®, the company's main product, for the treatment of r/r DLBCL, the market size almost doubled. Further, sales of the RTD liquid formulation began in early 2021, and an application for a rapid infusion (RI) formulation was completed in May of the same year. Through changes in formulation the company prolonged patent life and significantly increased profitability, securing its first profitable year in 2021. Looking ahead, the company plans to team up with academia in the development of new therapies using novel Treakisym® and brincidofovir mechanisms. The company also plans to expedite the global development of brincidofovir to treat viral infections following hematopoietic stem cell (HSC) transplantations. In fact, in February 2021 the company submitted an IND to the FDA for Phase 2 trials relating to adenovirus infections after HSC transplantations. Fast track status was acquired for trials on children. Further, the company is now also planning to develop in Japan a treatment for viral hemorrhagic cystitis following HSC transplantations. In this way, SymBio intends to use a certain percentage (15-20%) of operating revenues from Treakisym® to fund a second stage in global development to maximise the value of its product pipelines.

Will maintain earnings growth momentum and then evaluate development

Until Treakisym® reaches its sales peak it is likely to exhibit strong profit growth momentum, reflecting a high profit margin. While the imminent acceleration of brincidofovir development may deplete some of the momentum it seems more than likely that earnings will continue to grow until around 2026-2027. Treakisym® sales will then reach their peak and a pause in earnings growth will set in. However, the development of brincidofovir and of Treakisym® to treat solid cancers will by then be almost ready to produce future expansion. EPS growth may come to a halt, giving way to a phase of earnings multiple expansion.

Basic Report (revised)

Fair Research Inc.

Tsuyoshi Suzuki

Company Outline	
Location	Tokyo
President	Fuminori Yoshida
Established	March 2005
Capital	JPY17,070mil
Listed	Oct. 2011
URL	www.symbiopharma.com
Industry	Pharmaceuticals
Employees	127 (unconsol.)
Key Indicators as of May 31 2021	
Share price	1,889
52-week high	1,889
52-week low	337
Shares outstanding	38,414,806
Trading unit	100 shares
Market cap	JPY72,950 mil
Est. dividend	0.0
Forecast EPS	JPY30.1
Forecast PER	63.11X
Actual BPS	JPY100.64
Actual PBR	18.87X

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

Results	Revenues JPYmil	YoY %	Op. Income JPYmil	YoY %	R.P. JPYmil	YoY %	Net Income JPYmil	YoY %	EPS JPY	Share Price (JPY) High	Share Price (JPY) Low
2016/12 Actual	2,368	22.5	-2,127	NA	-2,316	NA	-2,313	NA	-58.8	509	170
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 Forecast	9,151	206.4	1,361	NA	1,350	NA	1,149	NA	30.1		

Company Outline and Philosophy

Business Model

The company is engaged in drug discovery without the risks presented by laboratories or manufacturing. It has evolved from a pharmaceutical venture operating a niche strategy in search of high returns to a global specialist pharma.

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

① Post-POC strategy
The company does not itself undertake drug discovery research but investigates 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 operating a high return, high market share niche strategy.
The company focuses its efforts on drugs for relatively rare indications 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 has selected, developing them in Japan and then licensing out to other pharmaceuticals companies. However, it has now set up its own sales function in Japan and has established itself as a pharma specialising in hematology.

③ Evolving into a global licensor
Further, in September 2019, SymBio acquired exclusive rights (development, production and sales) to brincidofovir, 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 or failure of this business model is dependent on 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, only around 7-8%. But SymBio managed to get its first product, Treakisym®, from adoption in 2005 to manufacturing and sales approval in 2010, a period of only five years. In July 2018 Treakisym® achieved recognition as a standard therapy in the area of malignant lymphomas. In the fifteen years since the company was founded, six products have been licensed in, and so far three of them are actually under development or at the planning stage.

SymBio is an unusual bio-venture in that its first product on the market took only five years from inception to regulatory approval

Its network and expertise are enhanced by an outstanding workforce

We believe this track record has been made possible by the expertise of the company's staff and by the way the company is organised. SymBio has a staff of 155, of whom 55 are involved in R&D (as of end of 2020). The drug search function is supported by a Scientific Advisory Board (SAB) of experts (including Nobel Prize candidates). Needless to say, a major role has been played by the company founder and CEO, Fuminori Yoshida, who developed the network and contributes his expertise.

Main 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 management 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 front-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 (INDPIRE) 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

Source: Compiled by Fair Research Inc. using securities reports and other sources

Main product pipelines

As of May 2021, the company's main product pipelines consist of Treakisym®, rigosertib and, since its introduction in September 2019, brincidofovir.

1. Treakisym® (SyB L-0501 (freeze-dried injection formulation)/SyB L-1701 (RTD liquid formulation)/SyB L-1702 (RI 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	Submitted a partial change application				

※ 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

Treakisym® (generic name: bendamustine) is a cancer drug developed in Germany in 1971. It is used to treat malignant lymphomas, particularly the less malignant non-Hodgkin's lymphoma and chronic lymphocytic leukemia.

Reference: malignant lymphomas

Lymphoma is a blood disease caused by the cancerisation of immunity cells called lymphocytes (a type of leukocyte). There are two major types: Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL). 94% of malignant lymphomas in Japan are NHL, which can be classified into the following three types depending on speed of disease progression (the NHL's for which Treakisym® is indicated are highlighted in red).

Types of malignant melanoma

Degree of Maligancy (speed of progression)	Type
Low-grade (measured in years)	Small Lymphocytic
	MALT
	Follicular(Grade 1-3a)
	Marginal Zone B cell
	Lympa Plasma cell
	Nodal marginal B cell
Medium-grade (measured in months)	Plasma cell tumor
	Mantle cell
	Follicular (Grade 3b)
	Diffuse large cell type
High grade (measured in weeks)	Precusor B Lymphoblastic
	Burkitt Lymphoma

Source: Eisai and SymBio's "Treatment Guide"

(1) Progressive expansion of authorised indications

Treakisym was approved within a mere five years of licensing-in, following which there was an expansion of indications

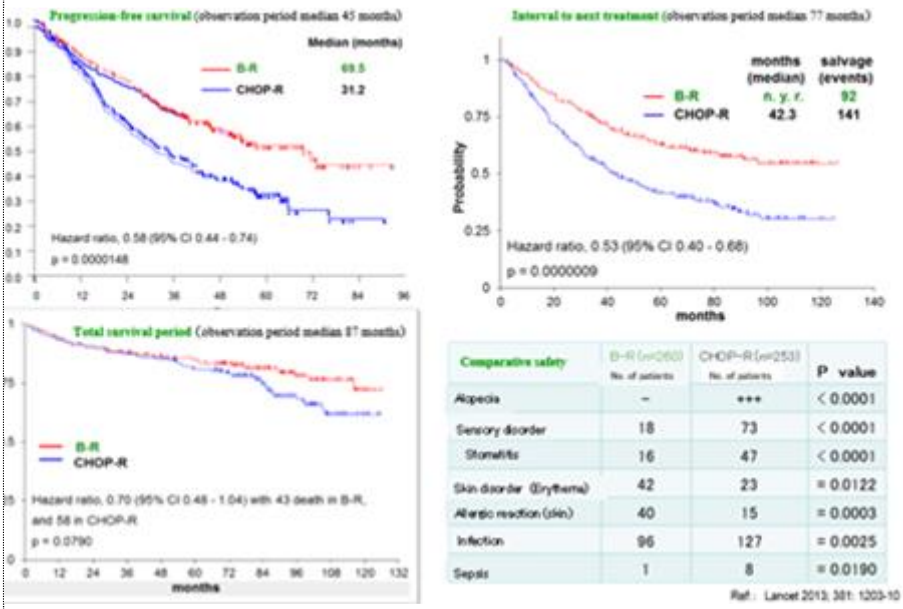
In December 2005, SymBio acquired exclusive development and sales rights to Treakisym® in Japan from the Astellas Pharmaceuticals European subsidiary (now named Astellas Deutschland GmbH). It began clinical trials and, within a mere 5 years, in October 2010, it received approval for two indications, low malignancy recurrent/refractory NHL and mantle cell lymphoma (below, MCL) and, in December, commenced sales. Further approvals were received in August 2016 for chronic lymphocytic leukemia (below, CLL), and in December for untreated low-malignancy NHL/MCL. Finally, in July 2018, with respect to all approved indications, Treakisym® was newly listed in the Guidelines for Clinical Practice in Hematopoietic Tumours for 2018 (edited by the Japanese Society of Hematology) as a standard treatment option.

After its initial authorisation in 2010 Telmelysin® was authorised for two further indications in 2016, with a consequent increase in market penetration

Treakisym has been used as a standard treatment since July 2018

Behind this was the demonstration of the superiority of the B-R therapy combining Treakisym® (generic name: bendamustine) and rituximab over the conventional standard CHOP-R therapy (see comparison of the two therapies in the chart below).

Comparative tests of 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 materials showing superior results of B-R therapy

Note: CHOP-R therapy
Chemotherapy combining the molecular targeted drug rituximab with the cancer drugs cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and the steroid prednisolone.

Market penetration proceeds well until 2018

Once it had established itself as a standard therapy Treakisym® carved out a rising market share, from an average annual level of 35% in 2017 to a level of 56% at the end of September 2018. It thus easily surpassed the erstwhile standard R-CHOP therapy, and in 2018, its 8th year, it chalked up domestic sales of JPY8.5 billion (regulated drug price basis).

After a short-tem period of stagnation sales are expected to bounce back with the extension of approved indications to r/r DLBCL

There was subsequently a temporary period of stagnating sales (in 2020 domestic sales totaled JPY8.1 billion on a regulated drug price basis) due to quality control problems at a supplier and swings in inventories as a result of the company's switch to in-house merchandising. However, this has been offset by a further expansion in authorised indications and the number of patients is expected to double. More

precisely, in March 2021 authorisation was received for the treatment of relapsed/refractory large B-cell lymphoma (r/r DLBCL) using the B-R therapy and the B-R + Polivy® therapy. We expect sales for the expanded indication to become more apparent in the second half. We estimate 2021 domestic sales at around JPY11.3 billion rising to a possible JPY15-17 billon eventually (see Treakisym® market size below).

Note: In Japan, the most common form of medium-malignancy NHL is the r/r DLBCL

Reference

Results of the Phase 3 trials of the B-R therapy targeting r/r DLBCL were announced at the European Hematology Association conference 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%. The release of data on the main endpoint, overall survival, is expected in the first half of 2021.

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

	(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 materials

About 73% of DLBCL patients are 65 years or over. They have traditionally been offered a multi-drug therapy but the side effects caused by taking a combination of multiple anticancer drugs has been a problem. Patient groups and academics have also petitioned for the early use of the B-R therapy.

(2) Increase in combination therapies

Treakisym® is estblishing itself as crucial in blood cancer therapies

Treakisym® is gradually becoming a crucial component in the area of treatments for blood cancers. In the field of hematological cancers targeted by Treakisym®, various new therapies have emerged in recent years (see below), but in each case, Treakisym® is used in combination with new drugs. We provide below a few examples:

A number of new combination therapies to supplememt the B-R therapy is on the way

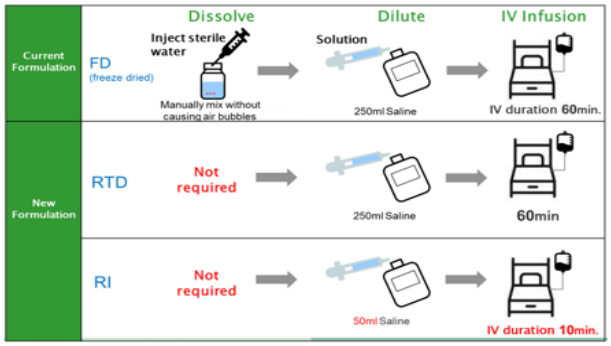
① In July 2018, a combination of the anti-CD20 antibody obinutuzumab (commercial name: Gazyva) and Treakisym® was approved for the treatment of CD20 positive follicular lymphoma, thereby providing a new therapeutic option.

Note: follicular lymphomas account for around 80% of low-malignity non-Hodgkin's lymphomas

② The CAR-T therapy (drug name: Kymriah) developed by Novartis is a well-known ground-breaking therapy for leukemia and other

	hematopoietic tumours. In March 2019, it was also approved in Japan for relapsed / refractory acute lymphocytic leukemia (ALL) and DLBCL. Treakisym® has been approved for use as a concomitant drug in CAR-T therapy pre-treatment, rather than as a CAR-T therapy competitor. ③ In June 2019, the FDA announced the expedited approval of a three-drug therapy for the treatment of surgery 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-CD79 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. However, we think the decision on whether to select the B-R therapy or the P-BR therapy will be made by doctors on the basis of the patient's condition and genotype, so neither will become dominant. ④ According to SymBio, a large number of new therapies for blood cancers combining other drugs, particularly immune checkpoint inhibitors, with the B-R therapy (B-R +X), are being developed in the US and Europe, As can be seen from the above, the B-R therapy has already become a crucial component in the area of hematopoietic tumours, and since new add-on therapies are being developed it is unlikely to be challenged by other treatments. Note: The B-R therapy results (response rates, progression free survival of 69.5 months) produce very high readings, such that new drug candidates are unlikely, as single agent therapies, to do meaningfully better.
	(3) Life-cycle management using formulation changes
Progress is also being made in life-cycle management through formulation changes	Until December 2020 the Treakisym® sold 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 is a risk of competition from generics. Preparations have therefore been made to extend the product's life to 2031 by means of new formulations.
Sales of the RTD formulation began in January 2021, and approval for expanded indications was received in March	As a first step, on 21st September 2017, SymBio announced it was licensing in ready-to-dilute (RTD) and rapid infusion (RI) formulations from the US company, Eagle Pharmaceuticals Inc. While the 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 cost. The company came to an understanding with the Pharmaceuticals and Medical Devices Agency (PMDA) that, since efficacy and method of administration was the same as for the FD formulation, no additional tests would be required and pharmacological stability data alone would suffice for approval application purposes. It then submitted an application in September 2019, received approval in September 2020 for the treatment of existing approved indications, and launched in the market on January 12, 2021. The RTD formulation was also approved for the additional r/r DLBCL indication in April 2021. Liquid formulations accounted for 20% of SymBio's output in the first quarter of 2021 but should reach 91% by the end of the year.

Comparison of the FD, RTD and RI formulations



Source: SymBio results meeting materials

Reference: Having launched a freeze-dried formulation in 2014, the US company, Teva Pharmaceuticals Industries, in January 2016 launched an RI preparation (product name: Bendeka®, licensed in from Eagle Pharmaceuticals) which is more easily administered). In only two years Bendeka® accounted for 97% of the Treakisym® market.

Has reached the application stage for the RI liquid formulation

Since the RI liquid preparation has a different concentration and administration time, a number of clinical tests to confirm safety and investigate pharmacokinetics were undertaken before submitting an application in May 2021. With its 10-minute administration time and low salt content it is regarded as particularly suitable for the many elderly patients with malignant lymphomas. Regulatory approval and market launch is expected for the second half of 2022. With the introduction of liquid formulations the product's life cycle will be extended until the end of 2031.

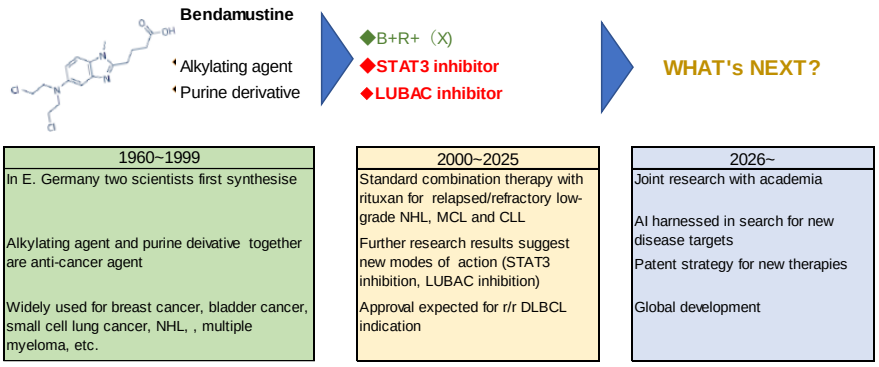
With the introduction of liquid formulations the product's life cycle is extended to 2031

(4) Search for new modes of action

Moving on to development of novel therapies outside the area of hematological cancers by focusing on novel Treakisym® mechanisms

The extension of indications to r/r DLBCL marks the completion of Treakisym development on malignant lymphomas. However, separate research has pointed to the existence of novel Treakisym® mechanisms (STAT3 inhibition, LUBAC inhibition). SymBio's policy is to expand its corporate value through joint research with academia, and by locking in on medical targets that make full use of AI, promoting research on the possibility of developing therapies for other cancer types, such as solid tumours, and the development of new therapies in combination with other drugs. By further developing Treakisym® it aims to make SymBio a global company.

The direction of further Treakisym® development



Source: SymBio company briefing materials
(the r/r DLBCL indication in the centre panel received approval in March 2021)

2. Rigosertib (SyB l-1101 injection formula; SyB C-1101 oral formula)

[Rigosertib]

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

Rigosertib is a cancer drug indicated mainly for myelodysplastic syndromes (MDS) developed by Onconova Therapeutics Inc. in the US. After Onconova completed Phase 2 clinical trials in July 2011, SymBio acquired sole development and sales rights for injectable and oral formulations in Japan and South Korea (the one-off contract payment is estimated at around JPY800 million).

(1) Development timeline

SymBio was responsible for the Japanese part of the joint international Phase 3 clinical trials targeting high-malignity MDS patients who had not responded to the standard treatment using hypomethylating agent (HMA) or who had experienced a recurrence after treatment.

Rigosertib was being developed as an injection and oral formula mainly for treating myelodysplastic syndrome

Onconova Therapeutics completed Phase 3 (ONTIME) trials targeting relapsed/refractory high-risk MDS in February 2014. The results of these trials showed no statistically significant difference in overall survival (OS) between the cohort receiving rigosertib and the control group (palliative care). However, there was a significant difference to overall survival when limited to patients who were resistant to the HMA standard treatment or whose condition had deteriorated during prior treatment. The OS for the patient cohort receiving rigosertib was 7.9 months versus 4.1 months for the control group. On the basis of these partial results Onconova revised the trial design and from August 2015 proceeded with international collaborative Phase III clinical trials (INSPIRE trials) targeting high risk MDS patients who were unresponsive to HMA or had a relapse after treatment. SymBio was responsible for the Japan segment of the Phase 3 trials.

Reference: The International Prognostic Scoring System classifies high-risk MDS into higher risk and medium risk, with the latter subdivided into two risk levels, the higher of which denotes a likelihood of transitioning to leukemia. Currently, the standard treatment is administration of azacitidine (trade name Vidaza) and decitabine (trade name Docagen), but some high-risk MDS occurrences are resistant to the standard treatment or relapse after treatment. Rigosertib is indicated for such relapsed or refractory high-risk MDS, and there are at present no competing approved drugs,

However, unforeseen difficulties became apparent in the development of the high-risk MDS injection formulation. On 24th August 2020, Onconova released the top-line results of the INSPIRE trials, the primary endpoint of which was overall survival (OS). Unfortunately, the results showed no significant difference in OS between injection rigosertib (6.4 months) and physician's choice of treatment (6.3 months) (The P value was 0.33).

Onconova conducted joint international Phase 3 trials of the oral formulation targeting untreated high-risk MDS, whose results suggested efficacy and safety (SymBio in 2019 completed tests confirming safety and tolerability).

(2) Onconova's development strategy

Elsewhere, Onconova is pursuing development which stresses rigosertib acting as a RAS mimicking molecule. On June 22, 2020, Onconova began patient registrations for an investigator-led study (Phase 1 / 2a) of the effect on KRAS (G12D)-positive advanced non-small cell lung cancer of a therapy combining immune checkpoint inhibitor nivolumab (Opdivo®) and rigosertib (orally administered). Further, on April 22, 2021, Onconova announced it had begun patient registrations for Phase 2 investigator-led tests of rigosertib (injection formula) as a treatment for locally advanced / metastatic squamous cell carcinoma related to recessive malnutrition-type epidermolysis bullosa.

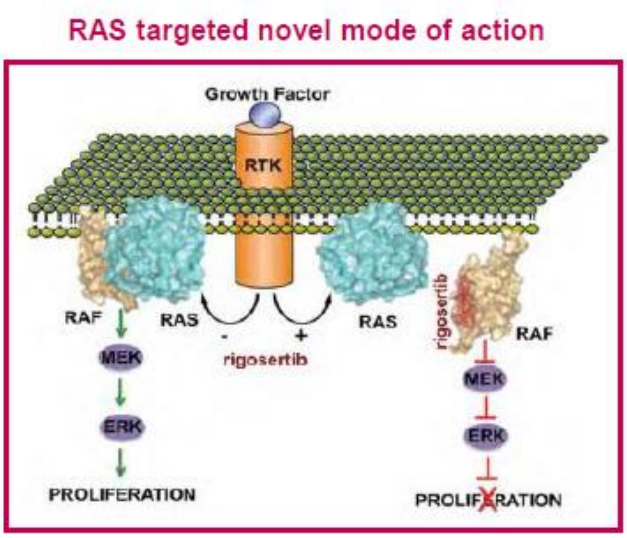
Reference: Rigosertib as a RAS mimicking molecule

It has been established that rigosertib acts as a RAS mimetic molecule. It is thought that rigosertib competitively inhibits the activated RAS from binding to signaling molecules (in the figure below these are RAF, and additionally PLK, RAL, and PI3K). In so doing it is thought to block the RAS-RAF-MAPK signaling pathway, suppressing RAS-generated carcinogenesis.

No significant difference observed in Phase 3 joint international trials

Rigosertib's mode of action

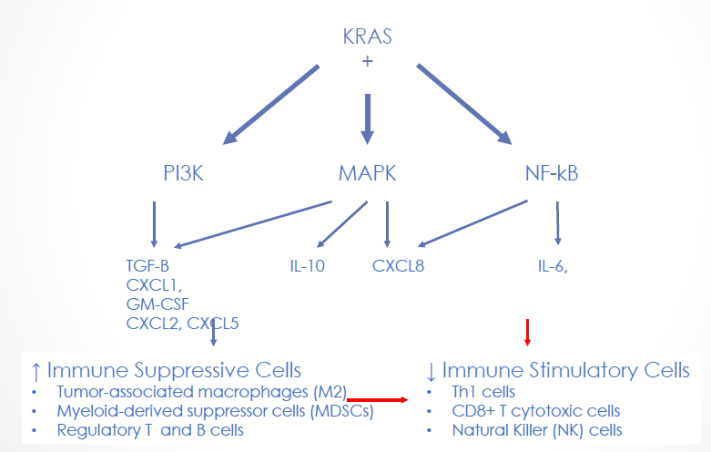
Onconova beginning development focused on RAS mimicking molecule effect



Source: Cell Magazine, 165 (3).643, April 21, 2016, quoted in SymBio's company briefing materials

In addition, it is thought that KRAS, a type of RAS, has a significant effect on the cancer micro-environment. That is, the activation of KRAS leads to enhancement of a type-II macrophage (M2) and MDSC, which suppresses immunity, and further enhancement of IL-6, which suppresses T cells and the like. KRAS inhibitors are thus thought to have a synergistic effect, altering the cancer immune environment and enhancing the effectiveness of immune checkpoint inhibitors.

KRAS signals and the cancer micro-environment



Source: Onconova Therapeutics. "Key Opinion Leader Meeting", February 7, 2019

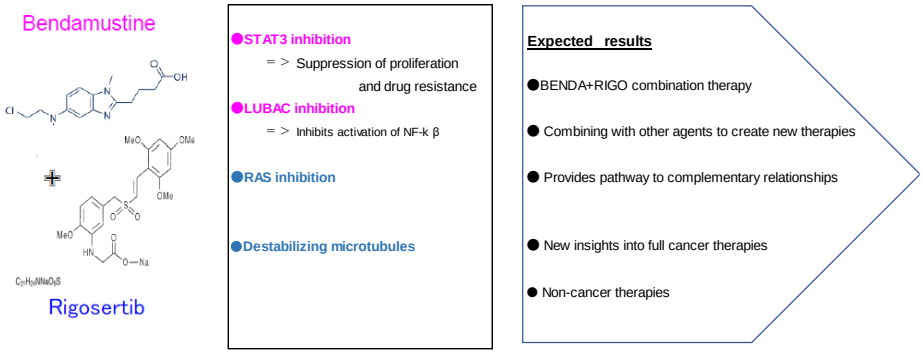
(3) SymBio's development strategy

SymBio is exploring the possibility of a therapy combining oral rigosertib and another drug

SymBio could be ready with a revamped development policy within 2021

SymBio will search for synergistic effects from different mechanisms of action and target new illnesses. To do this it will use additional analysis of the INSPIRE tests, joint research with the Institute of Medical Science of the University of Tokyo (contract concluded in January 2021), combined with analysis and hypothesis verification using artificial intelligence. It has been suggested that rigosertib has an inhibitory effect on microtubule polymerization (destabilizing microtubules) in addition to its action as a RAS mimetic molecule, in addition that the effects of Treakisym® and azacitidine may be enhanced by rigosertib. The company therefore intends to explore the possibility of oral combination therapies with existing drugs, including Treakisym® The company will also apparently use AI analysis techniques to identify potential new diseases to target and, within the year, will draw up a revamped rigosertib development plan.

Rigosertib and Treakisym® (bendamustine) combination possible



Source: SymBio company briefing materials

3. Brincidofovir（SyB V-1901）

BCV is an advanced antiviral drug

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

[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 (pediatric/ adult) (Global)	Start of global study				
SyB V-1901 Antiviral Drug (oral)	Formulation development (Global)	Beginning in 2020				

The company acquired exclusive global rights for all indications excluding smallpox

On October 1, 2019 SymBio announced it had acquired from the US company, Chimerix Inc., exclusive global rights (development, manufacturing and merchandising) to brincidofovir (BCV) for all indications except smallpox, making BCV the company's third strategic product after Treakisym® and rigosertib. SymBio had until now been an acquirer of licenses from overseas for mainly domestic development but this acquisition allows it to evolve into a provider of product licenses globally.

Reference: Why Chimerix retains all rights pertaining to smallpox

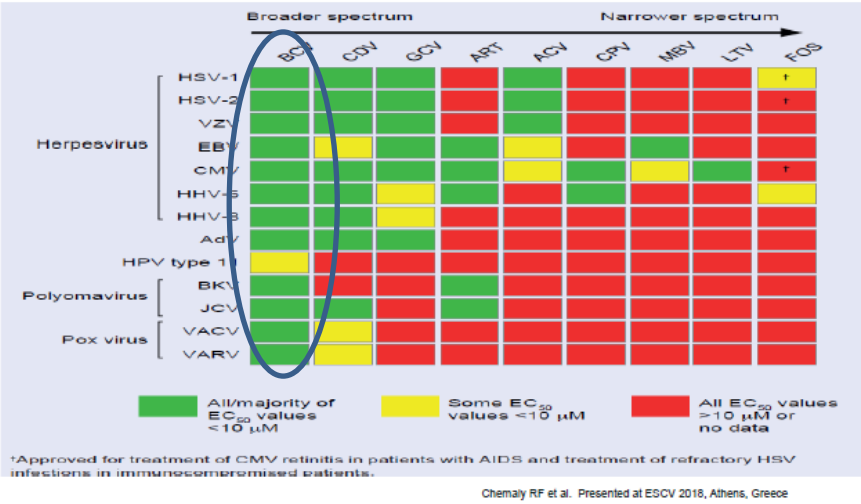
The US Biomedical Advanced Research and Development Authority (BARDA) has provided Chimerix with more than USD100 million to develop BCV as one element in countering bio-terror. The FDA has accorded BCV fast-track and orphan drug status, and Chimerix's application in December 2020 for approval of BCV targeting smallpox is expected to complete examination procedures on 7th July 2021.

(1) Brincidofovir characteristics

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

Compared to other antivirals, BCV is highly active and is effective across a broad spectrum

Brincidofovir (BCV) is highly active across a broad spectrum



Source: Chimerix Inc.

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

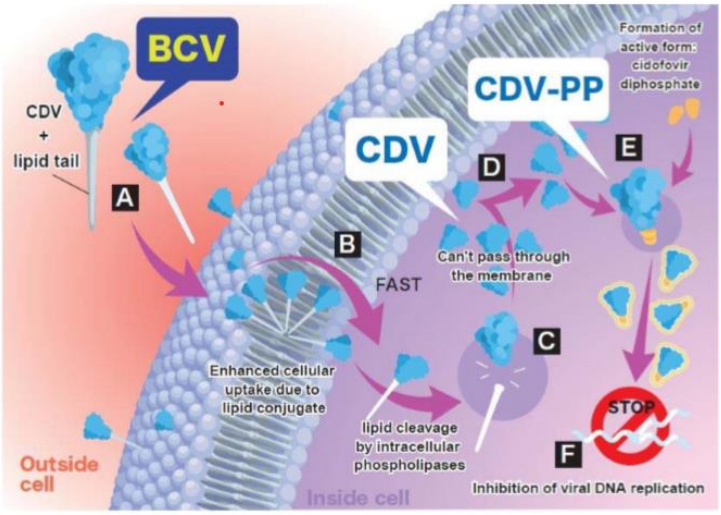
Reference: cidofovir (CDV)
Was approved by the FDA in 1996 for the treatment of cytomegalovirus retinitis in AIDS patients. CDV is a cytosine nucleotide analog which inhibits the replication of DNA viruses such as adenovirus, papillomavirus, and polyomavirus as well as the herpesvirus family. CDV is also effective against ganciclovir (GCV) resistance (UL97 gene mutation) and is thought to be of utility 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 (CVD) has a similar level of activity across as broad a spectrum as BCV. However, while CVD is nephrotoxic and difficult to use, BCV has low toxicity and is very safe despite being highly active.

(2) BCV mode of action

Additionally, highly stable and low nephrotoxicity

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 long time, 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 fatty chain, the rate of incorporation into cells is low, and a high concentration is required to enhance the effect, with nephrotoxicity the likely outcome.)



Source: SymBio IR materials

(3) Indications

The target indications are viral infections resulting from the transplantation of hamatopoietic stem cells, and viral infections caused by organ transplantations. The former would be given priority in light of the company's ambition of becoming a specialist pharma in the area of hematology

In general, in the case of hematopoietic stem cell (HSC) transplantations and organ transplantations（ZOT）, 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 risk of causing a nephrotoxic side-effect. Hence, the importance of BCV, which has low nephrotoxicity, to SymBio's goal of becoming a specialty pharmaceuticals company in the region of hematology.

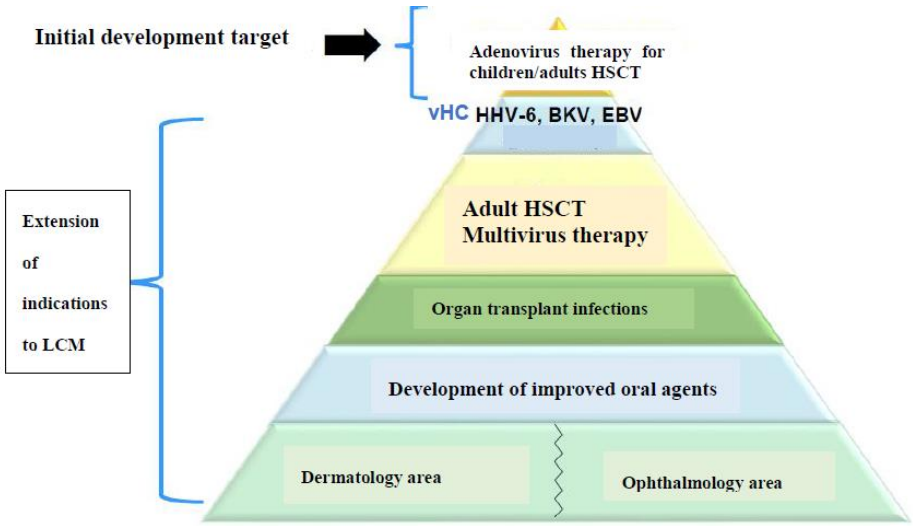
SymBio was planning to use BCV to treat viral infections after HSC transplantations, an area with poor prognosis, high lethality, and strong unmet medical needs. After a meeting of the company's Global Advisory Board in February

The company would make a start with adenovirus infections following HSC transplantations, within which it would prioritise children.

2020 it was decided that 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.

It is estimated that worldwide there are some 78,000 HSC transplantations a year, of which around 43,000 are autologous, and therefore less subject to rejection. There are some 35,000 allogeneic transplants in which immunoreactions need to be controlled to suppress rejection, and which are highly vulnerable to viral infection. These are on the rise.

BCV lifecycle management



Source: SymBio Pharmaceuticals results meeti

ng material, February 2019

Reference: hematopoietic stem cell transplantation

Transplantation of bone marrow, which contains hematopoietic stem cells, is carried out to effect a complete cure of blood diseases (notably leukemia and other blood cancers) which are not easily cured by cancer drug treatments (chemotherapy) or radiation therapy alone. Bone marrow transplantation includes autologous bone marrow transplantation using a relative's bone marrow, and allogeneic bone marrow transplantation using the bone marrow of another person with the same leukocyte type. The latter is growing in frequency.

In March 2021 The company submitted an IND application to the FDA for Phase 2 study of adenovirus infections following hematopoietic stem cell transplantation to the FDA and secured fast track status for paediatric therapies.

On 10th March 2021, SymBio submitted an application to the FDA to carry out Phase 2 trials on BCV to support an Investigational New Drug (Registration No: NCT04706923.) targeting adenovirus infections following HSC transplantations. Subsequently, on April 26, the FDA accorded fast-track status to development programs directed at adenovirus infections in children. If all proceeds smoothly, it is expected that the first patients will be registered in the second half of 2021. The first step is to conduct a staggered escalation of dose size to confirm safety and tolerability in trials of four groups of six patients each, ending in the second half of 2022. The plan is then to proceed to Phase 3 (several hundred cases) in 2023, and to file an NDA in 2026 prior to market launch in 2027 or after.

The company is planning to begin developing a drug for the treatment of viral hemorrhagic cystitis.

In Japan, the plan is to simultaneously develop a therapy for viral hemorrhagic cystitis (vHC) after hematopoietic stem cell transplantation. Phase 1 clinical trials in Japan should start in 2021. Additionally, Chimerix has recommenced development of an improved version of the oral preparation it had previously suspended.Reference: Viral hemorrhagic cystitis (extracted from SymBio IR materials)

Among the viral infections that frequently occur after HSC transplantations, adenovirus infections that cause hemorrhagic cystitis are generally intractable, and cause severely irritating symptoms such as frequent urination, abdominal pain, and dysuria, with dissemination and death when severe. Cases have been reported in which the adenovirus is transferred to the kidney and causes renal failure, resulting in death. It is particularly likely to occur with unrelated donors and umbilical cord blood transplants, which are frequently carried out in Japan, and are often extremely intractable due to the time required for reconstitution of the immune system. It is said to occur at a frequency of 8.6% to 24% in allogeneic transplants.

Reference: HHV-6 encephalitis (extracted from SymBio IR release)

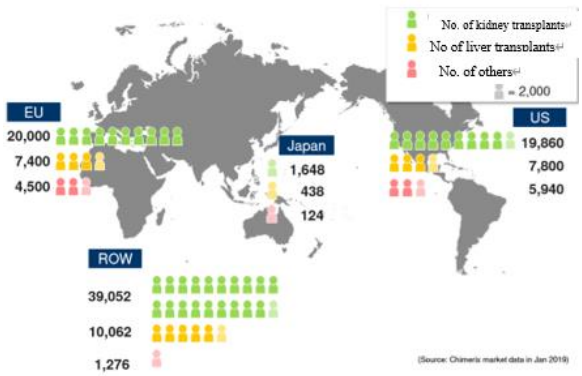
HHV-6 (human herpesvirus 6) is the sixth human herpesvirus to be discovered. In allogeneic hematopoietic stem cell transplantations, reactivation of HHV-6 occurs in 30-70% of patients, causing HHV-6 encephalitis. Most HHV-6 encephalitis cases develop at 2-6 weeks, with the most frequent occurring at 3 weeks after transplantation. The three major symptoms are memory impairment, impaired consciousness and, in 30-70% of cases, convulsions. In a typical case, symptoms gradually progress from memory impairment to impaired consciousness and convulsions. In the case of rapid progression, the neurological symptoms worsen every hour, and there are many cases where respiratory control is required for repeated convulsions and respiratory depression. In HHV-6 encephalitis cases early intervention is extremely important because a rapid deterioration in the patient's condition early on is common. Clinical guidelines* stipulate the first-line drug is foscarnet (FOS) or ganciclovir (GCV), and the second-line drug is cidofovir (CDV). CDV is considered a second-line choice because of its strong nephrotoxicity and the poor migration of the drug into the cerebrospinal fluid (CSF). However, no studies have been conducted to date on the clinical effects of these drugs, although effects have been confirmed in vitro on HHV-6 encephalitis cases.

*Guidelines for hematopoietic cell transplantation: prevention and treatment of viral infection HHV-6 (Japan Society for Hematopoietic Cell Transplantation, February 2018)

The company will need to partner up with a pharma in the US or Europe in order to develop a therapy for viral infections after organ transplants

The company is also planning to expand the scope of development beyond viral infections after HSC transplantation to viral infections from organ transplantation. Unlike Japan, organ transplants are quite frequently carried out in Europe and the US. For instance, looking at kidney transplants, in Japan there are 1,600 per year, compared with 20,000 in the five biggest countries of Europe, and the same number in the US. Of these, it is estimated that about one-third are infected with the BK virus or CMV (cytomegalovirus). While the number of cases does not exceed 560 or so in Japan, the total for the US and the five biggest countries of Europe is probably around 15,000. Since organ transplants are not part of the area SymBio specialises in, and there are not so many cases in Japan, SymBio will probably tie up with an overseas pharmaceuticals company to promote sales following organ transplants.

Number of organ transplants (ZOT)



Source: SymBio results meeting materials

Thought is also being given to ophthalmological and dermatological applications	The company is also looking beyond antiviral agents used during surgery to ophthalmological (eye drops) and dermatological (ointment) formulations. In these areas, anti-bacterial agents are mainstream but antiviral agents barely exist, and it is inferred there is a pronounced medical need. In addition, since cidofovir has been shown to exhibit antitumor action in brain tumours (GBM), BCV may also be indicated for GBM as a safer drug. BCV will thus become a drug with a protracted life cycle.

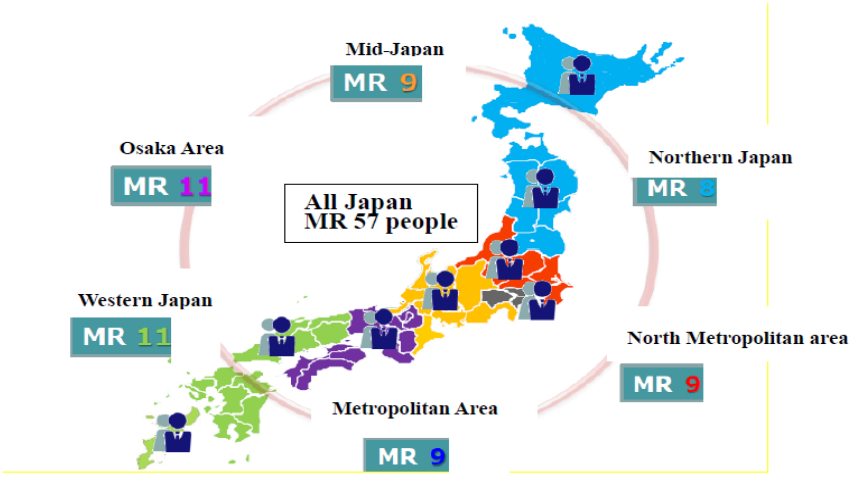
Start-up of the company's in-house sales

Approximately 400 hematology departments nationwide are divided into 6 blocks, and sales are promoted by 62 professionals.

There are an estimated 4,000 or so physicians in Japan specialising in hematology, and around 1,200 hospitals with hematology departments. SymBio sees itself covering around 400, or one-third, of the key facilities and will target around 1,200 physicians. Leading up to the launch of its in-house sales structure in 2021 it has been recruiting professional staff since 2018, with a view to having a total of 57 such staff serving six blocs nationwide.

The company successfully completed its recruitment on schedule in June 2020. It now has a sales group of 62 individuals, including 51 Medical Representatives highly qualified in the area of hematology, six RSM's (Regional Sales Managers), four HE's (Hematology Experts), and one person (KAM) coordinating the Key Opinion Leaders (KOL's). SymBio believes this is an extremely strong network, particularly because the KAM and HE's work so closely with the KOL's. Even in the context of the current coronavirus pandemic, appointments can be made and consultations held online between the highly qualified staff and KOL's. The size of the sales group compares favourably with other companies considering they are restricted to one area in oncology (Eisai has a staff of 150 MR's covering three oncology areas).

The in-house sales structure at SymBio



Source: SymBio company briefing materials

The distribution network, logistics centre and core management system are also up and running

On 7th September 2020, SymBio announced it was starting work to take over sales from Eisai. The tie-up with Eisai was terminated on 9th December 2020, following which the company's in-house sales force was activated. In addition, the company concluded basic agreements to transact with Suzuken and Toho Pharmaceutical with a view to using them as general agencies for the conduct of transactions. With the establishment of two logistic centres, one for East Japan and one for West, its logistics network was completed. The set-up of an ERP system controlling internal communications and the upgrading of the IT system were completed in the second quarter of 2020.

Potential market size for key products

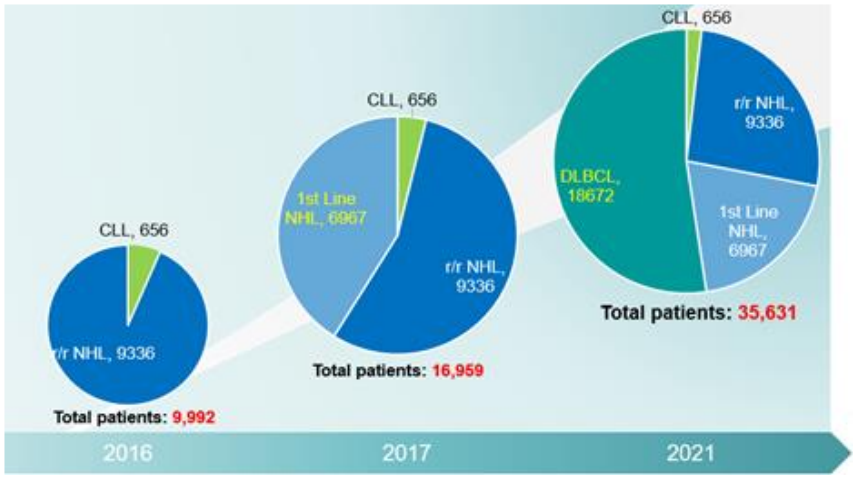
Potential market size for key products

1. Potential market size for Treakisym®

The company sees the three indications for which Treakisym® had received approval as of 2020 achieving sales of JPY8.7 billion

We see the market for Treakisym® growing, particularly on the back of the expansion in indications in 2021. Indications for which approvals had already been given and products launched as of 2020 are: ① Recurrent/refractory low malignancy NHL/MCL ②Chronic lymphocytic leukemia (CLL), and ③Untreated low malignancy NHL/MCL. Since the very first indication was approved in 2010 Treakisym® has already achieved a high degree of market penetration, which is likely to be maintained by new formulations. SymBio is targeting sales in 2021 of JPY4.1 billion (regulated drug price basis). Treakisym® was approved for indications ② and ③ above in 2016, so has already achieved market penetration. SymBio is assuming a target for annual sales in 2021 of JPY4.6 billion for indications ②and③ combined, and is likely to sustain that sales level.

Increase in patients due to additional approvals for Treakisym®



Source: SymBio company briefing materials

The market for recurrent/refractory medium/high malignancy NHL, for which approval was given in 2021, is estimated at JPY6-8 billion

Looking ahead, the biggest driver of market growth is going to be in the area of recurrent/refractory medium/high malignancy NHL (r/r DLBCL), for which approval was given in March 2021. It is estimated that there are in excess of 18,000 patients in this area. Assuming a market penetration of 40-50% we infer this area would have a market value of JPY6-8 billion. SymBio will start sales in the second quarter of 2021 and is assuming a target of JPY2.6 billion (regulated drug price basis) in the whole of that first year. Sales are expected to peak (at JPY6-8 billion) in 2024-2025.

Total sales for the three previously approved indications are expected to be JPY8.7 billion yen, and with the additional approval for r/r DLBCL in March 2021, sales are expected to be JPY15-17 billion.

2. Potential market size for brincidofovir

The size of the market for treating viral infections following HSC transplants

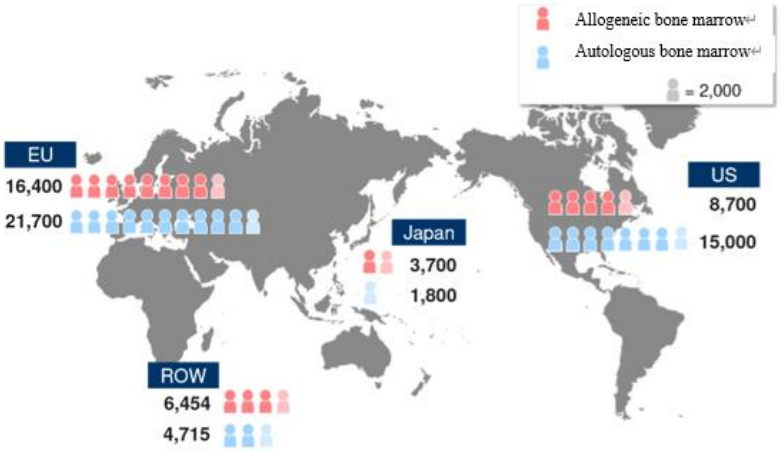
Here, we consider the implications for SymBio's own development policy of the market size of BCV in the area of viral infections after HSC transplantations.

There are an estimated 78,000 hematopoietic stem cell transplants carried out worldwide every year, and the autologous kind, which are less vulnerable to

rejection, total some 43,000. Allogeneic transplants (from someone other than the patient), which total around 35,000 a year, require the use of immuno-suppressants to inhibit rejection, and carry a high risk of viral infection.

SymBio expects that 50-60% of allogeneic transplants will be in Europe and the United States, and about 70% will be in Japan. This means 2,600 cases annually in Japan, and some 14,000 cases annually in the US and the five main countries in Europe. Outside of the main industrialised countries the population-adjusted rate of such transplants is only around 1/20th that of the industrialised regions but is bound to increase in the future.

No. of HSC transplants worldwide



Source: SymBio company briefing materials

The market for HSC transplants is valued at JPY8 billion in Japan and JPY42 billion in Europe+US. The Asia (incl. China) market potential is also substantial

If we assume, in the light of the cost of other antiviral drugs, that the drug cost per case is JPY3 million, the market size for treating viral infections after HSC transplantations would work out at JPY8 billion in Japan and an estimated JPY42 billion in the US and the five major European countries. The number of HSC transplantations in Asia is growing in number and, assuming that the population-adjusted number of cases is equivalent to that of Japan, the potential size of the Chinese market (approximately 1.4 billion people) could be in excess of JPY 83 billion. However, it is less than half when considering only the coastal areas where the medical environment is well-established.

Pipeline value simulation

Our calculation is based on a number of assumptions

We here estimate the value of the Treakisym® pipeline using the DCF method. The discount rate is set at 8% (previously 10%), given that while SymBio operates at a loss it is a low risk pharmaceuticals venture which does not use laboratories or manufacturing facilities, and is on the verge of profitability. Additionally, the application for the IND Phase 2 for brincidofovir has only just been submitted, and our assumptions are quite challenging. We also take into account whole company costs in calculating enterprise value.

The 8% discount rate reflects the company's proximity to profitability

1. Treakisym® assumptions

The assumtions we are making for our Treakisym® calculations are roughly in line with those for our previous simulation

In line with our earlier comments, we assume that peak sales will occur in the fourth year after market launch and will maintain at that level for the next 3-4 years, before shrinking at 5% per year and, from 2031, shrinking rapidly at 10% per year. Further, we set the probability of success in clinical trials directed at r/r medium/high-malignity NHL (r/r DLBCL) at 100%, reflecting the established position of Treakisym® as a standard therapy in the area of hematopoietic tumours.

Changes have been made only to milestone payments

From 2021 sales will be handled in-house and will in the same year be switched almost entirely to the liquid formulations (RTD and RI). Liquid formulations will have, we assume, a cost advantage over the conventional formulations. After switching, we assume the cost rate, including the payment of royalties to Eagle, should be in the area of 20-25%. Milestones will be payable on the achievement of JPY10 billion in sales and with the successful launch of the RI formulation. We anticipate payments of JPY550 million in each of 2022 and 2023.

All development costs (excluding milestone payments) are to be borne by SymBio itself but, since these extend only to the development of the RI formulation, should be in the area of JPY400-600 million.

Assuming a 62-person salesforce, annual sales expenses will come to JPY2 billion

Sales expenses, based on the 62-person salesforce discussed earlier, will amount to around JPY2 billion per year.

Reference: Brincidofovir assumptions

Estimates for brincidofovir are complicated by the number of uncertainties. The calculation therefore targets only HSC transplantations

Making estimates concerning brincidofovir are complicated by the number of uncertainties. We therefore restrict the extent of our calculations to five viral infections after HSC transplantations. The markets targeted by our assumptions are Japan, the US and Europe. We assume a Japanese market value of JPY8 billion and an overseas market value of JPY42 billion (the market sizes are higher than in our previous estimates because we use more viral infection indications).

We have posited a market size of JPY8 billion for Japan and JPY42 billion for the US and Europe

In terms of schedule, we assume development will start with adenovirus infections after HSC transplantation in the US, that Phase 2 will continue until 2022 and Phase 3 (400 subjects) from 2023 to 2026. We further assume an NDA application will be submitted in 2025 and market launch will occur in 2027. We believe that development of therapies targeting vHC, which have been given precedence in Japan, will be switched to global development in Europe and the United States. We further assume that the development of other therapies (for vHC, HHV-6, BKV and EKV) will take place sequentially after the adenovirus therapy with delays of 2 years each. The development costs for each indication will differ depending on the number of cases but for the sake of simplifying the calculation we are assuming such costs at JPY8 billion each.

Big expansion in develoment costs since previous estimate

Launch assumed to take place in 2027 or after

Under the terms of the licensing-in, SymBio is to pay Chimerix a total of JPY180 million in milestones (including the licensing-in payment of JPY5 million), and royalties at a fixed ratio of sales. The company has disclosed that the royalties percentage rate will be a two-digit sum, and for the purposes of our simulation we assume it is 12%.

Quite challenging assumptions

SymBio itself could handle the development of overseas sales but we are assuming sales rights will be licensed out. In that case, we are assuming a gross profit margin of 50% for SymBio. We are positing milestone income linked to a licensing-out totaling JPY42 billion at peak sales. Since

for milestones and gross profit

We are positing all-company costs (including basic research spending) at around an annual JPY2.2 billion

Treakisym® has a pipeline value of JPY62.8 billion. Adding in the values of brincidofovir and rigosertib the company's total pipeline value could exceed JPY100 billion

POC on human subjects has been established we are assuming an 80% probability of success.

The company has annually recurring administration costs and R&D spending to find and study new drug candidates. We posit R&D expenditure directed at the latter at JPY600 million, and all-company administrative costs at JPY1.6 billion, for a relatively high total of JPY2.2 billion.

2. Simulation results

The table below shows the results of our discounted present value calculation using the tentative suppositions given above. The value of Treakisym® comes in at JPY62.8 billion before tax, assuming a discount rate of 8%. For reference, brincidofovir for viral infections after HSC transplantations is valued at JPY33.3 billion before tax, which would bring the total to JPY96.1 billion. While we have excluded this from the present exercise, if we add the value of brincidofovir for organ transplants, Treakisym® for new indications, and rigosertib, the total pipeline value could be in excess of JPY100 billion.

Estimates of SymBio pipeline value (pre-tax)

(JPY100mil)

	Success Prob.	Disc. Rate 10%	Disc. Rate 8%
Treakisym®	100%	570	**628**
Brincidifovor (HSCT only)	80%	220	333
Sub Total		790	961
All company costs		-220	-275
Total		570	686

Source: Calculated by Fair Research Inc.

Note: No direct comparison can be made between pipeline value and market value; rigosertib pipeline value has not been included in the above

Trend in revenues and medium-term company plan

SymBio's revenues come from the sale of products and from rights income. It turned in an operating profit in the December/2008 period after receiving a lump-sum contract fee from Eisai for sole sales rights to Treakisym® in Japan, but then recorded operating losses in every subsequent period. In 2021, however, profitability is expected to return along with double-digit operating profits thereafter.

1. Results in 2020

Sales were lacklustre in 2020 mainly because of a product quality problem and an inventories adjustment due to the switch in sales channels

Sales in the December 2020 period totaled JPY2,987 million, most of which consisted of wholesale deliveries of Treakisym® to Eisai. Sales had temporarily fallen off because of quality problems in and after the Spring of 2019 with the freeze-dried Treakisym® formulation, and because of inventory adjustments made necessary by the switch in sales channels. However, more robust quality testing was introduced and this led to a recovery in the second half of 2020. For the defective products, JPY69 million yen was recorded as an inventory valuation loss in cost of sales (the 2019 inventory valuation loss was JPY187 million).

Excluding the payment of a milestone, savings were made on R&D. However, extra costs incurred on provision of in-house sales structure

R&D disbursements in 2020 came to JPY2,261 million, down from JPY2,442 million in 2019. The 2020 figure includes the JPY500 million milestone payable on the approval of the RTD formulation. Allowing for that, the decrease was really about JPY700 million. We assume that the increase in costs associated with the establishment of the sales structure led to enhanced efficiency in R&D activities.

Operating loss of JPY4.5 billion in 2020

SG&A expenditures other than R&D in 2020 rose JPY400 million from the previous year to JPY3,107 million. This was probably because of an acceleration in spending on the new sales structure. As a result, operating losses increased to JPY4.5billion in 2020.

Trends in P&L and balance sheet

(JPY mil.)

	2014/12	2015/12	2016/12	2017/12	2018/12	2019/12	2020/12
Sales	1,955	1,933	2,368	3,444	3,835	2,838	2,987
Product sales	1,940	1,933	2,137	3,444	3,809	2,811	2,977
Licensing	15	0	231	0	25	27	10
Cost of goods sold	1,428	1,483	1,737	2,413	2,662	1,973	2,120
SG&A	1,830	3,135	3,031	4,978	3,828	5,166	5,373
of which, R&D	774	2,035	1,667	3,017	1,832	2,442	2,266
Excl R&D	1,056	1,100	1,364	1,961	1,996	2,724	3,107
Op. profits	-1,303	-2,552	-2,127	-3,947	-2,656	-4,302	-4,506
Rec. Profits	-1,110	-2,630	-2,317	-3,976	-2,748	-4,377	-4,615
Pre-tax profits	-1,112	-2,628	-2,309	-3,974	-2,748	-4,372	-4,087
Net profits	-1,116	-2,632	-2,313	-3,978	-2,752	-4,376	-4,090
Liquid assets	7,290	4,827	6,685	4,037	6,038	4,887	5,815
of which, cash etc.	5,692	4,261	5,719	2,947	4,821	3,910	3,848
Fixed assets	164	158	193	216	200	386	459
Liquid liabs	488	551	942	1,011	1,336	872	1,615
Fixed liabs	2	2	451	1	1	1	2
of which, corp bonds	0	0	450	0	0	0	0
Net assets	6,964	4,432	5,485	3,239	4,901	4,400	4,657
Shareholders equity	6,763	4,132	5,054	2,702	4,372	3,779	4,037
of which, optioms	200	300	431	537	530	620	620
(Reference)							
Income from options issued/exrcised	54	0	687	1,178	4,301	3,771	4,244
Income from CB's issued	500	0	3,000	0	0	0	0
Event		IONSYS expenses, etc.		Treakisym liquid formula costs		BCV licensing in Preparation of In-house sales	Switch to in-house sales Milestone payment for RTD approval Received the settlement regarding IONSYS

Source: Fair Research Inc. using securities report filings

2. 2021 first quarter results

First-quarter sales maintained a recovery track, although not yet at cruising speed. The annual sales goal is attainable

Sales in the first quarter of 2021 came in at JPY1.42 billion yen, 157.6% of the same period of the previous year. This was mainly due to the correction in the sales price level (see note below) reflecting the start of the in-house sales system on December 10, 2020. We infer around JPY1.6 billion when translated to regulated drug price terms. Because of a number of one-off factors, such as the existence in the market of inventories (around JPY400 million) preceding the in-house sales system, and the effects of COVID-19, sales in the first quarter did not reach cruising speed (that is, JPY2.1-2.2 billion). However, these factors will abate from the second quarter, allowing plenty of room to meet the sales target in 2021 for indications (excluding r/r DLCBL) of JPY8.7 billion on a regulated drug price basis (around JPY7.0 billion in terms of SymBio shipments).

Sharp increase in gross profit due to rapid improvement in cost structure

At the same time, because of changes in the cost structure due to the introduction of in-house sales, the cost of sales ratio fell to 28.9% (same period of the previous year was 76.8%) and gross profit rose sharply on a YoY same-period basis from JPY 882 million to JPY1,009 million.

Sharp cut in opperating loss

Profitability on a monthly basis possible in the second quarter

There was an increase of JPY131 million in SG&A expenditures. This was due to expenditure of JPY473 million for BCV and RI formulation clinical development (up 8.0% from the first quarter of the previous year) and the increase in cost of sales associated with the switch to an in-house sales structure. As a result, first quarter operating profits were in the red to the tune of JPY210 million. This represents a JPY751 million cut in the loss compared to the first quarter of the previous year. It may be possible to reach profitability on a monthly basis during the second quarter in light of the switch to the RTD formulation and the expansion in indications to r/r DLBCL.

Q1 2021 results

(JPY100 mil)

	Q1/2020	Q1/2021	2021 Target
Sales	5.51	14.20 (COGS basis: JPY1.6 bn)	91.51 (COGS basis:11.3 bn) (of which, excl. r/r DLBCL JPY8.7) → For QTR JPY2.1-2.2 bil
COGS	4.23	4.10	21.94
COGS rate	76.8%	28.9%	24.0%
Gross profit	1.27	10.09	69.57
SG&A	10.89	12.20	55.96
of which, R&D	4.38	4.73	20.19
Op. profit	-9.61	-2.10	13.61

Source: Collated from securities report filings

Note: We believe that the wholesale price for Treakisym® sold by SymBio to Eisai was 50% of the regulated price, and that the price paid by SymBio to Astellas was 66% of. the wholesale price. With the switch to in-house sales, wholesale prices to Eisai are replaced by wholesale prices to the recipient medical facility, and Astellas will be replaced by Eagle as a supplier of the RTD and RI formulations. Since it will be easier to handle these formulations, distribution costs will be reduced. These changes mean the cost structure will change significantly.

3. Outlook for 2021

Sales are expected to jump in 2021 to the JPY9 billion level due to the switch to in-house sales and the launch of liquid formulations

Sales in 2021 are expected to see a marked change in level. This will be driven by the start of in-house sales on December 10, 2020, and additionally by the expansion of indications to r/r DLBCL approved in March. SymBio has set a target of JPY9,151 million for sales in 2021 (figure released in the medium-term management plan of February 2021; on the basis of regulated drug prices: JPY11.3 billion). The gross profit will improve significantly due to the rise in the sales price level accompanying the activation of the in-house sales system, and the switch to the RTD formulation. Thus, while the rate of gross profits in 2021 was only 29.0%, in 2021 it should be closer to 76.0%. Gross profit should therefore rise significantly to JPY6,957 million (in 2020, JPY866 million).

Big change in profit structure, with gross profit rate surging to 76%

R&D spending will fluctuate due to one-off factors such as lump sum payments for licensing-in contracts, or milestone payments. Excluding those, product development is on a growth trend

SG&A expenditure is expected to total JPY5,596 million, some JPY221 million higher than the previous year. Within this, R&D in 2021 is forecast to come in at JPY2.01 billion, a decline of JPY251 million. However, the 2021 forecast includes a milestone payment of some JPY500 million related to approval of the RTD formulation. Without this, the figure for 2021 R&D expenditure would be higher. The company plans to increase this by pressing forward with the development BCV. It plans to lift SG&A apart from R&D expenditures from JPY3,107 million in 2020 to JPY3,577 million in 2021 with spending on its in-house sales structure.

Increase in non-R&D SG&A due to spending on the in-house sales structure

With the major increase in gross profit and a relatively small increase in SG&A it is very likely the company will turn profitable (operating profit of JPY1,361 million) in 2021.

4. Medium-term management plan (2021-2023) and beyond

We can infer from the high rate of marginal profit of the liquid Treakisym® formulations, that the growth in profits generated by expanded inidications and higher sales could be sharp, but milestone payments and BCV's global development will restrain operating profit to the 15-20% range

In its medium-term management plan SymBio sees the effect of an expansion of Treakisym® indications filtering through to results. Revenues should rise 20% to JPY10,985 million in 2022 and a further 12.5% to JPY12,369 million in 2023.

The management plan posits operating profit of JPY1,738 million in 2022, rising to JPY2,099 million in 2023. We can infer from the high rate of marginal profit (about 80%) of the new Treakisym® formulations, based on the sales growth noted in the medium-term management plan, that operating profits could be higher than the planned value. However, in 2022 and 2023 operating income is expected to settle at the value noted in the medium-term management plan (operating income margin of 15-20%) due to the occurrence of milestone payments to Eagle (about JPY550 million yen each year) and the full-scale development of BCV.

Earnings growth momentum should be maintained for the time being

From 2024, SymBio will accelerate development to expand the viruses targeted by BCV, and also expects to undertake research and development of Treakisym® to target solid cancers. Given this, until around 2026 we expect Treakisym® sales expansion to continue but at a slightly reduced pace.

Even if Treakisym reaches peak sales and earnings growth plateau's, the development of BCV and others will be evaluated for their growth potential

Further, even after Treakisym® reaches peak sales, and if R&D spending as a percentage of sales proceeds at 25% or so, until the time of patent expiry in 2031 Treakisym® will continue to be SymBio's cash cow, able to provide returns of 15-20% on an ongoing basis. During this period, even if profit growth reaches a landing, it is expected that the progress in development of BCV and Treakisym® will become the source of future growth in enterprise value.

End to reliance solely on equity finance for funds

SymBio Pharmaceuticals 2021 company plan and medium-term company plan

(JPYmil)

	2020 (actual)	2021 (forecast)	2022 (med. term plan)	2023 (med.term plan)
Sales	2,987	9,151	10,985	12,369
Gross profit	866	6,957		
GP margin ratio	29.0%	76.0%		
SG&A	5,373	5,596		
of which, R&D	2,266	2,019		
Operating profit	-4,506	1,361	1,738	2,099
OP margin ratio		14.9%	15.8%	17.0%
Recurring Profit	-4,615	1,350	1,727	2,088
Net profit	-4,090	1,149	1,470	1,778

Source: Compiled by Fair Research Inc. from SymBio's medium-term management plan and securities report filings

Reference: Committed credit line agreement (upper limit JPY3 billion), December 2020

The company has usually relied on equity finance via the exercise of new share options to raise funds for operations. However, with the prospect of turning profitable in December 2020 it concluded committed credit line agreements with two banks (upper limit JPY3 billion). It seems that in the future the company will cover its working capital needs with bank loans. However, if the development of several Phase 3 BCV indications occur at the same time it may be necessary to raise funds externally, including via equity.

Conclusions

In 2020, SymBio set up is own sales structure and acquired brincidofovir, thereby establishing the foundations for its growth as a specialist pharma in the area of hematology with ownership of global licensing.

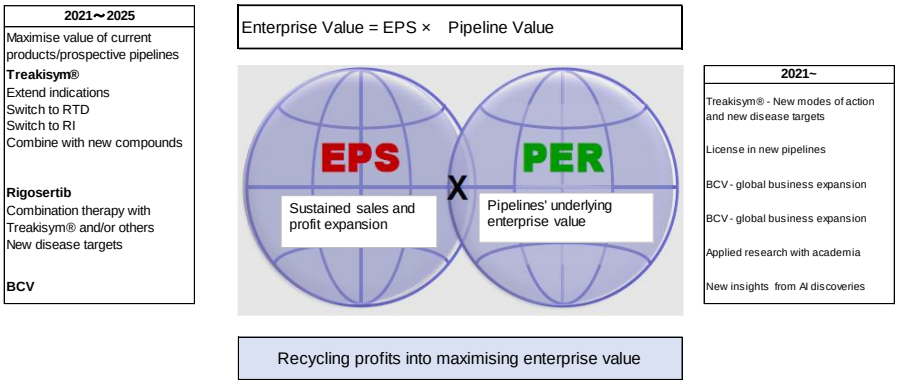
The period up to 2020 was for laying the foundations of a specialty pharma company

The year 2021 is the second stage: Takeoff

The addition of r/r DLBCL to approved indications for Treakisym®, SymBio's key product, and changes in formulation secured the company's path to profitability in 2021. Looking ahead, SymBio will seek to maintain an operating profit margin in the upper 10% level. At the same time it will use profits from Treakisym® as the funding source to maximise the business value of its pipelines by developing therapies using novel mechanisms of Treakisym® and rigosertib. The company will also promote the global development of brincidofovir (BCV) in the field of viral infections after hematopoietic stem cell transplantations. The Treakisym® pipeline on its own has a value of JPY62.8 billion. We infer that adding in the other product pipelines would produce a total value in excess of JPY100 billion. In the context of its profitability the company now has no need to rely purely on equity as a source of funding.

2021 will thus be the year that SymBio takes off as a global specialty pharma.

The second stage of development (2021-2025)



Source: SymBio company briefing materials

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