SymBio Pharmaceuticals Ltd.

(4582 JASDAQ) Issue date: April 7, 2020

The Last One Mile

From drug 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, and leading, drug is Treakisym®, which was approved five years after being adopted by the company and received standard treatment status in 2018. The company seeks out new formulations and new indications to extend product life. In addition, it is now preparing to switch the sales function to an in-house unit. It's ambition, now almost achieved, is to grow as a pharma specializing in blood diseases. In September 2019 the company licensed in Brincidofovir, and in so doing acquired the sole global license, covering development, manufacture and sales, and gaining a launch pad to expand as a licensor into Asia primarily but also globally, including the US.

On the verge of becoming profitable

Treakisym® sales have always been handled by Eisai Co Ltd. but in 2021 SymBio itself is supposed to take over. For this reason, precedence is being given to costs for systems development, such as an increase in sales personnel, the development of distribution networks, and the setting up of ERP systems. In addition, R&D expenditure is rising. In 2020, the development of different Treakisym® formulations and an expansion in indications will be more or less complete, and the development of the company's second product, Rigosertib, is expected to begin, using oral formulation in addition to ongoing injections The development of Brincidofovir is also expected to start. On the other hand, in order to switch to an in-house-sales system, Eisai's inventory must be cleared, so sales are not expected to rise much. For that reason, operating income in 2020 will record a bigger loss of JPY5 billion. In 2021, however, the company will overcome that, recording a surprising turnaround in operating income to JPY1 billion, due to the switch to Treakisym® in-house sales and the introduction of expanded indications which should boost total sales to JPY9 billion yen and increased profitability. With the announcement of a stock options issue on February 27, 2020 the company can now see its way clear to going the last one mile.

We estimate pipeline value at JPY89 billion (pre-tax)

We estimate total Treakisym® pipeline value at around JPY57 billion (pre-tax). The expansion of applications to r/r DLBCL is expected to double potential market size, and it is expected that the cost ratio will be significantly improved by switching to liquid formulations. Elsewhere, it is also expected that Rigosertib will be indicated for various cancer types as a RAS mimetic molecule, but even if it targets only high-risk myelodysplastic syndrome refractory to hypomethylating agents, the pipeline value (before tax) will still be around JPY24.9 billion. With regard to the company's third main pipeline, Brincidofovir, the indications are viral infections (viral cystitis and HHV-6 encephalitis) after hematopoietic stem cell transplantation and organ plantations. For the Japanese, US and European markets only in the area of hematopoietic stem cell transplantations , the pipeline value is estimated at JPY29.1 billion yen (before tax). Even after discounting company-wide administrative and basic research costs the total pipeline value is estimated at around JPY89 billion (before tax). This calculation relies on various assumptions but potential value is significant. An increase in indications for Treakisym®, applications for, and approvals of, formulation changes, and progress in financing will help with value creation.

Note: This report is the English-language version of the original Japanese-language report issued on April 7th, 2020, to which you should refer for precise details

Revised Basic Report

Fair Research
Tsuyoshi Suzuki

Company Information	
Location	Tokyo
President	Fuminori Yoshida
Established	March 2005
Capital	JPY14,870 mil.
Listed	Oct. 2011
URL	www.symbiopharma.com
Industry	Pharmaceuticals
Employees	107(non-con)
Key Indicators (April 6, 2020)	
Share price	315
52-week high	896
52-week low	264
Shares outstanding	28,112,681
Trading unit	100 shares
Market cap	JPY8,855 mill
Dividend	0
EPS	-181.8 yen
Forecast PER	NA
Actual BPS	143.07 yen
Actual PBR	2.20 times

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

Results	Revenues JPYmil	YoY %	Op.Income JPYmil	YoY %	RP JPY mil	YoY %	Net Income JPYmil	YoY %	EPS JPY	Share Price JPY High	Share Price JPY Low
2015/12 Actual	1,933	-1.1	-2,551	NA	-2,630	NA	-2,632	NA	-325.0	1,532	708
2016/12 Actual	2,368	22.5	-2,127	NA	-2,316	NA	-2,313	NA	-235.3	2,036	692
2017/12 Actual	3,444	45.4	-3,947	NA	-3,976	NA	-3,977	NA	-319.1	1,244	800
2018/12 Actual	3,835	11.4	-2,656	NA	-2,748	NA	-2,752	NA	-165.5	1,052	464
2019/12 Actual	2,837	-26.0	-4,301	NA	-4,376	NA	-4,376	NA	-189.0	1,088	600
2020/12 Forecast	3,404	20.0	-5,090	NA	-5,134	NA	-4,803	NA	-181.8		

Company outline and philosophy

Business Model

The company is evolving from drug venture to specialized global pharma but operates without labs or factories (“laboless-fabless”), suppressing the risk inherent in drug discovery and focusing on a high-return niche in the market

The determinants of commercial success are interactions with a network of drug discovery companies and expertise

The company is a bio-venture in the rare position of having a product which was approved and brought to market within five years of being adopted

The network and in-house expertise supported by a high quality work force and organizational strength are key

SymBio Pharmaceuticals has the following characteristics:

① Proof of concept (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. That is to say, 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 the major pharmaceuticals companies are unrepresented. Using this niche strategy, the company seeks high market share and high returns. The company’s business model thus far has involved entering into licensing agreements on new drug candidates it has selected, developing them in Japan and then licensing out to other pharmaceuticals companies. However, it is now planning to set up its own sales function by the end of 2020 and to establish itself as a specialist pharma in the area of hematology.

③ Evolving into a global licensor

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

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, around 7-8%. But SymBio managed to get its first product, Treakisym®, from adoption to manufacturing and commercial approval in only five years, and in July 2018 became recognised as a standard therapy. In its fifteen-year history the company has ultimately adopted 6 products, and at the moment 3 of these are under development or in the planning stage.

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 107, of whom 44 are involved in R&D. The drug search function is supported by a Scientific Advisory Board (SAB) of specialists (including Nobel Prize candidates). The company’s founder and CEO, Fuminori Yoshida, is of great value in terms of both the experience he brings and his extensive personal network (see CV below).

Career of Fuminori Yoshida, CEO

1949	Born in Tokyo
1971	Graduated from the Science Faculty (majored in Chemistry) of Gakushuin University
1973	Obtained master's degree from M.I.T (specialised in Life Sciences)
	Studied Management and Medical Policy Theory at Harvard University Graduate School
1975	Joined Mitsubishi Corporation
1977	Joined AHS Japan (currenty Baxter)
1980	Founded Japan Bio-Rad Laboratories
1991	Joined Japan Syntex (now Roche)
1993	CEO Amgen Japan, Vice-President Amgen Inc.
2005	Founded SymBio Pharmaceuticals Limited

Source: Fair Research Inc., using company filings

In 2018, Treakisym®, the company's leading product, became established as a standard therapy, and steady progress was seen in terms of expanded indications and formulation changes. The company's decision to set up its own internal sales structure demonstrated it was ready to evolve from bio-venture to specialist pharma in the area of hematology. In September 2019, the company acquired an exclusive license to the worldwide rights of Brincidofovir, thereby transforming itself into a global licensor.

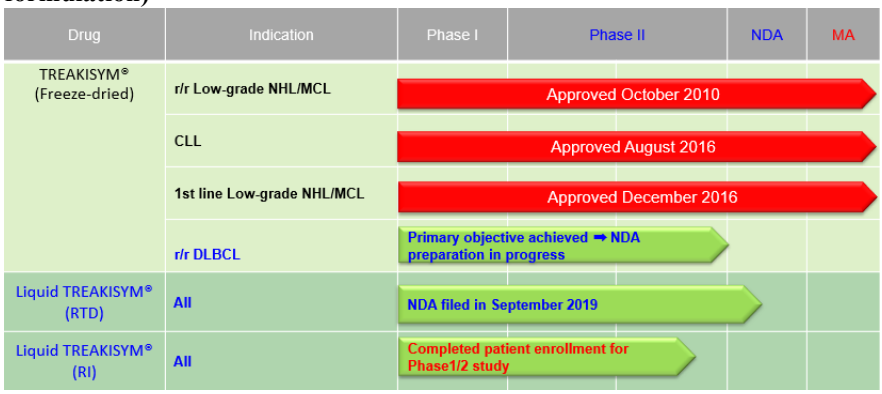
Main product pipelines

As of March 2020, the company's main products under development are Treakisym®, Rigosertib and Brincidofovir, introduced in September 2019.

(Supplementary information)

In October 2015 SymBio concluded an agreement with The Medicines Company in the United States under which it would license-in the self-administration pain control drug, IONSYS. The lump sum contract payment was JPY1 billion and Phase 3 clinical trials in Japan began in June 2016. In May 2017, however, the other party abruptly announced it was considering withdrawing from that business. Patient registration was therefore halted and in November 2017 the agreement was terminated. SymBio has requested the International Chamber of Commerce to arbitrate on its claim for compensation in the amount of JPY9 billion from The Medicines Company. In January 2020 the latter was bought by Novartis AG. The arbitration case was heard in June 2019 at the ICC Arbitration Court, and the arbitration procedures were completed in December. SymBio expects that an arbitration finding will be issued during the first half of 2020.

(1) Treakisym® (SyB L-0501 freeze-dried injection formulation) /SyB L-1701 (RTD formulation) / SyB L-1702 (RI formulation)/ SyB C-0501 (oral formulation)



Treakisym® (generic name: bendamustine) is an anticancer drug developed in Germany in 1971 and used mainly as a treatment for low-grade non-Hodgkin lymphoma and chronic lymphocytic leukemia.

(Reference) **malignant lymphoma**
Lymphoma is a blood disease caused by lymphocytes (a type of white blood cell that mainly act to provide immunity) becoming cancerous. There are two types of lymphoma: Hodgkin lymphoma (below, HL) and non-Hodgkin lymphoma (NHL). The majority (94%) of Japanese malignant lymphomas are NHL, classified into three types according to the rate of disease progression. Treakisym® is indicated for the NHL red areas in the chart.

Types of malignant lymphoma

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

Source: Therapy Handbook by Eisai and SymBio

<Licensing-in and development history>

In December 2005, SymBio acquired exclusive development and sales rights in Japan for Treakisym® from the Astellas Pharmaceuticals European subsidiary (now named Astellas Deutschland GmbH). Within a mere 5 years, in October 2010, it had received approval for two indications, low grade r/r 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 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.

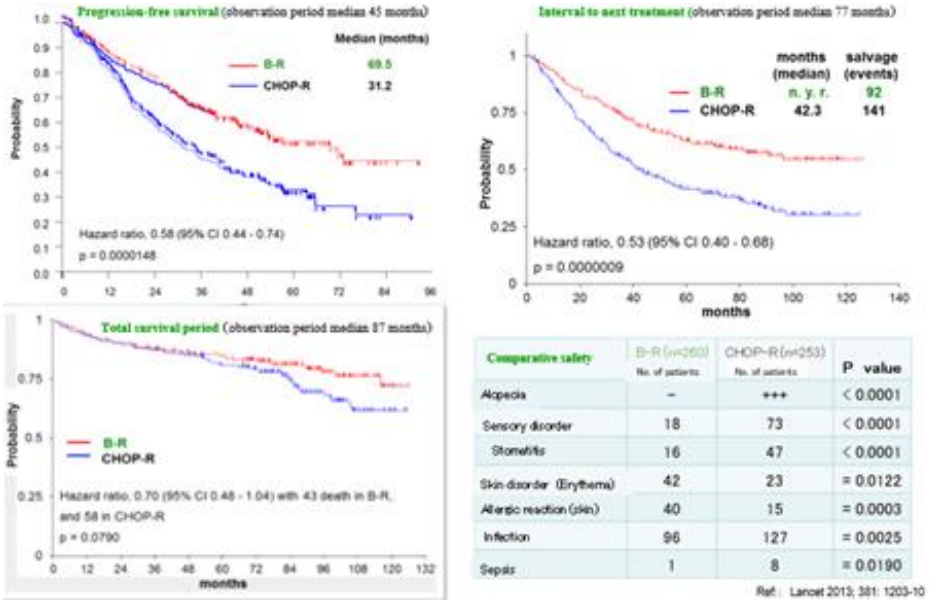
Treakisym® received approval in a mere 5 years following introduction, and since then has seen a series of additional indications

After receiving its first approval in 2010 two additional indications were approved in 2016, adding to market penetration

In July 2018 became eligible as a standard therapy

Behind this was the fact that the superiority of the B-R therapy using Treakisym® in combination with rituximab had been demonstrated over the conventional standard CHOP-R therapy (see note below on comparative tests of CHOP-R therapy and B-R therapy.)

Tests comparing CHOP-R therapy and B-R therapy



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: Company briefing materials: "The B-R therapy evinces better results

(Note) **CHOP-R therapy**

Therapy combining the molecule targeting rituximab with a chemotherapeutic combination of the anticancer drugs cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and the steroid prednisolone.

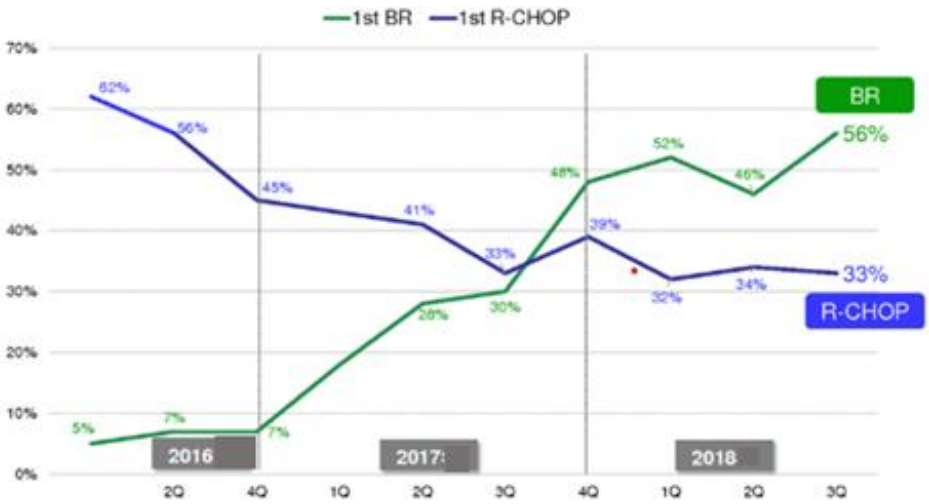
The elevation of Treakisym® to standard treatment helped boost its market penetration from an annual average of 35% in 2017 to 56% at the end of September 2018. It completely surpassed the erstwhile standard therapy, R-CHOP, and in 2018, its eighth year on the market, sales in Japan reached JPY8.5 billion (official drug price basis).

(Note) **Product quality problem**

Sales in 2019 were only slightly up on 2018. This was because of a product quality problem that had turned up in shipments of Treakisym® (freeze-dried preparation) imported from the manufacturing source (Astellas Deutschland GmbH). What in fact happened was that, in October 2018, 87% of the 25mg vials in a shipment were visibly disfigured, so that from the first quarter of 2019 a switch was made to importing only

the 100mg preparation. However, in the second quarter impurities and serious disfiguring were found in the new preparation, forcing a temporary halt to deliveries. The present situation is that the cause of the problem has been found and remedial measures have been carried out. Astellas has put a CAPA program (Corrective And Preventative Action plan) in place. SymBio has taken action to confirm the effectiveness of this program and has initiated steps to audit quality control. The joint actions of the two companies seems to have brought about the beginnings of a resolution to the problem.

The B-R therapy's market penetration



Source: SymBio using M3 market survey

In the area of blood cancers SymBio is establishing Treakisym® as the backbone of its business

<Expansion in combination therapies>

Treakisym® is in an interesting position. In the field of hematological cancers targeted by Treakisym®, various new therapies have recently emerged (see below). However, in each case, Treakisym® does not come to the fore, but is used in a combination therapy with a new drug.

Following on from the B-R therapy a variety of other combination therapies are coming to the fore

Following are examples of this:

① On July 2, 2018, a combination therapy of the anti-CD20 antibody obinutuzumab (trade name: Gazabia) and Treakisym® was approved for follicular lymphoma, adding a new treatment option.

(Note) Follicular lymphoma accounts for about 80% of low-grade non-Hodgkin lymphoma)

② CAR-T (trade name: KYMRIAH), was developed by Novartis and has proved to be a ground-breaking treatment for hematopoietic tumours including leukemia. In March 2019 it was approved for the treatment of relapsed or refractory acute lymphocytic leukemia (ALL) and DLBCL. Treakisym® has been approved for use in combination with CAR-T therapy rather than competing with it.

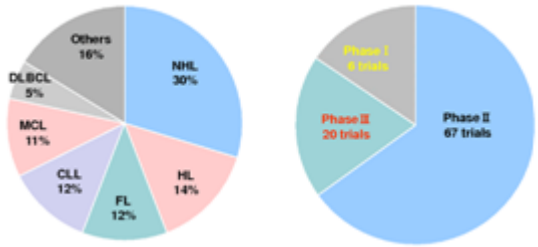
③ On June 10, 2019 the FDA gave rapid authorisation to a new combination of Genentech's anti-CD79b antibody, poratuzumab, and the drug vedotin-piiq, together with B-R therapy, for the treatment of relapsed or refractory non-Hodgkin lymphoma for transplant-ineligible patients. In Europe, also, on January 19, 2020, it was given rapid authorisation.

④ A SymBio survey in 2018 suggested that, in the area of blood cancers, there were almost 100 projects underway in the US and Europe trialing B-R therapy in combination with new drugs.

Looking at the foregoing, in the field of hematopoietic tumours, B-R therapy has already established itself as the mainstay, and new therapies have been developed as add-ons, so there is little likelihood of a competitive new therapy entering the picture.

Novel combinations now under development

By Disease By Stage



Source: SymBio using data from SyteLine, 2018

In addition to the above, with so many trials of combination therapies using immunity checkpoint inhibitors going on around the world it would not be surprising if new uses arose.

<Sales structure>

Sales has been in the hands of Eisai but preparations are now underway to take this function in house from 2021

In January 2008, SymBio licensed out to Eisai joint development rights and sole sales rights of Treakisym® in Japan. The arrangement involves SymBio buying Treakisym® from Astellas Deutschland GmbH and wholesaling it to Eisai in Japan, who then undertake sales (we assume that half the costs of developing Treakisym® in Japan were covered by Eisai). The licensing-out agreement with Eisai terminates in 2020. In October 2018, SymBio announced that, from 2021, it would set up its own sales structure with a view to making a complete switch in 2021 (we detail the in-house sales structure later).

<The current status of product development>

The company is looking to expand indications to r/r DLBCL. Phase 3 results were salutary and now preparing for an application

① **Additional indications :** Relapsed/ refractory moderate to high-grade non-Hodgkin lymphoma

Aiming to further expand indications the company is now pursuing product development by targeting relapsed/refractory medium to high-grade NHL (below, r/r DLBCL). In January 2018, the first cases were registered (FPI) for Phase 3 clinical tests, during the course of which, and following deliberations with the PMDA, the targeted number of cases was changed. The registration of cases was completed (LPI) in April 2019. Subsequently, on November 5, it was announced that the primary endpoint (expected response rate) had been exceeded (the full results should be announced at the ACH and other symposia during 2020).

The company is currently making preparations to submit an application to the authorities in the April-June period of 2020, prior to receiving approval in the second quarter of 2021 and product launch in the third quarter.

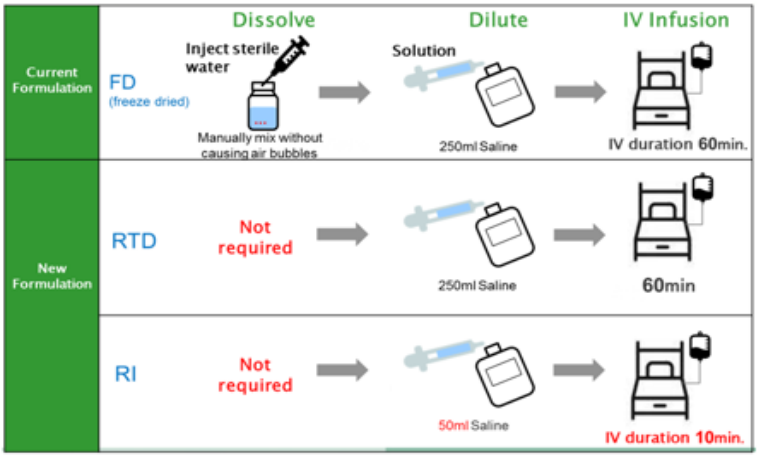
(Note) in Japan, among medium-grade NHL's, the most frequently occurring is the diffuse large B-cell lymphoma (DLBCL)

Steady progress being made in formulaton changes to manage product life cycles

② Formulation changes for life cycle management

Another important activity for the company's business is the use of formulation changes for the purpose of product life cycle management. In 2020, Treakisym® will have been authorised for 10 years, and in 2021 could be threatened by competition from generics. The company is using new formulations to extend product life (to 2031). To this end, SymBio on September 21, 2017 announced the introduction of RTD and RI liquid formulations from the US company, Eagle Pharmaceuticals Inc., to add to Treakisym's® existing freeze-dried formulation. The current freeze-dried formulation does have the advantage of storage at room temperature but has to be dissolved in liquid and diluted in saline solution before administration, which takes time and trouble. On the other hand, while the liquid formulation must be refrigerated, the preparation of a diluted saline liquid offers a time-saving alternative and reduces the burden on clinicians. In the US in 2014, Teva Pharmaceutical Industries launched an FD preparation, and in January 2016 launched an RI formulation which could be administered in a shorter time (trade name: BENDEKA®, introduced from Teva). In the short space of two years BENDEKA accounted for 97% of the Treakisym® market.

Comparison of the freeze-dried, ready-to-dilute ready to infuse formulations



Source: SymBio company briefing

RTD formulation approval in second half of 2020

As for the RTD formulation, since the efficacy and method of administration is the same as the FD formulation, it had been agreed with the PMDA that data showing stability would be enough to fulfill application requirements with no additional testing necessary. On this basis, an application was announced on September 26, 2019 with a view to launching at the beginning of 2021.

Steady progress being made in development of RI formulation

Introduction of liquid formulations should extend life cycle to end of 2031

With respect to the RI formulation, density and method of administration are different and therefore safety tests are necessary. However, the PMDA has agreed that only 36 cases will be needed, and in April 2019 registration of the first patients for clinical tests was completed. All registrations were completed in March 2020. Product approval could be given in the second half of 2022. These new formulations will extend product life cycle until the end of 2031.

③Selection and concentration

In the past, Phase 1 clinical trials of Treakisym® were progressed using oral formulations for advanced solid tumours and preclinical studies on systemic lupus erythematosus (SLE), a type of autoimmune disease. The results were gratifying but due to the potential to surpass existing drugs, and the expansion of the pipeline following the introduction of Brincidofovir, the decision was made to discontinue both (February 2020).

(2) Rigosertib (SyB L-1101: injection formulation, SyB C-1101 oral formulation)

Drug	Indication	Phase I	Phase II	Phase III	NDA	Approval
Rigosertib IV	Relapse/ refractory high risk MDS monotherapy	Completed patient enrollment for global phase III study				
Rigosertib Oral	Relapse/ refractory high risk MDS	Japan study completed				
	1st line high risk MDS Combination with AZA	In preparation				
	1st line high risk MDS Combination with AZA	Global phase II/III study in preparation				

Development underway of injection and oral formulations of Rigosertib targeting myelodyspatic syndromes (below, MDS)

Rigosertib is a cancer drug mainly targeting myelodysplastic syndromes (below, MDS) being developed in the US by Onconova Therapeutics, Inc. In July 2011, after Onconova had completed Phase 2 tests, SymBio acquired sole development and marketing rights regarding the injection formulation and the oral formulation in Japan and South Korea (the one-off contract payment estimated at JPY800 million). The current development status is as follows:

(a) **Injection formulation**

Joint international Phase 3 trials are being conducted on high-risk MDS patients who do not respond to the standard hypomethylating agent (HMA) treatment (HMA refractory), or relapse after treatment. SymBio is responsible for Phase 3 in Japan.

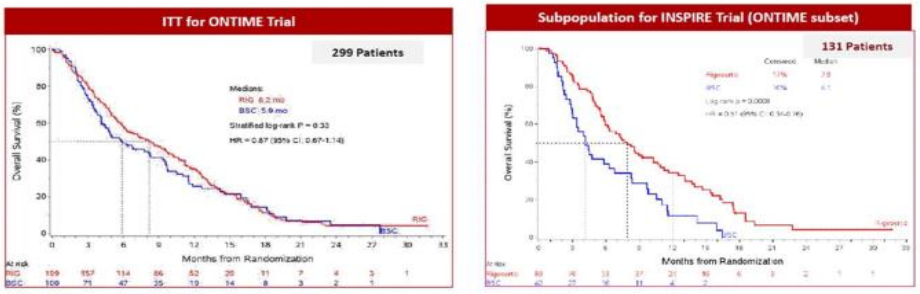
High-risk MDS is classified into two groups (higher risk) out of those determined as high risk by the IPSS (International Prognostic Scoring System) and those with medium risk, with a high risk of transition to leukemia and the like. Currently, the standard treatment is administration of azacitidine (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 no competing approved drugs yet.

Onconova completed Phase 3 (ONTIME) tests for r/r high risk MDS in February 2014. The results showed there was no statistically significant difference in overall survival between the cohort receiving Rigosertib and the control cohort receiving palliative care. However, looking only at HMA refractory patients or those whose

condition had deteriorated during previous treatment, a statistically significant difference was recognised: overall survival was 7.9 months for the Rigosertib cohort and 4.1 months for the control cohort. Onconova then redesigned the test design on the basis of this partial analysis. In August, 2015 it initiated joint international Phase 3 INSPIRE tests directed at high risk MDS patients who are HMA refractory or who have relapsed after treatment.

ONTIME results (left) and partial analysis - INSPIRE tests with same cases (right)

ITT OS analysis of ONTIME – HR = 0.87; NS survival benefit
ITT OS of proposed INSPIRE population – HR = 0.51; P = 0.0008



*Guillermo Garcia-Manero, Pierre Fenaux, Aref Al-Kali, Maria R Baer, Mikkael A Sekeres, Gail J Roboz, et al. Rigosertib versus best supportive care for patients with higher-risk myelodysplastic syndromes after failure of hypomethylating drugs (ONTIME): a randomised, controlled, Phase 3 trial; The Lancet Oncology 2016 (17): 496–508

Source: SymBio results meeting

The original developer, Onconova, changed test design – now in joint international Phase 3 with SymBio participating. On the basis of interim analysis, cases increased in January 2018. Top-line data due for release in 2H 2020

SymBio initiated Phase 1 tests on r/r high risk MDS in June 2012, completing them in October 2015. Subsequently, SymBio participated in the international Phase 3 INSPIRE tests, initiated by Onconova in December 2015, as the party responsible for Japanese clinical trials. In January 2018, on the basis of interim INSPIRE results Onconova increased the number of cases from 225 to 360, and in Japan SymBio did the same with a target of 50 cases. In March 2020 all 360 cases had completed registration for joint international Phase 3 (INSPIRE). The expectation now is for top-line data (interim report) possibly being released early in the second half of 2020. At the present time an application is scheduled for 2021 and approval for 2022.

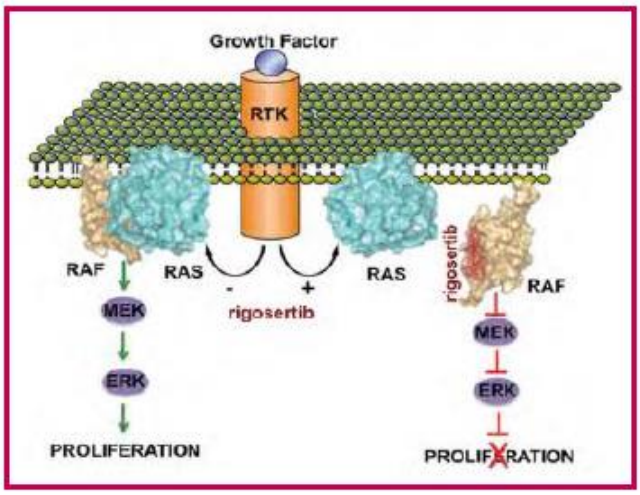
(b) **Oral formulation**

In Europe and the US, Phase 1 / 2 trials have already demonstrated the effectiveness and safety of the oral formulation on high-risk MDS in combination with azacitidine (2017, 14th international MDS symposium). Also, at the 2018 American Society of Hematology (ASH) symposium the results of Rigosertib oral formulation Phase 2 trials were published, showing good tolerability and superior rates of responsiveness for previously untreated HMA and r/r MDS patients.

Rigosertib Phase 2 clinical trial results (ASH, 2018)

Response rate (2006 IWG basis)	HMA untreated (1st line, 29 cases)	HMA refractory (2nd line, 26 cases)
Overall response rate(ORR)	26 cases (90%)	14 cases (54%)
Complete remission (CR)	10 cases (34%)	1 case (4%)
Partial remission (PR)	0 cases	1 case (4%)

Source: SymBio results meeting, 2018

SymBio scheduled to join international joint Phase 2/3 trials planned by Onconova	Onconova applied to the FDA in December 2018 for a special protocol assessment (SPA), planning Phase 3 trials in combination with azacitidine on untreated high risk MDS. As of December 2019, they have announced changes to the trial design and are considering Phase 2/3 adaptive trials. (Note) **SPA** An SPA involves an advance agreement with the FDA on the acceptability of Phase 3 trial methods, purpose, trial endpoints (primary and secondary) and analytical methods. Under the SPA system the findings are accepted as they are without changes to the protocol. SymBio plans to participate in the international joint Phase 2/3 adaptive trials scheduled by Onconova.
KRAS-positive cancer could become an additional indication	Rigosertib has been shown to act as a RAS mimetic molecule. Rigosertib competitively inhibits the activated RAS from binding to signaling molecules (RAF in the figure below, PLK, RAL, PI3K other than RAF). By blocking the Ras-Raf-Mapk transmission pathway by this inhibition, it is expected to suppress carcinogenesis by activated RAS. Onconova is planning an investigator-led study (Phase 1) of advanced KRAS-positive non-small cell lung cancer with a combination of an immune checkpoint inhibitor and Rigosertib. It is also planning Phase 1 for KRAS-positive colorectal cancer. RAS targeted novel mode of action  Source: Onconova presentation materials, October 2018

Has acquired an exclusive global license for inications except smallpox

(3) **Brincidofovir（SyB V-1901）**

On October 1, 2019 SymBio announced it had acquired the exclusive global rights (development, manufacturing and sales) to Brincidofovir (BCV) for all indications except smallpox from the US company Chimerix. BCV thus became SymBio's third strategic product after Treakisym® and Rigosertib. The company has previously licensed in products from overseas for development mainly in Japan, but with this acquisition it is now in an entirely new position, able to license out globally.

(Note) Why Chimerix retains all rights to the smallpox indication

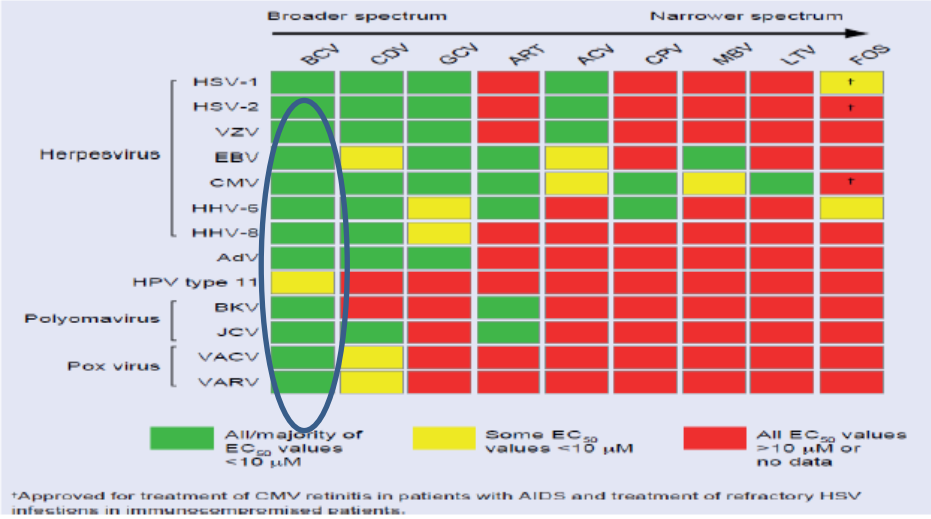
The US Biomedical Advanced Research and Development Authority (BARDA) has provided Chimerix with more than USD100 million to develop BCV as one element in countering bio-terror. The FDA has given BCV fast-track and Orphan status, and Chimerix expects to receive approval for smallpox in 2020.

<Characteristics of Brincidofovir>

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

BCV is more active across a broader spectrum than other anti-virals

BCV is active across a broad spectrum



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

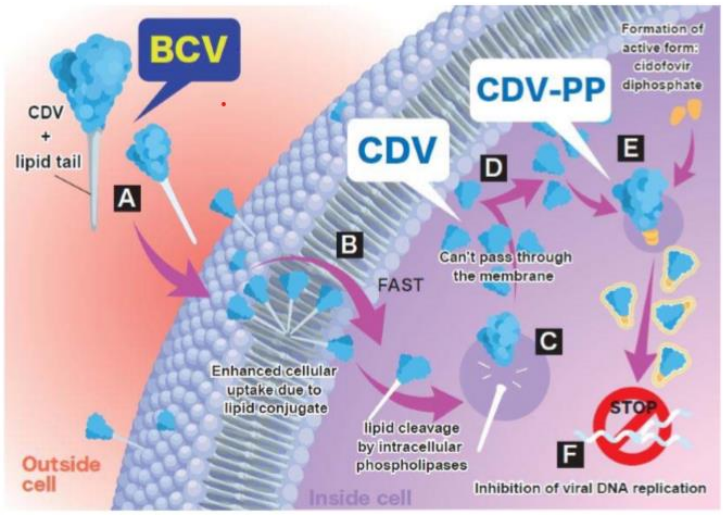
(Note) **EC50** (the concentration at which a drug or antibody shows a 50% maximum response from the lowest value) indicates that the lower the number, the higher the activity. In the upper figure, EC50 is color-coded depending on the level. Green has high activity and red has low activity. The left-most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

Source: Chimerix

(Reference) **Cidofovir (CDV)**

This was approved by the FDA in 1996 for the treatment of cytomegalovirus retinitis in AIDS patients. CDV is a cytosine nucleotide analog that inhibits the replication of DNA viruses such as adenovirus, papilloma virus, and polyoma virus as well as herpesviridae. CDV is also effective against ganciclovir (GCV) resistance (UL97 gene mutation) and is considered of utility when foscarnet (FOS) cannot be used due to the appearance of GCV resistance. It is an unapproved drug in Japan.

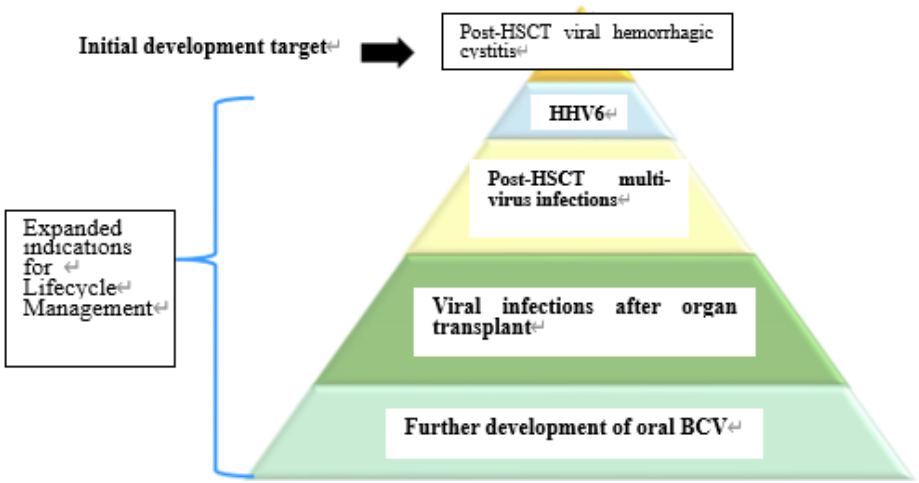
As can be deduced from the above chart, CDV is close to BCV in terms of activity level and broadness of spectrum. However, CDV is difficult to use because of its nephrotoxicity. BCV, on the other hand, has low toxicity and, despite being highly active, is extremely safe.

In addition, nephrotoxicity is low and safety excellent	**<BCV mode of action>** 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 fat 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 release 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 of administration is required to enhance the effect, with nephrotoxicity the likely outcome.)  Source: SymBio IR materials
Indications targeted: viral infections following hematopeoietic stem cell transplantation and organ transplantation	**<Indications>** SymBio uses the properties of BCV to target what is has described as a primary area for development: viral infections after hematopoietic stem cell transplantation, an area with poor prognosis, high lethality, and strong unmet medical needs. In general, in hematopoietic stem cell transplantation or organ transplantation, radiation or immunosuppressive agents are used to suppress rejection, but in doing so are rendering the patient easily susceptible to viral infections. Conventionally, other antiviral agents, such as CDV and FOS have been used, but with these there is a concern about the side-effect of nephrotoxicity. BCV is an important drug in helping SymBio achieve specialty pharma status in the area of hematology. The number of hematopoietic stem cell transplants worldwide is estimated at about 78,000 annually, of which some 43,000 are autologous with low rejection rates. 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.
Phase 1 viral cystitis trials due to start in Japan from the second half of 2020 Will draw up global	SymBio anticipates first undertaking drug development in Japan for viral hemorrhagic cystitis. Phase 1 clinical trials in Japan should start in the second half of 2020, and about 50 subjects will be included in Pivotal trials. After that, it is thought that the focus will shift to the development targeting HHV-6 encephalitis and multivirus infections. Overseas, a global development strategy will be formulated in the latter half of 2020, and it is assumed international joint clinical

development strategy

trials will take place. Also, in 2020, the company plans to start developing oral formulations.

BCV life cycle management



Source: Symbio results meeting materials

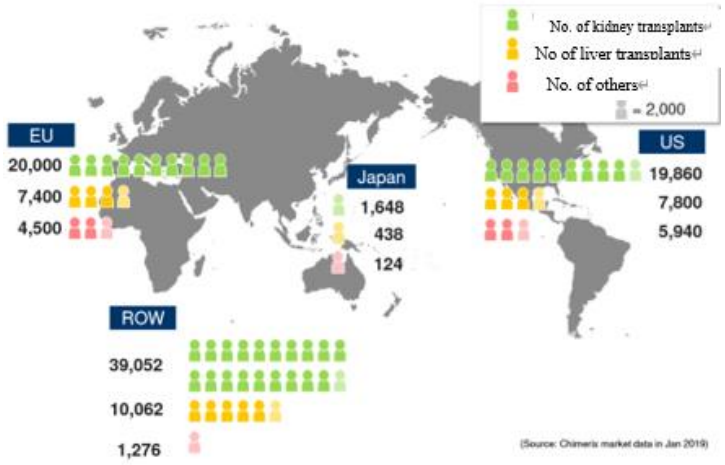
In the future it will be possible to use this therapy not only for hematopoietic stem cell transplantations, but also after organ transplantations, and it will be administered not only via injection but orally. In other words, long-term life cycle management will be possible.

It is anticipated that this product will have a prolonged existence due to an increase in indications and formulation changes

Unlike Japan, organ transplants in Europe and the US are quite common. For instance, in Japan there are 1,600 kidney transplants per year, compared with 20,000 (total) 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, SymBio will probably tie up with an overseas pharmaceuticals company to promote sales following organ transplants.

It will be necessary to find a European or US pharma partner in order to pursue the development of drugs for post-transplantation viral infections

Number of organ transplants (ZOT)



Source: SymBio results meeting

(Reference) **Hematopoietic stem cell transplantation**
Transplantation of bone marrow, which is a hematopoietic stem cell, is a treatment that aims to completely cure blood diseases (mainly haematological cancers such as leukemia) that are difficult to cure only by chemotherapy or radiation therapy. Bone marrow transplantation includes autologous bone marrow transplantation using the bone marrow of a relative, and allogeneic bone marrow transplantation, which is increasing in frequency, using the bone marrow of another person with the same white blood cell type.

(Reference) **Viral hemorrhagic cystitis** (extracted from SymBio IR data)
Among the viral infections that frequently occur after hematopoietic stem cell transplantation, adenovirus infections that causes hemorrhagic cystitis are generally intractable, and 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, which is fatal. It is particularly likely to occur with unrelated donors and umbilical cord blood transplants, which have a high ratio 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** (extract from SymBio IR data)

HHV-6 (human herpesvirus 6) is the sixth human herpesvirus to be discovered. In allogeneic hematopoietic stem cell transplantation, 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-encephalitis cases early intervention is extremely important because a rapid deterioration in the patient's condition early on is common. According to clinical guidelines*, 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 whose 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)

Plans to cover the 400 or so most significant hemalology departments nationwide, divided into 6 blocs and served by 62 sales staff specialised in hematology

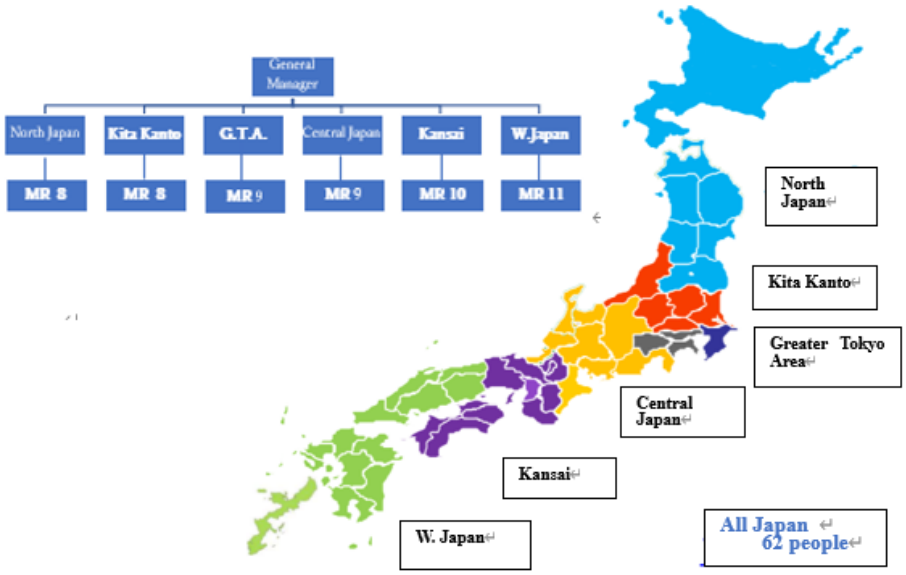
The necessary distribution system, logistics centers and core systems are in place

<Building an in-house sales function>

There are 1100-1200 hospitals and clinics in Japan with hematology departments, of which 800-900 are hospitals. SymBio believes it can cover the most significant ones, or one-third of the total. As it was getting closer to starting its own sales in 2021 it began recruiting a highly professional staff in 2018. The sales structure it is considering consists of 62 staff divided into 2 areas nationwide and 6 blocs. As of February 2020, it has already secured the services of 42 staff, and by April will mobilise the remainder on secondment from CSO. The company is simultaneously preparing two logistics centres and its distribution infrastructure should be in place by the second quarter of 2020. The ERP, which is the company's core systems component, is in place and IT is being upgraded in parallel, so all should be ready for the second quarter of 2020.

We estimate that the cost of MR's and promotional costs will push Treakisym® sales costs up to around JPY2 billion per year.

Teams of regional specialists in the area of hematology are to lead marketing



Source: SymBio results meeting, February 2019

Potential market size for three major products

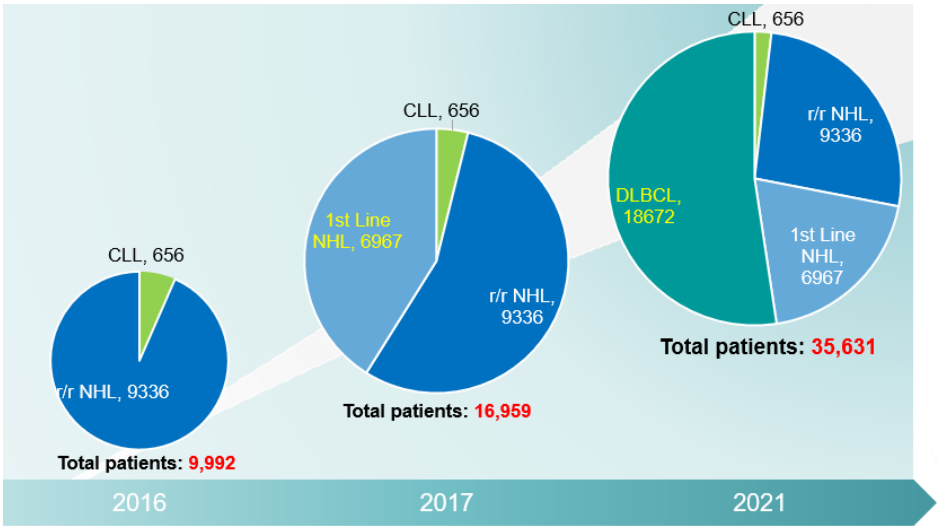
We posit the marke size of Treakisym's® three approved indications at JPY10.6 billion, and for Phase 3 r/r medium and high risk NHL at JPY9.8 billion

(1) Potential market size for Treakisym®

We see the market for Treakisym® rising on the back of higher market penetration and an expansion in indications. Those indications already authorised are: ① r/r low grade NHL/MCL ② Chronic lymphocytic leukemia（CLL）③ Untreated low grade NHL/MCL. Sales value for ① totals JPY4.72 billion. We see total patients at 9,336 and market penetration at 58%, with the level of sales likely to be maintained by changes in formulation. ② and ③ have only recently been authorised so sales of both together are around JPY2.68 billion for FY2017. We estimate 656 patients and 6,967 patients, respectively, with an average market penetration in 2017 of 35%, suggesting higher penetration to come. The market value of ② CLL would be JPY340 million at a market penetration of 55%, and for ③ untreated low-grade NHL/MCL a market penetration of 75% would yield an estimated market size of JPY5.57 billion. Further, there are an estimated 18,000 patients or so suffering from the three stages of r/r medium-high grade NHL (r/r DLBC), now at Phase 3. A maximum market penetration of 60% would yield a market value estimated at JPY9.77 billion.

From the above we can posit a total sales value of JPY1.06 billion for the three indications already approved. If we include r/r DLBCL, an additional indication now at Phase 3, total estimated sales value comes to JPY20.4 billion. We do not make any assumptions in our calculations for new combination therapies, such as CAR-T.

The market for Treakisym®



Source: SymBio company briefing, 2018

We posit a potential value of JPY4.6 billion for the Rigosertib injection formulation, and a potential value of JPY11.6 billion for the oral formulation

(2) Potential market for Rigosertib

The Rigosertib injection formulation is indicated only for those high-grade MDS patients who are HMA refractory. We therefore infer some 900 patients and, using the official price of Vidaza as a reference, we calculate sales of JPY4.6 billion. For the oral formulation, we infer 2300 patients, that being the number of high-grade MDS patients not receiving injections. The oral formulation market is therefore valued at JPY11.6 billion, and the total for both formulations is JPY16.0 billion. However, if KRAS-positive cancer qualifies as an additional indication in the future, the size of the market could fluctuate significantly.

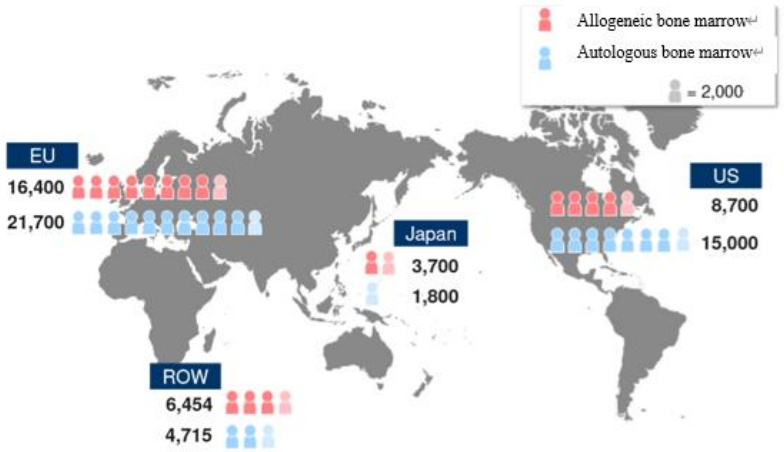
(3) Potential market size for Brincidofovir

Market size will be a function of viral infections following hematopietic transplants

Worldwide there are some 78,000 hematopoietic stem cell transplants each year, 43,000 of which are autologous and therefore with a low probability of rejection. There are some 35,000 allogeneic transplants each year and for these it is necessary to suppress the immune response to prevent rejection, which thereby increases the risk of infection.

SymBio anticipates that in Europe and the US, 50-60% of allogeneic transplants, and in Japan, 70% will require this. As a result, the number of cases in Japan could total around 2,600 each year, and in the US together with the five main European countries, could total around 1,500. Elsewhere, the population-adjusted incidence of hematopoietic stem cell transplants is still around one-twentieth that of the bigger economies. However, we expect this to rise in the future.

Frequency of hematopoietic stem cell transplants (HCT's)



Source: SymBio results meeting materials

The market for hematopoietic stem cell 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, given the cost of other antiviral drugs, that the drug cost per case is JPY3 million, the market size for treating viral infections after hematopoietic stem cell transplantations would work out at JPY8 billion in Japan and an estimated ¥ 42 billion in the US and Europe (i.e. the US and the five major European countries). The number of hematopoietic stem cell 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, almost half the potential demand is in the coastal areas where the medical environment is well-established.

Measuring pipeline value	Pipeline value simulation
Our calculation is based on a number of assumptions Discount rate: 10%	In order to model the company's value, we assume approved Treakisym® indications include r/rDBLCL, and our calculations discount the value of formulation changes and of the company's in-house sales structure. We then sum the resulting value with the value of the injection and oral formulations of Rigosertib (DCF method) and deduct whole-company costs (drug search costs and administration costs) again using the DCF method. The discount rate is set at 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 does have a launched product in the market. **< Assumptions for Treakisym®>**
We have amended the assumptions we made to calculate the cost of Treakisym® liquid formulations	In line with our earlier comments, we assume that peak sales will occur four years 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. Further, we set the probability of success in clinical trials directed at r/r medium-grade NHL (r/r DLBCL) at 100%, reflecting the established position of Treakisym® as a standard therapy in the area of hematopoietic tumours. Until 2020 sales will be made through Eisai, but from 2021 will be handled in-house. We have assumed the company will in the same year be switching almost entirely to the liquid formulations (RTD and RI). These 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% (in our previous Basic Report we assumed 30%). Milestone payments, which will become payable on regulatory approval of the RTD formulation, will be approximately JPY700 million.
We are setting sales costs at JPY2 billon, assuming a sales force of 62	All development costs (excluding milestone payments) will be borne by the company itself. For 2020, in addition to RI formulation development, r / r DLBCL regulatory application preparations, etc., will be assumed at about JPY900 million. For 2021-2022 it is thought that the only cost will be the development of the RI formulation so development outlays will fall to about JPY400-600 million. It is also assumed that a milestone payment to Eagle (JPY700 million) will occur in 2020, triggered by the approval of the RTD formulation. With a sales force of 62, as mentioned earlier, we are assuming cost of sales at an annual JPY2 billion yen.
We have revised our calculation of the injection formula's probability of success from 50% last time to 80%	**< Assumptions for Rigosertib>** As per the previous pages, we are assuming that sales will peak in the fourth year following launch, maintaining that level for approximately 3-4 years before contracting by 5% per year and by a sharper 10% from 2035. We are positing launch of the injection formulation in around 2023, and in around 2024 for the oral formulation. Reflecting different stages of development, we assume a probability of success of 80% for the Phase 3 injection formulation, and 50% for the Phase 3 preparatory oral formulation (the injection formulation has advanced from our previous calculation of 50% at an earlier point in clinical trials).
Rigosertib goes through the same sales channels as Treakisym®	Further, we are assuming that payments for supplies of the drug and royalties to Onconova will amount to some 25% of sales revenues. We believe that development costs (excluding milestone payments) will continue at a level of about JPY800 million annually from 2020 to 2022, and will amount to JPY300 million yen in 2023,

	because oral drug development will continue even after injectable drug development peaks. We have assumed milestone payments being made at the time of approval for the injection formulation and the oral formulation and amount to JPY 500 million and JPY1.5 billion, respectively. Sales expenses for Rigosertib are not recorded as they go through the same MR and the same sales channel as Treakisym® sales.
	<Assumptions for Brincidofovir>
We are taking a conservative view of market size: Japan JPY8 billion, overseas JPY32 billion	When SymBio licensed in Brincidofovir from Chimerix it was to pay a total of USD180 million (including a one-off contract fee of USD5 million) and royalties at a fixed proportion of sales. It was reported that the royalties rate was at a "two-digit" percentage level, which we have assumed to be 12% for our calculation purposes. Also for calculation purposes, we have narrowed our focus to the two viral infections occurring after hematopoietic stem cell transplants. As for markets under consideration, we start with Japan and China. The former has an assumed market value of JPY8 billion, and China market is accorded a more conservative value than was suggested in the previous pages, at JPY32 billion, or four times the Japanese level. In terms of development schedule, we first assume the development of a viral hemorrhagic cystitis therapy in Japan, to begin in the second half of 2020 and, using overseas data which includes Japanese natives, to be completed at an early date. From mid-2021, we anticipate registering some 50 individuals for the start of Pivotal tests. The registration should be competed in 18 months and the Pivotal tests in the first half of 2024. An application for approval should follow in 2025 and market launch in 2026. It is expected that studies in patients with HHV-6 encephalitis and those in patients with hemorrhagic cystitis will progress on a similar scale, with a delay of about one year. The overseas markets will wait on regulatory approval in Japan, so the company is now thought to be considering a strategic direction involving China and other parts of Asia.
We assume a market launch in or after 2026	
We have set quite challenging assumptions for milestones and gross margin	As described above, assuming 50 patients for each indication in the Pivotal tests, the development cost would be about JPY500 million per year at its peak. It is also assumed that the gross profit rate in Japan is 80%.
We have set whole-company costs (including basic research costs) at an annual JPY2.2 billion	Given the foregoing and assuming that there are 50 patients for each indication in the Pivotal tests, we have inferred development costs of around JPY500 million per year at the peak. It is also assumed that the gross profit rate in Japan is 80%. Although sales in overseas markets would be possible in-house, it is assumed that sales rights are licensed out. In that case, the gross profit of SymBio would be 50%, and the milestone income associated with the licensing-out we set at a total of JPY 10 billion, about one-third of peak sales. The probability of success is considered to be 80% or more because POC in humans has already been established.
	R&D costs to find and study new candidates for development are generated every year, along with whole-company administration costs. After analysing the company's revenues structure, we posit R&D costs generated by recurrent search activities at JPY600 million, and whole-company administration costs at JPY1.6 billion, for a relatively high total of JPY2.2 billion.

Even after allowing for whole-company costs the company's pipeline value comes to JPY88.9 billion (before tax), suggesting substantial latent value

<Results of our calculation>

We calculate the discounted present value using the preconditions touched on above, the results of which are given in the table below. Treakisym® has a pre-tax value of JPY57.0 billion, Rigosertib JPY24.9 billion, and Brincidofovir JPY29.1 billion, for a total JPY110.9 billion. Deducting all company costs we arrive at JPY88.9 billion (pre-tax).

Modelling the value of SymBio's product pipeline (pre-tax)

(JPY100 mil)

	Prob. of success	Discount rate 10%
Treakisym®	100%	570
Rigosertib	Injection 80% Oral 50%	249
Brincidofovir （for 2 infections after HSCT only ）	80%	291
sub-total		1,109
Company-wide costs		-220
Total		889

Source: Calculated by Fair Research Inc.

(Note) No direct comparison can be made between the company's pipeline value and the company's market cap

Earnings outlook	SymBio has two sources of revenue: proceeds from product sales and licensing fees. Apart from the period ending December 2008, when the company booked a contract fee from Eisai in exchange for sole domestic sales rights to Treakisym®, the company has never operated at a profit.
Revenues fell in 2019 mainly because of a product quality problem. In 2020, sales will again fall, perhaps to below 2018's level, as Eisai seeks to draw down inventories	SymBio recorded sales of JPY2,838 million in the December 2019 period, most of it the proceeds of sales of Treakisym® to Eisai. Because of product quality issues with Treakisym® wholesale deliveries to Eisai had been delayed, leading to a YoY fall in SymBio revenues of around JPY1 billion in 2019. In the December 2020 period we expect revenues to rebound on the back of a resolution to the product quality problem. However, from the beginning of 2021 SymBio is switching to its in-house sales structure, necessitating the compression of Eisai inventories. We expect sales to fall to around JPY3.4 billion, even lower than the level for 2018. (The size of the market using official drug prices was around JPY8.5 billion in 2018, and almost flat in 2019, but we expect a slight rise in 2020.)
However, in 2021 the switch to in-house sales, an increase in qualifying indications and the launch of liquid formulations should provide a jump in sales to the JPY9 billon level	In 2021, however, the start of in-house sales together with a switch to the Treakisym® RTD formulation and the inclusion of r/r DLBCL as an approved indication should mean a significant improvement in results, such that SymBio is forecasting sales in 2021 of JPY9 billion (as stated in the company's medium-term management plan of February 2020). It is quite possible that, in official drug price terms, the size of the Treakisym® market could top the important JPY10 billion level at this time. (Note) It is estimated that the wholesale price at which SymBio sells Treakisym® to Eisai is around 50% of the official drug price, and the acquisition cost which SymBio pays Astellas Deutschland GmbH is 66% of the wholesale price. When sales move in house, the company will not be paying a wholesale price to Eisai but a wholesale price to medical institutions. And with the switch to the RTD and RI formulations SymBio will be supplied not by Astellas but by Eagle. Because of ease of drug handling, logistics costs will fall and overall, there will be a significant impact on the cost structure.
R&D costs can change depending on incidental contract fees and milestone payments for products licensed in. But excluding such variability, the pace of development is expanding In the run-up to starting in-house sales, sharp upturn in non-R&D SG&A expected	R&D spending in 2019 was JPY2,441 million, an increase on the previous year's JPY1,832 million. However, for the previous year we infer JPY540 million of the R&D was accounted for by the one-off contract payment (for BCV) to Chimerix. Deducting that leaves JPY1.9 billion, which was used to maintain a steady program of development: around JPY1.1 billion was Treakisym® related, JPY500 million was Rigosertib related, and the remaining JPY300 million went on other drugs search costs. R&D spending rose JPY289 million to an anticipated JPY2,731 million in 2020. This includes a milestone payment of around JPY700 million that was due because of the approval of the RTD formulation. R & D expenses excluding one-time milestone payments are expected to increase to around JPY2 billion as development progresses and expands, including the start of BCV development.
Operating losses could expand to JPY4.3 billion in 2020, but could perform a U-turn in 2021 recording profits of JPY1.0 billion	SG&A expenditures excluding R&D costs came to JPY2,724 million in 2019, a sizeable increase of JPY728 million on the previous year. The increase arose as full –fledged preparations for in-house sales was getting underway. The company expects SG&A expenditures excluding R&D costs will expand to JPY 3.5 billion in 2020 and thereafter continue to increase steadily along with the sales growth. It is expected that in 2020 the company's operating loss will expand to JPY4.3 billion due to preparations for the in-house sales function and increased R&D costs. However, in 2022 the start of the new sales arrangement and changes to the Treakisym® cost structure should boost profitability and generate a JPY1 billion operating profit. Later, the effect of increased indications for Treakisym® will sink in, sales should grow by 20% and operating revenues could rise by almost JPY1.5 billion.

SymBio Pharmaceuticals – results and medium-term outlook

JPY mil.

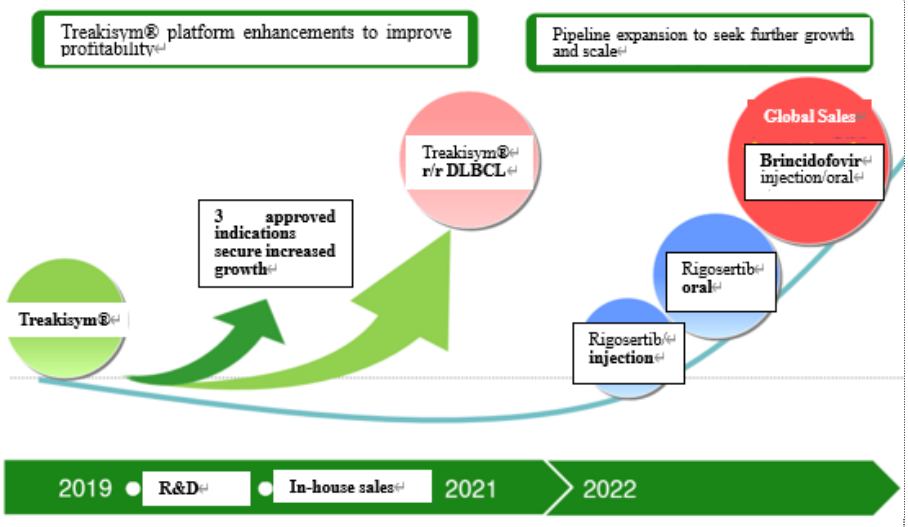
	Dec. 2013	Dec. 2014	Dec. 2015	Dec. 2016	Dec. 2017	Dec. 2018	Dec. 2019	Dec. 2020 (Company)	Dec. 2021 (med. term plan)	Dec. 2022 (med. term plan)
Sales	1,532	1,955	1,933	2,368	3,444	3,835	2,838	3,404	9,008	10,816
Product sales	1,432	1,940	1,933	2,137	3,444	3,809	2,811	3,404		
Licensing	100	15	0	231	0	25	27	0		
Cost of goods sold	1,214	1,428	1,483	1,737	2,413	2,662	1,973	2,258		
SG&A	1,999	1,830	3,135	3,031	4,978	3,828	5,166	6,236		
of which, R&D	1,053	774	2,035	1,667	3,017	1,832	2,442	2,731		
Excl R&D	946	1,056	1,100	1,364	1,961	1,996	2,724	3,505		
Op. profits	-1,681	-1,303	-2,552	-2,127	-3,947	-2,656	-4,302	-5,090	1,031	1,482
Rec. Profits	-1,601	-1,110	-2,630	-2,317	-3,976	-2,748	-4,377	-5,134	987	1,438
Pre-tax profits	-1,601	-1,112	-2,628	-2,309	-3,974	-2,748	-4,372			
Net profits	-1,605	-1,116	-2,632	-2,313	-3,978	-2,752	-4,376	-4,803	1,356	1,717
Liquid assets	7,634	7,290	4,827	6,685	4,037	6,038	4,887			
of which, cash etc.	6,163	5,692	4,261	5,719	2,947	4,821	3,910			
Fixed assets	53	164	158	193	216	200	386			
Liquid liabs	251	488	551	942	1,011	1,336	872			
Fixed liabs	3	2	2	451	1	1	1			
of which, corp bonds	0	0	0	450	0	0	0			
Net assets	7,433	6,964	4,432	5,485	3,239	4,901	4,400			
Shareholders equity	7,336	6,763	4,132	5,054	2,702	4,372	3,779			
of which, optioms	97	200	300	431	537	530	620			
(Reference)										
Income from options issued/exrcised	247	54	0	687	1,178	4,301	3,771	Options Nos. 50, 51		
Income from CB's issued	1,000	500	0	3,000	0	0	0			
Event			IONSYS expenses, etc.		Treakisym liquid formula costs		BCV licensing in In-house sales	Milestone payment on RTD Approval	Switch to in-house Sales RTD launch DLBCL approved	RI formulation received

Source: Fair Research Inc. using SymBio medium term management plan and securities reports

In 2022 SymBio will move to a second stage

From 2022 onwards, there will be several developments including the launch of Rigosertib and, in 2026 or thereabouts, plans for the launch of BCV. These developments will give SymBio a more secure footing as a specialty pharma with several products in the market, and ready to move to the next stage.

SymBio moves to the second stage



Source: SymBio results meeting, February 2019

Moving to the second stage is not without its difficulties

However, SymBio is not at present ideally placed to make this move. The financing plan announced in 2018 with the issuance of multi-year stock options (45th, 46th, 47th) will be exercised ahead of schedule (scheduled completion February 12, 2020), allowing the company to raise a total of about JPY7,326 million yen. However, cash on the balance sheet stood at JPY3.91 billion at the end of 2019, and net profits for 2020 could record a loss of JPY4,803 million, meaning that funds will be necessary to carry the company over for one year until profitability becomes a reality. Among the previously mentioned financings the amounts raised in January-February 2020 totalled JPY943 million. But to reliably carry out product

With the announcement on February 27, 2020 of a financing using an equity options issue the company seems to have found its way over the last one mile	development and to complete the in-house sales project, the company needs greater financial room for manoeuvre. If the company's arbitration application filed with the International Chamber of Commerce is successful (the amount of damages requested by SymBio is equivalent to approximately JPY9 billion), the company's position will be improved. But we should not stand on a satisfactory outcome to the arbitration which cannot be taken for granted. It was in this situation that Symbio announced stock options issues (No. 50 and No. 51) on February 27 to raise finance (JPY5.45 billion envisaged). Each has Commit issue conditions attached, designed to expedite exercise at a relatively early date. (Reference) Commit issue outline No. 50: 7 million shares, from date of issue 2.8 million shares within 56 trading days Entire no. of shares within106 trading days No. 51: 3 million shares Within 46 trading days of date stipulated by SymBio **Conclusions** With its own sales structure in place and the acquisition of Brincidofovir (BCV), SymBio has established the foundations for growth as a globally licensed blood specialty pharma. The total pipeline value (before tax) of its three cancer products (Treakisym®, Rigosertib, and Brincidofovir) is estimated at about JPY110 billion yen, or about JPY89 billion yen after deducting company-wide costs. The company's losses have recently expanded due to the upfront costs of switching to an in-house sales system and the increase in R & D expenses due to the development of core products. The company is now at a particularly difficult juncture in its development but once it overcomes this it should see a clear path to profitability in 2021. The financing plan announced on February 27 through the issuance of stock options will help it traverse this last mile.

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