SymBio Pharmaceuticals, Ltd.

(4582 JASDAQ) Issued: Nov.4 2020

Should turn profitable in 2021

Entering the second-time startup

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. In October 2019, the company announced its third product, acquiring the sole global license (development, manufacturing and sale) for Brincidofovir. The company thereby evolved into a licensor, not only in Japan but also globally, firstly in Asia generally (including China) and the US. At present, it is proceeding with an expansion of Treakisym® indications and undertaking a series of Treakisym® formulation changes as one plank in its lifecycle management policy. Furthermore, preparations have been completed for the launch in 2021 of in-house sales. The company has therefore entered the second phase of its existence as a pharmaceutical company specialising in hematology.

Revamping pipeline strategy

When Brincidofovir (BCV) was first adopted by Symbio the stated intention initially was to develop an injectable formulation for the prevention of viral hemorrhagic cystitis after hematopoietic stem cell transplantation, an area of poor prognosis and high lethality – i.e. strong unmet medical needs. However, on the basis of the consultations with the company's Global Advisory Board in February 2020 a new global development strategy was announced in August 2020. It was decided to give top priority to development in areas where no alternative therapeutic agent was available, where there was a strong unmet medical need and where there was a good expectation of success. On this basis it was decided to focus on adenovirus infections in children and adults during hematopoietic stem cell transplantation (HSCT). The company plans by itself to use overseas CRO's to pursue global development. Turning to rigosertib, the Phase III trials (INSPIRE trials) did not demonstrate a significant difference from physician's choice of therapy. However, based on cross-analysis with genome analysis and the analysis results of Japanese subjects alone a new approach is scheduled for next spring.

Could start turning profitable in 2021

Fair Research Inc. believes the company is now in sight of achieving profitability in 2021, followed by an earnings trajectory in the region of 10-20% in terms of 10-20% on an operating profits basis. In addition to the change in sales revenues due to direct sales by the company, there will also be an effect from a switch to the Treakisym® RTD formulation, leading to a reduction in costs. In addition, R&D spending will be curtailed by the peaking of Treakisym® development costs, the diminution of milestone payments for formulation changes, by the temporary review of rigosertib development and by a review of the BCV development plan. Starting in 2022, the successful expansion of indications to r/r DLBCL will gradually boost sales to double the prevailing level. At the same time, there will be a further fall in costs due to formulation changes. However, it is expected that the BCV development objectives will be expanded and rigosertib development will be resumed, and it is highly likely that new licensing and M&A investment activity will emerge in order to capture long-term growth opportunities. SymBio's management planning will have to strike a balance with company profits.

Follow-up Report

Fair Research Inc.

Tsuyoshi Suzuki

Company Information	
Location	Tokyo
President	Fuminori Yoshida
Established	March 2005
Capital	JPY16,519 mil.
Listed	Oct. 2011
URL	www.symbiopharma.com
Industry	Pharmaceuticals
Employees	125(unconsol.)

Key Indicators Nov. 2 2020	
Share price	355
52-week high	791
52-week low	264
Shares outstanding	35,198 thou
Trading unit	100 shares
Market cap	JPY12,495mil.
Est. dividend	0
EPS	-116.16 JPY
Forecast PER	NA
Actual BPS	147.68 JPY
Actual PBR	2.40X

(EPS、PER、BPS、PBR based on shares outstanding excl. treasury shares)

Results	Revenues JPY mil	YoY %	Op. Income JPY mil	YoY %	R.P. JPY mil	YoY %	Net Income JPY mil	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	-253.3	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	-189.03	1,088	542
2020/12 Forecast	3,043	7.2	-4,592	NA	-4,656	NA	-3,796	NA	-116.16		

Company outline and philosophy

Business Model The company is a specialty pharmaceutical company using a niche strategy and targeting high returns. It does not have laboratories or manufacturing facilities, avoiding the risks which they entail	SymBio Pharmaceuticals has the following 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. 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 where 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 has now set up its own sales function and is ready to enter phase 2 of its evolution 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 determinants of commercial success are interactions with a network of drug discovery companies and the company's 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, 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 it 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 125, of whom 44 are involved in R&D. The drug search function is supported by a Scientific Advisory Board (SAB) of experts (including Nobel Prize candidates).
Sets up own sales network Evolves into global licensor	In 2018, Treakisym®, the company's leading product, became established as a standard therapy, and steady progress has been 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.

Update on development of product pipelines

As of October 2020, SymBio's major development products are Treakisym® for relapsed / refractory diffuse large B-cell lymphomas (r / r DLBCL) and the RI preparation for product life cycle management of Treakisym®, together with injectable and oral rigosertib for myelodysplastic syndrome (MDS), and the antiviral agent Brincidofovir (BCV) for multiple viruses.

Phase 2 of the company's development calls for a review of pipelines

At the present time the company has completed preparations for the switch to in-house sales. It has also completed an application for an extension of Treakisym® approved indications to r/r DLBCL and has received approval for use of the RTD formulation (RTD = ready-to-dilute without dissolving). The company is therefore on the verge of entering its second phase of development and it appears a lot of pipeline revamping is going on behind the scenes.

(1) Treakisym® (generic name: bendamustine)

（SyB L-0501, SyB L-1701、SyB L-1702）

[TREAKISYM®]

Pipeline	Indication(s)	Clinical Trial Phase 1 / Phase 2 / Phase 3	NDA※1	MA※2
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	Partial Change Application submitted in May 2020 (BR therapy)		
SyB L-1701 (RTD)※	All	Approved September, 2020		
SyB L-1702 (RI)※	All	Completed patient enrollment for Phase1/2 study		

※ 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

Source: SymBio web page

Treakisym® (generic name: bendamustine) is an anti-cancer drug developed in Germany in 1971 and used to treat low-grade non-Hodgkin lymphoma and chronic lymphocytic leukemia.

In December 2005, SymBio acquired exclusive development and sales rights in Japan 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.

The company is currently working on development which will extend approved indications to relapsed /refractory diffuse large B-cell lymphomas (r/r DLBCL).

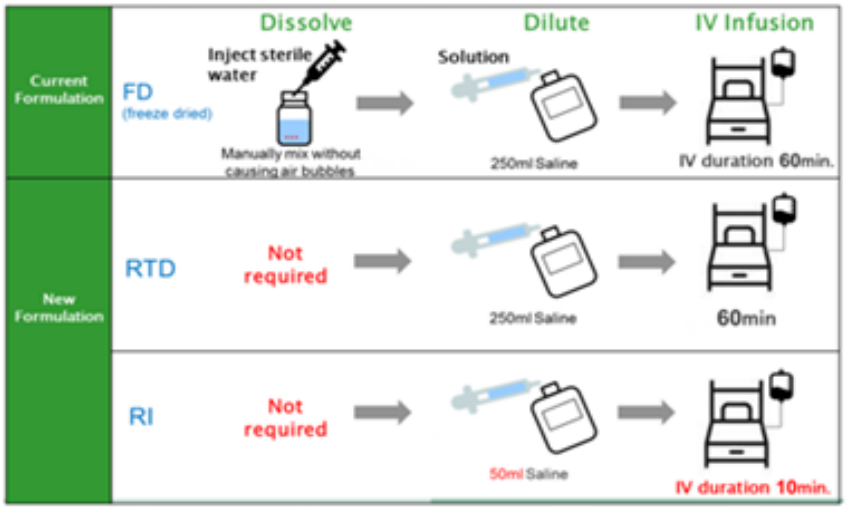
RTD formulation approved in September 2020

① Progress in product life-cycle management: RTD formulation approval

On September 18 2020 the RTD formulation for Treakisym® received regulatory approval, and in the first quarter of 2021 information on this formulation will be supplied to healthcare providers prior to product launch. In December 2020, the sales channel for Treakisym® will be switched from Eisai to direct sales and it is expected that the conventional freeze-dried (FD) formulation will rapidly be

The switch to direct sales in 2021 together with the change in formulation

should ease the problem of defective products	replaced by the RTD formulation. In addition, since the FD formulation supplier (Astellas Deutschland GmbH), will be replaced by the RTD supplier (the US company Eagle Pharmaceuticals Inc, it is hoped that there will be some amelioration of the problem over the last two years of defective products.



Source: SymBio company briefing materials

Development of the very convenient RI formulation is also proceeding steadily	At the same time there has been steady progress in the development of the RI formulation, which is convenient and quick. It was announced on March 17, 2020 that the last of 36 cases for clinical trials of this formulation had been registered, and on September 9, 2020 that the observation period for all subjects had been completed (last patient last visit). It is expected that approval will be given in the second half of 2022. In 2020, ten years will have passed since Treakisym® was first approved, but successful life cycle management means that its product life can be extended to 2031.
In May 2020, application submitted for expansion of approved indications to r/r DLBCL	② Application for expansion of approved indications to relapsed / refractory diffuse large B-cell lymphoma (r/r DLBCL) Good progress has also been made on development work to further expand approved indications. On September 18, 2019 the observation period was completed for of all patients in Phase 3 clinical trials of the B-R dual drug therapy combining Treakisym® (generic name: bendamustine) and Rituxan® (generic name: rituximab) for the treatment of relapsed/refractory diffuse large B-cell lymphomas (r/r DLBCL). On November 5 of the same year, the company announced that primary endpoint results had exceeded expectations. The company then, on May 11 2020, submitted an application for the approval of the B-R therapy for the treatment of r/r DLBCL. Details of this study were presented at the European Society of Hematology (EHA) in June 2020. It was reported that the overall response rate (ORR) was 76.3% and the complete response rate (CR) was 47.4%. A particularly noteworthy achievement was the high efficacy confirmed even in the case of elderly people (aged 65 years or older) whose treatment by hematopoietic stem cell transplantation is not the standard therapy. Even for non-GCB type DLBCL, which has a poor prognosis, the complete response rate (CR) was 39%

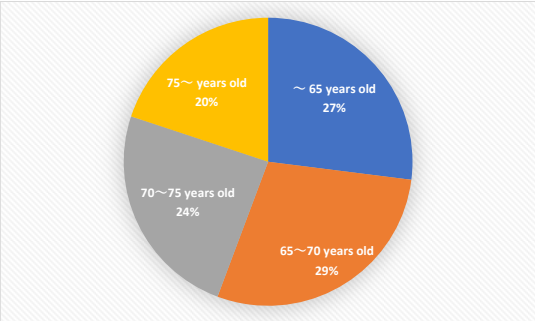
Results of Phase 3 clinical trials of the B-R therapy targeting r/r DLBCL

	(n)	ORR(%)	CR(%)	PR(%)
All patients	38	74.3	47.4	26.9
Response rate by age				
～65 years old	7	85.7	71.4	14.3
65～75 years old	20	75.0	45.0	30.00
75～ years old	11	72.7	36.4	36.3

Source: Symbio company briefing materials

r/r DLBCL is mostly confined to elderly patients (73% of patients are aged 65 and over) with multidrug therapy being the mainstream therapy for such patients. However, when multiple anticancer drugs are taken in combination, adverse side effects can be problematic. B-R therapy uses only two drugs, Treakisym® and Rituxan®, and has an excellent response rate and level of safety. It is very likely, therefore that it will be recognized as one of the standard therapies for this condition.

Age distribution of DLBCL patients (SymBio study)

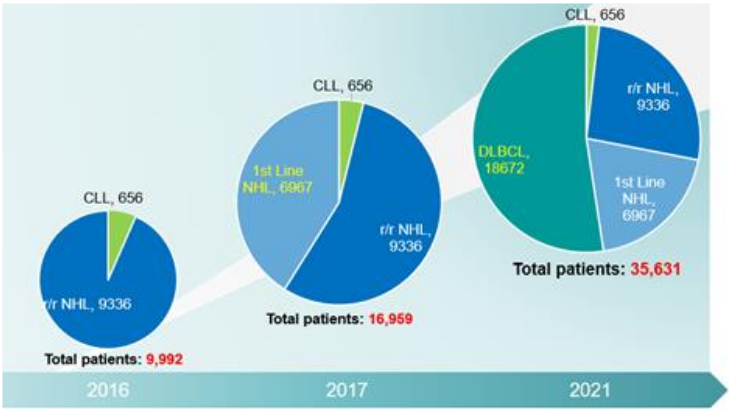


Source: SymBio company briefing materials

Expanded indications could mean doubling of market size

The expansion of indications could mean a doubling of patients being treated and a consequent major increase in the size of the Treakisym® market. The current expectation is that approval will come in the first half of 2021 for a product launch in the second half.

Trend in patient numbers with expanded indications for Treakisym®

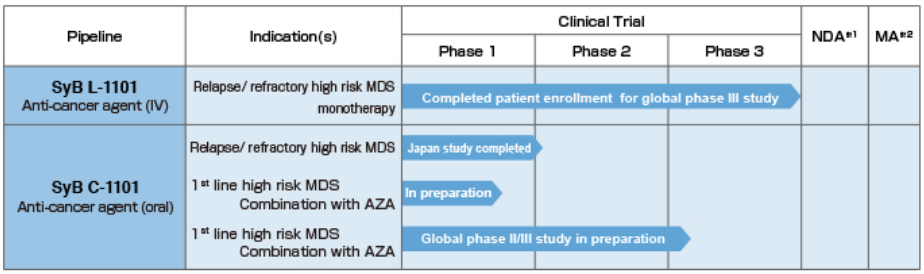


Source: SymBio company briefing materials

In July 2020 application also submitted for joint use of Polivy® in Japan	③ Application for approval of joint use with Polivy® (Japan) In June 2019 the FDA announced the expedited approval of a three-drug therapy for the treatment of relapsed or refractory non-Hodgkin lymphoma for transplant-ineligible patients. 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 joint B-R and Polivy® therapy was submitted in July 2020. While the amount of Treakisym® required for the B-R therapy alone is 120mg per administration, for the three-drug therapy it is 90mg. However, at present it seems that the three-drug therapy will be seen as supplementary to the B-R therapy (the B-R therapy has a longer OS) so we do not think there will be a big impact on the amount of Treakisym® used.
At the present time there appears to be no pressing competitition from other products	④ Development status of competing products Kyowa Kirin is developing as a single agent Zendelisib (phosphatidylinositol 3-kinase δ: PI3Kδ inhibitor) for low-grade B-cell non-Hodgkin's lymphoma in Japan, but has only just started Phase 2 trials (October 2020). The US company, Karyopharm Therapeutics, has developed a drug, Xpivo® (Selinexor), which received approval from the FDA in July 2019. It has a novel mechanism (XPO1: exportin 1 inhibitor) and was originally indicated for the treatment of 5-drug resistant multiple myeloma patients. Subsequently, in June 2020, it was given fast-track approval for the treatment of r/r DLBCL. In October 2017, the Japanese company, Ono Pharmaceutical Co., Ltd., concluded an exclusive licensing agreement with Karyopharm covering the development and merchandising of Selinexor and its successor, KPT-8602, for the treatment of all cancer types in Japan, S. Korea, Taiwan and Kong and the ASEAN countries. However, in early 2020, it ceased development for reasons of its own and surrendered its rights. Some developers of XPO1 inhibitors have suggested that Xpivo® is limited to multidrug-resistant cases due to its poor reversibility and worrying side effects.

(2) Rigosertib; SyB L-1101、SyB C-1101）

[Rigosertib]



Source: SymBio website

Rigosertib has been developed mainly to treat myelodysplastic syndromes (MDS)

Rigosertib is a cancer drug indicated mainly for myelodysplastic syndromes (MDS). Onconova Therapeutics Inc. in the US is an important developer of the drug. After Onconova completed Phase II 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 thought to be JPY800 million).

Onconova finished Phase III trials (ONTIME trials) targeting recurrent and very refractory MDS in February 2014.The results of these trials showed no statistically significant difference between the cohort receiving rigosertib and the control group (palliative care). However, the overall survival for the patient cohort receiving rigosertib was 7.9 months versus 4.1 months for the control group in cases where patients were resistant to the standard treatment using hypomethylating agents (MHA), or when during prior treatment the disease had progressed. This was recognised as significant and on this basis 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 III 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 no competing approved drugs yet.

The top-line results for the international Phase III clinical trials (INSPIRE trials) did not demonstrate a significant difference with physician's choice of treatment

① Top-line results for international collaborative Phase III trials (INSPIRE trials) for injectable drugs

On August 24 2020 Onconova, the product originator, released the top-line results of the INSPIRE trials. The primary endpoint was overall survival (OS). Unfortunately, the ITT-based results showed no statistically 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). However, safety analysis showed that rigosertib was generally well tolerated and serious adverse events were relatively rare.

Now conducting cross analysis of genome analysis. SymBio plans to re-examine its development policy on the basis of the results and on the basis of the Japan-only data

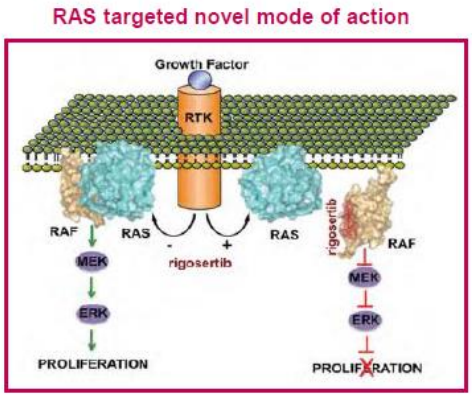
Onconova will conduct genome cross-analysis of registered patient cases and consider again the development of rigosertib. This is because, in recent years, gene mutation analysis of hematopoietic tumours has progressed rapidly with the development of genomic research, and much more is known about the relationship between therapeutic responsiveness and genomic mutation. In addition, SymBio will re-examine its development approach on the basis of cross-analysis and the analysis results of 50 Japanese cases from Onconova.

Rigosertib acts as a RAS inhibitor with an anti-cancer effect, and may additionally act synergistically as an immunity checkpoint inhibitor

② Rigosertib as a RAS pathway inhibitor

It has been established that rigosertib acts as a RAS mimicking 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.

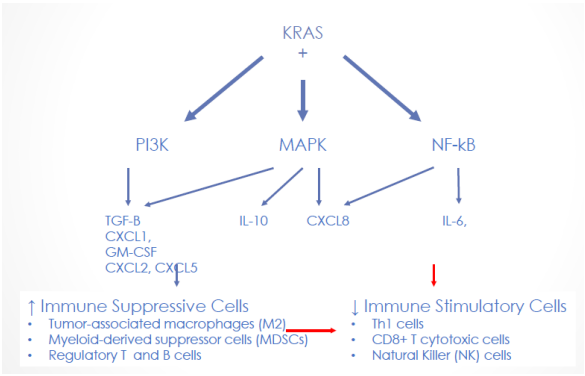
Rigosertib's mode of action



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

In addition, KRAS signals are thought to have a significant impact on the microenvironment surrounding cancer. That is, it is thought that KRAS activation leads to enhancement of a type-II macrophage (M2) and MDSC, which suppress 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. On June 22, 2020, Onconova began patient registrations for a physician-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.

KRAS signaling and the cancer micro-environment



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

SymBio could be ready with a revamped development policy by next Spring

While SymBio is closely watching the development of a KRAS inhibitor by Onconova, it plans to wait for the INSPIRE trial's genome cross-analysis data with the analysis of Japanese subjects only before deciding its future development policy. The new policy may shape up at the earliest around the spring of 2021.

(3) Brincidofovir（BCV; SyB V-1901）

[Brincidofovir]

Pipeline	Indication(s)	Clinical Trial			NDA※1	MA※2
		Phase 1	Phase 2	Phase 3		
SyB V-1901 Antiviral Drug (IV)	Treatment of Adenoviral infection immuno compromised / post hematopoietic stem cell transplantation patients (pediatric and adult) (Global)	Global phase II study in preparation				
SyB V-1901 Antiviral Drug (oral)	Formulation development (Global)	Beginning in 2020				

Source: SymBio web page

Acquired an exclusive global license for all indications except smallpox

On October 1, 2019 SymBio acquired from the US company, Chimerix Inc., exclusive global rights (development, manufacturing and merchandising) to Brincidofovir (BCV) for all diseases except smallpox, making BCV the company's third strategic product after rigosertib. SymBio had previously been an acquirer of licenses from overseas but this development allowed it to evolve into a provider of product licenses globally.

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

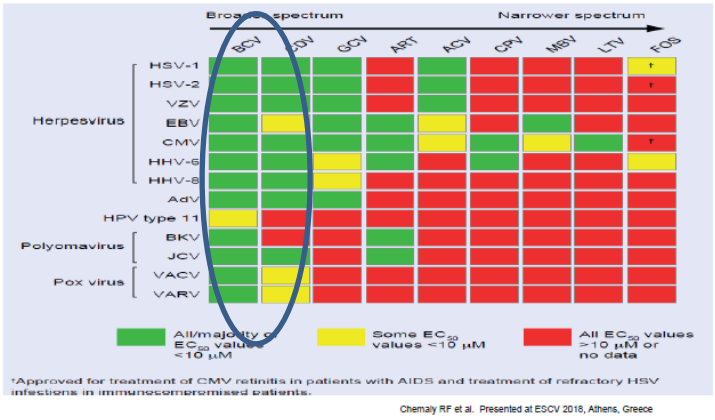
The US Biomedical Advanced Research and Development Authority (BARDA) has provided Chimerix with more than USD100 million to develop BCV as one element in countering bio-terror. In addition, the FDA has given BCV fast-track and Orphan Drug status, and Chimerix received approval in April 2020 to initiate a 'rolling application' (a staggered application for approval of a new drug), allowing it to complete the application within this year. It expects to generate cash flows of USD80-100 million per year for smallpox in the period from five years after launch up to 12 years.

Characteristics of Brincidofovir

BCV is a highly active antiviral drug which is effective across a broad spectrum

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

Brincidofovir (BCV) is highly active across a broad spectrum



Chemaly RF et al. Presented at ESCV 2016, 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

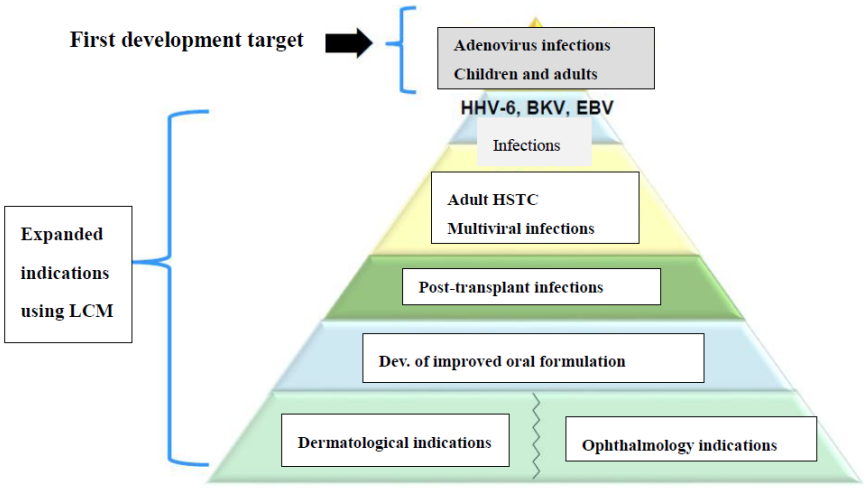
As can be discerned from the previous figure, cidofovir (CVD has a similar level of activity across as broad a spectrum as BCV. However, while CVD is nephrotoxic and difficult to use, BCV has low toxicity and is very safe despite being highly active.

At the time of licensing BCV in, SymBio indicated its first step would be to press forward with the development of an injection formulation of BCV to treat viral hemorrhagic cystitis after hematopoietic stem cell transplantation. This is an area which has a poor prognosis, is highly lethal, and is an area of strong unmet medical needs.

However, on the basis of consultations with the Global Advisory Board in February 2020 a new global development strategy was announced in August 2020. It was decided to give top priority to development in areas where no alternative therapeutic agent was available, where there was a strong unmet medical need and where there was a good expectation of success. On this basis it was decided to focus on adenovirus infections in children and adults following hematopoietic stem cell transplantation (HSCT). The company plans by itself to use overseas CRO's to pursue global development.

The company's initial target following licensing-in was viral hemorrhagic cystitis following HSCT, but changed this to adenovirus infections in children and adults following HSCT

BCV development strategy (August, 2020)



Source: SymBio company briefing materials

We see the company releasing its detailed plans in the Spring. The schedule is for dosage trials for children to be initiated in the US and Europe in the first half of 2021, expanding the dosage trials to adults

From the first half of 2021 the company at present plans to give priority to developing therapies for children where there is a stronger medical need. Now that Chimerix has produced data confirming safety, a start will be made on trials in Japan, the US and Europe to determine dosages (global Phase II clinical trials), following which, while the trials for children are underway, it is planned to begin determining adult dosages.

It seems that SymBio is now internally refining detailed plans, with the trial design and schedule likely to be released in around the Spring of 2021. It is hoped the company will include figures on market size for each BCV indication.

Subsequently, there will be a staged expansion of indications to other

Subsequently, the company will look at the interim results of Pivotal tests on adenovirus infections in children and, as with the original assumptions made at the time of the in licensing-in, will consider a staged expansion of indications to other viruses (such as HHV-6 and BKV). The plan then is to go beyond HSCT to organ

infections and post-organ transplantation infections	transplant infections. Elsewhere, an improved formulation of the oral drug discontinued by Chimerix is being developed.
There may be applications in the areas of dermatology (ointment) and ophthalmology (eye drops)	In the plan released in August, the company also indicated the possibility of expanding beyond antiviral use in surgical operations to ophthalmological (eye drops) and dermatological (ointment) formulations. It is thought there is a pronounced medical need in these areas, where anti-bacterial agents are mainstream but antiviral agents barely exist. SymBio has, it seems, been approached by several pharmaceutical companies with an interest in these areas to discuss BCV applications. Looking ahead, it is thought that several companies will pursue development in the light of compatibility between formulation (eye drops or ointment) and API.

Status of in-house sales capability

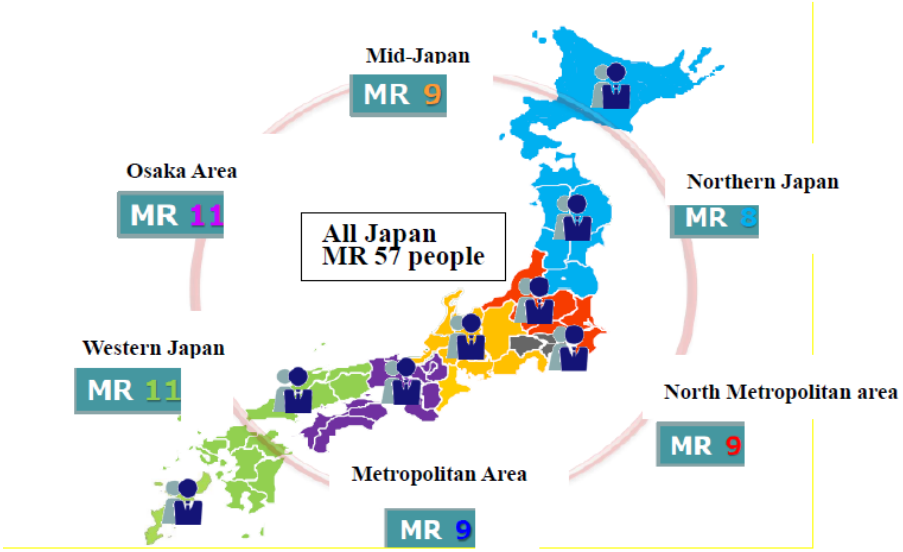
Progress made in building an in-house sales structure of sufficient size and quality

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 30%, 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.

In particular, there is a 7-person group consisting of the KOL manager and the Hematology Experts who network closely with the Key Opinion Leaders

The company successfully completed its recruitment on schedule in June 2020. It now has 51 Medical Representatives highly qualified in the area of hematology, six RSM's (Regional Sales Managers), six 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 is 57, which 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

Operations started to secure the takeover from Eisai

Completion of the logistics network and core systems

On September 7 SymBio announced it was starting work to take over from Eisai with a view to switching to its own sales structure after the termination of its tie-up with Eisai on December 9. In addition, the company concluded basic transaction agreements 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, it was then able to announce the completion of its logistics network. In parallel, both the construction of the ERP system and the upgrade of the IT system were completed in the second quarter of 2020.

Earnings outlook for 2020

Revision of 2020 results forecast and impact on mid-term management plan

The company's first half results were seriously affected by the coronavirus pandemic and by the lingering effects of a defective product problem. This was reflected in a revised earnings outlook released on September 17, 2020.

There are three main points:

Results in the first half were revised down to reflect the tough sales environment; but heading toward a recovery in the second half

① Sales for the 2020 full year were revised down by JPY360 million, and rose from JPY1.36 billion in the first half to JPY1.68 billion in the second. Demand for Treakisym® is greater in the second half than the first due to seasonality, in addition to which overseas sales are expected to rise in the second half.

Operating profit was revised up by JPY500 million, since costs were sevely limited to establishing the in-house sales structure and to preparing for BCV trials next period

② Operating profit was revised up by just under JPY500 million due to a big reduction in SG&A expenses. Top priority is being given to investments required for the in-house sales system starting on December 10, 2020, to undertake actions to achieve profitability in 2021, and to prepare for BCV's global Phase II trials scheduled for the first half of 2021. All other expenses are being pared back. Cost of sales and SG&A figures have not been released but R&D expenses come to about JPY2.2 billion (includes milestone income of JPY500 million from the approval of the RTD formulation). R&D aside, we expect SG&A expenses will be held at around JPY3.3 billion.

Adding in partial legal cost payments from the MDCO, net earnings was revised up by JPY1 billion

③ Net earnings have been revised up by around JPY1 billion. This is because of an upward revision in operating income, and extraordinary earnings from the expected USD495 million payment to SymBio from The Medicines Company (MDCO).

Results revisions for the 2020/December period

(JPY-mil)

	2020				(Ref.)		
	Initial	Revised	2020 H1	Revised H2	2019 Actual	2019 H1	H2
Sales	3,404	3,043	1,360	1,683	2,838	2,004	834
Cost of goods sold	2,258		1,030		1,973	1,475	498
SG&A	6,236		2,169		5,166	2,544	2,622
R&D	2,731	c.JPY2.2 bil	833		2,442	962	1,480
excl.R&D	3,505	c.JPY3.3 bil	1,336		2,724	1,582	1,142
Op. profits	-5,090	-4,592	-1,839	-2,753	-4,302	-2,015	-2,287
Rec. profits	-5,134	-4,656					
Net profits	-4,803	-3,796	-1,884	-1,912	-4,376	-2,069	-2,307

Notes: 2019 H2 R&D includes JPY540 mil. contract payment to Chimerix.
2020 R&D includes JPY500 mil. milestone payment to Eagle corp. for 2H

Source: Compiled by Fair Research Inc., using financial results and other filings

Note:

In October 2015, SymBio concluded a licensing-in contract (contract lump sum about JPY1 billion) with The Medicines Company (MDCO) in the United States for a patient-administered pain management drug, IONSYS. Phase III clinical trials started in Japan in June 2016. However, in May 2017, MDCO suddenly announced the possibility of withdrawal from the business, leading to the cancellation of patient registrations and, in November 2017, to the cancellation of the contract. An arbitration request for compensation was filed with the International Chamber of

Commerce (ICC) seeking compensation in the sum of JPY9 billion. (Incidentally, MDCO was acquired by Novartis AG in January 2020.) A hearing was conducted under the auspices of the ICC Arbitration Court in June 2019, the arbitration proceedings were completed in December, and an arbitration finding was handed down on July 21, 2020. Unfortunately, SymBio's claim for damages was not granted, but MDCO was required to pay SymBio half of the costs associated with the arbitration proceedings.

he company had cash on the balance sheet of JPY5.4 billion at the end of June 2020 so there is no concern in the meantime of running short of cash

While SymBio expects to record a JPY1.9 billion loss on a net earnings basis for the second half of 2020, as of June 2020 it does have cash on the balance sheet of around JPY5.4 billion. In addition, in October, investors will begin exercising rights for new shares on the company's 51st options issue (expected procurement: JPY1.6 billion), so there is very little possibility of running out of funds in the near term.

Note:

New investments in licensing-in and M&A to secure long-term growth opportunities will be put on the back-burner for the time being

On October 13 the company announced changes to the use of funds plan for the proceeds of the companys's 50th options issue (exercise completed) governed by a resolution in February, and for the proceeds of the 51st options issue (exercise underway), in addition to announcing the start of the exercise period for the 51st issue. The amount raised by the 50th issue failed to meet the targeted JPY3.8 billion. Because of weak market conditions it raised only JPY2.28 billion, less than the amount required for the development of new licensed-in product pipelines and financing of the company's in-house sales structure. For that reason the company is going to divert the proceeds of the 51st issue to prioritise product pipeline development and sales structure, and will consider raising funds again when the need arises in the future to finance long-term growth opportunities with new license acquisitions and M&A.

Changes to use of funds

(JPY-mil)

	Funds raised in 50th options issue	Funds rasised in 51st options issue	Total funds raised	Disbursements scheduled
①Dev. Of pipelines licensed in	2,375=>1,380	55=>1,059	2,430＝＞2,439	2020/3/1 ~2021/June
②In-house Sales unit	1,431＝＞900	54＝＞585	1,485＝＞1,485	2020/3/1 ~2021/June
③New licensing and M&A activity to secure long-term growth opportunities	0=>0	1,535＝＞0	1,535＝＞0	Initially: 2020/10/1 ~2021/June
Total	3,806＝＞2,280	1,644=>1,644		

Source: Compiled from SymBio company IR materials, October 13. 2020

The recent changes to the medium-term plan refer only to 2020. The years 2021-2022 are now being scrutinized and any changes to the figures will be released as soon as they are confirmed.

Changes to the medium-term plan are for 2020 only, with 2021 onwards now under consideration

Medium-term management plan (provisional)

(JPY-mil)

	2019 (Actual)	2020 (Rev. forecast)	2021 (Med.term plan)	2022 (Med. term plan)
Sales	2,837	3,043	9,008	10,816
Op. profit	-4,301	-4,592	1,031	1,482
Rec. profit	-4,376	-4,656	987	1,438
Net profit	-4,376	-3,796	1,356	1,717

Source: SymBio medium-term management plan (February 2020) and 2020 revised results (Sept. 2020)

	Fair Research Inc. believes SymBio will achieve profitability in 2021 and will then be on track for 10-20% in terms of operating profit margin. In 2021 the switch to the company's own sales force will mean a new level of sales for the company, and the switch to the Treakisym® RTD formulation will mean a fall in the product cost ratio. In addition, R&D expenses are going to be capped by the peak-out in Treakisym® R&D, by the falling milestone payments for formulation changes, the temporary review of rigosertib development, and changes made to the development plan for BVC (expanding indications beyond pediatric adenovirus)
It is now possible to see the path forward to profitability being achieved in 2021 and then operating earnings growth in the region of the mid-teens	From 2022, a contribution will come from the expansion of indications to r/r DLBCL with sales revenues gradually doubling from the 2021 level. In addition, as the switch to the RTD and RI formulations continue there will be further cuts to the cost of sales. However, earnings growth will not be completely one-sided, since there will also be expanded development of BCV and the resumption of rigosertib development. There is also the fact that the company remains enthusiastic for investments in licensing-in and M&A to secure long-term growth opportunities. SymBio's management planning will have to carefully balance these needs with profit potential.

Conclusion

The execution of the business plan is proceeding well and the company's second phase has begun

SymBio has, due to its establishment of an in-house sales structure and its acquisition of the license to brincidofovir (BCV), established itself firmly for growth as a specialist hematology pharma with a global license, thereby launching a second phase of its evolution. Recently, sales of the company's main product, Treakisym®, have inevitably been revised down due to the coronavirus pandemic and the product quality problems caused by another company, but additional indication approvals and formulation changes are proceeding well and preparations for the new sales structure are well underway.

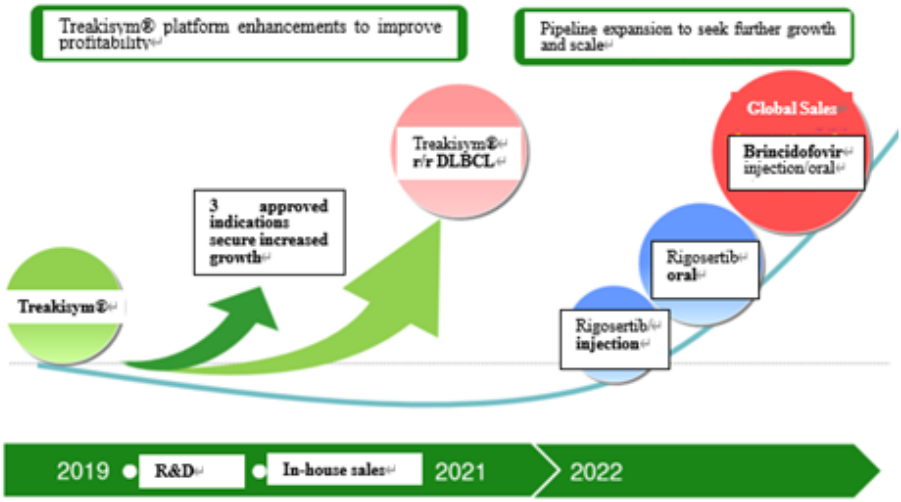
At this, the start of a second phase, a review of product pipelines will be undertaken

At this, the start of its second phase, the company will stand back to review its pipeline strategy. It plans to look again at the development strategy for rigosertib after the INSPIRE results are released and following further detailed analysis. With regard to BCV, it thinks it can reduce the scale of initial testing for targeted indications by switching to more assuredly unmet medical needs. Whether that is the case or not will be revealed at the time of its next medium-term management plan scheduled for release in February 2021.

The medium-term management plan the company expects to announce in February 2021 will be an opportunity to re-evaluate the revised development strategy

We see a very high probability of SymBio's operating profits turning positive in 2021 as a result of its in-house sales and pipeline review. Subsequently, our expectation is for operating profits to trend at 10-20%. Investors will be alert for a re-think of the company's potential when it releases its medium-term management plan in February 2021.

Symbio moving to a new stage



Source: SymBio results meeting materials

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