SymBio Pharmaceuticals Limited

(4582 JASDAQ) Issued: Nov. 7, 2019

Transformation to a Global Licensor

Specialty pharma with multiple promising new drugs

SymBio does not itself undertake drug discovery research but rather uses its insights and its links with drug discovery companies around the world to license in and develop promising new drugs. In particular, it focuses its development efforts on drugs for less common conditions in oncology and hematology, in which areas, despite a definite medical need, the major pharmaceutical companies show little interest. In these niche areas, the company seeks to maximise market share and revenues. In most cases, new drug candidates so selected have a proven track record of efficacy and safety, and therefore entail limited business risk. Thus, the company's first product success was Treakisym®, which went from licensing-in by the company through regulatory approval and market launch in a mere five years, and more recently achieved standard therapy status. The company is now pursuing the development of further applications and changes in formulation as steps in product life cycle management. At the same time, it is making preparations to have its own in-house sales force by 2020 and to evolve as a pharma specializing in blood conditions. Phase 3 clinical trials of rigosertib, the company's second product, targeting the blood disease myelodysplastic syndrome, seem to be going well. Further, in October 2019 the company announced it had acquired exclusive global rights to the drug Brincidofovir. This gives the company a foothold outside of Japan in China and other Asian countries and allows it to develop in the West, evolving as a licensor of pharmaceuticals.

Acquisition of exclusive global license for brincidofovir

Brincidofovir is an antiviral drug developed by Chimerix, Inc. in the United States, and targets viral infections following hematopoietic stem cell transplantation and organ transplantation, an area of high unmet medical needs. In hematopoietic stem cell transplantation and organ transplantation, an immunosuppressive agent is used to suppress rejection, thus facilitating infection. An estimated 20% of patients who undergo hematopoietic stem cell transplantation are said to develop viral cystitis. In addition, HHV-6 encephalitis can develop after hematopoietic stem cell transplantation. This can be fatal once it develops, and serious sequelae remain while the patient survives, so preventive measures are important. Brincidofovir is less toxic and more effective than other antiviral drugs that have been used in the past. For the time being, it is likely that in Japan Brincidofovir will first be developed as a treatment for viral cystitis after hematopoietic stem cell transplantation, then developed as a treatment for HHV-6 encephalitis after hematopoietic stem cell transplantation, followed by the expansion of sales in other Asian countries. Also, in Europe and the United States, where organ transplants are more common, there is a high possibility that it will be deployed via partnership arrangements.

Brincidofovir potential extremely high

The milestones to be paid by SymBio to Chimerix for licensing-in come to a total of $180 million (including a lump-sum $5 million contractual payment), and the royalties rate after launch is thought to be in the double digit range. It is estimated that in Japan the number of viral infections (viral cystitis + HHV-6 encephalitis) after hematopoietic stem cell transplantation is about 2,600 per year, and the market size is around JPY7-8 billion. In Europe and the US, there are some 14,000 cases annually. In developing regions, including Asia, the population-adjusted number of hematopoietic stem cell transplantations per year is still approximately 1/20 that of Japan, the US and Europe, and is expected to expand in the future. The number of cases of viral infection after kidney transplantation, which is expected to be the next application, is around 500 annually in Japan. However, the scale of organ transplantation overseas is extensive, amounting to some 15,000 cases annually in the US and Europe. We have conducted a trial calculation based on fairly challenging hypothetical conditions and posit pipeline value at JPY24-44 billion yen just for hematopoietic stem cell transplantation targets in Japan, the US and Europe. If we include the development of additional viral infections and organ transplants the figure could rise to JPY50 billion. The company's three main products could bring in a total of JPY90 billion.

Follow-Up Report

Fair Research Inc.

Tsuyoshi Suzuki

Company Outline	
Location	Tokyo
President	Fuminori Yoshida
Established	March 2005
Capital	JPY12,972 mil.
Listed	October 2011
URL	www.symbiopharma.com
Industry	Pharmaceuticals
Employees	102 (non-consol.)
Key Indicators (at Nov. 6, 2019)	
Share price	765
52-week high	1,088
52-week low	542
Shares outstanding	24,363thousand
Trading unit	100 shares
Market cap	JPY18,637 mil.
Dividend (est.)	0
EPS (company est.)	-167.66 yen
Forecast PER	NA
Actual BPS	198.87 yen
Actual BPR	3.85x

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

Results	Revenues JPY mil	YoY %	Op Income JPY mil	YoY %	RP JPY mil	YoY %	Net Income JPY mil	YoY %	EPS Yen	Share Price (yen) High	Low
2014/12 Actual	1,955	27.6	-1,303	NA	-1,110	NA	-1,115	NA	-145.0	1,572	784
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
2019/12Comp.Forecast	3,092	-19.4	-3,780	NA	-3,856	NA	-3,859	NA	-167.66		

Company outline and management philosophy

＜Business Model＞

Operating without laboratories, and thereby reducing the risks in new drug discovery, SymBio operates a niche strategy, evolving from a pharmaceuticals venture to a pharma company

SymBio Pharmaceuticals Ltd. has the following special characteristics

① **"Lableѕs" to reduce business risk**
Operates without laboratories, thereby controlling the risk of its operations. In terms of business model, the company itself does not conduct drug discovery research. Rather, it seeks out and carefully investigates new drug candidates developed by drug discovery ventures and pharmaceutical companies around the world. A new drug candidate selected as a result of this process can become the subject of a licensing agreement and, following development in Japan, can be licensed out to another company for commercialization, or can be commercialized by SymBio itself. Since the company undertakes development in Japan, it should be recognized as not simply a technology trader but as a bio-pharmaceutical company.

② **High market share and strong earnings from a niche business strategy**
The company focuses its development efforts on drugs for relatively rare conditions in, for example, oncology and hematology which, despite strong medical needs, the major pharma companies have mostly steered clear of. Using this niche strategy, it aims for high market share and strong revenues.

③ **Post-POC strategy**
In most cases Proof of Concept has already been established. By insisting on prior evidence of efficacy and safety in human subjects, the company reduces the development risks of new drug candidates.

The determinants of success are interactions with a network of drug discovery companies and the ability to discern, judge and evaluate

This business model, then, is one which seeks to control the risks inherent in drug discovery while at the same time securing good returns.

The success of this business model is dependent, obviously, on having a network of drug discovery companies worldwide, but also a keenly discerning eye for what is likely to succeed.

SymBio is one of those rare bio-ventures with a product on the market took five years to develop from licensing-in

That the company has what is needed is demonstrated by its 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 licensing-in to manufacturing and commercial approval in a mere five years, and in July 2018 it became the recommended standard therapy. To date, the company has licensed-in 6 products, of which 3 are currently slated for development.

Special attention to the support provided by the company's human resources and organization

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 workforce of 90, of whom 40 are involved in research & development. The drug search function is supported by a Scientific Advisory Board (SAB) of specialists (including Nobel Prize candidates) who review drug candidates.

In 2018 the company's leading product, Treakisym®, achieved standard therapy status. Smooth progress is being made on expanding indications and adding formulations which, together with the decision to build its own sales structure, means the company is making the leap from the bio-venture stage to full-fledged pharmaceuticals company.

＜The third pillar＞

Company acquires global license for Brincidofovir

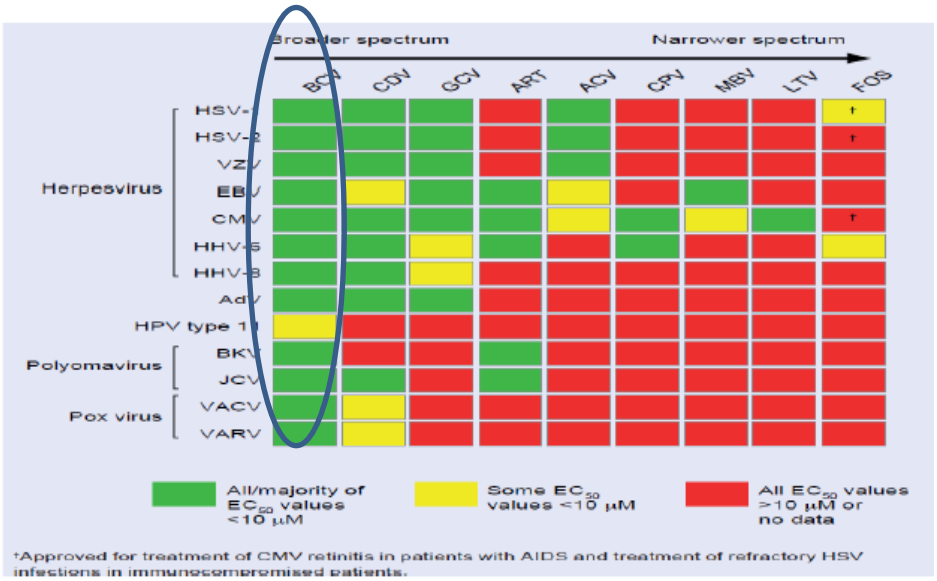
On October 1, 2019 SymBio announced its acquisition of the exclusive global licensing rights (development, manufacture and commercialization) to Brincidofovir (BCV). The acquisition, from the US company, Chimerix Inc., covers all applicable human indications excluding smallpox. This represents a major change for SymBio, which has until now licensed in from overseas and undertaken development mainly for the Japanese market. The contract arrangements on this occasion allow SymBio to license out on a global basis. BCV is to be the company's third strategic product, following Treakisym® and rigosertib.

BCV's distinctive characteristics

Compared to other antiviral drugs BCV is highly active with low toxicity

There are other antiviral drugs such as cidofovir (CDV) and foscarnet (FOS), but compared to these, BCV is a highly active multi-viral drug.

BCV demonstrates high activity versus various viruses



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

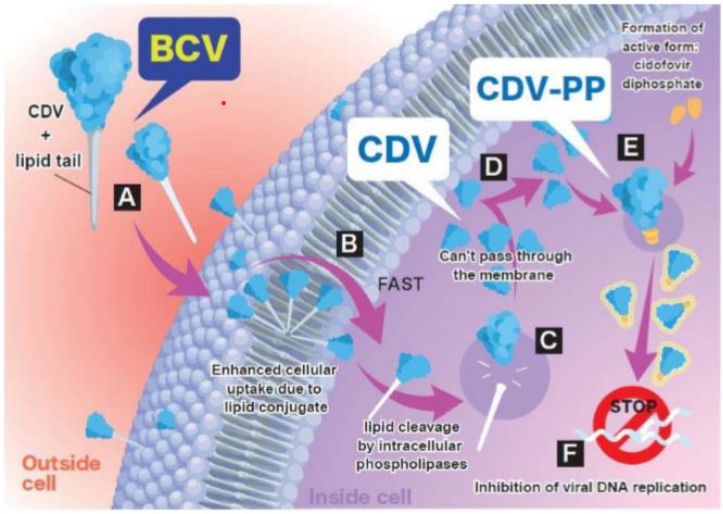
Note: The EC50 (effective concentration of a drug or antibody evincing the maximum response 50% from the lowest value) in which lower values indicate higher activity. In the above figure, at a minimum EC50 value the level of activity is color-coded, so that green has high activity and red has low. BCV on the left is green against various viruses. Source: Chimerix Inc.

Note: Cidofovir (CDV) (extract from SymBio IR materials)
In 1996 the FDA approved the use of cidofovir (CDV) for the treatment of cytomegaloviral retinitis in AIDS patients. CDV is a cytosine nucleotide analog that inhibits replication of DNA viruses such as adenovirus, papillomavirus, polyomavirus as well as herpesvirus. CDV is also effective against ganciclovir (GCV) resistance (UL97 gene mutation) and is considered useful when foscarnet (FOS) cannot be used when GCV resistance appears. In Japan, it is an unapproved drug that has not been developed.

In addition, Chimerix develops pharmaceuticals that behave like natural phospholipids, providing additional effectiveness by improving the metabolic distribution of drugs, and lower toxicity. Cidofovir (CDV) is a typical example of such a recognised antiviral drug (although not approved in Japan and limited to private import). However, BCV has a very different metabolic distribution from cidofovir, allowing the avoidance of nephrotoxicity. Further, while foscarnet (FOS), which is approved for HIV-6 encephalitis, is nephrotoxic, such toxicity can be avoided with Brincidofovir.

Reference: BCV's mechanism of action

BCV is a lipid conjugate of CDV with hexadecyloxypropyl (HDP), evincing a rapid incorporation to the plasma membrane with efficient cellular uptake due to the lipid conjugate. Once uptaken inside target cells, the lipid chain is cleaved by action of intracellular phospholipases releasing CDV, which is then converted to the active form, CDV-PP-CDV diophosphate. As a result of this being retained in the cell for an extended period, the antiviral activity of the drug is dramatically improved. Furthermore, BCV can greatly reduce the risk of nephrotoxicity associated with CDV because HDP conjugation brings no accumulation of CDV in renal tubular epithelial cells through the OAT-1 transporter, and low plasma exposure of CDV.



Source: SymBio IR materials

Targeted diseases

BCV targets viral infections after hematopoietic stem cell transplantation and organ transplantation

Symbio has announced that it will focus BCV development initially on viral infections following hematopoietic stem cell transplantation and kidney transplantation, which are characterized by poor prognosis and high lethality, and which constitute a strong unmet medical need. Generally, in hematopoietic stem cell transplantation and organ transplantation, radiation or an immuno-suppressive agent is used to suppress rejection, but this increases the likelihood of viral infection. Normally, other antiviral agents, such as CDV and FOS, have been used but there is a concern about the nephrotoxicity side effect. BCV is a key product in SymBio's ambition of becoming a specialist pharma in the area of renal medicine.

This product will give support to the company becoming a specialty pharma in the area of hematology

The first targeted disease areas will be:

① Viral hemorrhagic cystitis after hematopoietic stem cell transplantation
② Encephalitis due to HHV-6 infection after hematopoietic stem cell transplantation
③ Virus infection after kidney transplantation

Note: Hematopoietic stem cell transplantation（HCT）
Treatment that aims at complete cure for blood diseases (mainly blood cancers such as leukemia) that are difficult to treat with anticancer drug treatment (chemotherapy) or radiation therapy alone.

Note: Viral hemorrhagic cystitis (extract from SymBio IR materials)
Among viral infections that frequently occur after hematopoietic stem cell transplantation, adenoviral infections that causes hemorrhagic cystitis are generally refractory, and cause severe symptoms for patients, such as frequent urination, abdominal pain, and micturition pain. In serious cases it can be fatal. In addition, there have also been reports of cases where adenovirus is transferred to the kidney, causing renal failure and resulting in death. It tends to occur especially in the case of unrelated donors

and umbilical cord blood transplants, which have a high ratio in Japan. It is often extremely refractory due to the time required to reconstruct the immune system.

Note: HHV-6 encephalitis (extract from SymBio IR materials)
HHV-6 (human herpesvirus 6) is the sixth human herpes virus to be discovered. In allogeneic hematopoietic stem cell transplantation, reactivation of HHV-6 occurs in 30-70% of patients, causing HHV-6 encephalitis. This mostly happens in the second to sixth week, with the peak being in the third week following transplantation. Memory impairment, consciousness disorder, and convulsions are the three major symptoms. In typical cases, symptoms progress gradually from memory impairment to consciousness disorder and convulsions, with the reported incidence of convulsions being 30-70%. In fast-growing cases, neurological symptoms worsen over time, and many cases require ventilator management for repeated convulsions and respiratory depression. Early treatment is very important for patients with HHV-encephalitis as the patient's condition often deteriorates rapidly in a short time. According to clinical guidelines*, the first drug is foscarnet (FOS) or ganciclovir (GCV), and the second drug is cidofovir (CDV). CDV is the second-line drug because of strong nephrotoxicity and poor transfer of the drug into the cerebrospinal fluid (CSF). However, while the effects of these drugs have been confirmed in vitro, no tests to date have been conducted to confirm the clinical effects of these drugs on HHV-6 encephalitis cases.
* Guidelines for hematopoietic cell transplantation: Prevention and treatment of viral infections HHV-6 (Japan Society for Hematopoietic Cell Transplantation: February 2018 edition)

Potential market size and development strategy

The number of hematopoietic stem cell transplants is estimated to be around 78,000 annually worldwide, of which about 43,000 are autologous and have a low rejection risk. To reduce the risk of rejection it is necessary to suppress immune responses. There are about 35,000 allogeneic allografts that have a high risk of viral infection.

BCV is used to treat the estimated 8.6%-24% of the latter who contract viral hemorrhagic cystitis, and the 30-70% who contract HHV-6 encephalitis. The probability of contracting encephalitis in Japan is high due to the high proportion of unrelated donor transplants.

SymBio estimates that 50-60% of allogeneic transplantations in Europe and the US, and around 70% in Japan can be targeted. As a result, the annual number of cases in Japan comes to around 2,600, and in the West (US plus the five major countries in the EU) comes to around 14,000 cases. In the developing world, the incidence of population-adjusted stem cell transplants is still around one-twentieth of those countries, but the trend is likely to grow.

Number of stem cell transplantations (HCT) and organ transplantations (SOT) and use of BCV

TRANSPLANTS PER YEAR (population)	US (320M)	EU (550M)	Japan (130M)	ROW	Total
HCT					
Allogeneic	8,700	16,400	3,700	6,454	35,254
Autologous	15,000	21,700	1,800	4,715	43,215
HCT TOTALS	23,700	38,100	5,500	11,169	78,469
SOT					
Kidney	19,860	20,000	1,648	39,052	80,560
Liver	7,800	7,400	438	10,062	25,700
Other SOT	5,940	4,500	124	1,276	11,840
SOT TOTALS	33,600	31,900	2,210	50,390	118,100
TOTAL TRANSPLANT	57,300	70,000	7,710	61,559	196,569

＜SymBio Estimate＞

Indications	Estimated # of Patients in 2027	
	US + EU5	JAPAN
Post HSCT vHC・HHV-6 encephalitis	14,189	2,592
BKV・CMV infections post kidney transplant	15,386	558

Source: SymBio based on Chimerix data

Assuming a drug cost per case of JPY3 million to treat viral infections following stem cell transplantations yields a market value in Japan of approximately JPY8 billion, and

Potential market scale given incidence of stem cell transplants is JPY8 billion for Japan, and JPY42 billion for the US and Europe. The Asian market (including China) also has big potential

The company willl develop targeting of stem cell transplantations in Japan, and will then give consideration to expansion into Asia, including China

Initial viral hemorrhagic cystitis targeted development will be in 2020, with pivotal tests starting in the second half, and development targeting HHV-6 encephalitis expected to folllow a year later

As for the development of BCV for viral infections following organ transplantant, the company's strategy is to tie up with US and European pharma partners

in the US plus the five major EU countries in excess of JPY42 billion. We believe the incidence of stem cell transplantations is growing in Asia, but assuming the population-adjusted rate is the same as Japan, we estimate the potential size of the China market (population 1.4 billion) could be in excess of JPY83 billion. However, looking only at the coastal region, where most of the medical infrastructure is, the actual figure could be half of this.

SymBio is likely to initially concentrate development in Japan on viral hemorrhagic cystitis beginning in early 2020, using already existing data collated overseas to help advance the schedule. Pivotal studies in Japan are expected to begin in late 2020 on about 50 subjects. It will take around 18 months to complete the roster of cases, and in the second half of 2023 pivotal studies will be completed. It is thought that an application for approval will be made in 2024 and marketing will begin in 2025. Tests targeting HHV-6 encephalitis and hemorrhagic cystitis of around the same scale will follow with a delay of around one year. Overseas, development is likely to follow receipt of approval in Japan, with the initial emphasis on Asia including China.

Transplantation surgery is carried out more actively overseas than in Japan. For example, there are around 1,600 kidney transplantations per year in Japan, compared to some 20,000 in the US and the same in Europe (five main EU countries). An estimated one-third of these are infected with either the BK virus or the CMV (cytomegalovirus). Japan therefore has only about 560 cases, compared to some 15,000 cases in the US and the five main countries of the EU. Organ transplantation is not within SymBio's area of expertise, and Japan has relatively little exposure, which could lead SymBio to tie up with a US or European pharmaceutical company. The partner would probably handle development and merchandising of post-organ transplantation product strategies.

Reference: Modelling the BCV pipeline value

Under the agreement SymBio is to pay Chimerix a total of USD180 million in milestone payments (including a licensing-in sum of USD5 million), and royalties (said to be a fixed double-digit percentage based on sales). We assume this to be in the lower 10% range and have set it at 12% for the purposes of our modelling. Further, for the same purpose we have limited applications to those related to stem cell transplantations. As for markets, we have assumed Japan and Asia (including China) will be central to development. We have assumed a market size of JPY8 billion for Japan, and for the overseas markets a fairly conservative figure of 4 times that amount, or JPY32 billion. As for development costs, as noted earlier, this will depend on each condition, with an assumed 50 subjects undergoing pivotal tests at a cost of around JPY500 million per year. We further assume a gross product margin of 80% on the product in Japan. In overseas markets, it is possible that SymBio will conduct the sales function, but we assume for our calculations that there will be a licensing out, with SymBio receiving a gross profit margin of 50%. Milestone revenues associated with the licensing-out are assumed to total one-third of peak sales, or JPY10 billion. In addition, we assume probability of success is 80% since POC has been established for human subjects. Given these rather challenging assumptions we posit pipeline value at around JPY24-44billion. On the assumption that progress is made with other viral infections and organ transplantations we imagine there is a possibility that the BCV pipeline value could exceed JPY50 billion.

Modeling the BCV pipeline value（Pretax; only for HCT）

(100mil Yen)

		Success Rate	
		80%	100%
DCF discount rate	8%	328	436
	10%	241	325

Source: Calculated by Fair Research

In any case, with a pipeline value of at least JPY50 billion, and milestones amounting to USD180 million (JPY19 billion) and double-digit royalties, this acquisition looks like an extremely good deal for SymBio.

Chimerix will focus on the development of drugs for acute myeloid leukemia and BCV for smallpox	**Chimerix's situation** Chimerix had been concentrating on the development of Brincidofovir (BCV), an anti-viral drug, but has importantly changed its product strategy to concentrate mainly on the oncology area. In July 2019 it licensed in "CX-01" from Cantex Pharmaceuticals, Inc. CX-01 is now preparing for Phase 3 for acute myeloid leukemia (AML). In September 2019 Brincidofovir was licensed out on a global basis to SymBio Pharmaceuticals for all indications excluding smallpox. When Chimerix was concentrating on the development of Brincidofovir, hopes were high for the company's share price in the stock market. In December 2015, however, expectations were greatly diminished when, in Phase 3 trials on magalovirus infection after hematopoietic stem cell transplantation, it was announced that no significant reduction in infection was achieved. This is thought to be because of the need to administer high dose steroids in order to suppress GvHD, or graft versus host disease, in which donor leukocytes contaminated with transplanted hematopoietic stem cells attack the patient's cells. This can lead to reinfection. Chimerix continued the development after amending the trial design. Antiviral efficacy was demonstrated but a problematic side effect was noted with diarrhea. This caused patient registrations for the trials to dry up and development fell behind schedule. Chimerix developed both oral (100 mg) and intravenous (10 mg) versions, with the emphasis being on the high-dose oral drugs. However, SymBio is considering the development of an intravenous injection that is effective even when the dose is small and does not consider side effects such as diarrhea as problematic.

Update on the status of other product pipelines

As of October 2019, SymBio's main development drugs excluding Brincidofovir include Treakisym® for relapsed/refractory diffuse large B-cell lymphoma (r/rDLBCL), and the introduction of a number of RTD and RI formulations to help with Treakisym® life cycle management. In addition, there is an oral and injection formulation for rigosertib for the treatment of myelodysplastic syndrome (for details see our Basic Report issued on April 16, 2019). Below we present an update of developments since the issue of our last report.

(1) Treakisym®

[TREAKISYM®]

Pipeline	Indication(s)	Clinical Trial			NDA※1	MA※2
		Phase 1	Phase 2	Phase 3		
SyB L-0501 Anti-cancer agent	r/r Low-grade NHL/MCL	Approved October, 2010				
	CLL	Approved August, 2016				
	1st line Low-grade NHL/MCL	Approved December, 2016				
	r/r DLBCL	P3 initiated August, 2017 LPLV achived				
	RTD (ready-to-dilute) Injection (liquid formulation)	NDA September 2019				
	RI (Rapid Infusion) Injection (liquid formulation)	P1 & 2 initiated November 2018				
SyB C-0501 Anti-cancer agent (oral)	Advanced solid tumors	P1 initiated January 2018				
	SLE	Pre-clinical study ongoing				

※ 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 aims to market the RTD formulation in the first half of 2021, and launch the RI formulation on a subsequent date.

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

Source: SymBio home page

◎ Relapsed/refractory diffuse large B-cell lymphoma (r/rDLBCL)

Exceeded expected response rate in Phase 3 trials on recurrent refractory DLBCL. Development is proceeding smoothly

As also noted in our previous report, it was announced on April 8, 2019 that the case registration for Phase 3 clinical trials on a fourth indication, relapsed / refractory diffuse large B cell lymphoma (r/r DLBCL), has been completed. The observation period for all patients was completed on September 18, and on November 5 it was announced that overall response rates had exceeded expectations, thus demonstrating smooth progress in development. There is no change in plans to submit an application in the second quarter of 2020 and to begin marketing in the third quarter of 2021.

◎ RTD formulation

Announced on September 26 that an application had been submitted for an RTD formulation (Ready-to-Dilute; dilution without need for dissolution). Plan is still to release in the first quarter of 2021.

◎RI formulation

On April 10th 2019, the company announced it had administered its RI formulation (rapid intravenous formulation) to the first batch of 36 patients in clinical trials. Smooth progress reported in patient registration. No change in plan to release in first half of 2020.

◎ Oral formulation

Sixteen patients completed registration for Phase 1 clinical trials of the oral formulation in July 2019.

◎ Possibility of using in CAR-T therapy

On May 22 2019 Novartis Pharma KK announced that the Kymriah® antigen receptor T-cell (CAR-T cell) therapy, or Kymriah® Intravenous Infusion (generic name: Tisagenelcleucal), had been listed in the official drug prices for relapsed or refractory CD-19 positive B-cell acute lymphoblastic leukemia (B-ALL) and relapsed or refractory CD19- positive diffuse large B cell lymphoma (r/r DLBCL). Already in March 2019, partial changes in Treakisym® were approved for the pre-treatment of tumor-specific T-cell infusion therapy, allowing it to be used also for pre-treatment of Kymriah® intravenous infusion.

◎ Combined use with Polivy® approved by FDA

In June 2019, the FDA announced the rapid approval of a three-drug therapy consisting of bendamustine (Treakisym®) + rituximab (Rituxan®) (BR therapy) and the anti-CD79b antibody-drug complex polatuzumab vedotin (trade name Polivy, developed by Genentech and Roche) for non-transplantable, relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL). It is expected that an application for approval will be submitted in Japan in 2021. In B-R therapy, the amount of Treakisym® used is 120mg per dose but will be 90mg in the case of this three-way therapy. B-R therapy is thought to be supplementary and Treakisym® will have a relatively subsidiary effect.

◎ Status of competing products

It was announced on May 28 2019 that the FDA had approved a therapy combining Revlimid® (commercial name: Lenalidomide) and Rituxan for the treatment of follicular lymphoma and marginal zone lymphoma. Revlimid® is an oral immuno-modulator developed by Celgene which has already been approved for multiple myeloma (MM) and myelodysplastic syndrome with chromosome 5 long arm deletion (5q-MSD). On May 22 2019, Celgene announced it had applied for approval of a therapy combining rituximab and Revlimid® in patients with relapsed/refractory low-grade diffuse large B-cell lymphoma. However, most of the DLBCL cases were GCB-type and in tests evinced little effect. ROBUST study of non-GCB type is now ongoing. Provisional interim results did not show the expected promising results for ABC-type DLBCL's, which constitute most of the non-GCB type.

（2）Rigosertib

[Rigosertib]

Pipeline	Indication(s)	Clinical Trial			NDA※1	MA※2
		Phase 1	Phase 2	Phase 3		
SyB L-1101 Anti-cancer agent (IV)	Post-HMA Higher Risk MDS	Global P 3 (INSPIRE study)				
SyB C-1101 Anti-cancer agent (oral)	1.1st line Higher Risk MDS 2.With azacitidine (under preparation)	P 1 (monotherapy)				

Source: SymBio home page

◎ International phase III clinical trial of injections

As of August 2, 2019, the number of cases in Japan came to 44, approaching the target of 50 cases. According to a release by Onconova Therapeutics, Inc., the licensor, on October 24 2019, the enrollment of all patients (360 cases) will be close to 90% complete in the first half of 2020 and they will be ready to report on top-line (major endpoint) results. Development therefore seems to be progressing smoothly.

Progress made in registrateion of patients for Phase 3 injection formualtion. Development proceeding smoothly

	◎ Oral formulation (targeting untreated high-risk MDS) On October 24, 2019 Onconova Therapeutics announced that, following discussions with the FDA on a Special Protocol Assessment it applied for in January 2019, it would study Phase 2 clinical trial design (mainly to compare rigosertib/azacitidine combination and azacitidine mono-theraphy) targeting untreated high-risk MDS. ◎ Development status of competing drugs (target: untreated high-risk MDS) Drugs under development for high-risk myelodysplastic syndrome (MDS) include guadecitabine, a methylation inhibitor similar to azacitidine (being developed by Otsuka Pharmaceutical's US subsidiary, Astex Pharmaceuticals) and the molecular target drug Pevonedistat (under development in the U.S. by Millennium Pharmaceutical, and in Japan by Takeda Pharmaceutical), but all remain at Phase 3. In addition, US-based Karyopharm Therapeutics' XPOT1 inhibitor Selinexor® (rights held by Ono Pharmaceutical in Japan), which is approved for multi-drug resistant multiple myeloma, is also under development for myelodysplastic syndrome (MDS). It is still in Phase 2 clinical trials. Also, SY-1425 (oral) from Syros Pharmaceuticals seems to be prioritizing AML (acute myeloid leukemia) with RARα mutation over myelodysplastic syndrome (MDS) as the object of development.
Company likely to complete its hiring of 30 Treakisym managers by early 2020, and has already started work on a countrywide sales structure	**SymBio's in-house sales structure** As early as 2018 SymBio had secured a team of 10 very specialized individuals as Treakisym Managers (TM's) to undertake Treakisym® sales activities. The number was brought to 17 in July 2019, and sales activities across the country began. The company is planning to eventually have 30 TM's and to add secondment Medical Representatives (25-30). The hiring plan is going well at present so that by early 2020 it should have an in-house head count of 30 MR's (TM's).

Supplement: Revisions to 2019 results

In the October-December period of 2018 and the first half of 2019, there were product quality problems which necessitated downward revisions to corporate results

Because of a delay to Treakisym® shipments in August 2019 SymBio revised down its 12/2019 results. Sales were revised down by JPY1.372 billion from JPY4.465 billion to JPY3.092 billion. The cause of the revision was a problem with the quality of the lyophilized Treakisym® imported from the manufacturer, Astellas Deutschland GmBH. In the fourth quarter of 2018, too, there was a quality problem with the 25mg formulations, so that from the first quarter of 2019 the company switched to 100mg imports. In the second quarter, however, the 100mg formulations were found to contain impurities and numerous imperfections in appearance. This meant that almost all shipments planned in 2019 from the second quarter onwards could not be completed until the early part of 2020. The present situation is that the cause of the problem has been found, remedial measures are being put in place and the problem is being resolved.

To make up loss in profits by reducing all unnecessary expenses

The downward revision in operating income is less than the downward revision in sales. The reduced amount of operating income has been kept to JPY193 million by savings, relative to the initial budget, of JPY500 million on R&D expenses and JPY300 million on SG&A. The reduction in R&D is mainly in basic research, so that the development work necessary for profitability after 2021 has not been affected. SG & A expenses other than R&D expenses are higher than initially expected, probably due to front-loading the in-house sales structure.

Changes in P&L expectations for 12/2019

(Million Yen)

	Initial Plan (February)		Revised Plan (August)	Jan-Jun Result	Jul-Dec Plan (August)
Sales	4,465		3,092	2,005	1,087
Gross Profits	1,497		979	529	450
SG&A Cost	5,053		4,759	2,544	2,214
R&D Cost	2,508		2,029	962	1,067
Excl. R&D Cost	2,545		2,730	1,582	1,148
Operating Profit	-3,780		-3,780	-2,015	-1,765
Recurring Profit	-3,856		-3,856	-2,069	-1,787
Net Income	-3,859		-3,859	-2,070	-1,789

Source: Fair Research, Inc. using results filings

However, absence of costs for licensing-in BCV from the August 2019 plan makes a further revised outlook likely

However, the one-off payment for the licensing-in of Brincidofovir (BCV) is not included in the August revisions. In the final analysis, it is likely that operating revenues will be revised down by JPY500 million to a loss of JPY4.3 billion, and at the net level earnings will come in with a loss of around JPY4.4 billion. In the second half of 2019 both operating and net earnings will chalk up losses of around JPY2.3 billion.

Despite this, no concern for the time being that cash may be insufficient

On the other hand, cash on the balance sheet totaled around JPY6 billion at the end of June 2019, and the final tranche (around JPY3 billion) in the multi-year capital procurement program is expected at the end of 2020. There is no fear, therefore, of the company depleting its cash holdings for the next 1-2 years, despite costs arising from the establishment of an in-house marketing function and continued development of the company's three main products

The company plans to amend its medium-term management plan. The 2021 target for turning profitable is unchanged, but earnings growth post-2022 will be more subdued due to BCV development costs

Elsewhere, some progress has been made in the arbitration proceedings filed with the International Chamber of Commerce against The Medicines Company, and some sort of conclusion is expected at the end of this year or early next year (SymBio is seeking an amount equivalent to about JPY9 billion). This sum would further enhance the cash position.

The revised plan currently being formulated will reflect the 2019 results forecast after-effects and the effect of licensing in BCV. It is possible that part of the Treakisym® shipments that could not be completed in 2019 will be deferred until 2020. It should also be noted that the 2021 date for turning profitable is unchanged. Rather, there may be a change in attitude to earnings in and after 2022 given the weight of BCV development costs. Needless to say, this was a necessary investment for a company seeking additional growth and global specialty pharma status.

Previous medium-term earnings plan （as of Feb 2019）

	FY2019 Forecast	FY2020 Target	FY2021 Target	FY2022 Target
Net Sales	4,465	3,282	9,132	11,282 ～ 11,809
Operating Profit	-3,587	-5,180	1,225	2,084 ～ 2,464
Ordinary Profit	-3,612	-5,224	1,181	2,040 ～ 2,420
Net Profit	-3,616	-5,228	1,005	1,736 ～ 2,060

Note: Sales during the period of the medium-term plan are for Treakisym® since sales of rigosertib, etc. not scheduled. Until 2020 wholesale deliveries to Eisai, and then company's own sales

Source: SymBio Medium Term Management Plan, February 2019

Total value for three product pipelines exceeds JPY90 billion(pretax)

Opportunity for re-evaluation of SymBio

Conclusion

By developing an in-house sales capability and acquiring BCV, SymBio has built the foundations for growth as a global renal specialty pharma. We estimate its three main pipelines (Treakisym®, rigosertib and Brincidofovir) have a combined value (pre-tax) of over JPY90 billion (refer to our basic report dated April 16 2019 for details on the value of Treakisym® and rigosertib).

Symbio has recently been forced to make downward revisions due to quality issues arising at another company. On the plus side, the multi-year funding program will be completed soon, and we are optimistic the company will be re-evaluated by investors as it becomes profitable in 2021.

Note: Please note differences between pipeline value and corporate value

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