SymBio Pharmaceuticals Ltd.

（4582 JASDAQ） Report issued:19/Feb/2018

Pipeline value of JPY30 billion even after allowing for ongoing new drug search costs

A drug venture company seeking earnings without the risks of drug discovery

SymBio is not itself involved in the basic research and discovery of drugs. Rather, it is a bio-pharmaceuticals venture business which seeks to leverage its links with a network of drug discovery companies worldwide to select and bring to market promising new drugs.
It has a niche strategy, seeking to maximize market share and revenues by focusing its development efforts on drugs for relatively rare conditions in, for example, oncology, hematology and pain management which, despite strong medical need, the major pharmaceutical companies have mostly steered clear of.
Another element in its strategy is to minimize development risk by concentrating on candidate drugs which have already demonstrated effectiveness and safety.
As a result, the first product developed by SymBio, Treakisym, took only five years from licensing-in to reach the approval and commercialization stage.

Expanding indications for its key product, and product life-cycle management

Treakisym was approved for the treatment of recurrent and refractory non-Hodgkin's lymphoma and mantle cell lymphoma in 2010, and in 2016 for chronic lymphocytic leukemia, untreated low-grade non-Hodgkin's lymphoma and mantle cell lymphoma. As a result, sales in 2017, the seventh year since initial commercialisation, rose roughly 60% year-on-year and market size has expanded to JPY 7.6 billion (official drug price basis).
At present, development is underway with the aim of adding further indications, and patients are being enrolled for Phase 3 clinical trials on relapsed /refractory medium and high-grade malignant non-Hodgkin's lymphoma (DLBCL).
In addition, lifecycle management by drug type modification is also underway. There is a risk of TREAKISYM® being exposed to competition from generics in 2020, 10 years after approval, but the company intends to mitigate that risk by introducing an easy-to-administer liquid formulation from Eagle Pharmaceuticals in the United States to replace the current lyophilised preparation. Fair Research Inc. believes these measures could propel the TREAKISYM® market to a peak value of around JPY20.4 billion.

Pipeline value at around JPY30 billion (pre-tax) after new drug search costs

Assuming the company builds its own sales structure, and after allowing for the ongoing costs of searching for new drugs, we modelled the company's pipeline value, together with end-December 2017 cash on the balance sheet, at around JPY30.3 billion (before tax, using a discount rate of 10%. (Also, using a discount rate of 8% yields a value of approximately JPY36.6 billion).
Nevertheless, in the intervening three years before turning profitable in 2021, the company will continue operating at a loss, and the end-December 2017 cash may not be sufficient to cover costs for that period. The proceeds from the exercise of stock acquisition rights could help, as could payment of the company's compensation claim (now in arbitration) relating to the cancelled development of the IONSYS drug due to the circumstances of the licensor, but it should be borne in mind that the company is planning to raise cash.

Executive Summary

Fair Research Inc.
Tsuyoshi Suzuki

Company outlook	
Location	Minato-ku, Tokyo
CEO	Fuminori Yoshida
Establishment	March 2005
Capital	10,392million
Listed	Oct. 2011
URL	www.symbiopharma.com
Sector	Pharmaceuticals
Workforce	78 – consol. basis
Indicators as at	**2018/2/16**
Stock price	207
52 week closing high	311
52 week closing low	200
Shares issued	54,049thou.
Trading unit	100 shares
Market cap	JPY11,188 mil.
Forecast dividend	0.0
EPS-forecast	-56.55
Forecast PER	NA
Actual BPS	50.00
Actual PBR	4.14X

EPS, PER, BPS and PBR are on a total shares outstanding basis, excl. treasury shares

Results	Sales JPY mil.	YoY %	Op. profits JPY mil.	YoY %	Rec. profit JPY mil.	YoY %	Net profit JPY mil.	YoY %	EPS JPY	Year-end share price High	Low
2015/12 period actual	1,933	-1.1	-2,551	NA	-2,630	NA	-2,632	NA	-81.3	383	177
2016/12 period actual	2,368	22.5	-2,127	NA	-2,316	NA	-2,313	NA	-58.82	509	173
2017/12 period actual	3,444	45.4	-3,947	NA	-3,976	NA	-3,977	NA	-79.78	311	200
2017/12 1H actual	1,786	47.5	-1,235	NA	-1,268	NA	-1,266	NA	-26.09	311	200
2017/12 2H actual	1,658	43.2	-2,712	NA	-2,708	NA	-2,711	NA	-53.69	243	212
2018/12 period company forecast	4,201	22.0	-2,981	NA	-3,044	NA	-3,056	NA	-56.55		

Company outline – management philosophy

＜Business Model＞	SymBio Pharmaceuticals Ltd. is regarded as a bio-venture but has the following special characteristics:
Requiring neither labs nor factories SymBio is a pharmaceuticals venture with none of the risks assumed by drug discovery firms, operating a niche strategy focused on maximizing profits.	1. Controls risk and maximises earnings with a “lableless” and “fableless” strategy. In terms of business model, the company does not itself conduct basic research on new drugs. Rather, it seeks out and carefully investigates new drug candidates developed by drug discovery ventures and pharmaceutical companies around the world. A new drug selected as a result of this process is the subject of a licensing agreement and, following development in Japan, is either licensed out to another company for commercialization or commercialized by the company itself. (Since the company itself conducts drug development in Japan it should be recognized as not simply a technology trader but as a bio-drug company). 2. Targets large market share and high earnings using a niche strategy. The company focuses its development efforts on drugs for relatively rare conditions in, for example, oncology, hematology and pain management which, despite strong medical needs, the major pharmaceutical companies have mostly avoided. It seeks to maximize market share and profits using this niche strategy. 3. Post-POC (proof of concept) 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. This business model is one which seeks to control the risk inherent in drug discovery and, at the same time, secure good returns from pharmaceuticals. The success or failure of this business model is dependent on having a network of drug discovery companies worldwide and a keenly discerning eye, as evidenced by the company’s track record.
SymBio is one of those rare bio-ventures whose first product on the market took only five years from adoption to approval.	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 to 8%. But SymBio managed to get its first product, Treakisym, from adoption to manufacturing and commercial approval in around five years, and in the three years following launch captured 57% of the market. In the eleven or so years since founding, the company has screened 1,500 drug candidates, of which over 700 have been formally investigated in-house. And of these, five products have been adopted and two are currently under development. Development of two others was terminated, not for reasons of clinical trial failure, but because of circumstances on the licensor’s part, and in the case of the third terminated candidate, changes in the licensor’s business strategy led to changes in targeted indications and was terminated when Phase 2 trials did not demonstrate superior therapeutic performance (please refer to the Licensing and Development Timeline chart at the end of this report).
The determinants of commercial success are interactions with a network of drug discovery companies and the ability to discern and evaluate.	We believe this track record has been made possible by the expertise of the company’s staff and by the way the company is organized. SymBio has a workforce of 78, of whom around 40 are involved in research and development. The drug search function is supported by a Scientific Advisory Board (SAB) of specialists (including Nobel Prize candidates) who review drug candidates (a list of Board members is given below). Needless to say, the company’s founder and CEO, Fuminori Yoshida, is an important factor in terms of both his experience and his personal network (please refer to his career history below).

Members of the Scientific Advisory Board（SAB）

	**Chair: George Morstyn, M.D., Ph.D.** • Former Senior Vice-President of Development and CMO, Amgen Inc. • Currently chief executive officer of G & R Morstyn Pty Ltd.,
	**Robert Lewis, M.D., Ph.D.** • Former Senior Vice-President of US R&D, Aventis Pharmaceuticals; Chief Scientific Officer, Cell Therapeutics; Head of Discovery Research, Syntex Pharmaceuticals; Associate Professor, Harvard Medical School Currently serves as consultant in Immunology/Inflammation, Roche Palo Alto;
	**Tomomitsu Hotta, M.D.** • Honorary President, National Cancer Center • Honorary Director, NHO Nagoya Medical Center
	**Makoto Ogawa, M.D., Ph.D.** • Honorary President, Aichi Cancer Center
	**Tatsutoshi Nakahata, M.D., Ph.D.** • Adviser and Professor, Center for iPS Cell Research and Application (CiRA), Head of Drug Discovery Technology Development Office • Kyoto University
	**Toshio Suda, M.D., Ph.D.** • Professor, International Research Center for Medical Sciences, Kumamoto University • Professor, Cancer Science Institute of Singapore, National University of Singapore
	**Tsutomu Takeuchi, M.D., Ph.D.** • President of Keio University Hospital
	**Shinji Nakao, M.D., Ph.D.** • Professor, Kanazawa University. Institute of Medical, Pharmaceutical and Health Sciences, Faculty of Medicine, Department of Hematology / Respiratory Medicine • Executive Director of The Japanese Society of Hematology; Vice President of The Japanese Society of Hematopoietic Cell Transplantation; Councilor, The Japanese Society of Internal Medicine
	**Koichi Takahashi, MD** • Assistant Professor, Department of Leukemia and Genomic Medicine, The University of Texas MD Anderson Cancer Center

Source: SymBio HP

Fuminori Yoshida, CEO Biography

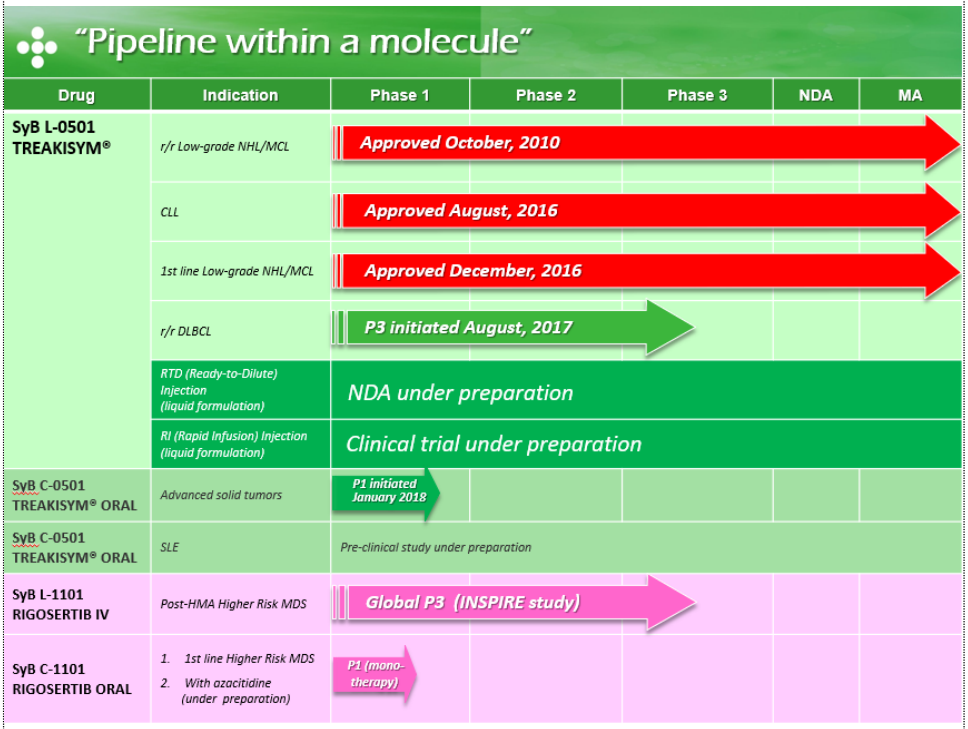
1949	Born in Tokyo
1971	Graduated from the Science Faculty (majored in Chemistry) of Gakushuin University
1973	Obtained master's degree from M.I.T (specialised in Life Sciences)
	Studied Management and Medical Policy Theory at Harvard University Graduate School
1975	Joined Mitsubishi Corporation
1977	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 Securities Report filings and other information

<Main Pipeline Products>

As of Feb.2018, the company's two mainstay pipelines are TREAKISYM® and rigorsertib.

Pipelines



Source: Company results meeting

(1) TREAKISYM® (SyB L-0501, freeze-dried injected preparation/ SyB L-1701, RTD preparation/ SyB L1702, RI preparation/ SyB-C-0501, oral preparation)

TREAKISYM® (generic name bendamustine) is a cancer drug developed in Germany in 1971. Among malignant lymphomas it is used in the treatment of low risk non-Hodgkin's lymphoma and chronic lymphocytic leukemia.

Malignant lymphoma

Lymphoma is a hematologic malignancy caused by the cancerization of lymphocytes (a type of white blood cell providing immunity). This condition comes in two main forms, Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL). The majority of Japanese patients with malignant lymphoma (94%) have the NHL form. NHL is divided into the three following types depending on the speed at which the disease progresses. The TREAKISYM® therapy is directed at NHL and is highlighted in red.

Types of malignant lymphoma

Degree of Maligancy (speed of progression)	Type
Low-grade (measured in years)	Small lymphocytic MALT Follicular(grade 1-3a) Marginall Zone B cell Rinpa Plasma cell Nodal marginal B cell
Medium grade (measured in months)	Plasma cell tumour Mantle cell Follicular (grade 3b) Diffuse large cell type
High grade (measured in weeks)	Precursor B lymphoblastic Burkitt's lymphoma

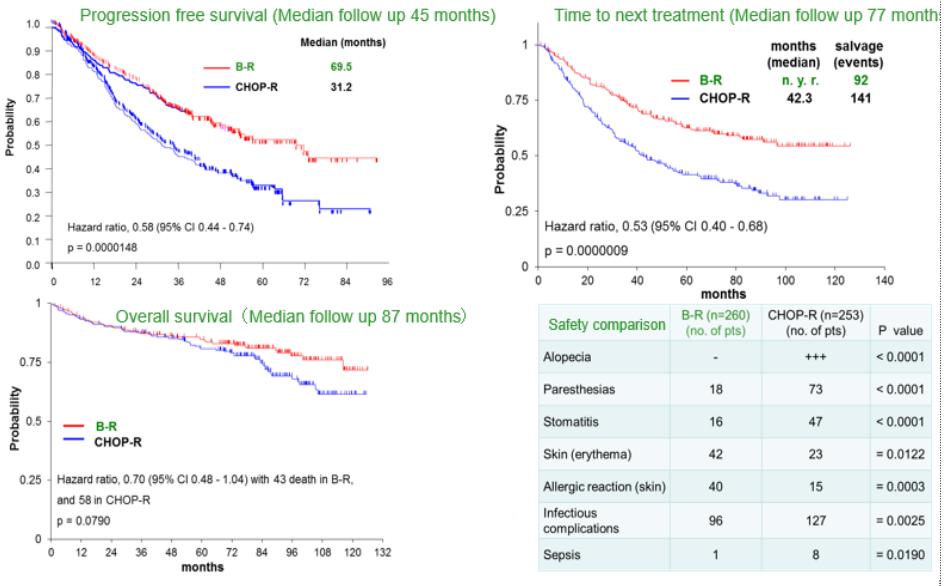
Source: “Treatment Guide” - Eisai and Symbio

TREAKISYM® went from licensing-in to approval in only 5 years, and additional indications are still being pursued.

Having received initial approval in 2010, TREAKISYM® was approved for two additional indications in 2016, leading to further penetration of the market.

In December 2005, SymBio acquired sole development and sales rights in Japan from Astellas Pharma’s European subsidiary, Astellas Deutsche. Subsequently, in October 2010, only five years after licensing-in, approval was granted for two indications, recurrent refractory low-risk NHL, and mantle cell lymphoma (MCL). Commercialization began in December of that year. Further, in August 2016, approval was granted for the treatment of chronic lymphocytic leukemia (CLL) and in December of the same year, for untreated low risk NHL/MCL. By 2017, the seventh year of commercialization, domestic sales had expanded to JPY7.6 billion (official drug price basis). The level of market penetration (2017 average) is 58% for recurrent/refractory low-risk NHL, but is still an estimated 35% for untreated low-risk NHL/MCL, for which approval was granted later, in 2016. Since for the latter indication the superiority of B-R therapy, using a combination of rituximab and TREAKISYM®, has been demonstrated against the current standard therapy (see the note to CHOP-R therapy below) it is expected that further market penetration can be achieved.

B-R Treatment Effectively against R-CHOP



Safety comparison	B-R (n=260) (no. of pts)	CHOP-R (n=253) (no. of pts)	P value
Alopecia	-	+++	< 0.0001
Paresthesias	18	73	< 0.0001
Stomatitis	16	47	< 0.0001
Skin (erythema)	42	23	= 0.0122
Allergic reaction (skin)	40	15	= 0.0003
Infectious complications	96	127	= 0.0025
Sepsis	1	8	= 0.0190

Source: SymBio pharmaceuticals IR meeting

Note: CHOP-R therapy

Chemotherapy treatment combining the molecular target drug rituximab and the anticancer drugs cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and the steroid drug prednisolone.

An additional development in August 2008 was the licensing-out to Eisai of joint development and sole sales rights in Japan for TREAKISYM®. The format is that SymBio buys in TREAKISYM® from Astellas Deutsche and releases to Eisai, which then sells domestically. We estimate that Eisai covers half the development costs of TREAKISYM®. The out-licensing contract with Eisai expires in 2020, and from 2021, although no firm decision has yet been made, SymBio is considering setting up its own in-house sales function.

At present, patient enrolment is proceeding for Phase3 trials directed at recurrent/refractory medium and high-risk NHL.

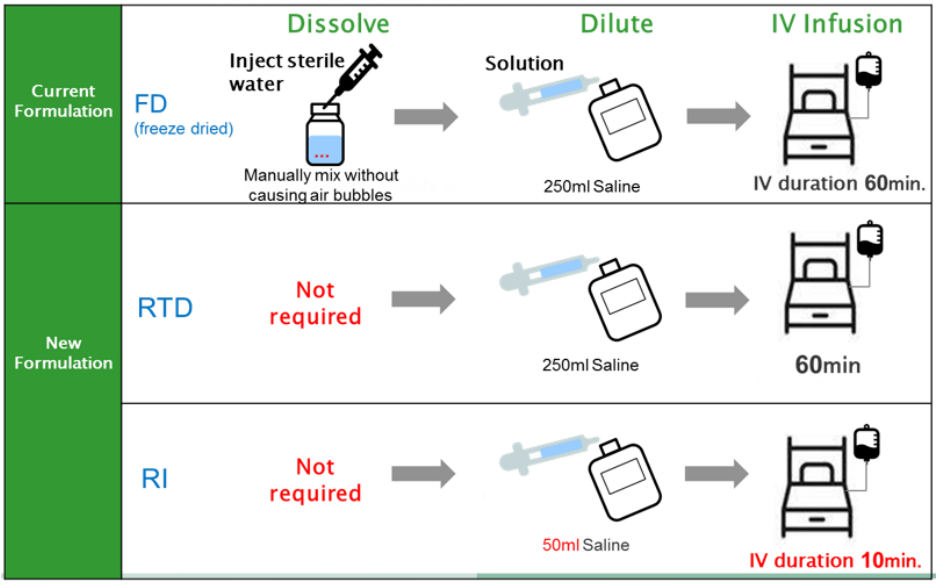
As of February 2018, development continues with the company looking to further expand the number of indications for TREAKISYM®. Looking particularly promising is the targeting of recurrent/refractory medium/high risk NHL (below, r/rDLBCL). The first patients for Phase 3 clinical tests were enrolled in January 2018. In addition, there was an announcement that Phase I clinical trials using an oral preparation and targeting progressive solid tumor subjects had begun.

Note: In Japan the most common form of medium-risk NHL is diffuse large B-cell lymphoma (DLBCL).

Progress is also being made in product life-cycle management through changes in the drug formulation.

A further important point to note is the issue of life cycle management through changes in drug formulation. In 2020 TREAKISYM® will be 10 years from receiving drug approval, and from 2021 will face the risk of competition from generics. The company plans to extend the product life span until 2031 by developing new formulations. On September 21st in 2017, the company announced it was introducing liquid ready-to-dilute (RTD) and rapid-infusion (RI) formulations from the US company, Eagle Pharmaceuticals Inc. to add to the existing freeze-dried (FD) formulation. The existing formulation does have the advantage of being storable at room temperature, but prior to administration it takes time and effort to dissolve with solvent and dilute with physiological saline. On the other hand, while the liquid formulation needs to be refrigerated it can be administered simply by diluting with physiological saline solution, thus shortening the dispensing work and reducing the burden on healthcare staff. The US company Teva Pharmaceutical Industries launched an RTD formulation in 2014, and in January 2016 brought to market an RI formulation (product name: BENDEKA®, licensed in from Eagle Pharmaceuticals) with a shorter administration time. In only two years, BENDEKA® has come to account for 97% of the TREAKISYM® market.

Comparison of FD, RTD and RI formulations

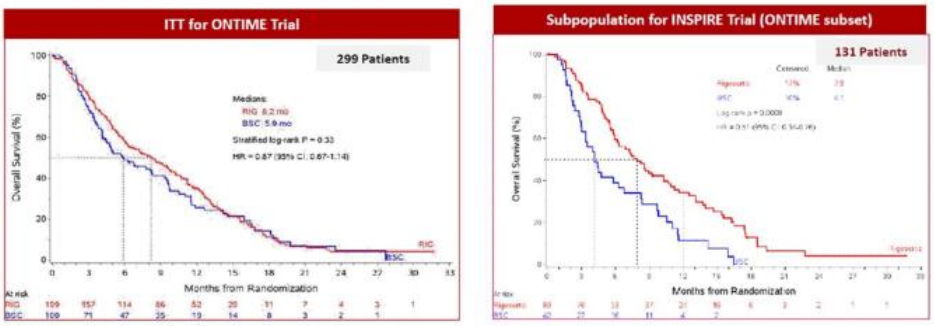


Source: SymBio IR materials

Introduction of liquid formulations likely to extend product life cycle to 2031	SymBio expects to commercialize an RTD formulation in 2021 without additional trials because its function and method of administration are the same as for the FD formulation. In the case of the RI formulation, the different concentration and different administration time mean that safety tests and other procedures are necessary. Nevertheless, due to results already obtained in the US, commercialization in Japan can probably be achieved in 2022-2023. These formulations will extend the TREAKISYM® life-cycle to 2031. As for drugs which could compete, it should be noted that in the area of NHL and CLL the absence of drugs with a sufficient level of safety and effectiveness using conventional chemotherapy alone has stimulated interest and there are now a number of pipeline drugs in development. In August 2017 Chugai Pharmaceutical applied for approval for obinutuzumab, but since it is targeted at CD20 positive B cell follicular lymphoma it is basically used in combination with TREAKISYM®, and we therefore believe it will have no adverse impact on sales. In addition, the EZH2 inhibitor (Tazemetostat) licensed in by Eisai from Epizyme Inc. is still at the Phase II level.
	(2) Rigosertib (SyB L-1101: injected preparation; SyB C-1101 oral preparation)
Rigosertib is under development for injection and oral preparations mainly to treat myelodysplastic syndrome (MDS).	SymBio is developing a cancer agent from the US company, Onconova Therapeutics, mainly for the treatment of myelodysplastic syndromes (MDS). In July 2011, when Onconova completed Phase 2 clinical trials, SymBio acquired sole development and sales rights in Japan and Korea for injected and oral preparations of this drug (estimated up-front lump sum payment of around JPY800 million). The current development status is as follows: (a) Injected preparations A joint international Phase 3 trial is underway for patients who do not benefit from the standard hypomethylating agent (=HMA) therapy (=HMA refractory), and for post-treatment patients with relapsed high risk MDS. SymBio is responsible for Phase 3 in Japan. High-risk MDS is identified as high risk by the International Prognostic Scoring System, and is judged to be in the intermediate 2 risk category (the higher risk group) with a high risk of transition to leukemia. Currently the standard treatment is the administration of azacitidine (trade name Vidaza®) and decitabine (trade name Dacogen), but some high risk MDS cases have shown a resistance to the standard therapeutic drugs or have a relapse after treatment. Rigosertib is indicated for such recurrent and refractory MDS, and at present there are no competing approved drugs. There is one competing candidate agent under development (Syros Pharmaceuticals' SY-1425), which is still in Phase 2 trials.
The original developer, Onconova, is continuing international joint Phase 3 trials using a revised trial design.	Onconova completed Phase 3 (ONTIME) trials for recurrent and refractory high risk MDS in February 2014. The test results showed no statistically significant difference in overall survival (OS) between the patient cohort treated with rigosertib and the control (palliative care) cohort. However, in terms only of HMA refractory patients and those whose disease advanced during pre-treatment, there was a significant difference in OS between the cohort treated with rigosertib (7.9 months) and the control cohort (4.1 months). Onconova then changed the test design to focus on this part of the results and in August 2015 initiated global joint Phase 3 trials (INSPIRE) targeting HMA refractory patients and high-risk MDS patients whose condition recurred after treatment.

ONTIME trial results (left chart) and subpopulation results (right chart using same cases as for INSPIRE trials)

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 IR materials

SymBio is also participating in the joint international trials.

As a result of the interim analysis in January 2018 trials proceeded with additional cases. An application for approval will be made in 2021 or later.

In June 2012, SymBio began Phase 1 trials targeting recurrent refractory high-risk MDS subjects. The trials were completed in October 2015. As a result of discussions with Onconova and the relevant authorities, SymBio joined the international joint Phase 3 trials (INSPIRE) conducted by Onconova from December 2015, becoming responsible for the clinical trials in Japan. In January 2018, based on the interim INSPIRE analysis, Onconova decided to continue the trial with an increased number of cases (from 225 to at least 360). In Japan, it was also decided to continue with an increased number of cases. Application and approval was therefore delayed for around 1.5 years, until about 2021 for application and until around 2022 for approval.

(b) Oral preparation

Following completion of tests in Japan for the oral preparation, SymBio plans to participate in the international joint Phase 3 trials currently being planned by Onconova.

In Europe and America, Phase 1/2 trials of rigosertib (in combination with azacitidine) directed at high-risk MDS have already demonstrated safety and efficacy (see chart below). In Japan, SymBio in June 2017 began Phase 1 monotherapy trials targeting high-risk MDS to confirm the safety of higher doses, and in October 2017 completed the first patient enrolments. After Phase 1 the company plans to start domestic trials in combination with azacitidine (product name: Vidaza®) and to participate in the international joint Phase 3 planned by Onconova.

Phase 2 Responses to Combination Treatment

Hematologic Response as per IWG 2016 Criteria		
Complete Remission (CR)	8 / 33	(24%)
Marrow Complete Remission (mCR)	16 / 33	(48%)
Hematologic Improvement (HI)	11 / 33	(33%)
Overall Response Rate (CR+mCR+HI)	***25 / 33***	***(76%)***
Median Duration of Treatment	6 cycles (Range: 1-37+)	
Overall Response for IPSS-R for VHR with an Effective Response as per IWG 2016 Criteria		
Very High Risk (CR+mCR)	9 / 13	(69%)

Phase 2 data was presented at the 14th International Symposium on Myelodysplastic Syndromes, 2017

Source: Compiled by SymBio Pharmaceuticals from papers presented at the 14th International MDS Symposium in 2017

<Revenue structure>

SymBio's sources of revenue consist of product sales and milestone payments. In the year ending December 2008, it registered an operating profit after receiving a lump sum contract payment from licensing out sole distribution rights for TREAKISYM® in Japan to Eisai. In each subsequent year, however, it has registered only operating losses.

We estimate that TREAKISYM® wholesale price is about 50% of the official price, and the cost of the medicine to SymBio is about 66% of the wholesale price.

In the period ending December 2017 the company recorded sales of JPY3.44 billion, mostly attributable to wholesaling TREAKISYM® to Eisai. The cost of goods (mostly the value of supplies from Astellas Deutschland) was JPY2.41 billion for a gross profit of JPY1.03 billion. SymBio's wholesale price of TREAKISYM® to Eisai was an estimated 50% of the official price, and SymBio's acquisition cost of supplies from Astellas Deutschland was around an estimated 66% of the wholesale price.

R&D costs came to JPY3.02 billion, of which we estimate JPY1.38 billion was attributable to a contract lump sum (liquid formula licensing-in) paid to Eagle. Breaking out the remaining JPY1.64 billion we get JPY300 million for TREAKISYM®-related costs, rigosertib-related costs of JPY350 million, and around JPY 400-500 million associated with the patient-controlled pain management drug IONSYS® (development discontinued in November 2017. Refer to "Timeline" section). We believe the residual JPY500-600 million or so is attributable to the R&D costs of recurrent new drug candidate search activities.

R&D costs associated with recurrent search activities came to JPY500 million, and we estimate total company administration costs came to around JPY1.4 billion.

Non-R&D SG&A came to JPY1.96 billion, of which sales costs came to around JPY300 million and non-R&D general administration to JPY1.6-1.7 billion. This is a somewhat larger amount than normal because in 2017 there were costs associated with licensing in the new TREAKISYM® formulations, and legal and other costs generated by IONSYS®. In a normal year, general administration expenses would come in at around JPY1.4 billion.

As a result, the company recorded an operating profit loss of JPY3.9 billion.

SymBio Pharmaceuticals – Balance sheet and P&L

(JPYmil)

Periods ending Dec.	2013	2014	2015	2016	2017	2018 Comp. forecast
Sales	1,532	1,955	1,933	2,368	3,444	4,201
Product revenue	1,432	1,940	1,933	2,137	3,444	
Milestone revenue	100	15	0	231	0	
Unit cost	1,214	1,428	1,483	1,737	2,413	2,832
SG&A	1,999	1,830	3,135	3,031	4,978	4,350
R&D	1,053	774	2,035	1,667	3,017	2,311
operating profit	-1,681	-1,303	-2,552	-2,127	-3,947	-2,981
Recurring profit	-1,601	-1,110	-2,630	-2,317	-3,976	-3,044
Pr-tax profit	-1,601	-1,112	-2,628	-2,309	-3,974	
Corp. tax, etc.	4	4	4	4	4	
Net profit	**-1,605**	**-1,116**	**-2,632**	**-2,313**	**-3,978**	**-3,056**
Liauid assets	7,634	7,290	4,827	6,685	4,037	
of which, cash	**6,163**	**5,692**	**4,261**	**5,719**	**2,947**	
Fixed assets	53	164	158	193	216	
Liauid liabilities	251	488	551	942	1,011	
of which, accounts payable	207	143	184	553	331	
Fixed liabilities	3	2	2	451	1	
of which,corp. bonds	0	0	0	450	0	
Shareholders equity	7,336	6,763	4,132	5,054	2,702	
Stock acquisition rights	97	200	300	431	537	
Net assets	7,433	6,964	4,432	5,485	3,239	

Source: compiled by Fair Research Inc. from Securities Report filings, etc.

< TREAKISYM® and rigosertib market size>

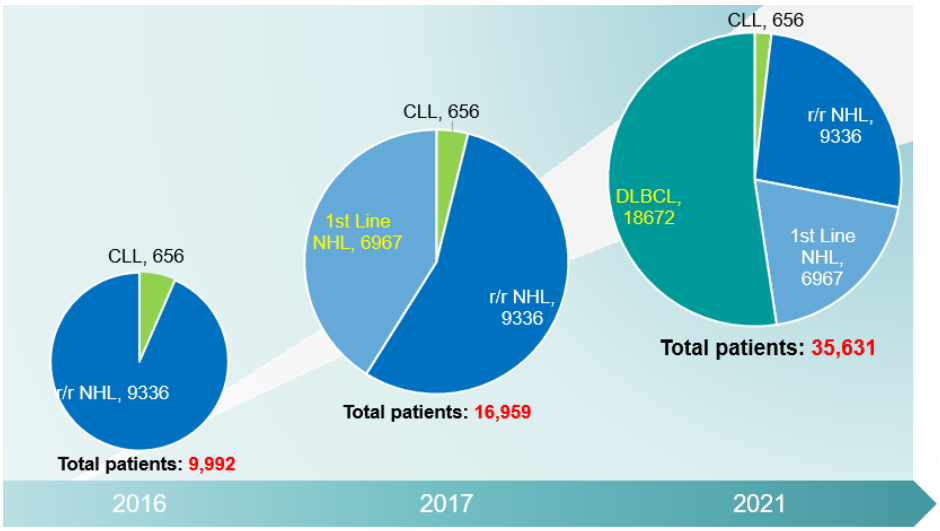
We model a market size of JPY10.6 billion for the three indications for which TREAKISYM® approval has been granted, and around JPY9.8 billion for recurrent/refractory medium-high risk NHL (now in Phase 3).

We anticipate an enlarged market for TREAKISYM® due to rising market penetration and an increase in the number of indications. Approvals have already been granted for the following areas: 1. recurrent/refractory low-grade NHL/MCL; 2. chronic lymphocytic leukemia (CLL); 3. 1st Line low-grade NHL/MCL. In area 1, sales have reached JPY4.72 billion but, as the number of patients is estimated at 9,336, we think market saturation has already reached 58%. We anticipate sales in this segment will be sustained by changes in formulation. For CLL and 1st Line low-grade NHL/MCL, for which approval has only relatively recently been granted, sales of the two together still stand at around the JPY2.68 billion level. The number of subject patients is estimated at 656 and 6967, respectively, with average market penetration in 2017 standing at around 35%. However, we anticipate further penetration is possible. If the CLL segment were to see a rise in penetration to 55%, this would suggest a market size of JPY340 million. And if we assume that the maximum market penetration for untreated intermediate grade NHL/MCL is 75%, this would infer a market size of JPY5.57 billion.

Again, in the case of relapsed/refractory medium/high risk NHL (r/r DLBCL), now in Phase 3, there are an estimated 18,000 plus patients, and assuming a market penetration of 60%, we would posit a potential market size of JPY9.77 billion.

Sales for the above three approved indications total JPY10.63 billion. Adding in sales of Phase 3 r/rDLBCL yields estimated potential total sales of JPY20.4 billion.

The market for TREAKISYM® (Number of patients)



Source: SymBio IR materials

We estimate the market size of injected rigosertib at JPY4.6 billion, and the potential market size for oral rigosertib at JPY11.6 billion.

Since the use of injected rigosertib on high-risk MDS patients is limited to MHA refractory patients, there are an estimated 900 subjects. Using the Vidaza® drug price for reference, we model an estimated market size of around JPY4.6 billion. As for the oral preparation, we model the number of subject patients at 2300, assuming it is that portion of the high-risk MDS patients who are not being treated with the injected preparation, and thereby posit a market size for the oral preparation of JPY11.6 billion. For the two preparations together, the total market size comes to around JPY16 billion.

<Modelling the product pipeline value and corporate value>

We now look at the corporate value of SymBio using a DCF model. This simulation posits a product value for TREAKISYM® (assuming that indications are expanded to r/rDBLCL, that formulation changes are made, and that the company will take over its own merchandising), and a product value for rigosertib (both the injected and oral formulations). From the sum of these two we deduct the DCF value of the company's costs attributable to drug search activities and administration. We model a discount rate of 10% to reflect the fact that the company, while continuing to operate at a loss, is a low risk lab-less and fab-less drug venture and does already have a product on the market.

<Assumptions made for TREAKISYM®>
Using the market size calculations described earlier we model peak sales being attained in the fourth year after going to market and sales staying at that peak level for the subsequent 3-4 years. We assume that the market will then decline at a rate of 5% per year before shrinking sharply (at an annualized 10%) from 2031 onwards. We are assuming an 80% probability of success in relapsed/refractory intermediate grade NHL (r/rDLBCL), now undergoing Phase 3 trials.

While we assume Eisai will provide the sales channel until 2020, sales will go in-house from 2021. We are modelling the ratio of cost of goods to sales at 26% at that time. In 2021 and after, supplies will have almost entirely switched to the liquid formulation (either RTD or RI) and we are assuming royalty payments to Eagle Pharmaceuticals as 22% of sales (estimated figure based on Eagle's materials and elsewhere). In addition, the milestone payment at the launch of the RI formulation should, we assume, be in the area of JPY700 million.

Assuming the company switches to self-merchandising in 2021 we model a discounted present value for TREAKISYM® (pre-tax) of JPY31.9 billion (discount rate 10%).

Development costs are not being shared evenly with Eisai but are assumed to be entirely by SymBio. The assumptions we made are shown in the "Development Costs" line in the chart. The costs associated with commercializing assume 40 medical representatives (MR) in 2020 and 50 from 2022 onwards. These and other promotional costs are as shown in the chart.

We therefore posit a value for TREAKISYM® of approximately JPY31.92 billion (before tax).

Modelling TREAKISYM® Value

(JPY100mil)

	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030
				RTD insertion		RI insertion							
Sales (official drug price basis)													
Treakisym total	101.1	102.4	104.5	120.5	136.3	166.3	196.3	204.0	198.7	193.6	184.0	174.8	166.0
NHL/MCL r/r low-risk NHL/MCL	47.2	47.2	47.2	47.2	47.2	47.2	47.2	47.2	44.8	42.6	40.5	38.4	36.5
Chronic lymphocytic leukemia	3.0	3.2	3.3	3.3	3.4	3.4	3.4	3.4	3.2	3.1	2.9	2.8	2.6
Untreated low-risk NHL/MCL	50.9	52.0	54.0	55.0	55.7	55.7	55.7	55.7	52.9	50.3	47.8	45.4	43.1
r/r medium-high risk NHL (DLBCL)	0.0	0.0	0.0	15.0	30.0	60.0	90.0	97.7	97.7	97.7	92.8	88.2	83.8
Sales Sales via Eisai (until 2020)	41.8	42.1	45.3										
Switch to own-merchandising				117.5	130.3	154.3	178.3	184.5	179.1	174.1	165.4	157.1	149.3
(Note: assuming r/r DLBCL success prob. 80%)													
Bulk powder cost (+manuf. costs) 26%	27.6	27.8	29.9	30.0	33.2	39.3	45.5	47.0	45.7	44.4	42.2	40.1	38.1
Milestone payments to Eagle						7.0							
Royalty payments to Eagle 22%	0.0	0.0	0.0	25.9	28.7	33.9	39.2	40.6	39.4	38.3	36.4	34.6	32.8
Development costs	13.0	16.9	15.6	7.8	5.2	1.3							
r/rDLBCL Ph3 ：Trial costs for 60 cases	6.0	7.0	6.0										
RTD and RI trials application	3.0	5.0	5.0	5.0	3.0								
Other direct costs	1.0	1.0	1.0	1.0	1.0	1.0							
Development staff costs	3.0	3.9	3.6	1.8	1.2	0.3							
Sales costs (incl. MR costs)	7.0	10.0	11.0	12.0	14.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0
Own MR costs	3.0	6.0	7.0	8.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0
Other sales costs	4.0	4.0	4.0	4.0	4.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Profits	-5.8	-12.6	-11.2	41.9	49.2	57.7	78.6	81.8	79.1	76.4	71.8	67.5	63.4

Disc. Rate	Discounted P.V.
10%	**319.2**

Source: Calculations by Fair Research Inc.

We model a 50% probability of success for the rigorsertib injected formulation, and 30% for the oral formulation, and posit a value of around JPY9 billion (discount rate 10%).

<Assumptions for rigosertib>

As described earlier, we assume peak sales four years after launch, a level which should be maintained for the subsequent 3-4 years. The market should then subside at a rate of 5% annually until 2035 when it will begin shrinking sharply at 10% per year. In terms of market launch, the timing has fallen behind schedule due to the results of the interim INSPIRE analysis and the attendant additional indications. We are now factoring in 2023 or thereabouts for the injected preparation and 2025 for the oral preparation. Probability of success reflects the stage of the trial, with the Phase 3 injected preparation posited at 50% and the Phase 1 oral preparation at 30%. Our simulation also posits payments for supplies of medicine from Onconova and royalties to Onconova coming in at 25% of sales. We assume milestone payments at launch of JPY500 million for the injected preparation and JPY1.5 billion for the oral preparation. We have assumed development costs as shown in the Development Costs line in the chart. Since the marketing channel and MR is the same as for TREAKISYM® we have omitted sales costs. As a result, we model a value for rigosertib of JPY8.96 billion (pre-tax).

Modeling Rigosertib Value

Event		No. of patients	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034
Injection (high-risk MDS)																			
			Intl. joint Ph3(+addit.cases)				File	Approved											
Oral (high -isk MDS)		Combined with AZA	Ph1			Intl. joint Ph3			File	Approved									
Sales	Injection (high-risk MDS)	900	0.0	0.0	0.0	0.0	0.0	20.0	30.0	40.0	46.0	46.0	46.0	43.7	41.5	39.4	37.5	33.7	30.3
	Oral (high-risk MDS)	With AZA 2300	0.0	0.0	0.0	0.0	0.0	0.0	0.0	40.0	80.0	90.0	100.0	116.0	116.0	116.0	110.2	104.7	99.5
Sales adj. for prob. of success		<-- probability of success	0.0	0.0	0.0	0.0	0.0	10.0	15.0	32.0	47.0	50.0	53.0	56.7	55.6	54.5	51.8	48.3	45.0
	Injection 50%, Oral 30%	25%																	
Bulk chem.+ manuf. cost + royalties			0.0	0.0	0.0	0.0	0.0	2.5	3.8	8.0	11.8	12.5	13.3	14.2	13.9	13.6	12.9	12.1	11.3
Milestone payments			0.0	0.0	0.0	0.0	0.0	5.0	0.0	15.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total development costs			4.9	6.2	7.5	7.8	6.5	5.2											
	Trial costs		3.0	4.0	5.0	5.0	4.0	3.0											
	Other direct costs		0.8	0.8	0.8	1.0	1.0	1.0											
	Development staff costs		1.1	1.4	1.7	1.8	1.5	1.2											
Profits			-4.9	-6.2	-7.5	-7.8	-6.5	-2.7	11.3	9.0	35.3	37.5	39.8	42.5	41.7	40.9	38.8	36.2	33.8

Disc. rate	Disc. P.V.
10%	89.6

(JPY100mil)

Source: Calculations by Fair Research Inc.

Taking into account recurrent drug search costs, all-company corporate administration costs and current cash on the balance sheet, we model a pre-tax value for SymBio of JPY30.3 billion (discount rate 10%).

Further costs are generated annually by search and examination activities for new drug candidates and by total company administration. Based on analysis of data in the earnings structure section we model JPY500 million for R&D costs related to ongoing exploration, and JPY1.4 billion for company administrative costs, for a total of JPY1.9 billion.

On the basis of the above assumptions we calculate discounted present value, yielding a present value for all-company costs of –JPY13.6 billion.

Looking next at the value (pre-tax) of the total SymBio pipeline, we take the present value of the company's two main drugs, the present value of the total company costs and the current cash on the balance sheet, arriving at a figure of JPY30.3 billion. Using a discount rate of 8% yields a figure of 36.6 billion.

Modelling the value of SymBio's product pipeline

(JPY 100mil.)

	Discount Rate	
	10%	8%
Total(before tax)	**302.6**	**366.0**
Treakisym	319.2	369.1
Rigosertib	89.6	113.9
Headquarter's costs	-135.7	-146.5
Cash	29.5	29.5

(Ref) Assuming eff.tax rate 31%

	Disc.rate 10%	Disc. rate 8%
Total (after tax)	208.8	252.5
2018/2/16 Market cap		111.9

Source: Calculations by Fair Research Inc.

<Adherence to medium term management plan and balance sheet risk>

On February 8th 2018, SymBio announced its results for FY2017 and simultaneously released its medium-term management plan. We provide the data below.

SymBio Pharmaceuticals medium-term management plan

(JPY million)

	FY2018 (forecast)	FY2019 (Target)	FY2020 (Target)	FY2021 (Target)
Sales	4,201	4,328	4,413	11,624 ～ 10,325
Operating profits	△2,981	△3,786	△3,709	1,777 ～ 878
Recurring profits	△3,044	△3,849	△3,772	1,724 ～ 825
Net profits	△3,056	△3,853	△3,776	1,467 ～ 702

Source: SymBio Pharmaceuticals

In the table below, we systematize the sales and earnings data for TREAKISYM® and rigosertib calculated in the previous pages. The data in the table conforms quite closely to the data in the company's medium-term management plan.

Long-term sales and profits trajectory

(JPY100mi

		2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030
Total sales		**41.8**	**42.1**	**45.3**	**117.5**	130.3	164.3	193.3	216.5	226.1	224.1	218.4	213.8	204
	Treakisym	41.8	42.1	45.3	117.5	130.3	154.3	178.3	184.5	179.1	174.1	165.4	157.1	149
	Rigosertib	0.0	0.0	0.0	0.0	0.0	10.0	15.0	32.0	47.0	50.0	53.0	56.7	55
Op. profits	total	**-29.7**	**-25.2**	**-37.7**	**15.1**	23.7	36.0	70.9	71.8	95.3	94.9	92.6	91.0	86
	Treakisym	-5.8		-11.2	41.9	49.2	57.7	78.6	81.8	79.1	76.4	71.8	67.5	63
	Rigosertib	-4.9	-6.2	-7.5	-7.8	-6.5	-2.7	11.3	9.0	35.3	37.5	39.8	42.5	41
	Other costs	-19.0	-19.0	-19.0	-19.0	-19.0	-19.0	-19.0	-19.0	-19.0	-19.0	-19.0	-19.0	-19

Turns profitable

Source: Fair Research.Simulation; Sales figures take account of probability

The company is forecasting a return to operating profit in 2021.

An important point to note is that both the company's medium-term plan and our simulation point to a return to operating profit in 2021. Even if the company defers on bringing the marketing in-house from 2021, preferring the option of a tie-up with another company, the terms of such a tie-up could contribute to an improvement in profitability. This, together with milestone income on the back of the introduction of liquid formulations, means the company, in our view, would still turn profitable in 2021.

One other important point to note over the three-year period from 2018 to 2020 concerns the level of development costs. These will continue to be elevated in order to fund an increase in the conditions for which TREAKISYM® is indicated, to fund the development of an RI formulation and to fund additional cases in rigosertib clinical trials. It will also be necessary to increase the number of MR's. This makes it likely that the company will continue to generate losses in excess of JPY3 billion every year and could exhaust development funds. At the end of 2017 the company held JPY2.95 billion in cash but over the next three years is expected to accumulate net losses totaling in excess of JPY10.7 billion, leaving a shortfall of approximately JPY7.7 billion. However, the cash position recovered to the JPY3.6 billion level at the end of January with the exercise of stock acquisition rights. This will help secure the company's needs for the current year 2018.

There is a possibility of a cash shortfall in the intervening three years prior to returning to profit.

It is also possible that the shortfall will be attenuated by compensation from The Medicines Company, the US firm which was the licensor for IONYS® until it abruptly withdrew from the business, forcing SymBio to terminate the project and triggering a demand for compensation of JPY9 billion via arbitration by the

The exercise of new stock acquisition rights and IONSYS®-related compensation may be sufficient, but the possibility of a cash call should be borne in mind.	International Chamber of Commerce (see Timeline below). SymBio had already made a JPY1 billion lump-sum contract payment to The Medicines Company and from 2016 to 2017 made annual payments of around JPY500 million for clinical trials. Direct costs alone therefore had totaled at least JPY2 billion. Indirect costs and future profits foregone makes up the remainder of SymBio's claim. The Medicines Company, however, does not agree with the claim. All things considered, it is as well to assume that SymBio is planning to raise cash.

Time-Line (reference)	SymBio was established in March 2005 by Fuminori Yoshida, who had previously been Corporate Vice President of the US company Amgen Inc., and had also served as President of Amgen Japan. Initial funding of JPY1 billion for the licensing-in and development of TREAKISYM® was provided by, among others, Daiichi Pharmaceutical Co., Ltd.., (now known as Daiichi Sankyo Inc.), EPS Corporation, and SBI Holdings, Inc. In December 2005, SymBio signed a licensing agreement with Astellas Pharma in Germany (now known as Astellas Deutsche) for the sole development and sales rights of Treakisym in Japan. The development of TREAKISYM® subsequently proceeded favourably and in August 2008 SymBio licensed out the sales rights to Eisai Co., Ltd. The company faced a shortage of funds for development following the "Lehman Shock" of September 2008. The president, Fuminori Yoshida, visited more than 50 venture capital funds and other institutions around the world and SymBio overcame its problems with an infusion of JPY1.5 billion from the bio-venture firm, Cephalon. The two companies maintained good relations subsequently. Cephalon is now a wholly-owned subsidiary of Teva Pharmaceutical Industries, having been bought out in May 2011. In October 2010, approval was given for the production and sale in Japan of TREAKISYM® for relapsed/refractory low-risk NHL (see section on types of malignant lymphoma). The product was launched in December, making SymBio a rare example in Japan of a bio-venture with an actual product in the market. The company then listed on JASDAQ in October 2011. While sales of TREAKISYM® continued to steadily grow, the company won approval to expand its application to chronic lymphoma leukemia in August 2016, and to untreated patients with low-grade NHL in December. Phase 3 Clinical trials are also underway with a view to expanding the indications to recurrent refractory high-risk NHL. At the same time, the company is working on product lifecycle management via drug formulation changes, and has signed a Japan development and commercialization rights agreement with the US company Eagle Pharmaceuticals Inc. covering easy-to-use liquid formulations (RTD and RI formulations). The company's second promising candidate drug after TREAKISYM® is rigosertib, which the company licensed in from the US company Onconova Therapeutics in July 2011. SymBio participated in Phase 3 international joint trials from December 2015 and continues to pursue development. As of January 2018, Phase 3 interim analysis has been released and tests are being continued on additional cases (refer to the earlier pipeline discussion). In October 2015, SymBio contracted to license in from the US company, The Medicines Company, the patient-controlled pain management drug, IONSYS® (lump sum contract payment JPY1 billion). Phase 3 trials began in Japan in June 2016 but in May 2017 the licensor abruptly announced it was withdrawing. Patient enrolment was therefore halted and in November 2017 the agreement was terminated. The company has applied for arbitration claiming compensation of approximately JPY9 billion. (Refer to "Licensing-in and development timeline" at the end of this report)

Licensing-in and development timeline

	1st in-licensed product	2nd in-licensed product	3rd in-licensed product	4th in-licensed product	5th in-licensed product	(Developed in-house)
	Treakisym (SyB L-0501,C-3501,L-1701,L-1702)	SyB D-0701 Antiemetic	SyB 1001 For systemic lupus erythematosus	Rigosertib (SyB L-1101 injection and C-1101 oral)	IONSYS (patient-controlled pain management) (SyB P-1501)	SyB 0702 HSP32 Inhibitor
Dec.2005	Licensing contract with Astellas Pharma (now Astellas Deutsche)					
	(Low-risk NHL)					
March. 2006	Phase 1 starts					
	(Medium/high-risk NHL)					
Sept. 2007	Phase 1 completed	Mar 2007 Abelle Licensing-in from				Aug 2007 Acquired exclusive rights worldwide for SyB 0702, effective for Gleevec-resistant leukemia cells. This was before the establishment of POC, because NEDO funding was obtained. Started development at the compound stage. Terminated
Dec.	Phase 1 starts	October Phase 1 starts				
Aug 2008	Grants Eisai joint development and sales	July 2008 Phase 1 completed				
October	Phase 1 starts					
Mar. 2009	Phase 2 completed					
October	Applic.to use on r/r low-risk NHL and mantle cell					
Mar. 2010	Phase 2 starts		June 2010 Licensed in Japan joint dev. rights from Cephalon Inc. subsid. Anesta			
October	Approved for use on r/r low-risk NHL and mantle cell					
December	Sales start in Japan	Dec.2010 Phase 2 starts	Oct. 2011 After being bought by Teva, dev. rights were ceded to ImmuPharma so dev. halted	July 2011 Licensing-in agreement with Onconova Therapeutics		
Nov. 2011	1st Line patients Phase 2 starts			June 2012 SymBio starts Phase 1 trials for r/r MDS		
May 2013	Chronic lymphoma leukemia Phase 2 starts	Dec. 2013 Development stopped due to change in licensor structure. Target changed but effectiveness not demonstrated		Feb. 2014 Onconova completes Phase 3 ONTIME trials		
				Aug. 2015 Onconova starts Phase 3 INSPIRE trials		
				Oct. 2015 SymBio completes Phase 1 trials for r/r MDS	Oct. 2015 Licensing-in agreement with The Medicines Company	
				Dec 2015 Symbio joins global Phase 3 INSPIRE trials	June 2016 Phase 3 starts	
Aug 2016	Approved for chronic lymphoma leukemia					
December	Approval for additional indication - 1st Line					
Aug 2017	Phase 3 trials start for r/r medium-high risk NHL.			June 2017 High-risk MDS SymBio Phase I (oral monotherapy)	May 2017 Licensor withdraws, patient enrollment terminated	
September	Contracts with Eagle Pharma for commercialisation of RTD and RI formulations in Japan					
Jan. 2018	Start of patient enrollment for Phase 3 r/r medium to high-risk NHL			Jan. 2018 INSPIRE: interim data leads to additional cases	November Licensing agreement cancelled, arbitration petitioned	
	Start of Phase 1 trials of oral formulation for solid cancers					

Source: compiled by Fair Research Inc. from multible materials

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