SymBio Pharmaceuticals / 4582

COVERAGE INITIATED ON: 2014.10.31
LAST UPDATE: 2018.12.07

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How to read a Shared Research report: This report begins with the trends and outlook section, which discusses the company's most recent earnings. First-time readers should start at the business section later in the report.

Executive summary

SymBio in-licenses drugs for development and sale

- SymBio Pharmaceuticals Ltd. is a specialty pharmaceutical company that buys the right to develop and commercialize drug candidates in order to address the underserved medical needs of patients in Japan and the rest of Asia. With its main focus on the areas of oncology, hematology, and pain management, the company typically seeks in-licensing opportunities for niche markets from pharmaceutical and biotech companies based in the US or EU.
- Notably, the company does not conduct basic research and outsources preclinical/clinical development, employing a fabless in-licensing approach. Using its proprietary in-house "search engine," the company identifies, assesses and in-licenses only quality drug candidates having proof-of-concept established in human subjects. The company first screens third-party drug candidates being tested in clinical trials, then presents the in-licensing opportunities to its Scientific Advisory Board for further assessment of the science behind each molecule, preclinical/clinical data, target market, and the feasibility of receiving marketing approval from Japanese regulatory authorities.
- According to the company, the typical development timeline of an oncology drug in Japan from preclinical studies to marketing approval is about 10 to 17 years. However, the company secured marketing approval for its first oncology drug under development in Japan, Treakisym®, in only four years after the first clinical trial was initiated, with product launch only two years after US marketing approval and around the same time that approval was granted in Europe. Within three years of its launch, Treakisym® captured more than 50% of the non-Hodgkin's lymphoma (NHL) and mantle cell lymphoma (MCL) market in Japan.
- As of February 2018, the company had received approval for, and started sales of Treakisym® (anticancer agent for hematologic malignancies) for the indications of relapsed or refractory low-grade NHL and MCL, first-line treatment of relapsed or refractory low-grade NHL and MCL, and chronic lymphocytic leukemia (CLL). Treakisym® is included in the Practical Guidelines for Hematological Malignancies 2018 edited and published by Japanese Society of Hematology as the standard treatment for relapsed or refractory low-grade B-cell NHL, MCL, and CLL, and as a treatment option for untreated low-grade NHL.
- Drugs in the development pipeline include Treakisym® for the indication of relapsed or refractory diffuse large B-cell lymphoma (DLBCL), liquid formulations (RTD and RI products) of Treakisym®, and rigosertib (anticancer agent for myelodysplastic syndromes) IV and oral formulations.

Earnings

- FY12/17 sales were JPY3.4bn (+45.5% YoY). Product sales totaled JPY3.4bn (+61.1% YoY) and milestone payments totaled JPY0mn (JPY231mn in FY12/16). The operating loss totaled JPY3.9bn (loss of JPY2.1bn). The company also reported a recurring loss of JPY4.0bn (loss of JPY2.3bn). Net loss was JPY4.0bn (loss of JPY2.3bn).
- As a result of sales growth of Treakisym®, SymBio forecasts FY12/18 sales of JPY4.2bn (+22.0% YoY), an operating loss of JPY3.0bn (operating loss of JPY4.0bn in FY12/17), a recurring loss of JPY3.0bn (recurring loss of JPY4.0bn), and a net loss of JPY3.1bn (net loss of JPY4.0bn).
- In its medium-term plan, with the aims of achieving sales growth and higher profit margins, SymBio projects sales of JPY10.3bn–JPY11.6bn and a net income of JPY702mn–JPY1.5bn in FY12/21. The company expects higher sales from increased market penetration of Treakisym® for approved indications and anticipated approval of additional indication of Treakisym® for relapsed or refractory diffuse large B-cell lymphoma (DLBCL). The company projects a significant increase in profit on higher sales as well as on higher GPM attributed to profit generated from the sale of Treakisym® following the shift to in-house sales of the product. The company has factored the cost of establishing and operating its own sales structure into its forecast, but Shared Research thinks the increase in GPM driven by the shift to in-house sales structure will easily offset the increase in costs. The company's own sales structure is specialized to the area of hematologic disorders, and will also handle the sale of rigosertib in addition to Treakisym®.

Strengths and weaknesses

Shared Research thinks SymBio's strengths include its unique candidate selection process, strong product development team, and business strategy focusing on niche markets. Weaknesses include the lack of its own sales force and funding needs (see Strengths and weaknesses).

Key financial data

Income statement (JPYmn)	FY12/09 Par.	FY12/10 Par.	FY12/11 Par.	FY12/12 Par.	FY12/13 Par.	FY12/14 Par.	FY12/15 Par.	FY12/16 Par.	FY12/17 Par.	FY12/18 Est.
Sales	**1,191**	**1,450**	**1,883**	**1,955**	**1,532**	**1,955**	**1,933**	**2,368**	**3,444**	**4,201**
YoY	-26.9%	21.7%	29.8%	3.9%	-21.6%	27.6%	-1.1%	22.5%	45.4%	22.0%
Gross profit	**1,191**	**1,212**	**658**	**593**	**318**	**527**	**583**	**904**	**1,031**	
YoY	-26.9%	1.7%	-45.7%	-9.9%	-46.4%	65.6%	10.7%	55.1%	14.1%	
GPM	100.0%	83.6%	35.0%	30.3%	20.8%	26.9%	30.2%	38.2%	29.9%	
Operating profit	**-208**	**-613**	**-2,067**	**-1,700**	**-1,681**	**-1,303**	**-2,552**	**-2,127**	**-3,947**	**-2,981**
YoY	-	-	-	-	-	-	-	-	-	-
OPM	-	-	-	-	-	-	-	-	-	-
Recurring profit	**-214**	**-638**	**-2,095**	**-1,729**	**-1,601**	**-1,110**	**-2,630**	**-2,317**	**-3,977**	**-3,044**
YoY	-	-	-	-	-	-	-	-	-	-
RPM	-	-	-	-	-	-	-	-	-	-
Net income	**-218**	**-642**	**-2,105**	**-1,733**	**-1,605**	**-1,116**	**-2,632**	**-2,313**	**-3,978**	**-3,056**
YoY	-	-	-	-	-	-	-	-	-	-
Net margin	-	-	-	-	-	-	-	-	-	-
Per share data (JPY)										
Shares issued (year end; '000)	101	112	19,131	19,131	30,634	30,634	32,391	46,531	54,049	-
EPS	-32.5	-59.3	-143.6	-90.6	-69.3	-36.3	-81.3	-58.8	-79.8	-56.6
EPS (fully diluted)	-	-	-	-	-	-	-	-	-	-
Dividend per share	-	-	-	-	-	-	-	-	-	-
Book value per share	402.8	365.4	345.3	254.7	239.5	208.8	127.6	108.6	50.0	-
Balance sheet (JPYmn)										
Cash and cash equivalents	4,121	4,016	6,511	4,840	7,264	6,591	4,261	5,719	2,947	
Total current assets	**4,218**	**4,213**	**7,178**	**5,421**	**7,634**	**7,290**	**4,827**	**6,685**	**4,037**	
Tangible fixed assets	13	22	17	14	9	49	53	75	47	
Investments and other assets	27	27	48	57	37	49	53	77	100	
Intangible fixed assets	2	1	13	11	8	66	52	42	69	
Total assets	**4,261**	**4,263**	**7,256**	**5,502**	**7,687**	**7,454**	**4,984**	**6,878**	**4,252**	
Accounts payable	-	1	309	330	-	306	320	322	604	
Short-term debt	-	-	-	-	-	-	-	-	-	
Total current liabilities	**205**	**178**	**646**	**599**	**251**	**488**	**551**	**942**	**1,011**	
Long-term debt	-	-	-	-	-	-	-	-	-	
Total fixed liabilities	**2**	**2**	**5**	**4**	**3**	**2**	**2**	**451**	**1**	
Total liabilities	**207**	**180**	**651**	**602**	**254**	**490**	**552**	**1,394**	**1,013**	
Net assets	**4,054**	**4,083**	**6,606**	**4,900**	**7,433**	**6,964**	**4,432**	**5,485**	**3,239**	
Total interest-bearing debt	-	-	-	-	-	-	-	-	-	
Statement of cash flows (JPYmn)										
Cash flows from operating activities	-211	-754	-2,074	-1,659	-1,677	-1,266	-2,272	-1,960	-3,817	
Cash flows from investing activities	-4	-116	-117	-411	-1,332	314	1,489	-44	-78	
Cash flows from financing activities	2,963	663	4,611	-1	4,057	544	-3	3,658	1,164	
Financial ratios										
ROA (RP-based)	-7.6%	-15.1%	-36.5%	-27.2%	-24.3%	-14.7%	-42.3%	-39.0%	-71.5%	
ROE	-8.1%	-15.8%	-39.4%	-30.2%	-26.3%	-15.8%	-48.3%	-50.4%	-102.6%	
Equity ratio	95.1%	95.8%	91.0%	89.1%	96.7%	93.4%	88.9%	79.7%	76.2%	

Source: Shared Research based on company data.
Note: Figures may differ from company materials due to differences in rounding methods.

Recent updates

Highlights

On **December 7, 2018**, Shared Research updated the report following interviews with SymBio Pharmaceuticals Ltd.

On **December 4, 2018**, the company announced that Onconova gave a presentation on phase II clinical trials of oral rigosertib at the American Society of Hematology conference.

Onconova Therapeutics, Inc. (Onconova), from whom the company had in-licensed the anticancer agent rigosertib in July 2011, gave a presentation on the results of phase II clinical trials of oral rigosertib at the 60th Annual Meeting and Conference of American Society of Hematology held in San Diego, California on December 1, 2018.

Summary of Onconova's presentation is as follows:
In a clinical trial of oral rigosertib 840mg or 1,120mg administered daily in combination with azacitidine, overall response efficiency (ORR) in 29 hypomethylating agent (HMA) naïve, myelodysplastic syndrome (MDS) patients was 90%, and of which 10 patients (34%) achieved complete remission (CR). Further, 26 HMA failed, relapsed or refractory MDS patients showed an ORR of 54%, with 8% achieving complete or partial remission. Except those related to the urinary system, adverse events of the combination therapy were identical to those of azacitidine administered as a single agent, and the incidence of urinary adverse events were mitigated with various safety measures implemented for high dosage (1,120mg) administration. In conclusion, oral rigosertib administered in combination with azacitidine demonstrated high tolerability and excellent ORR and CR in HMA naïve and relapsed or refractory MDS patients. The result of the clinical trial has opened the door to phase III clinical trials of rigosertib targeting untreated MDS.

Based on the results of clinical trial presented at the American Society of Hematology conference, SymBio plans to make preparations to participate in Onconova's global phase III clinical trials of rigosertib administered in combination with azacitidine targeting untreated, higher-risk MDS in Japan.

On **November 30, 2018**, the company announced that it has begun a clinical trial of Treakisym® liquid formulation (rapid infusion formulation).

The company has begun a clinical trial of Treakisym® liquid formulation (rapid infusion [RI] formulation, intravenous administration for 10 minutes) to primarily verify the drug's safety. A total of 36 patients are enrolled in the clinical trial. In addition to previously approved indications, the company will apply for approval of the drug as treatment for relapsed or refractory diffuse large B-cell lymphoma (DLBCL).

SymBio is preparing to apply for approval of the RTD formulation with the goal of launching the product in the first half of 2021. Regarding the RI formulation, the company will apply for approval upon completion of the clinical trial, with plans to launch the product in 2022.

On **November 9, 2018**, the company announced earnings results for Q3 FY12/18; see the results section for details.

On **October 16, 2018**, the company announced that it has begun preparing for own sales organization of anti-cancer agent Treakisym®.

According to the company, the business alliance agreement it has entered with Eisai Co., Ltd. regarding the sale of bendamustine (Treakisym®) will expire in December 2020. The company announced that it has begun preparing to establish its own sales organization to sell the anti-cancer agent in Japan after the expiration of the business alliance agreement.

SymBio is currently selling Treakisym® in Japan through Eisai as its sales distributor. However, upon reviewing the terms of business alliance with Eisai with the aims of moving into the black by FY12/21 and continually expanding earnings afterwards, the company has decided to establish its own sales organization for in-house sales of Treakisym®.

With an eye toward FY12/21, the company aims to establish a sales organization specialized for drugs targeting hematologic diseases. In addition to Treakisym®, it plans to sell Rigosertib (injections and oral agents) targeting myelodysplastic syndrome (MDS) currently under development using the sales organization. In doing so, SymBio aims to achieve high operational efficiency.

No revisions were made to the earnings forecasts for FY12/18 and four-year medium-term management plan announced in February 2018 as the impact of in-house sales of Treakisym® from FY12/21 has already been factored in.

On **September 27, 2018**, the company announced it has applied for approval of a partial revision regarding the use of Treakisym® as a pretreatment for regenerative medical products.

The company applied for approval of a partial revision to manufacture and marketing approval of anti-cancer drug Treakisym® (generic name: bendamustine hydrochloride) to enable its use as a pretreatment agent for regenerative medical products.

On April 23, 2018, Novartis Pharma K.K. filed for manufacture and marketing approval for the first chimeric antigen receptor T-cell (CAR-T) therapy in Japan for the treatment of relapsed or refractory B-cell acute lymphoblastic leukemia (ALL) in patients aged 25 years or younger and relapsed or refractory diffuse large B-cell lymphoma (DLBCL) in adult patients. If the therapy is approved, Treakisym® may be used as a pretreatment agent for CAR-T therapy for the treatment of ALL and DLBCL.

For previous releases and developments, please refer to the News and topics section.

Trends and outlook

Quarterly trends and results

Cumulative	FY12/17				FY12/18				FY12/18	
(JPYmn)	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	% of FY	FY Est.
Sales	870	1,786	2,417	3,444	888	1,928	3,032		72.2%	4,201
YoY	350.2%	47.5%	71.7%	45.4%	2.1%	8.0%	25.5%			22.0%
Gross profit	239	510	675	1,031	250	573	924			
YoY	323.0%	26.0%	41.0%	14.1%	4.4%	12.4%	37.0%			
GPM	27.5%	28.5%	27.9%	29.9%	28.1%	29.7%	30.5%			
SG&A expenses	764	1,746	4,183	4,978	964	1,898	2,832			
YoY	32.9%	42.5%	108.0%	64.2%	26.1%	8.7%	-32.3%			
SG&A ratio	87.9%	97.7%	173.1%	144.5%	108.5%	98.4%	93.4%			
Operating profit	-525	-1,236	-3,508	-3,947	-715	-1,325	-1,908		-	-2,981
YoY	-	-	-	-	-	-	-			-
OPM	-	-	-	-	-	-	-			-
Recurring profit	-583	-1,268	-3,547	-3,977	-749	-1,378	-1,938		-	-3,044
YoY	-	-	-	-	-	-	-			-
RPM	-	-	-	-	-	-	-			-
Net income	-583	-1,266	-3,546	-3,978	-760	-1,389	-1,941		-	-3,056
YoY	-	-	-	-	-	-	-			-
Net margin	-	-	-	-	-	-	-			-

Quarterly	FY12/17				FY12/18			
(JPYmn)	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Sales	870	916	631	1,028	888	1,040	1,104	
YoY	350.2%	-9.9%	220.3%	7.0%	2.1%	13.5%	75.1%	
Gross profit	239	271	165	357	250	324	351	
YoY	323.0%	-22.2%	123.8%	-16.2%	4.4%	19.5%	113.0%	
GPM	27.5%	29.6%	26.1%	34.7%	28.1%	31.1%	31.8%	
SG&A expenses	764	982	2,437	795	964	934	934	
YoY	32.9%	51.1%	210.1%	-22.1%	26.1%	-4.9%	-61.7%	
SG&A ratio	87.9%	107.1%	386.5%	77.4%	108.5%	89.8%	84.6%	
Operating profit	-525	-711	-2,272	-439	-715	-610	-583	
YoY	-	-	-	-	-	-	-	
OPM	-	-	-	-	-	-	-	
Recurring profit	-583	-685	-2,279	-430	-749	-629	-560	
YoY	-	-	-	-	-	-	-	
RPM	-	-	-	-	-	-	-	
Net income	-583	-684	-2,280	-432	-760	-629	-552	
YoY	-	-	-	-	-	-	-	
Net margin	-	-	-	-	-	-	-	

Source: Shared Research based on company data.
Note: Figures may differ from company materials due to differences in rounding methods.

Breakdown of SG&A expenses

Cumulative	FY12/17				FY12/18			
(JPYmn)	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
SG&A expenses	764	1,746	4,183	4,978	964	1,898	2,832	
YoY	32.9%	42.5%	108.0%	64.2%	26.1%	8.7%	-32.3%	
R&D expenses	395	840	2,711	3,018	416	839	1,293	
YoY	76.8%	62.0%	176.3%	81.0%	5.3%	-0.1%	-52.3%	
SG&A expenses excl. R&D	369	906	1,472	1,961	548	1,059	1,539	
YoY	5.0%	28.3%	42.9%	43.7%	48.5%	16.9%	4.6%	

Quarterly	FY12/17				FY12/18			
(JPYmn)	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
SG&A expenses	764	982	2,437	795	964	934	934	
YoY	32.9%	51.1%	210.1%	-22.1%	26.1%	-4.9%	-61.7%	
R&D expenses	395	445	1,872	307	416	423	454	
YoY	76.8%	50.8%	304.4%	-55.3%	5.3%	-4.9%	-75.7%	
SG&A expenses excl. R&D	369	537	566	489	548	511	479	
YoY	5.0%	51.3%	75.0%	46.1%	48.5%	-4.8%	-15.2%	

Source: Shared Research based on company data.
Note: Figures may differ from company materials due to differences in rounding methods.

Q3 FY12/18 results

Cumulative Q3 FY12/18 sales totaled JPY3.0bn (+25.5% YoY) mainly owing to domestic sales of Treakisym®.

Due to sales growth, gross profit rose 37.0% YoY to JPY924mn with the gross profit margin increasing 2.6pp YoY to 30.5%.

SG&A expenses fell 32.3% YoY to JPY2.8bn due to a 52.3% YoY drop in R&D expenses to JPY1.3bn, which included expenses for conducting clinical trials of intravenous and oral formulations of Treakisym® and rigosertib. Excluding the drop in R&D expenses, SG&A expenses would have risen by 4.6% YoY to JPY1.5bn.

As a result, operating loss narrowed to JPY1.9bn (versus a loss of JPY3.5bn in Q3 FY12/17). Recurring loss was JPY1.9bn (versus a loss of JPY3.5bn in Q3 FY12/17) due in part to the booking of non-operating expenses of JPY34mn (mainly on share issuance costs). Net loss was JPY1.9bn (versus a loss of JPY3.5bn in Q3 FY12/17). Losses were in line with the company's forecast.

Progress made in Q3 FY12/18 was as follows:

- ▷ Regarding anticancer agent Treakisym®, the company began a phase III clinical trial for the additional indication of relapsed or refractory diffuse large B-cell lymphoma (DLBCL), and completed enrollment of the first patient in January 2018.
- ▷ In January 2018, the company began a phase I clinical trial of oral Treakisym® for progressive solid tumors, aiming to examine the recommended dosage and dosage regimen, along with tolerability and safety of the formulation, and to identify potential target tumor types.
- ▷ In May 2018, with a view to evaluate the effect of oral administration of Treakisym® on the immune system, the company concluded a joint research agreement with Keio University to conduct a pre-clinical study to verify the therapeutic value of the formulation in the treatment of systemic lupus erythematosus (SLE), a form of autoimmune disease.
- ▷ In July 2018, the company obtained approval for a partial change to its manufacture and marketing authorization for Treakisym®, allowing its combined use with not only rituximab but also obinutuzumab (once it is launched), for the treatment of low-grade non-Hodgkin’s lymphoma (low-grade NHL).
- ▷ Also in July 2018, Treakisym® was newly included as a standard treatment option in the revised Clinical Practice Guidelines 2018 for healthcare professionals as a standard therapy.
- ▷ Regarding Rigosertib (IV form), based on the results of an interim analysis performed in January 2018, the company decided to continue the trial after increasing the number of patient enrollment in accordance with pre-determined statistical criteria.
- ▷ In February 2018, the company terminated development of patient-controlled pain management drug SyB P-1501.
- ▷ In April 2018, the company raised JPY10,413mn (net of expenses) through the issuance of 45th through 47th stock acquisition rights with exercise price revision clauses (Commit Issue Program) in order to secure the fund it needed during the three years from 2018 through 2020. The proceeds, which are slated for use between April 2018 and December 2020, will go to the development of in-licensed drugs (JPY4.7bn) and creation of an independent sales structure (JPY3.3bn). All of the 45th stock acquisition rights were exercised as of October 2018, raising JPY2.6bn in net proceeds.
- ▷ In September 2018, the company applied for approval of a partial revision to manufacture and marketing approval of Treakisym® to enable its use as a pretreatment agent for regenerative medicine products.
- ▷ In October 2018, the company announced that it had begun preparing for the sale of Treakisym® through its own sales structure. The business alliance agreement the company had concluded with Eisai Co., Ltd. in 2008 regarding the sale of Treakisym® will expire in December 2020. The company began making preparations to build its own sales structure to sell Treakisym® in Japan after the agreement expires. With an eye toward FY12/21, the company plans to establish a sales structure highly specialized for hematologic disorders, and use the structure to sell rigosertib (IV and oral formulation) targeting myelodysplastic syndrome (MDS) currently under development in addition to Treakisym®.

Domestic

Treakisym® (SyB L-0501[lyophilized injection]/SyB L-1701 [RTD]/SyB L-1702 [RI]/SyB C-0501 [oral]; anticancer agent; generic name: bendamustine hydrochloride)

The company markets the anticancer agent Treakisym® in Japan through its business partner, Eisai Co., Ltd. (TSE1: 4523) for the indications of relapsed or refractory low-grade non-Hodgkin's lymphoma (NHL) and mantle cell lymphoma (MCL), untreated low-grade NHL and MCL, and chronic lymphocytic leukemia (CLL). (The company obtained marketing approval for relapsed or refractory low-grade NHL and MCL in October 2010, for untreated low-grade NHL and MCL in December 2016, and for CLL in August 2016.)

As a result of additional indications, Treakisym® is steadily increasing its market share in the area of first-line treatment by replacing R-CHOP, the conventional standard treatment. The combination therapy of Treakisym® and rituximab (BR therapy) was newly included in the Practical Guidelines for Hematological Malignancies 2018 edited and published by Japanese Society of Hematology as a standard treatment option. Sales of Treakisym® based on the National Health Insurance (NHI) drug price grew steadily by 15.2% YoY, and product sales to Eisai also progressed in line with plan.

In addition to the above three approved indications, the company has started phase III clinical trials for the fourth indication of relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and is currently enrolling patients for the trial with an aim to obtain approval. In response to strong medical needs, the company began phase III clinical trials in August 2017, and with the enrollment of the first patient in January 2018, is working on enrolling patients.

In addition to efforts for new indications, in September 2017, the company concluded an exclusive licensing agreement with Eagle Pharmaceuticals (based in New Jersey, US) to develop, market, and sell liquid formulations of Treakisym® (RTD and RI formulations) in Japan for Treakisym®'s product life cycle management. The RTD and RI products offer significant value added to patients and healthcare professionals, and extend Treakisym®'s product life cycle until 2031. The company has already consulted with PMDA on the details of the application for approval of the RTD formulation and clinical trial design for the RI formulation, and is preparing for obtaining approval and launching Treakisym® liquid formulation in 2021 or later.

In July 2018, SymBio obtained approval for the partial revision to the marketing authorization of Treakisym®. As a result, Treakisym® can now be used in combination with not only rituximab but also obinutuzumab (launched in August 2018) for the treatment of CD 20-positive follicular lymphoma (FL), the most common histological type of low-grade NHL, enabling the company to provide patients with a new treatment therapy. According to the company, as of July 2018 there were over 160 drugs for lymphatic malignancies being developed in the US and Europe combining BR (bendamustine and rituximab) or just bendamustine with anti-CD20 antibodies (19 in phase III clinical trial, 104 in phase II, and 42 in phase I). The development of a treatment therapy combining immune checkpoint inhibitors with BR or just bendamustine is also under way. SymBio thinks the approval of these therapies will lead to increased market penetration and recognition of Treakisym®, without development costs. Further, in September 2018 the company applied for approval of a partial revision to the marketing authorization of Treakisym® to enable its use as a pretreatment agent for regenerative medical products.

To reinforce the position of Treakisym® at the core of its business to strengthen its business foundation, SymBio is developing an oral formulation of the drug in addition to the injection currently under development or on sale. The company commenced a phase I clinical trial for progressive solid tumors in January 2018, with the aim of examining the recommended dosage and schedule as well as tolerability and safety of the oral formulation of Treakisym®, and narrowing down the types of potential target tumors. With the enrollment of the first patient in May 2018, the company is currently working on enrolling more patients for the trial. To evaluate the effect of oral administration of Treakisym® on the immune system, the company concluded a joint research agreement with Keio University in May 2018 and began a preclinical study to verify the efficacy of the oral form of Treakisym® in treating systemic lupus erythematosus (SLE), a form of autoimmune disease.

Rigosertib Sodium (SyB L-1101 [IV]/SyB C-1101 [oral]; anticancer agent; generic name: Rigosertib Sodium)

Onconova Therapeutics, Inc., the licensor, is currently conducting a global phase III trial and SymBio Pharmaceuticals started the Japan trial in December 2015 (37 patients enrolled so far). The global phase III trial addresses higher-risk myelodysplastic

syndromes (higher-risk MDS), which do not respond to the current standard treatment with hypomethylating agents, which relapse after treatment under the current standard of care, or which are intolerant to hypomethylating agents, and is under way at clinical trial sites in more than 20 countries worldwide. Patient enrollments are smoothly accumulating. Based on the results of an interim analysis performed in January 2018, SymBio decided to continue the trial in an adoptive design agreed upon in advance with the US Food and Drug Administration (FDA), increasing the number of patient enrollment in accordance with pre-determined statistical criteria. Based on these results, the company plans to apply for approval in Japan at the same time as in the US and Europe.

Regarding the oral formulation of rigosertib, Onconova is conducting phase I/II clinical trials for the drug used in combination with azacitidine as first-line treatment for higher-risk MDS and phase II clinical trials for transfusion-dependent lower-risk MDS in the US. To verify the tolerability and safety of the oral formulation of rigosertib among Japanese patients, SymBio began phase I clinical trials in Japan in June 2017 and is steadily enrolling patients. After completing the phase I trials, the company plans to promptly start clinical trials for rigosertib used in combination with azacitidine, participate in global phase III clinical trials of the drug used in combination with azacitidine as first-line treatment for higher-risk MDS Onconova is planning, and apply for approval of the oral formulation of the drug in Japan at the same time as in the US and Europe. In regards to development of rigosertib for transfusion-dependent lower-risk MDS, the company is considering participating from Japan while monitoring Onconova's development progress.

SyB P-1501, a post-operative patient-controlled analgesia

Regarding SyB P-1501 licensed by the Medicines Company (through its wholly owned subsidiary Incline Therapeutics, Inc.) in October 2015, SymBio found a fact that raised concerns about the continuity of its business, and in the interests of patient welfare, it suspended further patient enrollment in April 2017. The license agreement was terminated in November 2017, and the development of the drug was terminated in February 2018.

The Company initiated an arbitration against The Medicines Company in October 2017, under the rules of the International Chamber of Commerce, seeking damages of USD82mn (approximately JPY9.0bn) arising from The Medicines Company's repudiation of the license agreement. Arbitration proceedings against The Medicines Company are still ongoing.

New drug candidates

From a long-term perspective, SymBio continues to search for and evaluate promising drug candidates, in a bid to acquire global licensing rights for these drugs and grow into a sustainable and profitable biopharmaceutical company with growth potential and profitability. The company is considering licensing rights for several drug candidates. Further, in May 2016, the company established SymBio Pharma USA, Inc., a wholly owned US-based subsidiary, as a strategic base for overseas business development. The company looks to leverage this subsidiary to actively acquire rights over new drug development candidates globally, and engage in development and commercialization in major markets including the US, Japan, and Europe to transition to a global specialty pharmaceutical company.

Overseas

The company marketed SyB L-0501 in Korea, Taiwan, and Singapore, and sales were largely in line with plans.

For details on previous quarterly and annual results, see the Historical performance section.

Full-year company forecasts

	FY12/17			FY12/18		
(JPYmn)	1H Act.	2H Act.	FY Act.	1H Act.	2H Est.	FY Est.
Sales	1,786	1,658	3,444	1,928	2,273	4,201
SG&A expensees	1,746	3,233	4,978	1,898	2,452	4,350
SG&A ratio	97.7%	194.9%	144.5%	98.4%	107.9%	103.5%
R&D expenses	840	2,177	3,017	1,059	1,252	2,311
SG&A excluding R&D	906	1,055	1,961	839	1,200	2,039
Operating profit	-1,236	-2,711	-3,947	-1,325	-1,656	-2,981
OPM	-	-	-	-	-	-
Recurring profit	-1,268	-2,709	-3,977	-1,378	-1,666	-3,044
RPM	-	-	-	-	-	-
Net income	-1,266	-2,712	-3,978	-1,389	-1,667	-3,056
Net margin	-	-	-	-	-	-

Source: Shared Research based on company data.
Note: Figures may differ from company materials due to differences in rounding methods.

Earnings outlook

The company forecasts sales of JPY4.2bn (+22.0% YoY) on sales growth of Treakisym®, breaking down into product sales of JPY4.2bn (+21.7% YoY) and royalty revenue of JPY9mn (zero in FY12/17). For product sales, the company mainly forecasts higher sales of Treakisym®.

According to the company, R-CHOP therapy—a combination of rituximab with CHOP chemotherapy drugs (cyclophosphamide, doxorubicin, vincristine, and prednisolone)—was standard first-line treatment for low-grade NHL and MCL in Japan prior to December 2016. However, leading overseas treatment guidelines such as the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines recommend the use of rituximab in combination with bendamustine (BR therapy) as first-line therapy for patients with untreated low-grade NHL and MCL (see Pipeline section).

SymBio received permission to add first-line low-grade NHL and MCL as indications in December 2016, which led to a 61.1% YoY increase in product sales in FY12/17. The company expects further sales growth in FY12/18 on progress with market penetration of BR therapy as first-line treatment of low-grade NHL and MCL. The company forecasts sales of JPY10.1bn (JPY7.6bn in FY12/17) on an NHI drug reimbursement price basis.

The company forecasts total SG&A expenses including R&D expenses of JPY4.4bn (JPY5.0bn in FY12/17), breaking down into R&D expenses of JPY2.3bn (JPY3.0bn) and other SG&A expenses JPY2.0bn (JPY2.0bn).

The company's R&D program comprises development of Treakisym® for the additional indication of relapsed or refractory DLBCL (aggressive NHL), oral and liquid formulations of Treakisym® (RTD and RI formulations), and oral and intravenous rigosertib products. Although in FY12/18 there will be no in-licensing costs for oral and liquid formulations of Treakisym® (RTD and RI formulations) recorded in FY12/17 (JPY12.5mm), the company expects to book development costs for the above products.

The company forecasts an operating loss of JPY3.0bn (operating loss of JPY4.0bn in FY12/17), recurring loss of JPY3.0bn (JPY4.0bn loss), and net loss of JPY3.1bn (JPY4.0bn loss).

Pipeline

Treakisym®

- ▷ Enrolments are currently accumulating for the phase III trial for relapsed or refractory DLBCL (aggressive NHL) that is under way. The company aims to register 48 out of 60 target patients for the trial in FY12/18.
- ▷ The company will progress development of liquid formulations (RTD and RI formulations) of Treakisym® in-licensed from Eagle Pharmaceuticals after finalizing development plans for the two products.
- ▷ The company aims to enroll the first patient for its phase I clinical trial of oral Treakisym®, which has already started, as soon as possible.

Intravenous and oral rigosertib

▷ The company is moving ahead with the accumulation of cases in Japan in the global phase III trial for the intravenous version of rigosertib. In Japan, the company aims to register 36 out of the 40 target patients.

▷ Clinical trials of the oral version of rigosertib for use in combination with azacitidine are to begin after safety of azacitidine monotherapy is confirmed in a domestic phase I study for which the company is still enrolling patients.

Others

▷ As of October 2018, the company markets the anticancer agent Treakisym® in Japan through its business partner, Eisai, but has announced that it has begun preparing to establish its own sales organization to improve profit margins. Its medium-term plan (FY12/18–FY12/21) assumes starting own sales of Treakisym® from FY12/21 onward after the business alliance agreement with Eisai comes to an end in FY12/20.

▷ With regard to financing, the company aims to raise at least JPY3.0bn in FY12/18.

Long-term outlook

Medium-term plan (FY12/18–FY12/21)

When it released its FY12/17 results, SymBio also announced a four-year medium-term plan for FY12/18 through FY12/21.

Medium-term plan

(JPYmn)	FY12/17 Act.	FY12/18 Est.	FY12/19 Target	FY12/20 Target	FY12/21 Target
Sales	3,444	4,201	4,238	4,413	11,624–10,325
Operating profit (losses)	-3,947	-2,981	-3,786	-3,709	1,777–878
Recurring profit (losses)	-3,977	-3,044	-3,849	-3,772	1,724–825
Net income (losses)	-3,978	-3,056	-3,853	-3,776	1,467–702

Source: Shared Research based on company data.

Turning profitable in FY12/21 is the main priority of the new medium-term plan. The company is working on the following measures.

- ▷ Expand sales of Treakisym® for approved indications: Make further progress with market penetration of BR therapy as first-line treatment of low-grade NHL and MCL to increase market share.
- ▷ Additional indications of Treakisym®: Complete phase III clinical trials targeting relapsed or refractory DLBCL on schedule and file for approval by 1H FY12/20
- ▷ Extend product life cycle of Treakisym®: Securing products to replace existing freeze-dried (FD) product (whose period of exclusive sales in Japan expires in 2H 2020) had been a priority for the company. It plans to gain approval for the ready-to-dilute (RTD) formulation in 1H FY12/21 and begin sales of the rapid infusion (RI) formulation by FY12/22, based on a licensing agreement that provides patent protection and extends Treakisym®'s product life cycle until 2031. The company plans to switch from RTD to the new formulations quickly after they go on sale.
- ▷ Develop oral formulation of Treakisym®: Progress phase I clinical trial of phase I clinical trials of oral Treakisym®, targeting indication for progressive solid tumors with the goal of commercializing the product.
- ▷ Target filing for approval of Rigosertib injection in FY12/21. The company plans to take part in a global phase III trial run by Onconova Therapeutics, Inc.
- ▷ Establishing its own sales organization: Considering the end of business alliance with Eisai regarding the sale of Treakisym® in December 2020 and launch timing of Rigosertib injection, the company has decided to establish its own sales organization. As of October 2018, the company markets the anticancer agent Treakisym® in Japan through its business partner, Eisai, but considers a transition to its own sales structure to improve profit margins as a top management priority. Its medium-term plan (FY12/18–FY12/21) assumes starting own sales of Treakisym® from FY12/21 onward after the business alliance agreement with Eisai comes to an end in FY12/20. In October 2018, the company announced that it has begun preparing to establish its own sales organization.
- ▷ While SymBio will continue to explore and evaluate new drug candidates and consider in-licensing, it will assess the impact on FY12/21 earnings performance before taking any action.

Main pipeline schedule

	FY12/17	FY12/18	FY12/19	FY12/20	FY12/21
Treakisym® (relapsed or refractory low-grade NHL and MCL)	Obtained approval (Oct-10)				
Treakisym® (first-line treatment of low-grade NHL and MCL)	Obtained approval (Dec-16)				
Treakisym® (CLL)	Obtained approval (Aug-16)				
Treakisym® (relapsed or refractory moderate- and high-grade NHL)	Phase Ⅲ clinical trials underway		Complete phase Ⅲ clinical trials	Apply for approval	Obtain approval
Treakisym®RTD (all indications)				Apply for approval	Obtain approval
Treakisym®RI (all indications)			Initiate phase Ⅲ clinical trials	Complete phase Ⅲ clinical trials	Apply for approval
Treakisym® (oral) (progressive solid tumors)		Phase I clinical trials			
Rigosertib (IV) (relapsed and refractory high-risk MDS)	Global phase Ⅲ clinical trials underway				Apply for approval
Rigosertib (oral) (high-risk MDS [in combination with azacitidine])	Phase I clinical trials underway	Complete phase I clinical trials			
Rigosertib (oral) (high-risk MDS [in combination with azacitidine])			Initiate phase I clinical trials	Complete phase I clinical trials	

Source: Shared Research based on company data

Earnings targets of medium-term plan (FY12/18–FY12/21)

Sales

Sales of Treakisym® accounts for the bulk of overall sales. The company set the performance targets for drug sales after analysis and discussions on market size projections (derived from estimated number of patients), competitive positioning and advantages compared with existing therapies, and sales performance after commencement of sales.

SymBio forecasts FY12/20 sales of JPY11.0–JPY12.0bn on an NHI drug reimbursement price basis versus JPY10.1bn estimate for FY12/18. The company forecasts sales of JPY10.3bn–JPY11.6bn for FY12/21 based on sales of Treakisym® through its own sales force. Sales of Treakisym® the company posted up until FY12/20 were sales to Eisai as its business partner. Sales of Treakisym® made by Eisai to hospitals include margin that goes to Eisai. Shared Research estimates Eisai's GPM to be around 50%. The business alliance agreement between SymBio and Eisai will expire in December 2020, and after the agreement expires, the company plans to sell Treakisym® using its own sales structure. Since the company will claim margin generated from the sale of Treakisym® from FY12/21 that previously went to Eisai, it expects sales to grow from FY12/21.

The company forecasts sales growth of Treakisym® in FY12/21 onward following approval of an additional indication of relapsed or refractory diffuse large B-cell lymphoma (DLBCL), which is expected in or after FY12/21. Its sales target range is calculated using an estimated market penetration rate range for the indication. The company commented that a conservative peak sales estimate for the relapsed or refractory DLBCL indication is JPY8.0–JPY10.0bn.

CoGS

CoGS is based on the terms and conditions of licensing and supply agreements with Astellas Deutschland GmbH (German subsidiary of Astellas Pharma Inc.) and Eagle Pharmaceuticals, Inc.

As mentioned above, up until FY12/20, Eisai acquired margin from the sale of Treakisym®, but from FY12/21 onward, the company will sell the product using its own sales structure and accordingly claim profit from the sales. Shared Research thinks that this will not only result in sales growth in FY12/21, but also push up GPM by a corresponding amount.

SG&A expenses

SG&A expenses are broken down into R&D expenses and other SG&A expenses. In the new medium-term plan, R&D expenses are expected to trend between JPY2.0bn and JPY2.5bn (versus an estimated JPY2.3bn in FY12/18), broken down as follows:

- ▷ Expenses associated with phase III clinical trials of Treakisym®, targeting indication for relapsed or refractory DLBCL (trials started in August 2017)
- ▷ Expenses associated with the filing and development of Treakisym® liquid formulations (RTD and RI), in-licensed from Eagle Pharmaceuticals after signing an exclusive licensing agreement in September 2017
- ▷ Expenses associated with phase I clinical trials of oral Treakisym®, targeting indication for progressive solid tumors (trials commenced in January 2018)

In regard to SyB L-1101 (Rigosertib IV), based on the results of an interim analysis performed in January 2018 the company plans to continue its clinical trial, increasing patient enrollment in Japan. Milestone payments that arise at the time of obtaining approval have not been factored into the forecasts.

In-licensing or development costs on new drug candidates other than those listed in the current pipeline are not accounted for, although the company plans to continue evaluation and discussion of these agents.

Other SG&A expenses are mainly associated with the marketing, production and distribution, business development, and administrative operations for Treakisym®. The company will begin sales of Treakisym® through its own sales force from FY12/21 onward, because the business alliance agreement with Eisai will come to an end in December 2020. As such, expenses for establishing and running its own sales force are accounted for from 2019 onward.

SymBio employs product managers, who are highly specialized and can provide technical information about its products. The company had five product managers as of December 2017, but plans to increase the number to around 10 in FY12/18, 20 in FY12/19, and 40–50 in FY12/20. Shared Research understands that the product managers will assume the role of medical representatives (MRs) in the company's own sales structure from FY12/21. The company estimates the costs of preparing to establish its own sales structure at around JPY1.6bn in FY12/20.

As mentioned above, after establishing its own sales structure, the company will claim profit generated from the sale of Treakisym® that had up until FY12/20 went to Eisai. Hence, the company expects a subsequent increase in GPM to easily offset preparation expenses for establishing its own sales structure and operating loss to improve substantially.

SymBio plans to establish a sales structure highly specialized for the area of hematologic disorders. For this reason, the company's sales force will sell rigosertib (IV and oral formulation) targeting myelodysplastic syndrome (MDS) in addition to Treakisym® with an aim of achieving a high level of operational efficiency.

Secured funds necessary for FY12/18 through FY12/20 by issuing 45th, 46th, and 47th stock acquisition rights

In April 2018, the company announced the issuance of 45th through 47th stock acquisition rights with exercise price revision clauses (Commit Issue Program) in order to raise funds required for the three years from FY12/18 to FY12/20. Proceeds from the issuance net of expenses came to JPY10,413mn.

The program is designed in such a way that the allottee of the stock acquisition rights EVO FUND is committed to exercising these rights for a pre-determined number of underlying common shares (45th stock acquisition rights: 20 million shares, dilution ratio of 37.0%; 46th: 15 million shares, 27.8%; 47th: 15 million shares, 27.8%). All rights will be exercised during their corresponding exercise periods: April 26 to October 23, 2018 for the 45th, April 26 to September 17, 2019 for the 46th, and April 27 to September 17, 2020 for the 47th stock acquisition rights. (All of the 45th stock acquisition rights were exercised as of October 2018, raising a net proceed of JPY2.6bn.)

The proceeds, which are slated for use between April 2018 and December 2020, will go to the development of in-licensed drugs (JPY4.7bn), and creation of an independent sales structure (JPY3.3bn).

The company also resolved to enter into a loan agreement with Evolution Japan Asset Management (EJAM), an affiliate of EVO FUND (the allottee of the stock acquisition rights) that will allow the company to respond to immediate funding needs including investment in new in-licensing and acquisitions. The loan amount under the agreement was JPY1.5bn (maximum), the loan period April 25, 2018 to April 25, 2021, and interest rate 0.5% per annum.

Business

Business description

SymBio licenses drugs for development and sale in Japan and Asia Pacific

President and CEO, Fuminori Yoshida, established SymBio in March 2005 to address underserved medical needs in Japan and the Asia Pacific region, with main focus on oncologic, hematologic and autoimmune diseases. The company aspires to be a leading specialty pharmaceutical company in the Asia Pacific region. Its strategic approach to drug development negates the need for costly and time-consuming investment in earlier-stage R&D activities with an in-house search and evaluation team to identify and assess only quality drug candidates having proof-of-concept established in human subjects.

Strategy Overview (details to follow)

- **Proof-of-concept**: The company reduces product development risk by focusing on drug candidates undergoing clinical development with preclinical/clinical data establishing safety and efficacy in human subjects.
- **Screening**: The company uses an in-house search and evaluation team to screen and evaluate drug candidates having a high unmet medical in Japan and other Asia Pacific markets with the potential to secure marketing approval in a shorter clinical development period. A select number of drug candidates will then undergo rigorous review by the company's Scientific Advisory Board (SAB).
- **Fabless**: The company outsources preclinical/clinical studies and manufacturing to reduce fixed costs.
- **New areas:** The company targets drugs with the potential to receive orphan drug designation and thus, secure a longer marketing exclusivity period due to high unmet medical needs—including oncology, hematology, and pain management—and smaller patient populations. Larger pharmaceutical companies may be reluctant to develop drugs in niche markets due to limited sales potential—SymBio sees an opportunity to avoid intense competition in the marketplace by focusing on the development of orphan or 'orphan-like' drugs.
- **Global expansion strategy**: The company identifies and capitalizes on opportunities to grow sales by acquiring the right to develop drug candidates in Japan and other international markets.

Proof-of-concept: Per company materials, "confirming the efficacy and safety of a new drug candidate in human subjects through clinical trials..."

The company have evaluated drug candidates rigorously, signing on four deals.

According to the company, the development of a drug—from preclinical studies to approval—usually takes 10 to 17 years. A newly developed chemical compound has a 1/100,000 chance of securing regulatory approval. By contrast, the company's first product, Treakisym®, received approval for domestic production only five years after signature of the License Agreement. The company achieved sales of JPY4.2bn in Japan in the third year after launch (FY12/13), equivalent to a market share of over 50%.

An example of the company's ability to identify and pursue quality in-licensing opportunities with proof-of-concept established is the license agreement signed for the development and commercialization right to rigosertib—currently in phase I clinical trials in Japan. In July 2011, once phase II clinical trials in the US established the drug's proof-of-concept, SymBio secured an exclusive right to all indications for rigosertib in Japan and South Korea from Onconova within seven months from the initial meeting between the two companies. The following year, Baxter International Inc. entered into an agreement with Onconova for the commercialization rights to rigosertib in Europe with a USD50mn upfront payment and USD337.5mn in pre-commercial milestones tied to MDS and pancreatic cancer indications (in addition to an existing equity investment with Onconova of USD55mn), a market that is approximately twice the size of Japan.

Four products under development: Treakisym® (FD), Treakisym® (RTD and RI), rigosertib (IV and oral), and SyB P-1501

Treakisym® (FD)

For patients that have developed resistance to other drugs, Treakisym® is safer and more effective than existing treatments. In October 2010, SymBio received approval to use the drug in Japan for relapsed or refractory low-grade NHL and MCL, having previously received orphan drug designation and priority review for these two indications.

Refractory conditions are difficult to treat, or do not respond to treatment.

The company received permission to add CLL as an indication for Treakisym® in August 2016, followed by permission to add first-line low-grade NHL and MCL as indications in December 2016.

In February 2018, SymBio announced that its phase III clinical trials for an additional indication of relapsed or refractory high-grade DLBCL (aggressive NHL) were under way.

Treakisym® (RTD and RI)

In September 2017, Eagle Pharmaceuticals and SymBio concluded a license agreement that licenses to SymBio rights to develop, market, and sell Eagle's bendamustine hydrochloride ready-to-dilute (RTD) and rapid infusion (RI) products in Japan. Securing products to replace existing freeze-dried (FD) product (whose exclusive sales rights in Japan expire in 2H 2020) had been a priority for the company. It plans to gain approval for the ready-to-dilute (RTD) formulation in 1H FY12/21 and begin sales of the rapid infusion (RI) formulation by FY12/22, based on a licensing agreement that provides patent protection and extends Treakisym®'s product life cycle until 2031. Once the RTD and RI products go on sale, the company plans to switch from existing FD products at an early stage.

Rigosertib

Rigosertib is a treatment for myelodysplastic syndromes (MDS). According to the company, rigosertib may be used alone or—due to its safety—in combination with other anticancer drugs. The drug is being developed in both intravenous (IV) and oral forms.

In February 2014, Onconova completed phase III clinical trials for the IV form of rigosertib in patients with relapsed or refractory MDS in Europe, and its efficacy was proven in subgroup analysis. SymBio also completed patient registration for phase I domestic clinical trials in January 2015. From August 2015, Onconova has been conducting global phase III clinical trials for patients with higher-risk MDS who had failed or relapsed after prior therapy with hypomethylating agents (HMAs) in more than 20 countries. Within Japan, the company has been conducting joint global phase III clinical trials in cooperation with Onconova. On the basis of results of an interim analysis performed in January 2018, Onconova decided to continue with the trial with a larger patient population based on pre-planned statistical criteria.

For the oral form of the drug, SymBio is conducting a phase I clinical trial for higher-risk MDS in Japan to evaluate safety. The company plans to begin a clinical trial in combination with azacitidine after confirming safety in the phase I clinical trials, and then it may participate in global phase III trials of rigosertib azacitidine combination therapy targeting higher-risk MDS that Onconova plans to launch in FY12/20.

Revenue: milestone payments and Treakisym®

Revenue comes from milestone payments and product sales. Operating losses have persisted since the company's foundation with the exception of FY12/08 when the company booked an operating profit due to a one-time contract payment from Eisai for an exclusive domestic right to sell Treakisym® (see Historical performance). For FY12/18, the company expects a JPY3.0bn operating loss, JPY3.0bn recurring loss, and net loss of JPY3.1bn. Over the course of the medium-term plan (FY12/18–FY12/21), the company expects to post annual operating losses of JPY2.9–3.8bn. In FY12/21, the company forecasts an operating profit of JPY878mn–1.8bn, and plans to remain in the black thereafter.

Business strategy

In-licenses drug candidates from pharma companies in the US or EU

Unlike conventional pharmaceutical companies, SymBio does not conduct basic research or develop its own drug candidates in labs or clinics. Rather, it in-licenses drug candidates from pharmaceutical and biotech companies based in the US or EU.

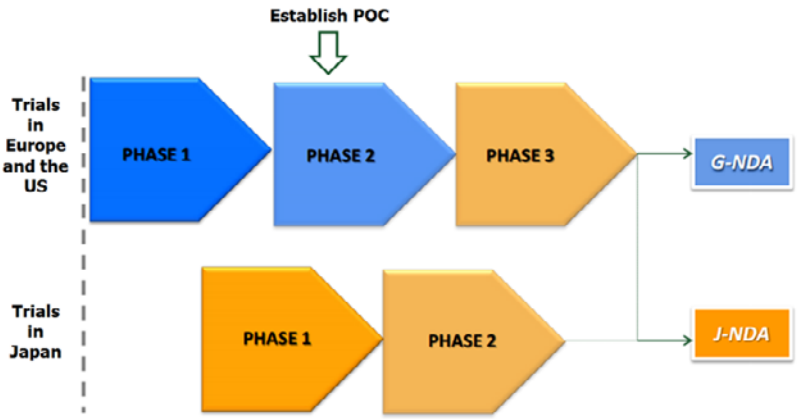
The company focuses on developing drugs that have strong safety and efficacy data in clinical trials, providing an opportunity to develop new drugs more likely to succeed and secure regulatory approval with the use of bridging data whenever possible to shorten development timelines. Because the company does not conduct basic research, the company can file an NDA and start selling a drug within five to six years of securing the development and commercialization right. The company increases the chance that drug candidates it in-licenses will be approved in the future through an effective in-house screening process and rigorous evaluation by the company's Scientific Advisory Board.

The overall aim is to reduce development risk, streamline expenses, and expand revenue opportunities. This hinges on the five strategies, namely post proof-of-concept, screening, fabless, niche market, and global expansion.

SymBio targets compounds with an established proof-of-concept

The pharmaceutical business requires substantial financial commitment in terms of upfront investment, not to mention the number of years of development required in order to realize a return on the investment and the high risk of failure in clinical studies from phase I through III. According to the company, the probability of a chemical compound having a signal with pharmacological activity in a particular disease being approved as a drug is 1/20,000 to 1/25,000, and only 15–20% of drugs that manage to enter the marketplace achieve profitability for the sponsor. Given the high rate of attrition of drug candidates in clinical development, SymBio reduces development risk by only targeting quality drug candidates undergoing clinical development with proof-of-concept established in human subjects and/or market sales. NDA filings that use clinical data generated overseas can expedite product development in Japan and other parts of Asia, slashing development costs and improving the overall success rate.

Post-proof-of-concept strategy



Source: Shared Research based on company data.

It may be possible for the company to file NDAs in Japan by bridging Japanese phase I clinical trials with foreign data through its participation in global phase III studies, thereby avoiding the need to complete domestic phase II and/or phase III studies for marketing approval.

Screening: independent search network plus evaluation experience

The company identifies quality chemical compounds owned by pharmaceutical and biotech companies in the US or EU using a proprietary "search engine" and rigorous evaluation process. These candidates are first screened in-house by the search and

evaluation team, whose members have extensive product development experience working at various pharmaceutical and biotech companies.

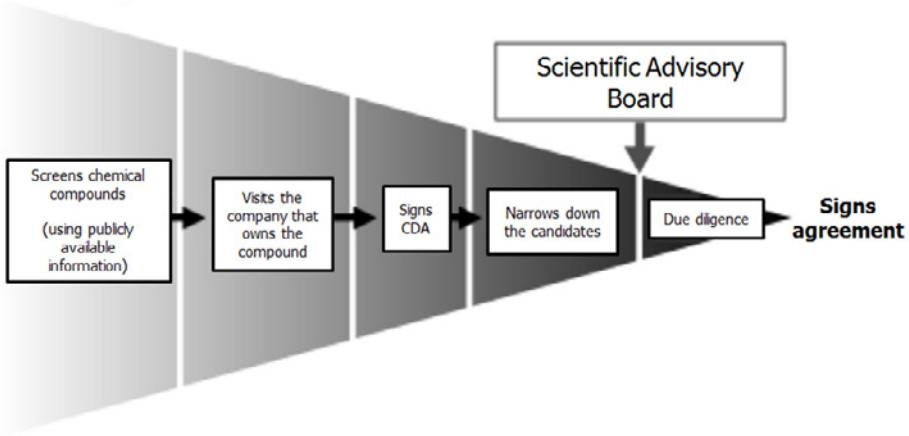
Onsite due diligence

After a select team visits the potential licensor to conduct due diligence, a decision is made regarding whether to pursue the in-licensing opportunity based on the results of onsite due diligence and input from the company's SAB members.

Only four new drug candidates have met the company's stringent criteria since its foundation

The company had screened several hundred new drug candidates since its foundation, of which it has in-licensed only a few that have met its stringent criteria. The first was Treakisym®, which Eisai Co., Ltd. (TSE1: 4523) sells in Japan. Clinical trials for additional Treakisym® indications are underway, as are preparations to file for approval of, and begin clinical trials of RTD and RI Treakisym® products. In addition, the company is also developing intravenous and oral versions of rigosertib, an anti-cancer drug for myelodysplastic syndromes.

Drug candidate selection process



Source: Shared Research based on company data.
CDA = confidential disclosure agreement

Scientific Advisory Board

The Scientific Advisory Board is comprised of former directors of pharmaceutical companies, researchers, and doctors, and meets three times a year. Typically, the SAB panel evaluates two to three drug candidates that have been selected via the company's in-house screening process. This in-house screening of only those drug candidates having proof-of-concept established in human subjects with supportive efficacy and safety data followed by SAB assessment enables the company to reduce development risk and to pursue only those opportunities having the best chance of reaching the marketplace.

Scientific Advisory Board members

Name	Profile
George Morstyn, M.D., Ph.D.	Presently Chairman GBS Venture Capital firm, Deputy Chairman Victorian Comprehensive Cancer Centre, Director of Co-operative Research Centre for Cancer Therapeutics and Proacta. Former Senior Vice-President of Development and CMO at Amgen Inc.
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; Adjunct Faculty Member, Rockefeller University, New York
Tomomitsu Hotta, M.D.	Honorary President, National Cancer Center Honorary Director, Nagoya Medical Center
Makoto Ogawa, M.D., Ph.D.	Honorary President, Aichi Cancer Center
Tatsutoshi Nakahata, M.D., Ph.D.	Deputy Director and Professor of Center for iPS Cell Research and Application (CiRA), Institute for Integrated Cell-Material Sciences, Kyoto University Honorary member, The Japanese Society of Hematology

Toshio Suda, M.D., Ph.D.	Professor, Keio University School of Medicine (Chair in Developmental and Differential Biology) Guest Professor, Institute of Molecular Embryology and Genetics, Kumamoto University Vice President, The Japanese Society of Hematology in 2012
Tsutomu Takeuchi, M.D., Ph.D.	Professor of Medicine, Keio University, School of Medicine (Division of Rheumatology, Clinical Immunology, Department of Internal Medicine)
Shinji Nakao, M.D., Ph.D.	Professor, Kanazawa University College of Medical, Pharmaceutical and Health Sciences, Division of Cancer Medicine Cellular Transplantation Biology (Hematology/Respirology) Executive Director, The Japanese Society of Hematology in 2012
Koichi Takahashi, M.D.	Assistant Professor, Department of Leukemia, Division of Cancer Medicine, MD Anderson Cancer Center, The University of Texas

Source: Shared Research based on company data.

A fabless strategy with a lean management team

SymBio seeks to reduce costs and raise profits by finding the right partner(s) to develop and commercialize drugs nimbly and efficiently through flawless execution.

Specifically, the company designs clinical trial protocols and whenever possible, will participate in global phase III studies being conducted by its partner(s) overseas with the aim of shortening development timelines in Japan. It may be possible to file NDAs in Japan using foreign data to support or "bridge" data generated in Japanese clinical trials, thereby avoiding the need to complete domestic phase II and/or phase III studies for marketing approval. The company uses its well-established network for bendamustine to coordinate with medical professionals, outsourcing routine development duties. Production is also outsourced either to the company that originally granted the product license, or to other domestic or foreign manufacturer(s). The company is preparing to establish its own sales organization to start in-house sales from FY12/21, but as of February 2018, marketing rights are granted to outside partners.

Focusing on niche markets: oncology, hematology, and pain management

SymBio focuses on drugs for underserved medical needs—even when the market may be as small as JPY10bn—rather than focusing on blockbuster drugs with sales in the hundreds of billions of yen. It aims to take advantage of therapeutic areas that tend to be overlooked in the pharmaceutical industry and thus, lack effective drugs. Specifically, the company specializes in therapeutic areas with high barriers to entry, such as oncology, hematology, and pain management.

According to the company, globally Japan has the third largest oncology market after the US and EU, and the market is expected to continue to expand due to Japan's aging population. However, regarding the type of tumors that anticancer drugs can effectively treat, there is a considerable range of indications with a limited number of patients who will benefit from approved cancer treatments, particularly in the elderly population where the occurrence of serious adverse events can be prohibitive. As a result, barriers to entry are high—developing cancer drugs for niche markets is especially difficult and requires a high level of expertise. Concerns about having sufficient profit margins from marketed drugs to fund large operations means that major pharmaceutical companies may be reluctant to target indications with limited patient numbers for development, presenting an opportunity with fewer competitors in the marketplace for smaller and more specialized pharmaceutical companies such as SymBio. The company can also increase value added of niche disease areas by additional indications and putting new products on the market. For example, its first in-house proprietary drug Treakisym® has gained over 50% market share three years after going on sale.

Strategy for global expansion

The company is seeking to develop new drugs that are complementary to Treakisym® and rigosertib to sell in China/Hong Kong, Taiwan, South Korea, and Singapore, as well as in Japan.

Pipeline

Name/Code	Category	Licensed country	Indications	Development stage	Sales partner
Treakisym® SyB L-0501 (FD)	Anti-cancer agent	Japan	Relapsed or refractory low-grade NHL and MCL	Approval obtained (Oct. 2010)	Eisai Co., Ltd. (co-developed: exclusive sales rights granted to Eisai)
			Relapsed or refractory DLBCL (aggressive NHL)	Phase III clinical trials underway	
			Untreated low-grade NHL and MCL	Approval granted (Dec. 2016)	
			CLL	Approval granted (Aug. 2016)	
		Singapore	Low-grade B-cell NHL CLL	Approval granted (Jan. 2010)	Eisai Co., Ltd. (Exclusive development and sales rights granted to Eisai)
		South Korea	CLL MM	Approval granted (May 2011)	Eisai Co., Ltd. (Exclusive development and sales rights granted to Eisai)
			Relapsed or refractory low-grade NHL	Approval granted (Jun. 2014)	
		China	Low-grade NHL	Clinical trials underway	Cephalon, Inc. (US) (Exclusive development and sales rights granted to Eisai)
		Hong Kong	Low-grade NHL	Approval granted (Dec. 2009)	
			CLL		
		Taiwan	Low-grade NHL	Approval granted (Oct. 2011)	InnoPharmax, Inc. (Taiwan) (Exclusive development and sales rights granted to Eisai)
			CLL		
Treakisym® SyB L-1701 (RTD)		Japan	All indications	In talks with PMDA regarding preparation to file for approval	
Treakisym® SyB L-1702 (RI)		Japan	All indications	Preparing for clinical trials	
Treakisym® SyB C-0501 (oral)		Japan	Systemic lupus erythematosus (SLE)	Preparing for preclinical trials	
Rigosertib (IV) SyB L-1101	Anti-cancer agent (IV)	Japan	Relapsed or refractory higher-risk MDS	Global phase III clinical trials underway	—
Rigosertib (oral) SyB C-1101	Anti-cancer agent (oral)	Japan	Higher-risk MDS (single drug)	Phase I clinical trials	—
			Higher-risk MDS (with azacitidine)	Preparing for phase I clinical trials	—

Source: Shared Research based on the company website

As of February 2018, the main drugs for which SymBio was preparing filing for approval or in the development pipeline were as follows:

- ▷ Treakisym®, targeting indication for relapsed or refractory DLBCL (aggressive NHL)
- ▷ Treakisym®, preparing to file for approval of RTD formulation and developing RI formulation
- ▷ Treakisym® (oral form), targeting indication for progressive solid tumors
- ▷ Rigosertib (intravenous form), targeting indication for relapsed or refractory higher-risk myelodysplastic syndrome (MDS)
- ▷ Rigosertib (oral form), targeting indication for higher-risk MDS

SyB L-0501 (generic: bendamustine HCl; product name: Treakisym®)

SyB L-0501 (Treakisym®) or bendamustine hydrochloride is an anticancer agent. It is used as a treatment for low-grade NHL, MCL, MM and CLL.

*Bendamustine was developed in 1971 by Jenapharm in former East Germany, where it was approved as a first-line treatment for low-grade NHL, MM, and CLL. After the unification of Germany in 1990, bendamustine was again evaluated for its effectiveness against these indications. In 2005, Germany approved the use of the drug for untreated low-grade NHL, MM and CLL. The drug was also approved in several other European countries in 2007. In the US, Treanda (bendamustine) was approved in March 2008 for relapsed or refractory NHL and CLL, with sales in October the same year. A separate application was filed in the US (2008) for the additional indication of previously untreated CLL.

According to the company, no cross-resistance (resistance to drugs with a similar structure or action as the study drug) has been shown for this drug, which means it is safer and more effective than existing treatments for target indications. In October 2010, SymBio received regulatory approval in Japan to market the drug for relapsed or refractory low-grade NHL and MCL. Eisai has been selling the drug since its launch in December 2010. The company received permission to add CLL as an indication for Treakisym® in August 2016, and first-line treatment of low-grade NHL and MCL in December 2016.

In August 2017, the company announced the initiation of phase III clinical studies of Treakisym® for an additional indication of relapsed or refractory DLBCL (aggressive NHL).

Lymphatic cancer

Lymphatic cancer is a malignant growth of lymphatic corpuscles in white blood cells. It causes inflammation of the lymphatic nodes. Lymphatic cancer is divided into Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL). Among the Japanese population, only 4% of lymphatic malignancies are HL. About 70-80% of NHL cases affect B-cells; the remaining 20-30% affect T/NK cells. Physicians examine tissue and determine the method of treatment depending on the type of cancerous cells observed: they look at the grade (high, intermediate, or low, depending on the aggressiveness of the disease) and clinical staging, which shows to what extent the cancer has spread.

Lymphatic malignancy: frequency by type

Category	Frequency
Non-Hodgkin's lymphoma	94%
B lymphocytes	69%
T/NK lymphocytes	25%
Hodgkin's lymphoma	4%
Other	2%

Source: Japanese Society for Lymphoreticular Tissue Research (JSLTR)

Treakisym® in-licensed from Astellas; Eisai handles sales

In December 2005, SymBio signed a license agreement for the exclusive right to bendamustine in Japan with Astellas Deutschland GmbH ("Astellas"), a subsidiary of Astellas Pharma Inc. The company entered into a second license agreement with

Astellas in March 2007 to extend its exclusive development and commercialization right for bendamustine to China/Hong Kong, Taiwan, South Korea, and Singapore.

In August 2008, SymBio granted Eisai Co., Ltd. ("Eisai") the co-development and exclusive marketing right for Treakisym® in Japan. Under the agreement, SymBio receives one-time payments from Eisai as well as milestone payments based on the clinical trial stage for a particular indication, plus revenues after supplying Treakisym® to Eisai. Eisai shoulders half of the development costs for Treakisym®, including labor costs for researchers and outsourcing costs for clinical trials (see Earnings structure).

SymBio has granted exclusive marketing rights for Treakisym® to InnoPharmax, Inc. in Taiwan, Cephalon, Inc. in China, and Eisai in South Korea and Singapore. In return, SymBio receives one-time milestone payments, and books revenue from the sale of the drug to these companies.

Approval for relapsed or refractory low-grade NHL, MCL in October 2010

In October 2010, five years after acquiring the right to Treakisym®, SymBio received marketing approval in Japan for relapsed or refractory low-grade NHL and MCL. In FY12/16—six years after the domestic launch of the drug in December 2010—Treakisym® sales to end users reached JPY4.7bn on an NHI drug price basis.

According to the company, Japan has about 4,700 patients who suffer from relapsed or refractory NHL and MCL. SymBio thinks annual Treakisym® sales could reach JPY4.5bn-JPY5.0bn.

Treakisym®: additional indications, RTD, RI, and oral forms

Approval for first-line treatment of low-grade NHL, MCL in December 2016 and additional indication for CLL in August 2016

In December 2016, Treakisym® was approved in Japan for first-line treatment of low-grade NHL/MCL and for CLL in August 2016. In August 2017, the company announced the start of phase III clinical studies for relapsed or refractory DLBCL (aggressive NHL) as part of its plans to add indications

Market for Treakisym® and number of patients

		Non-Hodgkin's Lymphoma		Chronic Lymphatic Leukemia
		Low-grade B-cell	Moderate- to high-grade	
First-line	Number of patients	6,967		656
	Approval	Obtained		Obtained
	Development status	Dec. 2016 approval obtained		Aug. 2016 approval obtained
Relapsed and refractory	Number of patients	9,336	18,672	
	Approval	Obtained	Completed phase II clinical trials in Japan	
	Development status	Approval obtained in Japan in Oct. 2010	Phase III clinical trials underway in Japan	

Source: Shared Research based on company data.

First-line treatment of low-grade NHL and MCL

According to the company, R-CHOP therapy—a combination of rituximab with CHOP chemotherapy drugs (cyclophosphamide, doxorubicin, vincristine, and prednisolone)—was standard first-line treatment for low-grade NHL and MCL in Japan prior to December 2016. In July 2018, Treakisym® was newly included as a standard treatment option in the Guidelines for Tumors of Hematopoietic and Lymphoid Tissues 2018 issued by the Japan Society of Hematology.

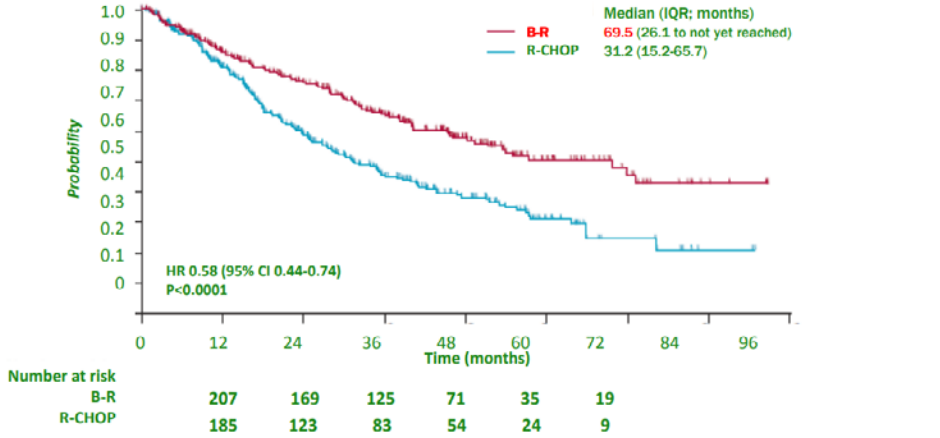
Phase III clinical trials conducted overseas have demonstrated that rituximab in combination with bendamustine (BR therapy) was safer and more efficacious than standard R-CHOP therapy for previously untreated low-grade B-cell NHL. These findings were

presented at the American Society of Hematology Annual Meeting in December 2012. Based on these results, the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines recommend the use of BR therapy as first-line therapy for patients with untreated low-grade NHL.

The subject phase III clinical trials were conducted at 81 facilities in Germany, treating patients who were newly diagnosed between September 2003 and August 2008 with stage III or IV low-grade NHL or MCL. The trials involved a comparison between R-CHOP and the bendamustine-rituximab (BR) regimen (bendamustine is marketed as Levact®, Ribomustin®, or Ribovact® in Europe). A total of 275 patients underwent R-CHOP therapy, while 274 were administered the BR combination. The median follow-up period was 45 months. Clinical results showed that the median progression-free survival period was 69.5 months for the bendamustine hydrochloride-rituximab group while that for the R-CHOP group was 31.2 months ($p<0.0001$), demonstrating the superiority of the BR therapy. Comparison of overall survival and safety between the two groups also showed superior results for the BR group.

p-value: In statistics, the p-value indicates the randomness of an observed result, or how trustworthy the sample is. A p-value of 0.01 indicates that an observed result will occur randomly one out of 100 times. Generally, if the value is below 5%, the result is statistically significant.

Results of trial comparing B-R and R-CHOP therapies as first-line treatment for patients with low-grade NHL/MCL



Progression-free survival
B-R=bendamustine plus rituximab
R-CHOP=CHOP plus rituximab.

Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, Phase 3 non-inferiority trial.
Rummel, Mathias J et al.
The Lancet, Volume 381, Issue 9873, 1203 - 1210, 6 April 2013

Source: Company data

Treakisym® approved in December 2016 for first-line treatment of low-grade NHL and MCL

In December 2016, SymBio received approval to manufacture and sell in Japan Treakisym® targeting first-line treatment of low-grade NHL and MCL. The company expects the shift from R-CHOP to BR therapy to progress domestically in the medium term.

Untreated low-grade NHL and MCL: Patient population

SymBio estimates that there are 6,967 first-line low-grade NHL and MCL patients in Japan. Although fewer than the number of patients with relapsed or refractory low-grade NHL and MCL, the company expects higher market penetration amid the trend of switching from R-CHOP to BR therapy. Treakisym® sales could reach JPY5.0–7.0bn as the Japanese population continues to age.

Treakisym® targeting chronic lymphocytic leukemia (CLL)

Astellas' European subsidiary has obtained approval in the US and the EU to market Treakisym® for the indication of CLL. In Japan, Treakisym® was designated as an orphan drug (drug for the treatment of rare diseases) in June 2012 by the Review Committee on Unapproved or Off-Label Drugs with High Medical Needs after it was determined that this drug met critical demand for new therapies to treat CLL.

Additional indication for CLL granted in August 2016

In Japan, SymBio completed a pivotal phase II trial for Treakisym® in CLL as a joint project with Eisai in October 2015. In August 2016, the company received permission to add CLL as an indication for Treakisym®.

Potential patient population, expected sales

SymBio estimates that there are about 656 CLL patients in Japan. Shared Research estimates that sales could reach JPY300mn–JPY350mn. This estimate is based on Treakisym® sales per patient with relapsed or refractory low-grade NHL or MCL.

Treakisym® indicated for relapsed or refractory DLBCL (aggressive NHL)

Diffuse large B-cell lymphoma (DLBCL), or aggressive NHL, progresses rapidly but recovery may be expected in patients for whom anti-cancer drugs are effective. R-CHOP is the standard initial therapy for relapsed or refractory DLBCL, the most common type of NHL.

But according to the company, 40% of untreated patients treated with R-CHOP relapse or become refractory, and only patients who are 65 or younger can undergo chemotherapy at higher doses together with autologous stem cell transplants. Because the majority of relapsed or refractory DLBCL patients are elderly, physicians must consider potential side effects when selecting a suitable treatment. Weaker patients—due to age or other illnesses—have limited choices for treatment, and there is a need for a safer, more effective method of treatment such as Treakisym®.

R&D status: Began phase III clinical trials of Treakisym® to treat relapsed or refractory DLBCL in August 2017

In March 2012, the company completed final analysis and evaluation of data from its phase II clinical trials using Treakisym® in combination with rituximab for relapsed or refractory DLBCL (aggressive NHL). The trial, with clinical trial sites in both Japan and South Korea, demonstrated an improved prognosis as well as clinically manageable side effects in elderly patients.

Following consultations with the Pharmaceuticals and Medical Devices Agency (PMDA), the company commenced phase III clinical trials using Treakisym® in combination with rituximab for relapsed or refractory DLBCL. The purpose of the study is to test the efficacy and safety of BR therapy, with the overall response rate (ORR; antitumor effect) as the primary endpoint and an enrollment target of 60 patients. The company plans to conduct the study over 24 months and aims to file NDA in 2H 2019.

In April 2018, Novartis Pharma K.K. applied in Japan for approval of CTL019, chimeric antigen receptor T cell (CAR-T) therapy, for the treatment of adult patients with CD19 positive relapsed or refractory DLBCL. In May 2018, Novartis obtained approval in the US for use of CTL019 to treat adult patients with relapsed or refractory DLBCL after two or more lines of systemic therapy. Since the use of CTL019 is limited to adult patients for whom two or more lines of therapy have proved ineffective, Shared Research understands that CTL019 is different from Treakisym® and that the two companies do not compete in this area. In September 2018, the company applied for approval of a partial revision to manufacture and marketing approval of Treakisym® to enable its use as a pretreatment agent for CTL019 targeting relapsed or refractory B-cell acute lymphoblastic leukemia (ALL) and relapsed or refractory diffuse large B-cell lymphoma (DLBCL) in adults.

Potential patient population

According to SymBio, the number of relapsed or refractory diffuse large B-cell lymphoma (DLBCL; aggressive NHL) patients in Japan is approximately 18,672. We estimate annual peak sales for the indication (NHI drug reimbursement price basis) at JPY8.0–10.0bn.

Concluded license agreement for RTD and RI formulations of bendamustine hydrochloride (marketed as Treakisym® in Japan) in September 2017

In September 2017, Eagle Pharmaceuticals and SymBio concluded a license agreement that licenses to SymBio rights to develop, market, and sell Eagle's bendamustine hydrochloride ready-to-dilute (RTD) and rapid infusion (RI) products (marketed in the US by Teva Pharmaceutical Industries as BENDEKA®) in Japan. SymBio will pay Eagle a USD12.5mn upfront payment and a milestone payment upon approval. The company will also pay additional milestone payments on the achievement of cumulative sales thresholds and royalties on future sales of licensed bendamustine products.

RTD and RI products do not require reconstitution; RI product can be administered in one sixth of the time as FD product

The FD powder injection product currently available must be reconstituted manually before administration by intravenous infusion. Since RTD and RI products are already liquidized, they do not require the time-consuming process of reconstitution and substantially reduce the workload of healthcare professionals. RI products also do not require reconstitution and can be administered by intravenous infusion in 10 minutes instead of 60 minutes for FD powder injection and RTD products, which reduces stress on patients.

Comparison of RTD/RI products and currently available (freeze-dried) product

	RTD products	RI products	Currently available products
Generic name	bendamustine hydrochloride		
Dosage form	Liquid		Freeze-dried powder injection
Reconstitution	Not required		Required (manual reconstitution)
Dilution	Dilute with 250ml physiological saline	Dilute with 50ml physiological saline	Dilute with 250ml physiological saline
Administration time	60 minutes	10 minutes	60 minutes
Dosage form	100mg/4mL		100mg/vial 25mg/vial
Storage	Refrigerated storage (2°C–8°C)		Room temperature

Can extend life cycle of Treakisym® until 2031

The re-examination term for the FD product of Treakisym® ends in 2020, after which generics can go on the market. SymBio believes that by selling the RTD and RI products that offer the advantages of reducing healthcare professionals' workload and stress on patients after 2020, it can extend the exclusive sales period until 2031. This increases the possibility of prolonging the life cycle of Treakisym® and limiting the spread of generics.

Bendamustine hydrochloride RTD and RI injection products are marketed in the US by Teva Pharmaceutical Industries as BENDEKA®, which has 97% share of the US bendamustine market within two years after its sales.

R&D status: Aim to begin selling bendamustine hydrochloride RTD product in 1H 2021

As of February 2018, the schedule for filing for approval of the bendamustine hydrochloride RTD product and development of the RI product were under discussion.

SymBio commented that it is likely to be allowed to file for approval of the RTD product without conducting clinical trials, because the ingredients, efficacy, and administration time are identical to the Treakisym® FD product; the only difference being that it does not need reconstitution. The company aims to begin selling the RTD product in 1H 2021, based on the estimated time required to prepare filing documentation and review period from filing to approval.

However, the company expects clinical trials will be required for the RI product, because the administration time is different from the FD product. Given that the trials will only be comparing the safety and efficacy of the RI product and the FD product (which has already been approved) rather than the usual phase III clinical trial of a new drug, SymBio expects that the required number of patients in the study will be small. The company plans to begin preparing for the sale of the RI product after the RTD product goes on sale.

Treakisym® (oral) SyB C-0501

SymBio is exploring the possibility of expanding the business by progressing development of the oral form of Treakisym® targeting new indications such as solid tumors and autoimmune diseases. As part of this project, the company has started a phase I clinical trial to evaluate dosage and dosing schedule, tolerability, and safety of the oral form on select types of cancer.

Treakisym® as a pretreatment agent for a regenerative medicine product (CAR-T cell therapy)

In September 2018, the company applied for approval of a partial revision to manufacture and marketing approval of anti-cancer drug Treakisym® to enable its use as a pretreatment agent for regenerative medical products.

In April 2018, Novartis Pharma K.K. filed for manufacture and marketing approval for the first chimeric antigen receptor T-cell (CAR-T) therapy (CTL019) in Japan for the treatment of relapsed or refractory B-cell acute lymphoblastic leukemia (ALL) in patients aged 25 years or younger and relapsed or refractory diffuse large B-cell lymphoma (DLBCL) in adult patients. If the therapy is approved, Treakisym® can be used as a pretreatment agent for CAR-T therapy for the treatment of ALL and DLBCL. Further, the approval would mark the addition of regenerative medicine as a new area of indication for Treakisym®.

CAR-T cell therapy genetically modifies T-cells collected from patients' blood samples to express chimeric antigen receptors (CARs) on their surface at a cell processing center. Then, the genetically modified T-cells (CAR-T cells) are infused back into the patients where they assume the role of immune system and specifically attack cells that express target proteins including cancer cells. CTL019 is an immune cell therapy that collects T-cells from patients' blood samples and genetically modifies them so that they specifically recognize CD19 proteins expressed on cancer cells among others and attack them. CTL019 therapy requires only a single administration.

SyB L-1101 (intravenous)/SyB C-1101 (oral) (generic name: rigosertib)

Rigosertib is a tumor-specific dual-specificity inhibitor, which inhibits both the PI3K (phosphoinositide 3-kinase) and the PLK (polo-like kinase 1) pathway. It is being developed in the US and EU by Onconova as a treatment for myelodysplastic syndromes (MDS) as well as in other indications such as first-line MDS and AML (in combination with Vidaza), and head and neck cancer (solid tumor).

According to SymBio, rigosertib's high safety profile enables the drug to be used as both a monotherapy and in combination with other anticancer drugs. It is being developed in both intravenous and oral forms.

Onconova: A US biopharmaceutical company. Established in 1998, Onconova focuses on discovering and developing small molecule drug candidates to treat cancer.

Myelodysplastic Syndromes (MDS)

MDS is a refractory disease with a poor prognosis and progression to acute myeloid leukemia (AML) in approximately 30% of cases. It leads to abnormalities in hematopoietic stem cells that produce blood cells, resulting in a lack of blood. Blood cells produced this way are abnormally shaped. This change in the cells is called dysplasia. The disease typically leads to frequent anemia with some patients dying from infection or bleeding due to the reduction in blood cells. The average survival period is about three to five years, with some patients surviving 10 years or longer. It is still not clear what environmental or genetic factors are responsible for the occurrence of MDS, although those who have received radiation treatment or taken anti-cancer drugs may have a higher risk of developing the disease (source: Japan Adult Leukemia Study Group: JALSG).

The seriousness of MDS is determined with the use of the International Prognostic Scoring System (IPSS). The IPSS score is calculated based on the ratio of myeloblasts (immature blood cells) in the bone marrow, chromosome analysis, and the results of a general laboratory blood test. The risk level is assessed based on the number of years that the patient is expected to live, disease progression, and the probability that the disease may lead to acute myeloid leukemia. Risk categories: low, intermediate-1, intermediate-2, and high. Lower-risk MDS refers to low and intermediate-1 patients, while higher-risk MDS refers to intermediate-1 and high in the IPSS risk categories.

Acquired rights from Onconova to develop and sell rigosertib in Japan, Korea

In July 2011 SymBio bought the exclusive right to develop and sell the intravenous (IV) and oral forms of rigosertib following completion of Onconova's phase II US clinical trial for the IV form. In September 2012, Baxter International Inc. acquired the exclusive right to develop and sell rigosertib in Europe.

Development status of rigosertib

As of February 2018, SymBio is developing the IV form of rigosertib for the indication of relapsed or refractory higher-risk MDS, and the oral form for higher-risk MDS.

Onconova has been conducting joint global phase III clinical trials in over 20 countries since August 2015 for the intravenous form of rigosertib in higher-risk MDS patients who had failed or relapsed after prior therapy with hypomethylating agents (HMAs). In the Japanese market, the company has been conducting the joint global phase III clinical trials in cooperation with Onconova since December 2015.

The company had started phase I clinical trials for the oral form of rigosertib for the indications of higher-risk MDS (in combination with azacitidine) in December 2015. The supply of the study drug from Onconova had been delayed, but SymBio restarted phase I clinical trials in Japan in June 2017. After establishing safety in phase I clinical trials, the company plans to resume the trial of rigosertib in combination with azacitidine and participate in global phase III clinical trials planned by Onconova.

Market for Rigosertib (oral form) and number of patients

		Low-risk MDS First-line	High risk MDS First-line	Relapsed and refractory
Intravenous	Number of patients			3,200
	Approval			Obtain approval in FY12/19 (expected)
	Development status			Global phase III trials
Oral	Number of patients	7,800	3,200	
	Approval	TBC	TBC	
	Development status	Phase II trials underway in the US	Phase II clinical trials underway in the US Phase I clinical trials underway in Japan	

Source: Shared Research based on company data.

IV form of Rigosertib for post-HMA higher-risk MDS

Higher-risk MDS (patients in the Intermediate-2 risk and High-risk groups based on International Prognostic Scoring System) is likely to cause a decline in blood cells or lead to leukemia. Treatment may involve stem cell transplants, depending on the patient's age, condition, and the compatibility of the donor. In the US and Europe, Vidaza (azacitidine) and Dacogen (decitabine) are standard drug therapies for this treatment. In Japan, Vidaza (being marketed by Nippon Shinyaku) is also administered in cases where stem cell transplants are not used. (for Vidaza, see Market and value chain)

However, some cases of higher-risk MDS show resistance to standard treatment with hypomethylating agents (HMAs) such as Vidaza and Dacogen, including relapse following treatment. The most advanced research being conducted for rigosertib was for the treatment of patients with higher-risk MDS who had progressed on, failed or relapsed after prior therapy with HMAs. According to the company, no drugs have been approved for the treatment of post-HMA higher-risk MDS patients as of February 2018.

R&D status: ongoing joint global phase III clinical trials in patients with relapsed higher-risk MDS following HMA therapy

In February 2014, Onconova completed its phase III ONTIME clinical trial for the intravenous form of the drug in MDS patients in the US who showed resistance to standard treatment with HMAs, or who experienced recurrence of the disease after treatment with HMAs.

Of the 299 patients enrolled in the phase III clinical trial, 199 were administered rigosertib and 100 were placed in the control group. The overall survival (OS) period for those who received rigosertib was 8.2 months, while OS for the control group (BSC) was 5.8 months. However, with a p-value of 0.27, there was no statistically significant difference between the two groups.

Among patients whose condition had deteriorated or not responded to previous treatment using hypomethylating agents (184 of 299 people, or 62%), the overall survival period for higher-risk MDS patients who received rigosertib was 8.5 months, while for those in the control group (BSC) it was 4.7 months. The p-value was 0.022, showing a statistically significant difference. The hematological toxicity of the conventional anti-cancer agent was approximately 60%. With rigosertib, toxicity of Grade 3 or above did not exceed 7%, and non-hematological toxicity did not exceed 3%, confirming safety of the drug.

In August 2015, Onconova submitted plans to US Food and Drug Administration (FDA) and regulatory agencies in England, Germany, and Australia for global phase III comparative trials of rigosertib for patients who did not see results from low methylation, or experienced higher-risk refractory or relapsed MDS following HMA treatment. These global trials are currently ongoing.

SymBio responsible for operation of global phase III clinical trials within Japan

Based on the outcome of discussions with the FDA and European regulatory agencies and Onconova's future development, the company has been operating the global phase III clinical trials within Japan since December 2015. The first patient was registered in July 2016 and 30 patients had been registered as of end-February 2018 versus the target 25–30. Onconova decided to proceed with the clinical trial on the basis of results of an interim analysis performed in January 2018 by increasing the number of patients registered from 225 to 360 based on preplanned statistical criteria. SymBio plans to increase the number of patients registered to 40 to continue the trial.

Oral form of rigosertib for first-line higher-risk MDS

R&D status: phase I and II clinical trials underway

Onconova, the anticancer drug rigosertib's licensor, presented phase II clinical trial data on oral rigosertib for patients with higher-risk myelodysplastic syndromes (MDS) at the 58th American Society of Hematology (ASH) Annual Meeting held in December 2016.

The data on the efficacy and safety of oral rigosertib and azacitidine combination for 33 MDS patients (20 HMA naïve; 13 HMA resistant) was presented at the poster presentation, "Combination of Oral Rigosertib and Injectable Azacitidine in Patients with Myelodysplastic Syndromes (MDS): Results from a Phase II Study." The complete remission (CR) rate amongst HMA-naïve patients was higher (35%) and responses occurred more rapidly and durably with the oral rigosertib combination compared to the single-agent azacitidine. The median duration of CR was eight months, comparing very favorably to the historic duration of CR of 3.2 months with single-agent azacitidine.

As of February 2018, Onconova is making efforts toward finalizing the design for a pivotal phase III oral rigosertib/azacitidine combination trial for higher-risk MDS patients.

Domestic phase I clinical trials

In FY12/16, the company launched phase I clinical trials to confirm the safety of the drug in combination with azacitidine for treatment of higher-risk MDS. However, patient enrollment had not started because of delayed supply of the study drug from Onconova Therapeutics. After the supply of the study drug resumed in June 2017, the company restarted the domestic phase I clinical trial to confirm the safety of the drug at high doses (an additional requirement for phase III clinical trials conducted by Onconova in the US for the indication of untreated and relapsed or refractory higher-risk MDS). After establishing safety in the phase I clinical trial, the company plans to resume the trial of the drug in combination with azacitidine and participate in global phase III clinical trials conducted by Onconova

Patient population, estimated sales

According to SymBio estimates, patients with lower-risk MDS in Japan number about 7,800, with 3,200 MDS patients classified as higher-risk.

Nippon Shinyaku Co., Ltd. (TSE1: 4516) has been selling azacitidine in Japan as first-line therapy for MDS under the product name Vidaza since March 2011. According to Nippon Shinyaku, sales of Vidaza were JPY14.1bn for FY03/17 (+14.0% YoY) and

forecast to reach JPY15.9bn in FY03/18. Shared Research thinks that sales of the intravenous and oral forms of rigosertib could match or exceed sales of Vidaza, used for patients who have not received treatment with Vidaza or in combination therapy with Vidaza.

Earnings structure

(JPYmn)	FY12/09	FY12/10	FY12/11	FY12/12	FY12/13	FY12/14	FY12/15	FY12/16	FY12/17
Sales	1,191	1,450	1,883	1,955	1,532	1,955	1,933	2,368	3,444
YoY	-26.9%	21.7%	29.8%	3.9%	-21.6%	27.6%	-1.1%	22.5%	45.4%
Product sales	-	326	1,632	1,955	1,432	1,940	1,933	2,137	3,444
YoY	-	-	401.3%	19.8%	-26.8%	35.5%	-0.3%	10.6%	61.1%
Treakisym sales to end users (reference	-	644	3,390	3,940	4,230	4,320	4,760	4,720	7,600
Product sales / Sales to end users	-	50.6%	48.2%	49.6%	33.9%	44.9%	40.6%	45.3%	45.3%
Royalty revenue	1,191	1,124	250	-	100	15	-	231	-
Sales to Eisai	1,085	1,446	1,872	1,930	1,486	1,908	1,852	2,265	3,382
Non-Eisai sales	106	4	10	26	46	47	81	104	62
CoGS	-	238	1,224	1,362	1,214	1,428	1,350	1,464	2,413
CoGS / Product sales	-	73.1%	75.0%	69.7%	84.8%	73.6%	69.8%	68.5%	70.1%
CoGS / Sales to end users	-	37.0%	36.1%	34.6%	28.7%	33.1%	28.4%	31.0%	31.7%
Product procurement	-	238	1,434	1,322	1,175	1,550	1,242	1,606	2,589
Gross profit	1,191	1,212	658	593	318	527	583	904	1,031
Product gross profit	0	87	408	593	218	512	583	673	1,031
GPM	-	27%	25%	30%	15%	26%	30%	32%	30%
Royalty revenue	1,191	1,124	250	-	100	15	-	231	-
SG&A expenses	1,399	1,825	2,725	2,293	1,999	1,830	3,135	3,031	4,978
Personnel expenses	323	343	365	413	441	479	488	541	554
R&D expenses	817	1,118	1,945	1,438	1,053	774	2,035	1,667	3,018
Other	259	364	415	442	505	577	612	823	1,406
Operating profit	-208	-613	-2,067	-1,700	-1,681	-1,303	-2,552	-2,127	-3,947

Source: Shared Research based on company data.

Sales

The company's sales are made up of product sales and royalty revenue. Per the above table, most of the sales have originated from Eisai.

Product sales

Product sales are revenue from selling Treakisym®. The company began booking product sales in FY12/10, when it obtained approval for Treakisym® and started selling the anti-cancer agent in December 2010. ThroughFY12/16, the company booked sales of Treakisym® indicated for relapsed or refractory low-grade malignant NHL and MCL.

In FY12/17, the company booked sales of additional indications of untreated low-grade malignant NHL and MCL, resulting in a strong sales YoY.

Royalty revenue

Royalty revenue includes one-time contract payments and milestone payments. Since granting the exclusive marketing right for Treakisym® to Eisai in August 2008, SymBio books one-time payments and milestone payments in accordance with clinical trial stage.

CoGS

Cost of goods sold refers to procurement costs for drugs. SymBio purchases Treakisym® from Astellas Deutschland GmbH. Astellas supplies Treakisym® to the company for about 70% of SymBio's wholesale price. Margins may improve as sales increase.

SymBio pays Astellas in euros, with these transactions usually taking place several months apart. Thus, the company faces the risk that euro-yen forex rates will change during this period. The company hedges this risk with forward foreign-exchange contracts, and by reporting gains and losses on forex as a non-operating profit (or loss).

SG&A expenses

Personnel and R&D are the main SG&A expenses. Personnel expenses have been trending upward in line with business growth. R&D expenses fluctuate depending on the progress of clinical trials and new license agreements from in-licensing activities. According to the company, in-licensing expenses are between JPY500mn and JPY1bn per drug, and domestic clinical trials cost between JPY1bn and JPY2bn. Note: Eisai pays half of the development costs for Treakisym® in Japan.

R&D expenses increased YoY in FY12/17, because the company incurred expenses for in-licensing liquid formulations of Treakisym® (RTD and RI products).

Strengths and weaknesses

Strengths

- **Unique candidate selection process:** SymBio makes decisions on in-licensing new drug candidates based on an initial assessment and screening process by its in-house search and evaluation team. The final decision is made by the company after evaluation by a team of medical experts—the Scientific Advisory Board (SAB). President Yoshida's extensive range of contacts in the pharmaceutical industry built during his tenure at Amgen Japan and Amgen Inc. is a significant hurdle for competitors attempting to emulate the quality of the company's search and evaluation team, SAB panel and selection process.
- **Strong product development**: Treakisym® (bendamustine hydrochloride)—the first drug the company developed—received marketing approval in Japan just five years after the license agreement was signed with Astellas. Treakisym®, launched by the company in December 2010, is being used by a number of Japanese physicians and is considered to be an essential drug for the treatment of relapsed or refractory low-grade NHL and MCL. The company's success with Treakisym® demonstrates its strong product development capabilities and nimbleness.
- **Strong share in niche markets**: SymBio focuses on niche markets for rare oncologic and hematologic diseases and pain management. The company takes advantage of a less competitive environment by developing drugs for indications that serve a limited number of patients and require a high degree of in-house expertise. Thus, the company has succeeded in securing more than 50% of the target market for Treakisym® in relapsed or refractory low-grade NHL and MCL in the third year after launch.

Weaknesses

- **Lack of sales force:** The company does not currently have its own sales force, thus Treakisym® is being sold through Eisai, an alliance partner. The company says that it aims to build up its own sales and marketing organization in the longer term, but Eisai will be responsible for sales of Treakisym® in Japan through FY12/20.
- **Funding needs**: It takes time and significant investment for pharmaceutical and biotech companies to develop and commercialize drugs, and they must secure funding on a regular basis to cope with the uncertainty of their earnings. For SymBio, cash and equivalents plus short-term investments totaled about JPY2.9bn at the end of FY12/17. But the company expects a total net loss of JPY10.7bn over the first three years of its medium-term plan (FY12/18–FY12/21). The company's operations would be affected if it fails to secure additional funding.
- **Dependence on a single individual**: Founding President and CEO, Fuminori Yoshida, has played a central role in all aspects of SymBio's management since its foundation. If for any reason Mr. Yoshida is unable to perform his duties, this could have an impact on company operations.

Market and value chain

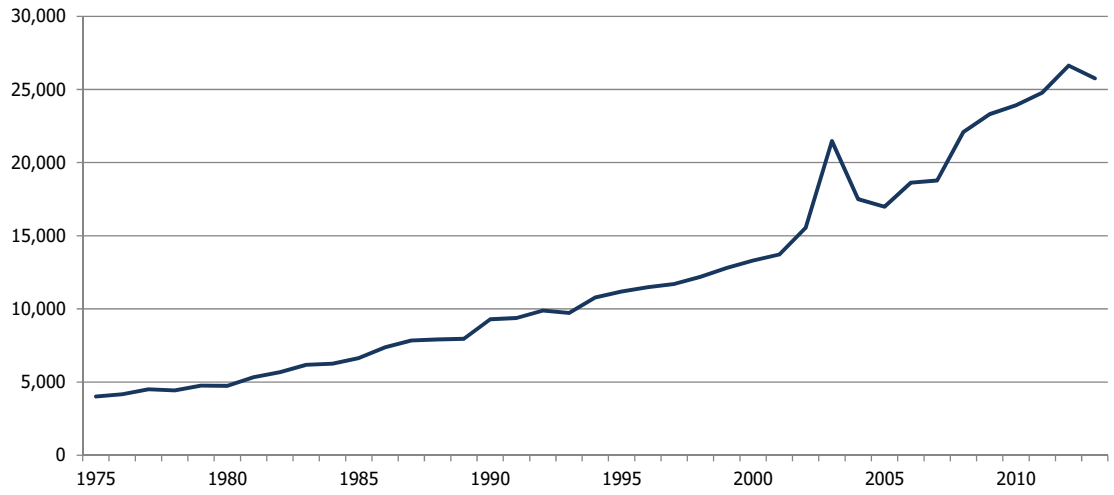
Market strategy

Lymphatic cancer: patient population, market size, drugs

Newly diagnosed patients with lymphatic cancer

In 2013, the number of people diagnosed with lymphatic cancer in Japan was 25,761 (-3.3% YoY; average annual increase in past 10 years is 1.8%), according to the Center for Cancer Control and Information Services. Of these, 20,327 (+2.0%), or 78.9% (77.9% in 2011), were 60 years or older. Of the 862,452 (-0.3%) people diagnosed with cancer, those diagnosed with lymphatic cancer accounted for only 3.0%, but their number increased 39.4% between 2003 and 2013 versus a 39.1% increase in the number of people newly diagnosed with cancer.

Patients newly diagnosed with lymphatic malignancy



	1975	1980	1985	1990	1995	2000	2005	2010
Number of patients	4,013	4,741	6,635	9,297	11,195	13,307	16,991	23,919
Incidence rate (per 100,000)	3.6	4.1	5.5	7.5	8.9	10.5	13.3	18.7

Source: Shared Research based on data from Center for Cancer Control and Information Services, National Cancer Center.

Market for anticancer drugs to expand

According to the Fuji Keizai Group, the domestic market potential l for anticancer agents was JPY1.6tn (+12.2% YoY) in 2016. The market is growing amid new products going on sale and additional indications, and is expected to hit JPY1.4tn by 2025.

Treakisym® market potential and patient population

The company estimates that the number of patients being treated for relapsed or refractory low-grade NHL and MCL in Japan is 9,336 and the number of patients with untreated low-grade NHL and MCL is 6,967. Treakisym® sales reached JPY7.6bn (+60.9%) in FY12/17.

The company estimates that the number of Japanese patients with relapsed or refractory DLBCL for which the company is considering application for approval of an additional indication is 18,672.

Treakisym® indications and number of patients

Indications	Patients	Progress	Notes
Relapsed or refractory low-grade NHL and relapsed or refractory MCL	9,336	Approval granted	Sales: JPY7.6bn (FY12/17)
Untreated low-grade NHL, and untreated MCL	6,967	Approval granted	
CLL	656	Approval granted	
Relapsed or refractory NHL	18,672	Clinical trials underway	

Source: Shared Research based on company data.
*Sales based on NHI prices.

Drugs competing with Treakisym®

As of February 2015, these include rituximab and ibritumomab tiuxetan.

Rituximab (product name: Rituxan)

The drug, co-developed by the US companies IDEC Pharmaceuticals and Genentech, Inc. received US approval in November 1997 as the world's first monoclonal antibody.

Rituxan consists of a portion of both mouse antibody and IgG, a human antibody. It attaches itself to the CD20 antigen that appears on B cells in the body and fights tumors through complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity effects (source: Chugai, Zenyaku Kogyo).

In Japan, Zenyaku Kogyo and Chugai have been jointly selling the drug since September 2001. Chugai's Rituxan sales were JPY33.4bn (+4.0% YoY) in FY12/17.

Ibritumomab tiuxetan (product name: Zevalin)

Like Rituxan, the antibody drug Zevalin targets CD20 antigen on B cells. It combines the antibody with a radioactive substance and attacks B cells with radiation. The treatment is only available at medical institutions authorized to handle radioactive elements.

Zevalin was approved in January 2008 as a treatment for refractory lymphatic cancer (low-grade B-cell NHL). It is sold by Fujifilm RI Pharma Co., Ltd., a subsidiary of Fujifilm Holdings Corporation.

MDS patients, drugs

Market potential and number of patients

MDS patient population estimated at 11,000

A high proportion of people aged 60 or older suffer from MDS. The number of patients totaled 9,000 in 2008, with 2,781 deaths from the disease according to Japan's Ministry of Health, Labour and Welfare (MHLW). SymBio estimates that there are currently about 11,000 MDS patients in Japan amid a larger elderly population. Even though the number of patients continues to rise, there is a high unmet medical need in Japan with no effective treatment available.

Rigosertib indications and number of patients

Condition	Patients
Low-risk MDS	7,800
High-risk MDS	3,200

Source: Shared Research based on company data.

Drugs competing with rigosertib

According to the company, as of February 2018, Nippon Shinyaku Co., Ltd.'s Vidaza is the only IV drug approved in Japan for the main indication of MDS.

Azacitidine (product name: Vidaza)

Vidaza, developed by Pharmion Corporation (now Celgene Corporation) in the US, is a treatment for first-line intermediate and higher-risk MDS. Nippon Shinyaku Co., Ltd. signed a license agreement with Pharmion in 2006 to sell this drug in Japan, obtaining marketing approval in January 2011 following the completion of domestic clinical trials.

In addition to killing cancerous cells, azacitidine inhibits DNA methylation. It becomes effective after use for three to six months, with bone marrow suppression as the main side effect (a decline in white blood cells and platelets). However, while the use of hypomethylating agents such as azacitidine and decitabine (Dacogen) in the treatment of MDS has improved the outcome of patients who tend to have very poor survival, about half of MDS patients do not respond, progress, or relapse at different times after their response on these HMAs, followed by an extremely poor prognosis.

According to Nippon Shinyaku, Vidaza is the only approved drug in Japan for the first-line treatment of higher-risk MDS, with no effective treatment available once patients treated with Vidaza relapse. Nippon Shinyaku booked Vidaza sales of JPY14.1bn in FY03/17 (+14.0% YoY) and expects sales of JPY15.9bn in FY03/18.

Historical performance

1H FY12/18 results

1H FY12/18 sales totaled JPY1.9bn (+8.0% YoY) mainly owing to domestic sales of Treakisym®, which increased 22.3% YoY based on the National Health Insurance (NHI) drug price. Overseas sales of Treakisym® also increased by over 20% YoY. Product shipment to Eisai Co., Ltd. at end-Q2 was pushed back to Q3. Excluding this factor, overall sales increased 21% YoY.

Due to the sales increase, gross profit came to JPY573mn (+12.4% YoY). Gross profit margin was 29.7% (+1.2pp).

SG&A expenses rose 8.7% YoY to JPY1.9bn. R&D expenses came in at JPY839mn (-0.1% YoY). There were expenses for clinical trials for intravenous and oral formulations of Treakisym® and rigosertib. SG&A expenses excluding R&D expenses were up 16.9% at JPY1.1bn. In an effort to bolster marketing of Treakisym®, the company hired additional product managers who are highly specialized and capable of providing product information, but these additions led to higher personnel costs.

As a result, operating loss totaled JPY1.3bn (loss of JPY1.2bn in 1H FY12/17). The company also reported a recurring loss of JPY1.4bn (loss of JPY1.3bn in 1H FY12/17) partly due to non-operating expenses of JPY54mn (mainly on forex losses). Net loss was JPY1.4bn (loss of JPY1.3bn in 1H FY12/17).

Progress made in 1H FY12/18 was as follows.

- ▷ Regarding anticancer agent Treakisym®, the company began a phase III clinical trial for the additional indication of relapsed or refractory diffuse large B-cell lymphoma (DLBCL), and completed enrollment of the first patient in January 2018.
- ▷ In January 2018, the company began a phase I clinical trial of oral Treakisym® for progressive solid tumors, aiming to examine the recommended dosage and dosage regimen, along with tolerability and safety of the formulation, and to identify potential target tumor types.
- ▷ In May 2018, with a view to evaluate the effect of oral administration of Treakisym® on the immune system, the company concluded a joint research agreement with Keio University to conduct a pre-clinical study to verify the therapeutic value of the formulation in the treatment of systemic lupus erythematosus (SLE), a form of autoimmune disease.
- ▷ In July 2018, the company obtained approval for a partial change to its manufacture and marketing authorization for Treakisym®, allowing its combined use with not only rituximab but also obinutuzumab (once it is launched), for the treatment of low-grade non-Hodgkin's lymphoma (low-grade NHL).
- ▷ Also in July 2018, Treakisym® was newly included as a standard treatment option in the revised Clinical Practice Guidelines 2018 for healthcare professionals as a standard therapy.
- ▷ Regarding Rigosertib (IV form), based on the results of an interim analysis performed in January 2018, the company decided to continue the trial after increasing the number of patient enrollment in accordance with pre-determined statistical criteria.
- ▷ In February 2018, the company terminated development of patient-controlled pain management drug SyB P-1501.
- ▷ In April 2018, the company raised JPY10,413mn (net of expenses) through the issuance of 45th through 47th stock acquisition rights with exercise price revision clauses (Commit Issue Program) in order to secure the funds it needed during the three years from 2018 through 2020. The proceeds, which are slated for use between April 2018 and December 2020, will go to the development of in-licensed drugs (JPY4.7bn) and creation of an independent sales structure (JPY3.3bn).

Domestic

Treakisym® (SyB L-0501/SyB L-1701 (RTD) /SyB L-1702 (RI) /SyB C-0501 (oral); anticancer agent; generic name: bendamustine hydrochloride)

The company markets the anticancer agent Treakisym® in Japan through its business partner, Eisai Co., Ltd. (TSE1: 4523) for the indications of relapsed or refractory low-grade non-Hodgkin's lymphoma (NHL) and mantle cell lymphoma (MCL), untreated

low-grade NHL and MCL, and chronic lymphocytic leukemia (CLL). (The company obtained marketing approval for relapsed or refractory low-grade NHL and MCL in October 2010, for untreated low-grade NHL and MCL in December 2016, and for CLL in August 2016.)

As a result of additional indications, Treakisym® is steadily increasing its market share in the area of first-line treatment by replacing R-CHOP, the conventional standard treatment, and sales of Treakisym® based on the National Health Insurance (NHI) drug price grew significantly by22.3% YoY. Product sales to Eisai is also progressing in line with plan.

According to the company, the market share of Treakisym® targeting relapsed or refractory low-grade non-Hodgkin's lymphoma (NHL) and mantle cell lymphoma (MCL) was around 60%. Further, the market share of BR therapy (use of rituximab in combination with Treakisym®) targeting untreated low-grade NHL reached around 55% as of July 2018, exceeding that of the R-CHOP (combination of rituximab with chemotherapy drugs cyclophosphamide, doxorubicin, vincristine, and prednisolone) therapy.

In July 2018, Treakisym® was newly included as a standard treatment option in the Guidelines for Tumors of Hematopoietic and Lymphoid Tissues 2018 issued by the Japan Society of Hematology. The guidelines were revised to include as indications of Treakisym® mantle cell lymphoma and chronic lymphocytic leukemia in addition to relapsed or refractory low-grade B-cell non-Hodgkin's lymphoma. Further, Treakisym® was newly included as a treatment option for untreated low-grade NHL. According to the company, inclusion of all approved indications of Treakisym® in the guidelines positioned the drug as standard treatment for malignant lymphoma. The company believes these developments will lead to further market penetration of Treakisym®.

In addition to the aforementioned three approved indications, the company has started phase III clinical trials for the fourth indication of relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and is currently enrolling patients for the trial with an aim to obtain approval. In response to strong medical needs, the company finished consultation with the Pharmaceuticals and Medical Devices Agency (PMDA) and began phase III clinical trials toward the addition of an indication in August 2017, enrolling the first patient in January 2018. As of end-July 2018, patient enrollment has reached 20.

In September 2017, the company concluded an exclusive licensing agreement with Eagle Pharmaceuticals (based in New Jersey, US) to develop, market, and sell liquid formulations of Treakisym® (RTD and RI formulations) in Japan for Treakisym®'s product life cycle management. The RTD and RI products offer significant value added to patients and healthcare professionals, and extend Treakisym®'s product life cycle until 2031. The company has already consulted with PMDA on the details of the application for approval of the RTD formulation and clinical trial design for the RI formulation. It looks to launch Treakisym® liquid formulation in Japan in 2021 or later, and is preparing application documents for the RTD formulation and creating a clinical trial plan for the RI formulation.

In July 2018, SymBio obtained approval for the partial revision to the marketing authorization. As a result, Treakisym® can now be used in combination with not only rituximab but also anti-CD20 antibodies for the treatment of low-grade NHL, enabling the company to provide patients with a new treatment therapy. According to the company, as of July 2018, there were over 160 drugs for lymphatic malignancies being developed in the US and Europe combining BR (bendamustine and rituximab) or just bendamustine with anti-CD20 antibodies (19 in phase III clinical trial, 104 in phase II, and 42 in phase I). The development of a treatment therapy combining immune checkpoint inhibitors with BR or just bendamustine is also under way. SymBio thinks the approval of these therapies will lead to increased market penetration and recognition of Treakisym®, without development costs.

SymBio will explore further expansion of the Treakisym® business by developing an oral formulation in addition to the injection currently under development or on sale to treat solid tumors and autoimmune diseases. In this context, the company commenced a phase I clinical trial for progressive solid tumors in January 2018, with the aim of examining the recommended dosage and schedule as well as tolerability and safety of the oral formulation of Treakisym®, and narrowing down the types of potential target tumors. The enrollment of the first patient was completed in May 2018, and four patients have been enrolled as of end-July 2018. To evaluate the effect of oral administration of Treakisym® on the immune system, the company concluded a

joint research agreement with Keio University in May 2018 and began a preclinical study to verify the efficacy of the oral form of Treakisym® in treating systemic lupus erythematosus (SLE), a form of autoimmune disease.

Rigosertib Sodium (SyB L-1101 [IV]/SyB C-1101 [oral]; anticancer agent; generic name: Rigosertib Sodium)
Onconova Therapeutics, Inc., the licensor, is currently conducting a global phase III trial and SymBio Pharmaceuticals started the Japan trial in December 2015 (36 patients enrolled so far). The global phase III trial addresses higher-risk myelodysplastic syndromes (MDS), which do not respond to the current standard treatment with hypomethylating agents, which relapse after treatment under the current standard of care, or which are intolerant to hypomethylating agents, and is under way at clinical trial sites in more than 20 countries worldwide. Patient enrollments are smoothly accumulating. Based on the results of an interim analysis performed in January 2018, SymBio decided to continue the trial, increasing the number of patient enrollment in accordance with pre-determined statistical criteria. Based on these results, the company plans to apply for approval in Japan at the same time as in the US and Europe.

Regarding the oral formulation of rigosertib, Onconova is conducting phase I/II clinical trials for the drug used in combination with azacitidine as first-line treatment for higher-risk MDS and phase II clinical trials for transfusion-dependent lower-risk MDS in the US. To verify the tolerability and safety of the oral formulation of rigosertib among Japanese patients, SymBio began phase I clinical trials in Japan in June 2017 and six patients have been enrolled as of end-July 2018. After completing the phase I trials, the company plans to promptly start clinical trials for rigosertib used in combination with azacitidine, participate in global phase III clinical trials of the drug used in combination with azacitidine as first-line treatment for higher-risk MDS Onconova is planning, and apply for approval of the oral formulation of the drug in Japan at the same time as in the US and Europe. In regards to development of rigosertib for transfusion-dependent lower-risk MDS, the company is considering participating from Japan while monitoring Onconova's development progress.

SyB P-1501, a post-operative patient-controlled analgesia
Regarding SyB P-1501 licensed by the Medicines Company (through its wholly owned subsidiary Incline Therapeutics, Inc.) in October 2015, SymBio found a fact that raised concerns about the continuity of its business, and in the interests of patient welfare, it suspended further patient enrollment in April 2017. The license agreement was terminated in November 2017, and the development of the drug was terminated in February 2018.

The Company initiated an arbitration against The Medicines Company in October 2017, under the rules of the International Chamber of Commerce, seeking damages of USD82mn (approximately JPY9.0bn) arising from The Medicines Company's repudiation of the license agreement. Arbitration proceedings against The Medicines Company are still ongoing.

New drug candidates
From a long-term perspective, SymBio continues to search for and evaluate promising drug candidates, in a bid to acquire global licensing rights for these drugs and grow into a sustainable and profitable biopharmaceutical company with growth potential and profitability. The company is considering licensing rights for several drug candidates. Further, in May 2016, the company established SymBio Pharma USA, Inc., a wholly owned US-based subsidiary, as a strategic base for overseas business development. The company looks to leverage this subsidiary to actively acquire rights over new drug development candidates globally, and engage in development and commercialization in major markets including the US, Japan, and Europe to transition to a global specialty pharmaceutical company.

Overseas
The company marketed SyB L-0501 in Korea, Taiwan, and Singapore, and sales were largely in line with plans.

Q1 FY12/18 results
In Q1 FY12/18 sales totaled JPY888mn (+2.1% YoY) mainly owing to domestic sales of Treakisym®, and marked a 32.4% YoY leap on an NHI drug reimbursement price basis (details to follow).

Due to the sales increase, gross profit came to JPY250mn (+4.4% YoY). Gross profit margin was 28.1% (+0.6pp).

SG&A expenses rose 26.1% YoY to JPY964mn. R&D expenses increased 5.3% to JPY416mn. There were expenses for clinical trials for intravenous and oral formulations of Treakisym® and rigosertib. SG&A expenses excluding R&D expenses were up 48.4% at JPY548mn. In an effort to bolster marketing of Treakisym®, the company hired additional product managers who are highly specialized and capable of providing product information, but these additions led to higher personnel costs.

As a result, operating loss totaled JPY715mn (loss of JPY525mn in Q1 FY12/17). The company also reported a recurring loss of JPY749mn (loss of JPY583mn in Q1 FY12/17) partly due to non-operating expenses of JPY35mn (mainly on forex losses). Net loss was JPY760mn (loss of JPY583mn in Q1 FY12/17).

Progress made in Q1 FY12/18 was as follows.

- ▷ Regarding anticancer agent Treakisym®, the company began a phase III clinical trial for the additional indication of relapsed or refractory diffuse large B-cell lymphoma (DLBCL), and completed enrollment of the first patient in January 2018.
- ▷ In January 2018, the company began a phase I clinical trial of oral Treakisym® for progressive solid tumors, aiming to examine the recommended dosage and dosage regimen, along with tolerability and safety of the formulation, and to identify potential target tumor types.
- ▷ In May 2018, with a view to evaluate the effect of oral administration of Treakisym® on the immune system, the company concluded a joint research agreement with Keio University to conduct a pre-clinical study to verify the therapeutic value of the formulation in the treatment of systemic lupus erythematosus (SLE), a form of autoimmune disease.
- ▷ Regarding Rigosertib (IV form), based on the results of an interim analysis performed in January 2018, the company decided to continue the trial after increasing the number of patient enrollment in accordance with pre-determined statistical criteria.
- ▷ In February 2018, the company terminated development of patient-controlled pain management drug SyB P-1501.
- ▷ In April 2018, the company raised JPY10,413mn (net of expenses) through the issuance of 45th through 47th stock acquisition rights with exercise price revision clauses (Commit Issue Program) in order to secure the funds it needed during the three years from 2018 through 2020. The program is designed in such a way that the allottee of the stock acquisition rights EVO FUND is committed to exercising these rights for a pre-determined number of underlying common shares (45th stock acquisition rights: 20 million shares, dilution ratio of 37.0%; 46th: 15 million shares, 27.8%; 47th: 15 million shares, 27.8%). The exercise periods are April 26 to October 23, 2018 for the 45th, April 26 to September 17, 2019 for the 46th, and April 27 to September 17, 2020 for the 47th stock acquisition rights. The proceeds, which are slated for use between April 2018 and December 2020, will go to the development of in-licensed drugs (JPY4.7bn) and creation of an independent sales structure (JPY3.3bn).

Domestic

Treakisym® (SyB L-0501/SyB L-1701 (RTD) /SyB L-1702 (RI) /SyB C-0501 (oral); anticancer agent; generic name: bendamustine hydrochloride)

The company markets the anticancer agent Treakisym® in Japan through its business partner, Eisai Co., Ltd. (TSE1: 4523) for the indications of relapsed or refractory low-grade non-Hodgkin's lymphoma (NHL) and mantle cell lymphoma (MCL), untreated low-grade NHL and MCL, and chronic lymphocytic leukemia (CLL).

As a result of additional indications, Treakisym® has steadily increased its market share in the area of first-line treatment by replacing R-CHOP, the conventional standard treatment. According to the company, the market penetration of BR therapy (use of rituximab in combination with bendamustine) targeting untreated low-grade NHL reached 50%, exceeding that of R-CHOP that stood at 32%. Sales of Treakisym® based on the NHI drug reimbursement price grew significantly by 32.4% YoY, and product sales to Eisai also made progress in line with plan.

In addition to the above three approved indications, the company has started phase III clinical trials for the fourth indication of relapsed or refractory diffuse large B-cell lymphoma (DLBCL, or aggressive NHL) and is currently enrolling patients for the trial

with an aim to obtain approval. In response to strong medical needs, the company finished consultation with the Pharmaceuticals and Medical Devices Agency (PMDA) and began phase III clinical trials toward the addition of an indication in August 2017, enrolling the first patient in January 2018.

In addition to efforts for new indications, in September 2017, the company concluded an exclusive licensing agreement with Eagle Pharmaceuticals (based in New Jersey, US) to develop, market, and sell liquid formulations of Treakisym® (RTD and RI formulations) in Japan for Treakisym®'s product life cycle management. The ready-to-dilute (RTD) and rapid infusion (RI) products offer significant value added to patients and healthcare professionals, and extend Treakisym®'s product life cycle until 2031. For the RTD formulation, the company completed consultation with PMDA and is preparing for approval. We understand that SymBio will be allowed to file for approval of the RTD product without conducting clinical trials, because its ingredients, efficacy, and administration time are identical to those of the Treakisym® freeze-dried (FD) product; the only difference being that it does not need reconstitution. For the RI formulation, it is in the process of preparing for a clinical trial, including consultation with PMDA.

SymBio is exploring further expansion of the Treakisym® business by developing an oral formulation in addition to the injection currently under development or on sale to treat solid tumors and autoimmune diseases. In this context, the company commenced a phase I clinical trial for progressive solid tumors in January 2018, with the aim of examining the recommended dosage and schedule as well as tolerability and safety of the oral formulation of Treakisym®, and narrowing down the types of potential target tumors. To evaluate the effect of oral administration of Treakisym® on the immune system, the company concluded a joint research agreement with Keio University in May 2018 to conduct a preclinical study to verify the efficacy of the oral form of Treakisym® in treating systemic lupus erythematosus (SLE), a form of autoimmune disease.

> SLE, which affects an estimated 60,000 to 100,000 patients in Japan, is an intractable autoimmune disease that can affect many parts of the body. Currently, treatment options for SLE are limited, and steroids are mainly used. If treatment with steroids is ineffective, the immunosuppressive drug cyclophosphamide is used as the standard treatment. However, treatment with cyclophosphamide is associated with side effects such as hair loss and myelosuppression, and there is an urgent need to develop effective treatments with reduced side effects.

Rigosertib Sodium (SyB L-1101 [IV]/SyB C-1101 [oral]; anticancer agent; generic name: Rigosertib Sodium)
Onconova Therapeutics, Inc., the licensor, is currently conducting a global phase III trial and SymBio Pharmaceuticals started the Japan trial in December 2015 (30 patients enrolled so far). The global phase III trial addresses higher-risk myelodysplastic syndrome (MDS) patients who do not respond to treatment or relapsed after treatment with hypomethylating agents (HMAs), the current standard of care ("Primary HMA Failure") and is under way at clinical trial sites in more than 20 countries worldwide. Patient enrollments are smoothly accumulating. Based on the results of an interim analysis performed in January 2018, SymBio decided to continue the trial, increasing the number of patient enrollment in accordance with some pre-determined statistical criteria. Based on these results, the company plans to apply for approval in Japan at the same time as in the US and Europe.

Regarding the oral formulation of rigosertib, Onconova is conducting phase I/II clinical trials for the drug used in combination with azacitidine as first-line treatment for higher-risk MDS and phase II clinical trials for transfusion-dependent lower-risk MDS in the US. To verify the tolerability and safety of the oral formulation of rigosertib among Japanese patients, SymBio began phase I clinical trials in Japan in June 2017 and is steadily enrolling patients. After completing the phase I trials, the company plans to promptly start clinical trials for rigosertib used in combination with azacitidine, participate in global phase III clinical trials of the drug used in combination with azacitidine as first-line treatment for higher-risk MDS Onconova is planning, and apply for approval of the oral formulation of the drug in Japan at the same time as in the US and Europe. In regards to development of rigosertib for transfusion-dependent lower-risk MDS, the company is considering participating from Japan while monitoring Onconova's development progress.

SyB P-1501, a post-operative patient-controlled analgesia
Regarding SyB P-1501 licensed by the Medicines Company (through its wholly owned subsidiary Incline Therapeutics, Inc.) in October 2015, SymBio found a fact that raised concerns about the continuity of its business, and in the interests of patient welfare, it suspended further patient enrollment in April 2017. The license agreement was terminated in November 2017, and the development of the drug was terminated in February 2018.

The Company initiated an arbitration against The Medicines Company in October 2017, under the rules of the International Chamber of Commerce, seeking damages of USD82mn (approximately JPY9.0bn) arising from The Medicines Company's repudiation of the license agreement.

New drug candidates

From a long-term perspective, SymBio continues to search for and evaluate promising drug candidates, in a bid to acquire global licensing rights for these drugs and grow into a sustainable and profitable biopharmaceutical company with growth potential and profitability. The company is considering licensing rights for several drug candidates. Further, in May 2016, the company established SymBio Pharma USA, Inc., a wholly owned US-based subsidiary, as a strategic base for overseas business development. The company looks to leverage this subsidiary to actively acquire rights over new drug development candidates globally, and engage in development and commercialization in major markets including the US, Japan, and Europe to transition to a global specialty pharmaceutical company.

Overseas

The company marketed SyB L-0501 in Korea, Taiwan, and Singapore, and sales were in line with plans.

Full-year FY12/17 results

FY12/17 sales totaled JPY3.4bn (+45.4% YoY) thanks to domestic sales of Treakisym®. Sales broke down into product sales of JPY3.4bn (+61.1% YoY) and zero royalty revenue (JPY231mn in FY12/16).

The company obtained approval for additional indications for Treakisym® of first-line treatment of low-grade malignant NHL and MCL in December 2016. Sales of Treakisym® indicated for first-line treatment of low-grade malignant NHL and MCL overall Treakisym® sales (product sales). For royalty revenue, the company booked revenue for reaching a sales milestone of SyB L-0501 in Taiwan in FY12/16, but received no milestone payments in FY12/17.

Due to the sales increase, gross profit came to JPY1.0bn (+14.1% YoY). Gross profit margin was 29.9% (-8.2pp). GPM fell in FY12/17, because the company received no milestone payments as note above, and GPM on product sales fell 1.6pp.

SG&A expenses rose 64.2% YoY to JPY5.0bn. R&D expenses increased 81.0% to JPY3.0bn. There were expenses for clinical trials for Treakisym®, the intravenous and oral formulations of Rigosertib Sodium and SyB P-1501, and the USD12.5mn cost of in-licensing liquid formulation products of Treakisym® (RTD and RI formulations). SG&A expenses excluding R&D expenses were up 43.7% at JPY2.0bn. Fees and commissions paid totaled JPY567mn (+313.2%) due to an increase in expert consultations.

As a result, operating loss totaled JPY4.0bn (loss of JPY2.1bn in FY12/16). The company also reported a recurring loss of JPY4.0bn (loss of 2.3bn in FY12/16), partly due to non-operating expenses of JPY34mn (mainly on share issuance costs of JPY14mn, forex losses of JPY10mn, and fees and commissions paid of JPY9mn). Net loss was JPY4.0bn (loss of JPY2.3bn in FY12/16).

Progress made in FY12/17 was as follows.

- ▷ The company announced in August 2017 that it would begin phase III clinical trials in Japan for anticancer agent Treakisym® for the additional indication of relapsed or refractory diffuse large B-cell lymphoma (DLBCL; aggressive NHL), and registered the first patient in January 2018.
- ▷ In January 2018, the company began phase I clinical trials of oral Treakisym®, targeting indication for progressive solid tumors.
- ▷ In June 2017, the company restarted domestic phase I clinical trials for oral Rigosertib, because the supply of the study drug had resumed, and registered the first patient in October 2010.
- ▷ The Medicines Company (MDCO) had filed a report (Form 8-K) with the US Securities and Exchange Commission in June 2017 stating that it would withdraw the patient-controlled pain management drug IONSYS® (SyB P-1501) from the US market and suspend commercial activities. In May 2017, SymBio announced temporary suspension of new patient enrollment in the

domestic phase III clinical trial of SyB P-1501. In October 2017, the company initiated an arbitration against MDCO under the rules of the International Chamber of Commerce, seeking damages of USD82mn (approximately JPY9bn) arising from MDCO's repudiation of the license agreement.

▷ In November 2017, the company announced that the license agreement it had entered with MDCO for the exclusive rights to develop and commercialize SyB P-1501 (IONSYS in the US) for the short-term management of acute post-operative pain has terminated. In conjunction with the termination of the license agreement, the development of SyB P-1501 was terminated in February 2018.

▷ In August 2017, the company announced the subscription for its 42nd stock acquisition rights by third-party allotment (8,800,000 residual shares corresponding to 17.97% of outstanding shares) to raise JPY1.9bn on an estimated net proceeds basis, and all stock acquisition rights were exercised as of January 2018. The funds are mainly to be used for expenses related to development of Treakisym® indicated for relapsed or refractory DLBCL (aggressive NHL) totaling JPY900mn and expenses for obtaining rights to the oral formulation of Treakisym® and development after obtaining the rights totaling JPY1.0bn.

▷ In September 2017, the company concluded a license agreement with Eagle Pharmaceuticals, Inc. (Eagle) for bendamustine hydrochloride ready-to-dilute (RTD) and rapid infusion (RI) injection products. The agreement licenses to SymBio rights to develop, market, and sell Eagle's bendamustine hydrochloride RTD and RI injection products (marketed in the US by Teva Pharmaceutical Industries as BENDEKA®) in Japan.

Domestic

Treakisym® (SyB L-0501/SyB L-1701 (RTD) /SyB L-1702 (RI) /SyB C-0501 (oral); anticancer agent; generic name: bendamustine hydrochloride)

The company markets the anticancer agent Treakisym® in Japan through its business partner, Eisai Co., Ltd. (TSE1: 4523) for the indications of relapsed or refractory low-grade non-Hodgkin's lymphoma (NHL) and mantle cell lymphoma (MCL), untreated low-grade NHL and MCL, and chronic lymphocytic leukemia (CLL).

As a result of additional indications, sales of Treakisym® based on the National Health Insurance (NHI) drug price grew 60.9% YoY, and accordingly product sales to Eisai increased 62.7%.

In addition to the above three approved indications, the company has filed an NDA for a fourth indication to help patients who need new treatments and maximize the value of the product. The company has completed phase III clinical trials for relapsed or refractory diffuse large B-cell lymphoma (DLBCL, or aggressive NHL). In response to strong medical needs, the company finished consultation with the Pharmaceuticals and Medical Devices Agency and began phase III clinical trials toward the addition of an indication in August 2017, enrolling the first patient in January 2018.

In addition to ongoing efforts to add new indications, in September 2017, the company concluded an exclusive licensing agreement with Eagle Pharmaceuticals (based in New Jersey, US) to develop, market, and sell liquid formulations of Treakisym® (RTD and RI formulations) in Japan for Treakisym®'s product life cycle management. The RTD and RI products offer significant value added to patients and healthcare professionals, and extends Treakisym®'s product life cycle until 2031.

SymBio is exploring further expansion of the Treakisym® business by developing an oral formulation in addition to the injection currently under development or on sale to treat solid tumors and autoimmune diseases. In this context, the company commenced a phase I clinical trial for progressive solid tumors in January 2018, with the aim of examining the recommended dosage and schedule as well as tolerability and safety of the oral formulation of Treakisym®, and narrowing down the types of potential target tumors.

Rigosertib Sodium (SyB L-1101 [IV]/SyB C-1101 [oral]; anticancer agent; generic name: Rigosertib Sodium)
Onconova Therapeutics, Inc., the licensor, is currently conducting a global phase III trial and SymBio Pharmaceuticals started the Japan trial in December 2015 (30 patients enrolled so far). The global phase III trial addresses higher risk myelodysplastic syndrome (MDS) patients who do not respond to treatment or relapsed after treatment with hypomethylating agents (HMAs), the current standard of care ("Primary HMA Failure") and is under way at clinical trial sites in more than 20 countries worldwide. The company completed the first patient enrollment in July 2016 and enrollments are smoothly accumulating. Based on the results of an interim analysis performed in January 2018, SymBio decided to continue the trial, increasing the number of patient enrollment in accordance with some pre-determined statistical criteria.

SymBio planned to start domestic phase I clinical trials for the oral form of Rigosertib (used in combination with azacitidine) for higher-risk myelodysplastic syndrome (MDS), however, due to delays in the supply of drugs by Onconova for the trials, patient enrollment did not make progress. Since Onconova resumed the supply of clinical trial materials, SymBio initiated a phase I clinical trial in Japan in June 2017 and enrolled the first patient in October. The purpose of the Japanese phase I study is to confirm the safety of high-dose oral rigosertib, which was added to the ongoing US phase II study by Onconova in untreated or relapsed/refractory patients with higher-risk MDS. After demonstrating the safety of high-dose oral rigosertib, SymBio intends to immediately recommence an oral rigosertib/azacitidine combination trial in Japan, and participate in the global phase III study in untreated higher-risk MDS patients that Onconova is planning.

SyB P-1501, a post-operative patient-controlled analgesia
The company started a domestic phase III clinical trial for SyB P-1501—licensed by the Medicines Company (through its wholly owned subsidiary Incline Therapeutics) in October 2015—for the short-term management of acute post-operative pain during hospitalization in June 2016. The company enrolled the first patient in November 2016 and was making progress with case accumulation. However, SymBio later found a fact that raises concerns about the continuity of The Medicines Company's SyB P-1501 business. In the interests of patient welfare, SymBio has suspended further patient enrollment since April 2017 and is in talks with The Medicines Company regarding how the SyB P-1501 clinical trial and commercialization in Japan would be affected. The license agreement with Incline Therapeutics, Inc. was terminated in November 2017.

The Company initiated an arbitration against The Medicines Company in October 2017, under the rules of the International Chamber of Commerce, seeking damages of USD82mn (approximately JPY9.0bn) arising from The Medicines Company's repudiation of the license agreement.

In conjunction with the termination of the license agreement, the Company terminated the development of SyB P-1501 in February 2018.

New drug candidates
From a long-term perspective, SymBio continues to search for and evaluate promising drug candidates, in a bid to acquire global licensing rights for these drugs and grow into a sustainable and profitable biopharmaceutical company with growth potential and profitability. At present, the company is considering licensing rights for several drug candidates. Further, in May 2016, the company established SymBio Pharma USA, Inc., a wholly owned US-based subsidiary, as a strategic base for overseas business development. The company looks to leverage this subsidiary to actively acquire rights over new drug development candidates globally, and engage in development and commercialization in major markets including the US, Japan, and Europe to transition to a global specialty pharmaceutical company.

Overseas
The company marketed Treakisym® in Korea, Taiwan, and Singapore, and overseas sales were ahead of target.

FY12/16 results
FY12/16 sales totaled JPY2.4bn (+22.5% YoY) thanks to domestic sales of Treakisym® (SyB L-0501). Products sales totaled JPY2.1bn (+10.6%). It also booked a royalty revenue of JPY230mn (zero in FY12/15) resulting from achieving the sales milestone of SyB L-0501 in Taiwan.

SG&A expenses fell 3.3% YoY to JPY3.0bn. R&D expenses fell to JPY1.7bn (-18.1% YoY). There were expenses for clinical trials for Treakisym®, the intravenous and oral formulations of Rigosertib Sodium, and SyB P-1501, but declined from FY12/15, when the company booked costs for licensing-in SyB P-1501. The company set an initial R&D expense budget of JPY2.2bn, but spent less than planned because of delays with the development of the oral formulation of rigosertib sodium. SG&A expenses excluding R&D expenses were up 24.0% at JPY1.4bn.

As a result, operating loss totaled JPY2.1bn (loss of JPY2.6bn in FY12/15). The company also reported a recurring loss of JPY2.3bn (loss of JPY2.6bn last year) partly due to non-operating expenses of JPY196mn (mainly on forex losses of JPY159mn). Net loss was JPY2.3bn (loss of JPY2.6bn).

Domestic

Treakisym® (SyB L-0501; anticancer agent; generic name: bendamustine hydrochloride)

The company markets the anticancer agent Treakisym® in Japan through its business partner, Eisai Co., Ltd. (TSE1: 4523) for the indications of relapsed or refractory low-grade non-Hodgkin's lymphoma (NHL) and mantle cell lymphoma (MCL).
Though product sales based on the National Health Insurance (NHI) drug price declined slightly by 0.8% YoY, product sales to Eisai were largely in line with plan.

Regarding chronic lymphocytic leukemia (CLL), the company filed an NDA in December 2015, and obtained approval for the additional indication in August 2016. The company developed and applied for this indication upon request of the Ministry of Health, Labour and Welfare in Japan as one of the "Unapproved or Off-Labeled Drugs with High Medical Needs." This is the second approval after the approval of an NDA for the indication of relapsed or refractory low-grade NHL and mantle cell lymphoma which the company has already received in October 2010.

In Japan, the company submitted a new drug application (NDA) to Japan's Pharmaceuticals and Medical Devices Agency (PMDA) in December 2015 for a first-line treatment of low-grade NHL and MCL and obtained approval for the additional indication in December 2016. Meanwhile, in Europe, though the company received notification on January 2016 from Astellas Pharma that its application had been withdrawn, it continued with the domestic approval process upon consulting with the PMDA, resulting in the approval of the additional indication.

Rigosertib Sodium (SyB L-1101 [IV]/SyB C-1101 [oral]; anticancer agent; generic name: Rigosertib Sodium)

Regarding these agents, for which a licensing agreement was entered into in July 2011, the company changed their generic name from "Rigosertib" to "Rigosertib Sodium" in accordance with the notice of decision on its Japanese Accepted Names for Pharmaceuticals (JAN) received in October 2016. Onconova Therapeutics, Inc., the licensor, is currently conducting a global phase III trial and SymBio Pharmaceuticals started the Japan trial in December 2015. The global phase III trial addresses higher risk myelodysplastic syndrome (MDS) patients who do not respond to treatment or relapsed after treatment with hypomethylating agents (HMAs), the current standard of care ("Primary HMA Failure") and is under way at clinical trial sites in more than ten countries worldwide. The company has taken steps to register patients, and completed the first patient enrollment in July 2016. Enrollments are currently accumulating.

SymBio started domestic phase I clinical trials for the oral (IV) form of Rigosertib Sodium (used in combination with azacitidine) for higher-risk myelodysplastic syndrome (MDS) in December 2015. Due to delays in the supply of drugs for the joint trials, patient enrollment has not started as of November 11, 2016. The company is looking to start patient registration upon resolution of this issue, and complete joint trials in line with its plans. SymBio is considering participating in the global clinical trial to be conducted by Onconova.

SyB P-1501, a post-operative patient-controlled analgesia

The company started a domestic phase III clinical trial for SyB P-1501—licensed by the Medicines Company (through its wholly owned subsidiary Incline Therapeutics)—for the short-term management of acute post-operative pain during hospitalization in June 2016. The company is looking to complete the phase III clinical trial quickly, and obtain regulatory approval in 2019.

New drug candidates

From a long-term perspective, SymBio will continue to search for and evaluate promising drug candidates, and acquire global rights for these drugs to become a sustainable and profitable pharmaceutical company with growth potential and profitability. Further, in May 2016, the company established SymBio Pharma USA, Inc., a wholly owned US-based subsidiary, as a strategic base for overseas business development. The company looks to leverage this subsidiary to actively acquire rights over new drug development candidates globally, and engage in development and commercialization in major markets including the US, Japan, and Europe to accelerate the process of turning into a global specialty pharmaceutical company.

Overseas

The company marketed Treakisym® in Korea, Taiwan, and Singapore, and overseas sales were steady.

FY12/15 results

FY12/15 sales totaled JPY1.9bn (-1.1% YoY) due to domestic and overseas sales of SyB L-0501 (Treakisym®).

Treakisym® domestic sales rose 24.0% YoY, but overseas sales fell 76.1% on factors including the earlier booking of orders in Korea in FY12/14.

SG&A expenses rose 71.3% YoY to JPY3.1bn due to expenses incurred for clinical trials for oral and intravenous rigosertib and Treakisym®, and the booking of R&D expenses of JPY2.0bn (+162.8%) in conjunction with the in-licensing expenses for SyB P-1501 (IONSYS for post-operative patient-controlled analgesia) and “other” SG&A expenses of JPY1.1bn (+4.2%).

As a result, operating loss totaled JPY2.6bn (versus a loss of JPY1.3bn the preceding year). The company also reported a recurring loss of JPY2.6bn (JPY1.1bn loss) due to non-operating expenses of JPY96mn (mainly on forex losses of JPY86mn). Net loss totaled JPY2.6bn (JPY1.1bn loss the preceding year).

Progress towards FY12/16 targets is as follows.

Domestic

Treakisym® (SyB L-0501; anticancer agent; generic name: bendamustine hydrochloride)
The company markets the anticancer agent Treakisym® in Japan through its business partner, Eisai Co., Ltd. (TSE1: 4523) for the indications of relapsed or refractory low-grade non-Hodgkin’s lymphoma (NHL) and mantle cell lymphoma (MCL). Sales through Eisai increased as expected. NHI price-based sales rose 10.3% YoY.

Phase II clinical trial of Treakisym® for the first-line treatment of low-grade NHL and MCL had already been completed and the company submitted a new drug application (NDA) to Japan’s Pharmaceuticals and Medical Devices Agency (PMDA) in December 2015. Meanwhile, in Europe, review of the application by Astellas Pharma is under way by European authorities.

Regarding the phase II clinical trial for chronic lymphocytic leukemia (CLL), the company filed an NDA in December 2015. Treakisym® was designated as an orphan drug (drug for the treatment of rare diseases) for CLL in June 2012, and the Evaluation Committee on Unapproved or Off-Labeled Drugs with High Medical Need has also submitted a development request to the company.

In addition to the 100mg dosage of Treakisym®, SymBio Pharmaceuticals also filed in December 2015 for approval of a smaller 25mg dosage as an amount that could actually be used at medical facilities.

SymBio is still considering applying for approval for use of the drug for relapsed or refractory aggressive NHL.

Rigosertib (SyB L-1101 [IV]/SyB C-1101 [oral]; anticancer agent)

The company is conducting a domestic phase I clinical trial for the intravenous (IV) form of rigosertib in relapsed or refractory higher-risk myelodysplastic syndromes (MDS), a hematological malignancy. Patient enrollment was completed in January 2015, and the trial was completed in October 2015.

Onconova Therapeutics, Inc., the US licensor, is currently conducting a global phase III trial and SymBio Pharmaceuticals started the Japan trial in December 2015. The global phase III trial addresses higher risk MDS patients who do not respond to treatment with hypomethylating agents (HMAs), the current standard of care ("Primary HMA Failure") and is under way at clinical trial sites in more than ten countries worldwide.

SyB P-1501, a post-operative patient-controlled analgesia

In October 2015 SymBio reached an in-licensing agreement with The Medicines Company (through its wholly owned subsidiary Incline Therapeutics) for the development and commercialization of SyB P-1501, a post-operative patient-controlled analgesia known as IONSYS in the US. SymBio acquired exclusive development and marketing rights for Japan. Preparations are under way to start a domestic phase III clinical trial in 2016.

Overseas

The company marketed Treakisym® in Korea, Taiwan, and Singapore. Product sales were mostly in line with targets.

Income statement

Income statement (JPYmn)	FY12/09 Par.	FY12/10 Par.	FY12/11 Par.	FY12/12 Par.	FY12/13 Par.	FY12/14 Par.	FY12/15 Par.	FY12/16 Par.	FY12/17 Par.
Total sales	**1,191**	**1,450**	**1,883**	**1,955**	**1,532**	**1,955**	**1,933**	**2,368**	**3,444**
YoY	-26.9%	21.7%	29.8%	3.9%	-21.6%	27.6%	-1.1%	22.5%	45.4%
CoGS	0	238	1,224	1,362	1,214	1,428	1,350	1,464	2,413
Gross profit	**1,191**	**1,212**	**658**	**593**	**318**	**527**	**583**	**904**	**1,031**
GPM	100.0%	83.6%	35.0%	30.3%	20.8%	26.9%	30.2%	38.2%	29.9%
SG&A expenses	1,399	1,825	2,725	2,293	1,999	1,830	3,135	3,031	4,978
SG&A ratio	117.5%	125.8%	144.8%	117.3%	130.4%	93.6%	162.1%	128.0%	144.5%
Operating profit	**-208**	**-613**	**-2,067**	**-1,700**	**-1,681**	**-1,303**	**-2,552**	**-2,127**	**-3,947**
YoY	-	-	-	-	-	-	-	-	-
OPM	-	-	-	-	-	-	-	-	-
Non-operating income	20	13	56	7	114	215	17	7	5
Non-operating expenses	26	38	85	37	35	22	96	196	34
Recurring profit	**-214**	**-638**	**-2,095**	**-1,729**	**-1,601**	**-1,110**	**-2,630**	**-2,317**	**-3,977**
YoY	-	-	-	-	-	-	-	-	-
RPM	-	-	-	-	-	-	-	-	-
Extraordinary gains	-	-	-	-	-	2	3	9	17
Extraordinary losses	-	0	5	0	-	3	1	1	15
Tax charges	4	4	4	4	4	4	4	4	4
Implied tax rate	-	-	-	-	-	-	-	-	-
Net income	**-218**	**-642**	**-2,105**	**-1,733**	**-1,605**	**-1,116**	**-2,632**	**-2,313**	**-3,978**
YoY	-	-	-	-	-	-	-	-	-
Net margin	-	-	-	-	-	-	-	-	-

Source: Shared Research based on company data.
Note: Figures may differ from company materials due to differences in rounding methods.

See the Earnings Structure section for more information about specific items (from total sales to recurring profit) on the company's income statement. There are no matters requiring special mention regarding non-operating profit/loss, extraordinary profit/loss, corporate income tax, etc.

Historical forecast accuracy

Results vs. Initial Est. (JPYmn)	FY12/09 Par.	FY12/10 Par.	FY12/11 Par.	FY12/12 Par.	FY12/13 Par.	FY12/14 Par.	FY12/15 Par.	FY12/16 Par.	FY12/17 Par.
Sales (Initial Est.)	-	-	1,933	2,338	1,927	1,785	1,785	2,339	2,903
Sales (Results)	-	-	1,883	1,955	1,532	1,955	1,933	2,368	3,444
Results vs. Initial Est.	**-**	**-**	**-2.6%**	**-16.4%**	**-20.5%**	**9.5%**	**8.3%**	**1.2%**	**18.6%**
Operating profit (Initial Est.)	-	-	-2,351	-1,625	-1,889	-1,654	-1,654	-2,778	-3,238
Operating profit (Results)	-	-	-2,067	-1,700	-1,681	-1,303	-2,552	-2,127	-3,947
Results vs. Initial Est.	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Recurring profit (Initial Est.)	-	-	-2,398	-1,652	-1,922	-1,650	-1,650	-2,811	-3,303
Recurring profit (Results)	-	-	-2,095	-1,729	-1,601	-1,110	-2,630	-2,317	-3,977
Results vs. Initial Est.	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Net income (Initial Est.)	-	-	-2,407	-1,656	-1,926	-1,654	-1,654	-2,815	-3,306
Net income (Results)	-	-	-2,105	-1,733	-1,605	-1,116	-2,632	-2,313	-3,978
Results vs. Initial Est.	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**

Source: Shared Research based on company data.
Note: Figures may differ from company materials due to differences in rounding methods.
Note: The company listed its common shares in October 2011, so the forecasts are from FY12/11 onward.

Balance sheet

Balance sheet (JPYmn)	FY12/09 Par.	FY12/10 Par.	FY12/11 Par.	FY12/12 Par.	FY12/13 Par.	FY12/14 Par.	FY12/15 Par.	FY12/16 Par.	FY12/17 Par.
Assets									
Cash and deposits	3,902	2,314	4,559	4,540	6,163	5,692	4,261	5,719	2,947
Marketable securities	219	1,701	1,953	300	1,100	899	-	-	-
Accounts receivable	-	6	162	148	-	273	301	487	490
Inventories	-	-	207	165	125	245	133	273	363
Other current assets	97	191	297	268	245	181	131	205	237
Total current assets	**4,218**	**4,213**	**7,178**	**5,421**	**7,634**	**7,290**	**4,827**	**6,685**	**4,037**
Buildings (net)	3	3	2	3	2	22	22	31	28
Tools, furniture, and fixtures (net)	11	19	15	11	6	27	31	43	18
Total tangible fixed assets	**13**	**22**	**17**	**14**	**9**	**49**	**53**	**75**	**47**
Total other fixed assets	**27**	**27**	**48**	**57**	**37**	**49**	**53**	**77**	**100**
Software	2	1	10	8	6	62	51	42	66
Other	-	-	3	3	2	4	1	-	3
Total intangible fixed assets	**2**	**1**	**13**	**11**	**8**	**66**	**52**	**42**	**69**
Total fixed assets	**42**	**50**	**78**	**82**	**53**	**164**	**158**	**193**	**216**
Total assets	**4,261**	**4,263**	**7,256**	**5,502**	**7,687**	**7,454**	**4,984**	**6,878**	**4,252**
Liabilities									
Accounts payable	-	1	309	330	-	306	320	322	604
Accounts payable–other	182	124	278	196	207	143	184	553	331
Short-term debt	-	-	-	-	-	-	-	-	-
Other current liabilities	23	52	59	73	44	39	47	68	76
Total current liabilities	**205**	**178**	**646**	**599**	**251**	**488**	**551**	**942**	**1,011**
Long-term debt	-	-	-	-	-	-	-	-	-
Other fixed liabilities	2	2	5	4	3	2	2	451	1
Total long-term liabilities	**2**	**2**	**5**	**4**	**3**	**2**	**2**	**451**	**1**
Total interest bearing debt	-	-	-	-	-	-	-	-	-
Total liabilities	**207**	**180**	**651**	**602**	**254**	**490**	**552**	**1,394**	**1,013**
Net assets	4,060	4,083	6,606	4,873	7,336	6,764	4,132	5,054	2,703
Capital stock	3,378	3,711	6,025	6,025	8,059	8,331	8,331	9,948	10,762
Capital surplus	3,348	3,681	5,995	5,995	8,029	8,301	8,301	9,918	10,732
Retained earnings	-2,666	-3,309	-5,413	-7,146	-8,752	-9,868	-12,500	-14,813	-18,791
Subscription rights to shares	-	-	-	27	97	200	300	431	537
Total net assets	**4,054**	**4,083**	**6,606**	**4,900**	**7,433**	**6,964**	**4,432**	**5,485**	**3,239**
Working capital	-	5	61	-17	125	212	114	439	249
Total interest-bearing debt	-	-	-	-	-	-	-	-	-
Net debt	-3,902	-2,314	-4,559	-4,540	-6,163	-5,692	-4,261	-5,719	-2,947

Source: Shared Research based on company data.
Note: Figures may differ from company materials due to differences in rounding methods.

Assets

SymBio does not have its own manufacturing facilities, clinical facilities or salesforce: the company outsources manufacturing, clinical development, and sales and marketing. Therefore, most of the company's assets are cash and deposits.

Within current assets, inventory assets consist of Treakisym® merchandise inventory.

Liabilities

The company does not have interest-bearing liabilities. Booked liabilities are accounts payable and arrears.

Net assets

Capital and capital reserves are increasing as a result of fundraising efforts. However, the deficit in retained earnings is expanding as the company continues to post losses.

Cash flow statement

Cash flow statement (JPYmn)	FY12/09 Par.	FY12/10 Par.	FY12/11 Par.	FY12/12 Par.	FY12/13 Par.	FY12/14 Par.	FY12/15 Par.	FY12/16 Par.	FY12/17 Par.
Cash flows from operating activities (1)	-211	-754	-2,074	-1,659	-1,677	-1,266	-2,272	-1,960	-3,817
Cash flows from investing activities (2)	-4	-116	-117	-411	-1,332	314	1,489	-44	-78
Free cash flow (1+2)	-215	-870	-2,191	-2,069	-3,010	-952	-783	-2,004	-3,894
Cash flows from financing activities	2,963	663	4,611	-1	4,057	544	-3	3,658	1,164
Depreciation and amortization (A)	4	7	8	9	8	13	24	26	30
Capital expenditures (B)	-3	-14	-12	-3	-	-109	-24	-28	-57
Working capital change (C)	-	5	56	-78	142	86	-98	325	-190
Simple FCF (NI + A + B - C)	-217	-655	-2,165	-1,650	-1,739	-1,298	-2,534	-2,640	-3,815
Cash and cash equivalents (year-end)	4,121	3,916	6,311	4,240	5,294	5,092	4,261	5,719	2,947

Source: Shared Research based on company data.
Note: Figures may differ from company materials due to differences in rounding methods.

Cash flows from operating activities

Cash flows from operating activities almost matches the company's current net loss before tax.

Cash flows from investing activities

Purchases of tangible fixed assets and intangible assets are limited as SymBio outsources manufacturing, clinical development, and sales and marketing. But investment in time deposits and securities meant outflow from investing activities widened in FY12/12 and FY12/13. SymBio booked an inflow of JPY1.5bn in FY12/15 due to payments from time deposits and the redemption of securities.

Cash flows from financing activities

The company has reported a series of inflows from financing activities. As the table below shows, the company has raised capital on multiple occasions in order to finance its operations in the face of continuous operating losses.

Main sources of funding

Date	Change in shares issued	Total shares issued	Change in capital stock and capital surplus (JPYmn)	Capital stock and capital surplus (JPYmn)	
Mar. 2009	7,404	66,017	888	4,643	Paid-in private placement
Nov. 2009	8,334	90,268	500	6,104	Paid-in private placement
Dec. 2009	9,553	100,651	573	6,727	Paid-in private placement
Feb. 2011	11,032	122,769	772	8,164	Paid-in private placement
Feb. 2011	17,368	140,137	1,216	9,380	Paid-in private placement
Oct. 2011	5,100,000	19,130,900	2,628	12,019	Paid-in public offering (price determined by the book building process)
Jan. to Dec. 2013	3,921,257	23,052,157	1,244	13,263	Exercise of stock options attached to convertible corporate bonds and other stock options
Dec. 2013	6,720,200	29,772,357	2,504	15,767	Paid-in public offering (price determined by the book building process)
Dec. 2014	1,756,666	32,390,923	544	16,632	Exercise of stock options attached to convertible corporate bonds and other

					stock options
Jan. to Dec. 2016	14,139,901	46,530,824	3,235	19,867	Exercise of stock options attached to convertible corporate bonds and other stock options
Jan. to Dec. 2017	7,518,400	54,049,224	1,627	21,523	Exercise of stock options attached to convertible corporate bonds and other stock options

Source: Shared Research based on company data.

Other information

Claim for damages

SymBio initiated arbitration against The Medicines Company, seeking damages of USD82mn

The license agreement the SymBio entered with The Medicines Company (MDCO) on October 5, 2015 for the exclusive rights to develop and commercialize the patient-controlled pain management drug SyB P-1501 (IONSYS in the US) has terminated effective November 30, 2017, pursuant to the terms of the subject agreement.

As disclosed in MDCO's Form 10-Q filing of November 9, 2017, the company initiated an arbitration against MDCO on October 11, 2017, under the rules of the International Chamber of Commerce, seeking damages of USD82mn (approximately JPY9bn) arising from MDCO's repudiation of the license agreement. In the Request for Arbitration, SymBio claims that MDCO failed to provide SymBio with adequate assurances of performance of MDCO's contractual obligations under the license agreement in the light of MDCO's decision to (1) discontinue and withdraw the drug (IONSYS®) from the markets in the US and EU and (2) cease related commercialization activities. SymBio claims such failure by MDCO to be a repudiation and material breach of the license agreement, resulting in its termination.

> The International Chamber of Commerce, a Paris-based international organization, has around 130 participating countries including Japan. Its flagship institution, the International Court of Arbitration, aims to solve disputes arising from international commercial agreements not by lawsuits, but by arbitration. When one party does not obey the court's judgment, the other party may perform compulsory execution.

History

SymBio was established in March 2005 by Fuminori Yoshida, former Corporate Vice President of Amgen Inc., and founding President and CEO of the Japanese subsidiary, Amgen Japan. Mr. Yoshida's desire to address the unmet medical needs of patients in underserved markets often overlooked by the pharmaceutical industry due to limited patient numbers inspired him to create SymBio Pharmaceuticals.

> In 2013, Amgen Inc. was the largest biopharmaceutical company in the world by revenue. It was established in 1980 in Thousand Oaks, California as Applied Molecular Genetics. Mr. Yoshida established Amgen Japan in May 1993, serving as President and CEO for 12 years prior to founding SymBio Pharmaceuticals in March 2005. In February 2008, Takeda Pharmaceutical Co. Ltd. acquired Amgen Japan.

After its establishment, SymBio obtained financing totaling JPY1bn from Daiichi Pharmaceutical Co., Ltd. (now Daiichi Sankyo, Inc.; TSE1: 4568), Medical & Biological Laboratories Co., Ltd. (JASDAQ: 4557), EPS Corporation (TSE1: 4282), and SBI Holdings, Inc. (TSE1: 8473). The company used the cash raised to in-license its first drug candidate, bendamustine hydrochloride, from Astellas Pharma GmbH in December 2005 with the exclusive right to develop and commercialize the drug in Japan.

After the global financial crisis of September 2008, the company experienced a shortage of capital as Treakisym® was advancing in the clinic. Mr. Yoshida visited at least 50 venture capital firms in Japan and elsewhere in December 2008, eventually raising JPY1.5bn in capital from Cephalon, Inc. (acquired by Teva Pharmaceutical Industries Ltd. (NASDAQ: TEVA) in October 2011).

SymBio obtained Japanese marketing and manufacture approval for Treakisym® in October 2010 and began domestic sales in December of that year.

As of February 2018, Treakisym® for relapsed or refractory low-grade NHL and MCL is the company's mainstay product. Clinical trials are also in preparation or under way toward attaining domestic approval for additional Treakisym® indication, RTD and RI products of Treakisym®, and anti-cancer drug rigosertib for myelodysplastic syndromes.

March 2005	SymBio Pharmaceuticals Limited established with JPY30mn in capital.
December 2005	License Agreement finalized with Astellas Pharma GmbH for SyB L-0501 (bendamustine) development and commercialization rights in Japan.
March 2006	Manufacturer's License (packaging, labeling and storage) obtained from Tokyo Metropolitan Government (License #13AZ200010).
March 2007	Abeille Pharmaceuticals licensed SyB D-0701 (granisetron patch) to SymBio Pharmaceuticals for development & commercialization in Japan, China (HK), Taiwan, Korea and Singapore.
March 2007	License Agreement finalized with Astellas Deutschland GmbH for SyB L-0501 (bendamustine) development & commercialization rights in China (HK), Taiwan, Korea and Singapore.
August 2008	License Agreement finalized with Eisai Co., Ltd. for co-development and commercialization rights of SyB L-0501 (bendamustine) in Japan.
March 2009	SymBio Pharmaceuticals concluded Sublicense Agreement with Cephalon, Inc. for development and commercialization rights of bendamustine hydrochloride in China (HK).
May 2009	License Agreement finalized with Eisai Co., Ltd. for co-development and commercialization rights of SyB L-0501 (bendamustine) in Korea and Singapore.
September 2010	SymBio Pharmaceuticals and Eisai launch SYMBENDA® (bendamustine) in Singapore for the treatment of Low-grade Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukemia.
October 2010	Announced NDA Approval of Treakisym® (bendamustine) in Japan.
December 2010	Launched Treakisym® in Japan.
July 2011	Onconova and SymBio Pharmaceuticals completed License Agreement for SyB L-1101/SyB C-1101 (rigosertib, a phase III stage multi-kinase inhibitor for Myelodysplastic Syndromes).
October 2011	Launched Symbenda® (bendamustine hydrochloride) in Korea for the treatment of Chronic Lymphocytic Leukemia and multiplemyeloma.
October 2011	Listed on Osaka Securities Exchange JASDAQ Growth Market.
February 2012	Launched Innomustine® (bendamustine hydrochloride) in Taiwan for the treatment of Low-grade Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukemia.
October 2015	Obtained exclusive development and marketing rights to Ionsys (patient-controlled analgesia system) in Japan from The Medicines Company (US).
August 2016	Received approval for Chronic Lymphocytic Leukemia to be added as indication for Treakisym®.
December 2016	Announced approval of the anti-cancer drug Treakisym® for the additional indication of first-line treatment of low-grade non-Hodgkin's lymphoma and mantle cell lymphoma.
September 2017	Concluded license agreement with Eagle Pharmaceuticals, Inc. (US), granting SymBio exclusive rights to develop, market, and sell Eagle's bendamustine hydrochloride RTD and RI products in Japan.

News and topics

July 2018

On **July 30, 2018**, the company announced inclusion of anti-cancer agent Treakisym® as standard therapy in revised Clinical Practice Guidelines 2018 for healthcare professionals.

The company announced that anti-cancer agent Treakisym® (generic name: bendamustine hydrochloride) was newly included as a standard treatment option in the Guidelines for Tumors of Hematopoietic and Lymphoid Tissues 2018 issued by Japan Society of Hematology on July 20, 2018. The guidelines were revised to include as indications of Treakisym® mantle cell lymphoma and chronic lymphocytic leukemia in addition to relapsed or refractory low-grade B-cell non-Hodgkin's lymphoma (relapsed or refractory low-grade NHL). Further, Treakisym® was newly included as a treatment option for untreated low-grade NHL. According to the company, inclusion of all approved indications of Treakisym® in the guidelines positioned the drug as standard treatment for malignant lymphoma. As a result, Treakisym® can potentially replace conventional standard therapy and penetrate the market even further.

On **July 2, 2018**, the company announced it has obtained approval for combined use of Treakisym® with Anti-CD20 antibodies.

The company obtained approval for a partial change to its manufacture and marketing authorization for the anticancer agent Treakisym® (non-proprietary name: bendamustine hydrochloride).

In Europe and the US, a significant number of new anti-CD20 antibodies* are being developed for treatment of low-grade B-cell non-Hodgkin's lymphoma (low-grade NHL). The approval permits the use of Treakisym® in combination with rituximab or other new anti-CD20 antibodies and will expand the treatment options available to patients. On the same day, Chugai Pharmaceutical Co., Ltd. obtained manufacture and marketing approval for Gazyva® (non-proprietary name: obinutuzumab) for CD20-positive follicular lymphoma, a typical histologic type of low-grade NHL. After the launch of Gazyva®, the approval will allow the combined use of Treakisym® and Gazyva® for the treatment of CD20-positive follicular lymphoma.

* CD20 is a transmembrane phosphoprotein that is a surface-membrane molecule specifically expressed on lymphocyte B cells. Anti-CD20 antibodies recognize and bind to CD20 in vivo, and target the binding to kill B cells by natural killer cells.

May 2018

On **May 28, 2018**, the company announced the first patient enrollment in the phase I clinical trial for oral Treakisym® for progressive solid tumors.

The company completed enrollment of the first patient for the phase I clinical trial for oral Treakisym® in patients with progressive solid tumors; the phase I trial was initiated on January 22, 2018.

Treakisym® acquired manufacture and marketing approval for three indications of malignant lymphoma (first-line and relapsed or refractory low-grade B-cell non-Hodgkin's lymphoma and mantle cell lymphoma, and chronic lymphocytic leukemia) and is currently used as treatment for numerous patients in each therapeutic area. The objective of the clinical trial is to investigate the recommended dose, dosage regimen, tolerability, and safety of the new oral formulation of Treakisym®, and to narrow down the types of advanced solid tumors suitable for future clinical trials.

April 2018

On **April 9, 2018**, the company announced it has issued 45th through 47th stock acquisition rights with exercise price revision clauses (Commit Issue Program) and concluded an unsecured loan facility agreement.

At the Board of Directors meeting held on the same day, the company resolved the following:

▷ Issuance of 45th through 47th stock acquisition rights via third party allotment to EVO FUND

▷ Conclusion of a third-party allotment agreement on stock acquisition rights (Commit Issue Program) with EVO FUND

▷ Conclusion of an unsecured loan facility agreement with Evolution Japan Asset Management Co., Ltd. simultaneously with the third-party allotment agreement

Overview of the stock acquisition rights

Allotment date	April 25, 2018
Total number of stock acquisition rights	50,000,000 units 45th stock acquisition rights: 20,000,000 units 46th stock acquisition rights: 15,000,000 units 47th stock acquisition rights: 15,000,000 units
Issue price	JPY23mn 45th stock acquisition rights: JPY0.54 per unit 46th stock acquisition rights: JPY0.44 per unit 47th stock acquisition rights: JPY0.38 per unit
Number of residual shares from the issuance	50,000,000 (one share per stock acquisition right) (Dilution rate of 92.5%; however, as the stock acquisition rights are scheduled to be exercised in three tranches over the course of three years, the dilution rate will be 37.0% in the first year, and 27.8% in the second and third years)
Amount of funds raised	JPY10,413mn
Exercise price and conditions for revision to the exercise price	Initial exercise price 45th stock acquisition rights: JPY207 46th stock acquisition rights: JPY209 47th stock acquisition rights: JPY211 The exercise price of the stock acquisition rights shall be initially revised on April 27, 2018, with revisions occurring at each passing of five price calculation dates that follow. Price calculation dates are days on which trading sessions take place on the Tokyo Stock Exchange but on which market-disrupting events do not occur. The exercise price shall be revised on the next trading day following the fifth price calculation date counted from the date on which the exercise price was previously revised; the exercise price shall be revised to an amount obtained by multiplying the simple average value of the VWAP (volume weighted average price) of SymBio's common shares on each price calculation date for the five consecutive price calculation dates prior to the revision date by the exercise price revision ratios of 92% for the 45th, 93% for the 46th, and 94% for the 47th stock acquisition rights.
Method for subscription or allotment	Third party allotment

Commit Issue Program

The target numbers of SymBio's common shares underlying each of the stock acquisition rights (45th: 20,000,000 shares; 46th 15,000,000 shares; 47th: 15,000,000 shares) are determined in advance, and such stock acquisition rights are designed so that the allottee EVO FUND commits to their exercise. The exercise period comprises a combination of Full Commitment Period (when all stock acquisition rights are exercised) and a First Half Commitment Period (when a portion of the acquisition rights are exercised). By distributing the exercisable timing of the stock acquisition rights (45th through 47th stock acquisition rights), a high probability of funding will be provided over the upcoming three-year period.

	45th stock acquisition rights	46th stock acquisition rights	47th stock acquisition rights
Number of stock acquisition rights issued	20,000,000 units	15,000,000 units	15,000,000 units
Total issue price	JPY10.8mn	JPY6.6mm	JPY5.7mn
Total exercise price	JPY4,140mn	JPY3,135mn	JPY3,165mn
Expected exercise period	In principle, a period of approximately 6 months after issuance	In principle, a period of approximately 4.5 months one year after issuance	In principle, a period of approximately 4.5 months two years after issuance
Exercise price	92% of the average VWAP over a period of five calculation days	93% of the average VWAP over a period of five calculation days	94% of the average VWAP over a period of five calculation days
Full Commitment	Commitment, in principle, to exercise all of the stock acquisition rights issued within 122 price calculation days	Commitment, in principle, to exercise all of the stock acquisition rights issued within 97 price calculation days	Commitment, in principle, to exercise all of the stock acquisition rights issued within 97 price calculation days

First Half Commitment	Commitment, in principle, to exercise 40% or more of the stock acquisition rights issued within 67 price calculation days	Commitment, in principle, to exercise 40% or more of the stock acquisition rights issued within 52 price calculation days	Commitment, in principle, to exercise 40% or more of the stock acquisition rights issued within 52 price calculation days
Expected start date of initial exercise	April 26, 2018	April 26, 2019	April 27, 2020
Expected final date of Full Commitment	October 23, 2018	September 17, 2019	September 16, 2020
Acquisition conditions	Yes	Yes	Yes

Unsecured loan facility agreement

The company resolved to enter into a loan agreement with Evolution Japan Asset Management, an affiliate of EVO FUND (the allottee of SymBio's stock acquisition rights), simultaneously with the issuance of stock acquisition rights, so that it can respond to immediate funding needs such as investment in new in-licensing, M&A, and other means of ensuring long-term growth opportunities.

Overview of loan agreement

Effective date	April 25, 2018
Loan amount (maximum)	JPY1,500mn
Period	April 25, 2018 to April 25, 2021
Interest rate	0.5% per annum

Amount of capital raised (estimated net proceeds)

Total amount paid	JPY10,463mn
Approximate amount of issue-related expenses	JPY50mn
Estimated net proceeds	JPY10,413mn

Specific fund usage

Specific uses	Amount (JPYmn)	Expected timing of expenditure
Development of in-licensed drugs	4,700	April 2018 to December 2020
Creation of an independent sales structure	3,300	April 2018 to December 2020
Investment in new in-licensing, M&A, and other means of ensuring long-term growth opportunities	2,413	April 2018 to December 2020

February 2018

On **February 9, 2018**, the company announced the termination of the development of patient-controlled pain management drug SyB P-1501.

The company terminated the development of SyB P-1501 (IONSYS in the US), a drug for patient-controlled, short-term management of acute postoperative pain during hospitalization. SymBio was developing the drug in Japan under a license agreement entered on October 2, 2015 with The Medicines Company (MDCO), which terminated effective November 30, 2017.

SymBio initiated an arbitration against MDCO on October 11, 2017, under the rules of International Chamber of Commerce, seeking damages of USD82mn (approximately JPY9bn) arising out of MDCO's repudiation of the license agreement.

On **February 7, 2018**, the company announced its new four-year medium-term plan (FY12/18–F12/21).

Medium-term plan targets

(JPYmn)	FY12/17 Act.	FY12/18 Est.	FY12/19 Target	FY12/20 Target	FY12/21 Target
Sales	3,444	4,201	4,238	4,413	11,624–10,325
Operating profit (losses)	-3,947	-2,981	-3,786	-3,709	1,777–878
Recurring profit (losses)	-3,977	-3,044	-3,849	-3,772	1,724–825
Net income (losses)	-3,978	-3,056	-3,853	-3,776	1,467–702

Source: Shared Research based on company data.

Main pipeline schedule

	FY12/17	FY12/18	FY12/19	FY12/20	FY12/21
Treakisym® (relapsed or refractory low-grade NHL and MCL)	Obtained approval (Oct-10)				
Treakisym® (first-line treatment of low-grade NHL and MCL)	Obtained approval (Dec-16)				
Treakisym® (CLL)	Obtained approval (Aug-16)				
Treakisym® (relapsed or refractory moderate- and high-grade NHL)	Phase III clinical trials underway		Complete phase III clinical trials	Apply for approval	Obtain approval
Treakisym®RTD (all indications)				Apply for approval	Obtain approval
Treakisym®RI (all indications)			Initiate phase III clinical trials	Complete phase III clinical trials	Apply for approval
Treakisym® (oral) (progressive solid tumors)		Phase I clinical trials			
Rigosertib (IV) (relapsed and refractory high-risk MDS)		Global phase III clinical trials underway			Apply for approval
Rigosertib (oral) (high-risk MDS [in combination with azacitidine])	Phase I clinical trials underway	Complete phase I clinical trials			
Rigosertib (oral) (high-risk MDS [in combination with azacitidine])			Initiate phase I clinical trials	Complete phase I clinical trials	

Source: Shared Research based on company data.

Earnings targets of medium-term plan (FY12/18–FY12/21)

Sales

Sales of Treakisym® accounts for the bulk of overall sales. The company set the performance targets for drug sales after analysis and discussions on market size projections (derived from estimated number of patients), competitive positioning and advantages compared with existing therapies, and sales performance after commencement of sales. The company's forecast for FY12/21 is based on sales of Treakisym® through its own sales force.

The company forecasts sales growth of Treakisym® in FY12/21 onward following approval of an additional indication of relapsed or refractory diffuse large B-cell lymphoma (DLBCL), which is expected in 1H FY12/21. Its sales target is calculated using an estimated market penetration rate range for the indication.

CoGS

CoGS is based on the terms and conditions of licensing and supply agreements with Astellas Deutschland GmbH (German subsidiary of Astellas Pharma Inc.) and Eagle Pharmaceuticals, Inc.

SG&A expenses

SG&A expenses are broken down into R&D expenses and other SG&A expenses. In the new medium-term plan, R&D expenses are broken down as follows:

- ▷ Expenses associated with phase III clinical trials of Treakisym®, targeting indication for relapsed or refractory DLBCL (trials started in August 2017)
- ▷ Expenses associated with the filing and development of Treakisym® liquid formulations (RTD and RI), in-licensed from Eagle Pharmaceuticals after signing an exclusive licensing agreement in September 2017
- ▷ Expenses associated with phase I clinical trials of oral Treakisym®, targeting indication for progressive solid tumors (trials commenced in January 2018)

In regard to SyB L-1101 (Rigosertib IV), based on the results of an interim analysis performed in January 2018 the company plans to continue its clinical trial, increasing patient enrollment in Japan. Milestone payments that arise at the time of obtaining approval have not been factored into the forecasts.

In-licensing or development costs on new drug candidates other than those listed in the current pipeline are not accounted for, although the company plans to continue evaluation and discussion of these agents.

Other SG&A expenses are mainly associated with the marketing, production and distribution, business development, and administrative operations for Treakisym®. The company expects to begin sales of Treakisym® through its own sales force from 2021 onward, because the business alliance agreement with Eisai comes to an end in December 2020. As such, expenses for establishing and running its own sales force are accounted for from 2019 onward.

January 2018

On **January 22, 2018**, the company announced that it has initiated a phase I study in Japan for oral Treakisym® in patients with progressive solid tumors.

The purpose of the phase I study is to evaluate the recommended dose, dosage regimen, the tolerability* and the safety of oral Treakisym®, as it is a new formulation, and to identify types of solid tumors that show promise for treatment.

*Tolerability refers to the degree to which overt adverse effects of a drug can be tolerated by a human subject.

The company will evaluate safer dosage regimens with no adverse effect on efficacy by leveraging the pharmacokinetic traits of the oral formulation, specifically, lowering Cmax and administration in lower doses during the treatment period.

On **January 15, 2018**, the company announced that the first patient has been enrolled in the domestic phase III clinical trial for anti-cancer drug Treakisym® (non-proprietary name: bendamustine hydrochloride) targeting relapsed or refractory diffuse large B-cell lymphoma (DLBCL).

The objective of the phase III trial is to confirm the efficacy and safety of the phase II trial. The company aims to file an NDA for relapsed or refractory DLBCL as an additional indication in 2H FY12/19.

November 2017

On **November 30, 2017**, the company announced the termination of license agreement with The Medicines Company.

The company announced that the license agreement it entered with The Medicines Company (MDCO) on October 5, 2015 for the exclusive rights to develop and commercialize the patient-controlled pain management drug SyB P-1501 (IONSYS in the US) has terminated effective November 30, 2017, pursuant to the terms of the subject agreement.

As disclosed in MDCO's Form 10-Q filing of November 9, 2017, the company initiated an arbitration against MDCO on October 11, 2017, under the rules of the International Chamber of Commerce, seeking damages of USD82mn (approximately JPY9bn) arising from MDCO's repudiation of the license agreement. In the Request for Arbitration, SymBio claims that MDCO failed to provide SymBio with adequate assurances of performance of MDCO's contractual obligations under the license agreement in the light of MDCO's decision to (1) discontinue and withdraw the drug (IONSYS®) from the markets in the US and EU and (2) cease related commercialization activities. SymBio claims such failure by MDCO to be a repudiation and material breach of the license agreement, resulting in its termination.

MDCO's Form 10-Q filing of November 9, 2017 stated that the license agreement had terminated in October 2017, but SymBio disagrees with this statement and has advised MDCO accordingly. In conjunction with the termination of the license agreement, the development of SyB P-1501 (including the currently-suspended domestic phase III clinical trial) will be terminated by March 31, 2018.

On **November 13, 2017**, the company announced the initiation of an arbitration against The Medicines Company (MDCO), a licensor of the company's post-operative patient-controlled analgesia, SyB P-1501.

SymBio initiated an arbitration against The Medicines Company on October 11, 2017, under the rules of International Chamber of Commerce, seeking damages arising out of MDCO's repudiation of the license agreement entered into between SymBio and MDCO on October 5, 2015 for the exclusive rights to develop and commercialize the patient-controlled pain management drug SyB P-1501 (called IONSYS in the US). MDCO's alleged breaches relate to its decision to discontinue and withdraw IONSYS® from the US and European markets and failure to provide adequate assurances of its performance under the license agreement. SymBio seeks damages of USD82mn (approximately JPY9bn).

In its quarterly report (Form 10-Q) to the US Securities and Exchange Commission on November 9, 2017, MDCO disclosed that an arbitration case has taken place, in violation of the provisions of the license agreement, and the possibility of counterclaims against SymBio. The company said it believes that MDCO's counterclaims are groundless and that it will severely refute any of MDCO's claims.

October 2017

On **October 10, 2017**, the company announced that it had enrolled the first patient in a domestic phase I clinical trial of anticancer agent rigosertib monotherapy for higher-risk myelodysplastic syndrome (MDS).

SymBio registered the first patient in its domestic phase I clinical trial of anticancer agent rigosertib (oral formulation) monotherapy for higher-risk myelodysplastic syndrome (MDS) started in June 2017.

The purpose of the trial is to confirm safety of high-dose oral rigosertib –an additional requirement in the phase II clinical trial conducted by Onconova Therapeutics, Inc. in the US with relapsed or refractory MDS patients. Once safety has been confirmed, SymBio plans to perform a domestic trial of combination therapy with azacitidine and participate in the global phase III study of rigosertib-azacitidine combination therapy with untreated higher-risk MDS patients planned by Onconova.

The company has not made any revisions to its FY12/17 earnings forecast associated with the start of the domestic phase I clinical trial.

September 2017

On **September 21, 2017**, the company announced revisions to its full-year FY12/17 earnings forecasts.

Revised FY12/17 company earnings forecasts

- ▷ Sales: JPY3.6bn (previous forecast: JPY2.9bn)
- ▷ Operating loss: JPY3.9bn (JPY3.2bn)
- ▷ Recurring loss: JPY4.0bn (JPY3.3bn)
- ▷ Net loss: JPY4.0bn (JPY3.3bn)

Reasons for revisions

The company expects sales of JPY3.6bn, exceeding its previous forecast by JPY680mn, because sales of Treakisym® in Japan grew faster than expected following approval for the new indication of first-line treatment of low-grade non-Hodgkin's lymphoma (NHL) and mantle cell lymphoma (MCL) in December 2016. The company expects operating profit, recurring profit, and net profit to be lower than its previous forecast due to the upfront payment relating to the license agreement with Eagle Pharmaceuticals, Inc., for the liquid formulation products of bendamustine hydrochloride, although SG&A expenses have been solidly controlled within budget.

On **the same day**, the company announced that it had concluded a license agreement with Eagle Pharmaceuticals, Inc., for the bendamustine hydrochloride ready-to-dilute (RTD) and rapid infusion (RI) injection products.

On **September 20, 2017**, Eagle Pharmaceuticals and SymBio concluded a license agreement that licenses to SymBio rights to develop, market, and sell Eagle's bendamustine hydrochloride RTD and RI injection products (marketed in the US by Teva Pharmaceutical Industries as BENDEKA®) in Japan.

SymBio received approval for the new indication of first-line treatment of low-grade B-cell non-Hodgkin's lymphoma (NHL) and mantle cell lymphoma (MCL) in December 2016. As a result of patent protection conferred by the license agreement with Eagle Pharmaceuticals for the liquid formulation products of bendamustine hydrochloride, the company will be able to extend the product life cycle of Treakisym® until 2031. Switching from the currently available freeze-dried (FD) powder injection to the RTD product (which is already liquidized) will reduce the dispensing workload. The company also plans to develop a RI product to shorten the administration time from 60 minutes to 10 minutes. SymBio aims to begin selling the RTD product in early 2021, followed by the RI product.

SymBio will pay Eagle a USD12.5mn upfront payment and a milestone payment upon approval. The company will also pay additional milestone payments on the achievement of cumulative sales thresholds and royalties on future sales of licensed bendamustine products.

RTD and RI bendamustine products are marketed in the US by Teva Pharmaceutical Industries as BENDEKA®, which accounts for 97% of the bendamustine market. Teva estimates that the North American market for bendamustine products at around USD600mn–USD660mn.

RTD and RI products: RTD products are ready to dilute, which eliminates the time-consuming process of reconstitution and substantially reduces the workload of healthcare professionals. Rapid infusion (RI) products can be administered by intravenous infusion in 10 minutes instead of 60 minutes, which reduces stress on patients.

Comparison of RTD/RI products and currently available (freeze-dried) product

	RTD and RI products	Currently available products
Generic name	bendamustine hydrochloride	
Dosage form	Liquid	Freeze-dried powder injection
Reconstitution	Not required	Required
Administration time	60 minutes (RTD product) 10 minutes (RI product)	60 minutes
Dosage form	100mg/4mL	100mg/vial

		25mg/vial
Storage	Refrigerated storage (2°C–8°C)	Room temperature

August 2017

On **August 31, 2017**, the company announced the initiation in Japan of the phase III clinical trial of the anti-cancer drug Treakisym® for the indication of relapsed or refractory diffuse large B-cell lymphoma.

The company announced that it initiated a phase III study in Japan of the anti-cancer drug Treakisym® (non-proprietary name: bendamustine hydrochloride) for the indication of relapsed or refractory DLBCL.

Although DLBCL accounts for about one-third of malignant lymphoma in terms of the number of patients, a standard chemotherapy for treatment of DLBCL is currently not available, thus multiple drug therapies are administered. Multiple drug therapies, however, tend to have strong adverse effects, placing a burden on patients, and accordingly a new therapy is much-awaited.

Having completed a phase II study for bendamustine-rituximab (BR) therapy, SymBio obtained clinical trial results for the treatment of patients with relapsed or refractory DLBCL.

Based on the achievements of this clinical study, BR therapy has been recommended in the NCCN (National Comprehensive Cancer Network) Guidelines in the US, the standard for clinical policy in oncology, since 2012. After consultation with Pharmaceuticals and Medical Devices Agency (PMDA) of Japan, SymBio has now initiated a phase III study. The objective of the study is to confirm the efficacy and safety of BR therapy. The disease, relapsed or refractory DLBCL, falls under a therapeutic area with high unmet medical needs, where a new drug therapy is much-awaited, as the strong need for the development of BR therapy has been voiced by a patient group and relevant academic societies.

Swiftly enrolling patients in the study, SymBio aims to file an NDA (new drug application) for relapsed or refractory DLBCL in the second half of 2019. This event will not impact the company's FY12/17 forecasts.

On **August 9, 2017**, the company announced the issuance of the 42nd stock acquisition rights by third-party allotment.

The company resolved to issue its 42nd stock acquisition rights (placement through third-party allotment) as outlined below.

42nd stock acquisition rights

- ▷ Allotment date: August 25, 2017
- ▷ Number of stock acquisition rights issued: 88,000 units
- ▷ Issue price: JPY32,560,000 (JPY370 per unit)
- ▷ Number of underlying shares: 8,800,000 (17.97% of all issued shares)
- ▷ Total funding amount: JPY1,910mn (net of cost)
- ▷ Exercise price and exercise price amendment provisions: Initial exercise price: JPY215

  On February 26, 2018, the exercise price shall be amended to an amount equivalent to 90% of the closing price of SymBio's common shares on February 23, 2018, but in the event that the price falls below the minimum exercise price, the minimum exercise price shall be the exercise price after amendment.

Uses of proceeds to be raised

Specific use of funds to be raised	Amount	Scheduled disbursement timing
Expenses for the development of Treakisym® (SyB L-0501) for relapsed or refractory	JPY900mn	August 2017–December 2018

aggressive non-Hodgkin lymphoma (diffuse large B-cell lymphoma, or DLBCL)		
Expenses related to acquisition of rights and subsequent development of the oral form of Treakisym®	JPY1,009mn	August 2017–December 2018

Phase II clinical trials for Treakisym® (SyB L-0501) for the additional indication of relapsed or refractory aggressive NHL (DLBCL) have been completed with favorable results, and SymBio has considered applying for approval in order to further enhance the product value of Treakisym® through additional indications. SymBio is currently formulating the details of a phase III clinical trial plan, and plans to submit a trial plan within 2017 and begin the trials. Of the total development period for these phase III clinical trials, the amount of expenditure expected until the end of December 2018 is stated.

With regard to the acquisition of rights for the oral form of Treakisym®, SymBio will expand the rights it holds on Treakisym® in order to promote indications in addition to blood cancer, such as for solid cancer and autoimmune diseases. Expenses related to the acquisition of rights and expenses related to the implementation of phase I clinical trials currently under consideration are stated.

On **the same day**, the company announced the current status of the domestic phase III clinical trial of the patient-controlled pain management drug SyB P-1501.

On May 11, 2017, SymBio announced temporary suspension of new patient enrollment in the domestic phase III clinical trial of the patient-controlled pain management drug "SyB P-1501." On June 5, 2017, the company announced that The Medicines Company, the licensor of SyB P-1501, had filed a report (Form 8-K) with the US Securities and Exchange Commission.
In an update on the current status of the domestic phase III clinical trial of the drug, SymBio said that it is continuing to discuss with The Medicines Company (MDCO) the effects of MDCO's decision to discontinue and withdraw IONSYS® (the product name for SyB P-1501 in the US) from the US market, in particular on the SyB P-1501 clinical trial and commercialization in Japan. SymBio will make a timely disclosure once it makes a decision pending the results of the ongoing discussions with MDCO.

June 2017

On **June 30, 2017**, the company announced that it has initiated in Japan a phase I clinical trial of single-agent oral rigosertib in higher-risk myelodysplastic syndromes (MDS).

The company initiated the phase I clinical trial since Onconova Therapeutics, Inc., the licensor for oral rigosertib, resumed the supply of clinical trial materials after completing a change of manufacturing sites.

The purpose of the Japanese phase I study is to confirm the safety of high-dose oral rigosertib, which was added to the ongoing overseas phase II study by Onconova in untreated or relapsed/refractory patients with higher-risk MDS. After demonstrating the safety of high-dose oral rigosertib, SymBio intends to immediately recommence an oral rigosertib/azacitidine combination trial in Japan, and participate in the global phase III study in untreated higher-risk MDS patients that Onconova is planning. In initiating the subject phase I study, SymBio has terminated the phase I combination study for oral rigosertib/azacitidine.

The enrollment of patients is currently underway in the global phase III clinical trial for the intravenous version of rigosertib in relapsed or refractory patients with higher-risk MDS, which SymBio has been taking part in.

The initiation of this phase I study will not impact the company's FY12/17 forecasts.

On **June 5, 2017**, the company announced a US SEC filing (Form 8-K) by The Medicines Company as the licensor of the patient-controlled pain management drug SyB P-1501.

On May 11, 2017, the company announced it has suspended further registration of new patients in a domestic phase III clinical trial of SyB P-1501 indicated for the short-term management of acute post-operative pain during hospitalization. In relation to this, the Medicines Company, the licensor of this product, filed a Form 8-K with the US Securities and Exchange Commission on June 2, 2017.

The Form 8-K states that The Medicines Company commenced implementation of a workforce reduction on June 1, 2017 in connection with the discontinuation and market withdrawal of IONSYS® (US product name of SyB P-1501) in the US and the cessation of related commercialization activities, while the New Drug Application for IONSYS® is to remain open until December 31, 2017.

SymBio will discuss with The Medicines Company the effects of the 8-K filing on the clinical trial plan of SyB P-1501 and plans to make timely disclosures accordingly.

May 2017

On **May 11, 2017**, the company announced that it has suspend further patient enrollment for the phase III trial of SyB P-1501 (patient-controlled analgesia for pain management).

SymBio decided to suspend further registration of new patients in a domestic phase III trial of SyB P-1501 indicated for the short-term management of acute post-operative pain during hospitalization.

In a quarterly report submitted to the US Securities and Exchange Commission (SEC) in May 2017, The Medicines Company, the licensor of SyB P-1501, stated that it was considering a business alliance or company split for the SyB P-1501 business and that it may suspend commercialization of the agent unless an acceptable agreement is concluded by Q2 FY12/17 (April–June 2017).

SymBio started the domestic phase III trial of SyB P-1501 in June 2016, enrolled the first patient in November, and has made progress with case accumulation. However, on April 21, 2017, The Medicines Company notified the company of its intentions as outlined in the quarterly report. SymBio, which is committed to the primacy of patient welfare, interrupted patient enrollment on the same day given concerns about the continuity of The Medicines Company's SyB P-1501 business. Accordingly, SymBio notified medical institutions participating in the study and the Pharmaceuticals and Medical Devices Agency (PMDA) that it would suspend further patient enrollment.

SymBio will not register new patients in the trial until The Medicines Company makes a further announcement about the commercialization of SyB P-1501. The company intends to disclose without delay any impact on the implementation plan of the trial if an announcement is made.

February 2017

On **February 24, 2017**, the company announced a notice concerning the appointment of a representative director.

At a Board of Directors' meeting held on the same day, the company decided to formally propose the approval of the appointment of a new representative director at its ordinary general meeting of shareholders to be held on March 29, 2017, and at a Board of Directors' meeting to be held immediately following the shareholders meeting.

Change of positions

Name	New position	Current position
Kazuo Asakawa	Representative Director, Executive Vice President, COO, and Head of the Japan Business Unit	Corporate Officer, Executive Vice President, COO, and Head of the Japan Business Unit

January 2017

On **January 31, 2017**, the company announced the sales launch in Japan of the anti-cancer drug Treakisym® Intravenous Infusion 25 mg.

The company, through Eisai Co., Ltd. (Eisai), launched sales in Japan on January 31, 2017 of Treakisym® Intravenous Infusion 25 mg, a standard low-dose product (non-proprietary name: bendamustine hydrochloride) for the treatment of low-grade B-cell

non-Hodgkin's lymphoma and mantle cell lymphoma, and chronic lymphocytic leukemia. Based on a license agreement between the company and Eisai, Eisai will be exclusively in charge of marketing the drug.

December 2016

On **December 19, 2016**, the company announced approval of the anti-cancer drug Treakisym® for the additional indication of first-line treatment of low-grade non-Hodgkin's lymphoma and mantle cell lymphoma.

SymBio obtained approval for the additional indication of first-line treatment of this disease after filing a new drug application on previously untreated patients in December 2015, based on the results of a domestic phase II clinical trial and the outcome of an overseas phase III clinical trial. The company made no changes to its forecast of FY12/16 earnings based on this approval for manufacture and marketing of the drug.

On **December 6, 2016**, the company announced that Onconova presented phase II clinical trial data on oral rigosertib at the 2016 American Society of Hematology (ASH).

SymBio began handling the anticancer drug rigosertib in July 2011. Onconova Therapeutics, Inc., the drug's licensor, presented phase II clinical trial data on oral rigosertib for patients with higher-risk myelodysplastic syndromes (MDS) at the 58th American Society of Hematology (ASH) Annual Meeting in San Diego, California. The meeting lasted from December 3 to 6.

The data on the efficacy and safety of oral rigosertib and azacitidine combination for 33 MDS patients (20 HMA naïve; 13 HMA resistant) was presented at the poster presentation, "Combination of Oral Rigosertib and Injectable Azacitidine in Patients with Myelodysplastic Syndromes (MDS): Results from a Phase II Study." The complete remission (CR) rate amongst HMA-naïve patients was higher (35%) and responses occurred more rapidly and durably with the oral rigosertib combination compared to the single-agent azacitidine. The median duration of CR was eight months, comparing very favorably to the historic duration of CR of 3.2 months with single-agent azacitidine.

The global joint phase III clinical trial is currently underway for patients with relapsed or refractory higher-risk MDS. Onconova is also making efforts toward finalizing the design for a pivotal phase III oral rigosertib/azacitidine combination trial for higher-risk MDS patients.

Major shareholders

Top shareholders	Shares held ('000)	Shareholding ratio
Fuminori Yoshida	3,120,000	5.80%
Cephalon, Inc. (Standing proxy: TEVA Pharmaceutical K.K.)	2,589,000	4.80%
Japan Securities Finance Co., Ltd.	1,812,000	3.40%
Matsui Securities Co Ltd	993,800	1.80%
Daiwa Securities Group Inc	853,000	1.60%
Eisai Co., Ltd.	833,400	1.50%
Waseda No. 1 Investment LP	684,000	1.30%
SBI Securities Co., Ltd	595,300	1.10%
BNY GCM CLIENT ACCOUNT JPRD AC ISG (FE-AC) (Standing proxy: The Bank of Tokyo-Mitsubishi UFJ, Ltd.)	577,700	1.10%
Rakuten Securities, Inc.	532,500	1.00%
SUM	12,590,700	23.30%

Source: Shared Research based on company data.
As of end-December 31, 2017
Note: Shareholding ratio calculated excluding treasury shares from shares issued

Top management

Representative Director, President and CEO, Fuminori Yoshida established SymBio Pharmaceuticals Limited, his third company, in March of 2005. As founding president of two other major healthcare companies, Nippon BioRad Laboratories (1980) and Amgen Japan (1993), he has earned high visibility and credibility within Japan's healthcare and academic communities. Following his

graduation from Gakushuin University in 1971 with a B.S. in Organic Chemistry, he went on to receive an M.S. in Molecular Biology from MIT (1973) and M.S. in Health Policy and Management from Harvard University Graduate School (1975). He possesses dual experience and expertise in the management of major Japanese and American corporations due to his prior work experience at various companies, including Mitsubishi Corporation and AHS Japan, Syntex Japan (1993) as President and CEO, and Amgen Inc. where he served concurrently as Corporate Vice-President, President and CEO of Amgen Japan, for 12 years.

Employees

SymBio had a total of 78 employees as of December 31, 2017.

Other

Overview of clinical trials

Development of a new drug takes between 10 and 17 years

The development process of a new drug follows the four stages described below. It usually takes 10 to 17 years for a new drug to win regulatory approval, according to the company.

Ordinary process and periods of developing new drugs

Process	Period	What is done
Basic research	2-3 years	Creation of new substances and decision on candidates for drugs
Preclinical test	3-5 years	Confirmation of efficacy and safety through experiments on animals
Clinical trials	3-7 years	Phase I: Confirmation of safety and pharmacokinetics with a small number of healthy people
		Phase II: Confirmation of efficacy and safety with a small number of patients
		Phase III: Confirmation of efficacy and safety with many patients in comparison to existing drugs
Application and approval	1-2 years	Examination by the Ministry of Health, Labour and Welfare

Source: Shared Research based on company data.

Probability of a compound receiving drug approval is 1/100,000

The probability of a chemical compound receiving regulatory approval is said to be 1/100,000, according to the company.

According to the 2013 edition of the Thomson Reuters Pharmaceutical R&D Factbook, the success rate of pharmaceutical companies around the globe from 2006 to 2009 at various stages in the development process was:

- ▷ Preclinical: 67%
- ▷ Phase I clinical trials: 46%
- ▷ Phase II clinical trials: 19%
- ▷ Phase III clinical trials: 77%
- ▷ Regulatory approval: 90%.

The success rate of cancer drugs tends to be lower than that of other drugs. The success rate of cancer drugs that went through clinical trials in the US between 2004 and 2011 was only 6.7%, compared with 12.1% for other drugs, according to BIOtechNow. The success rate of cancer drugs that went through phase III clinical trials was 45%, while other drugs had a 64% success rate.

Ethnic factors in the acceptability of foreign clinical data

Japan's Ministry of Health, Labour, and Welfare (MHLW) in 1998 released a report entitled Ethnic Factors in the Acceptability of Foreign Clinical Data (ICH-E5 Guideline) to spell out the government's stance on the use of data on clinical trials conducted outside Japan. The report discusses whether the use of such extrapolated data is acceptable.

Applications for drug approval in Japan normally require pharmacokinetic data, dose-responsive data, and clinical trial data on efficacy for Japanese people. However, data from overseas clinical trials are acceptable if a bridging study demonstrates that such data can be used for Japanese people.

Pharmacokinetic data: Data concerning the fate of substances administered externally to a living organism: absorption, distribution, metabolization, and excretion (ADME).

Glossary

Antigen

Normally, a protein or other substance carrying bacteria and viruses that the body rejects as foreign, causing an antigen-antibody reaction (AAR). When antigens enter the body, they either stimulate the production of antibodies or combine with them.

Bridging Data

Data generated from overseas clinical trials that can be applied to Japanese patients and used in Japan regulatory filings for marketing approval. The goal is to shorten the number of preclinical/clinical studies required for marketing approval in Japan by avoiding the need to repeat the same studies that have already been carried out overseas (e.g., dispense with the need to do a phase II and/or III clinical trial in Japan).

Chronic Lymphocytic Leukemia (CLL)

A disease in which white blood cells, called lymphatic corpuscles, become cancerous.

Contract Research Organization (CRO)

Pharmaceutical companies often outsource some of their work to contract research organizations so they can focus on core operations. Outsourced work may include monitoring of clinical trials to ensure that they are proceeding according to plan, and the management of clinical trial data.

Dose-Responsiveness

Does-responsiveness shows the relationship between the dosage and efficacy of a drug. It is used to determine the method and dosage. Under normal circumstances, the effectiveness of a drug corresponds to its dosage.

First-line Drug

The first drug given to a patient for a disease that is typically part of a standard set of treatments such as surgery followed by chemotherapy and radiation. When used by itself, first-line therapy is the one accepted as the best treatment. If it doesn't cure the disease (the patient has a relapse) or causes severe side effects, other treatments (second-line, third-line etc.) may be added or used instead.

Immunoglobulin G (IgG)

The main antibody isotype found in blood and extracellular fluid which protects the body from infection by binding to many kinds of pathogens such as viruses, bacteria, and fungi —it does this via several immune mechanisms: IgG-mediated binding of pathogens causes their immobilization and binding together.

Iontophoresis

A method for transdermal administration of ionized drugs using a tiny electric current.

Key Opinion Leader (KOL)

Key opinion leaders are physicians whose opinions concerning the treatment of certain illnesses have a strong influence on other doctors.

Mantle-Cell Lymphoma (MCL)

A type of fast-growing B-cell non-Hodgkin's lymphoma that normally affects people over a certain age. It is characterized by small and medium-sized cancer cells that appear in lymphatic nodes, the spleen, bone marrow, blood, and the digestive system.

Monoclonal Antibody

A single antibody molecule taken from a single cell. It is possible to produce large amounts of these special antibodies and use them in the development of antibody drugs.

Multikinase Inhibitor
Multikinase inhibitor blocks tyrosine kinases, which play an important role in transmitting signals involving the multiplication and division of cells. Tyrosine kinases can be energized due to genetic mutations. If this happens, the number of cells rapidly increases, causing cancer or other illnesses.

Myelodysplastic Syndromes
Myelodysplastic Syndrome leads to abnormalities in hematopoietic stem cells that produce blood cells, resulting in a lack of blood. Blood cells produced this way are abnormally shaped. This change in the cells is called dysplasia. The disease typically leads to frequent anemia with some patients dying from infection or bleeding due to the reduction in blood cells. The disease is most common among the elderly. 10 to 20% of MDS patients progress to acute leukemia.

Non-Hodgkin's Lymphoma (NHL)
A group of ailments associated with all types of malignant tumors other than Hodgkin's lymphoma.
In Japan, many of these diseases are diffuse large cell lymphomas.

Overall Survival (OS)
Overall survival refers to the duration between the initiation of treatment and a patient's death.

Progression-Free Survival (PFS)
Progression-free survival refers to the duration between the initiation of treatment, and either death or disease progression.

Proof-of-Concept (POC)
A proof-of-concept, when applied to drug development, is the concept that the efficacy and safety of a new drug candidate must be validated through data generated in clinical trials.

Rare Disorders
Rare disorders are illnesses that affect few people, although they may be serious and/or life-threatening. Drugs designed to treat rare medical conditions are called 'orphan drugs', and pharmaceutical companies often receive government incentives for the development of these drugs.

In Japan, the Ministry of Health, Labour and Welfare seeks to promote the development of orphan drugs by offering subsidies. When a drug is designated as an orphan, it is placed on a fast track for approval (the time between the application and approval is reduced). The period of market exclusivity can also be extended to 10 years, and a system is in place to keep the NHI price of orphan drugs above a certain level.

R-CHOP therapy
A combination of rituximab with chemotherapy drugs cyclophosphamide, doxorubicin (hydroxydaunomycin), vincristine (Oncovin®), and prednisolone. R-CHOP is an acronym derived from the names of the drugs used. It is the standard initial treatment for low-grade non-Hodgkin's lymphoma (NHL) and mantle-cell lymphoma (MCL).

Special Protocol Assessment (SPA)
A system under which the US Food and Drug Administration (FDA) approves the protocol or design of a planned phase III clinical trial, such as target illness, purpose, primary and secondary endpoints, and method of data analysis – the protocol may be revised following FDA consultation prior to the start of the study. The SPA is intended to shorten the review period of new drug applications (NDAs) by the FDA.

Standard Therapy
Standard therapy refers to treatment that is considered to be the best therapy currently available. It is a treatment widely recommended to patients by physicians.

Company name

SymBio is derived from the words “symbiosis” and “biotechnology.” The company’s corporate philosophy emphasizes the symbiotic or mutually supportive relationship that exists among major players in the healthcare industry, and is reflected in the company’s logo which symbolizes physicians, scientists, regulators, and investors, with patients at its center. The color of the logo represents the evergreen tree—the company’s endeavor to create and sustain a life-giving force.

Company profile

Company name	Head office
SymBio Pharmaceuticals Limited	Toranomon 30 Mori Building, 3-2-2 Toranomon Minato-ku, Tokyo, JAPAN 105-0001
Phone	**Listed on**
+81-3-5472-1125	TSE JASDAQ Growth
Established	**Exchange listing**
March 25, 2005	October 20, 2011
Website	**Fiscal year-end**
http://www.symbiopharma.com/index_e.html	December
IR contact	**IR web**
Tsutomu Abe	http://www.symbiopharma.com/ir_e/01.html
IR mail	**IR phone**
tabe.ta02@symbiopharma.com	+81-3-5472-1125

We offer corporate clients comprehensive report coverage, a service that allows them to better inform investors and other stakeholders by presenting a continuously updated third-party view of business fundamentals, independent of investment biases. Shared Research can be found on the web at http://www.sharedresearch.jp.

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ADJUVANT COSME JAPAN CO., LTD.
Aeon Delight Co., Ltd.
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AnGes Inc.
Anicom Holdings, Inc.
Anritsu Corporation
Apaman Co., Ltd.
Arealink Co.,Ltd.
Artspark Holdings Inc.
AS ONE CORPORATION
Ateam Inc.
Aucfan Co., Ltd.
AVANT CORPORATION
Axell Corporation
Azbil Corporation
AZIA CO., LTD.
BEENOS Inc.
Bell-Park Co., Ltd.
Benefit One Inc.
B-lot Co.,Ltd.
Canon Marketing Japan Inc.
Carna Biosciences, Inc.
CERES INC.
Chiyoda Co., Ltd.
Chugoku Marine Paints, Ltd.
cocokara fine Inc.
COMSYS Holdings Corporation
CRE, Inc.
CREEK & RIVER Co., Ltd.
Daiseki Co., Ltd.
DIC Corporation
Digital Arts Inc.
Digital Garage Inc.
DIGITAL HEARTS HOLDINGS Co., Ltd
Don Quijote Holdings Co., Ltd.
Dream Incubator Inc.
EARTH CHEMICAL CO., LTD.
Elecom Co., Ltd.
Emergency Assistance Japan Co., Ltd.
en-Japan Inc.
euglena Co., Ltd.
Evolable Asia Corp.
Ferrotec Holdings Corporation
FIELDS CORPORATION
Financial Products Group Co., Ltd.
FreeBit Co., Ltd.
FRONTEO, Inc.
Fujita Kanko Inc.
FURYU CORPORATION
Gamecard-Joyco Holdings, Inc.
GCA Corporation
Grandy House Corporation
Hakuto Co., Ltd.
Happinet Corporation
Harmonic Drive Systems Inc.
HOUSEDO Co., Ltd.
IDOM Inc.
IGNIS LTD.
Inabata & Co., Ltd.
Infocom Corporation
Infomart Corporation
Intelligent Wave, Inc.
istyle Inc.
Itochu Enex Co., Ltd.
JSB Co., Ltd.
JTEC Corporation
J Trust Co., Ltd
Japan Best Rescue System Co., Ltd.
JINS Inc.
JP-HOLDINGS, INC.
KAMEDA SEIKA CO., LTD.
Kenedix, Inc.
KFC Holdings Japan, Ltd.
KI-Star Real Estate Co., Ltd.
Kumiai Chemical Industry Co., Ltd.
Lasertec Corporation
LUCKLAND CO., LTD.
MATSUI SECURITIES CO., LTD.
Medical System Network Co., Ltd.
MEDINET Co., Ltd.
Milbon Co., Ltd.
MIRAIT Holdings Corporation
Monex Goup Inc.
NAGASE & CO., LTD
NAIGAI TRANS LINE LTD.
NanoCarrier Co., Ltd.
Net One Systems Co.,Ltd.
Nichi-Iko Pharmaceutical Co., Ltd.
Nihon Denkei Co., Ltd.
NIPPON PARKING DEVELOPMENT Co., Ltd.
Nisshinbo Holdings Inc.
NS TOOL CO., LTD.
NTT URBAN DEVELOPMENT CORPORATION
Oki Electric Industry Co., Ltd
ONO SOKKI Co., Ltd.
ONWARD HOLDINGS CO.,LTD.
PARIS MIKI HOLDINGS Inc.
PIGEON CORPORATION
RACCOON HOLDINGS, Inc.
RESORTTRUST, INC.
ROUND ONE Corporation
RVH Inc.
RYOHIN KEIKAKU CO., LTD.
SanBio Company Limited
SANIX INCORPORATED
Sanrio Company, Ltd.
SATO HOLDINGS CORPORATION
SBS Holdings, Inc.
Seikagaku Corporation
Seria Co.,Ltd.
SHIP HEALTHCARE HOLDINGS, INC.
SIGMAXYZ Inc.
SMS Co., Ltd.
Snow Peak, Inc.
Solasia Pharma K.K.
SOURCENEXT Corporation
Star Mica Co., Ltd.
Strike Co., Ltd.
SymBio Pharmaceuticals Limited
Synchro Food Co., Ltd.
TAIYO HOLDINGS CO., LTD.
Takashimaya Company, Limited
Take and Give Needs Co., Ltd.
Takihyo Co., Ltd.
TAMAGAWA HOLDINGS CO., LTD.
TEAR Corporation
Tenpo Innovation Inc.
3-D Matrix, Ltd.
TKC Corporation
TOKAI Holdings Corporation
Tri-Stage Inc.
VISION INC.
VISIONARY HOLDINGS CO., LTD.
VOYAGE GROUP, INC.
WirelessGate, Inc.
YELLOW HAT LTD.
YOSHINOYA HOLDINGS CO., LTD.
YUMESHIN HOLDINGS CO., LTD.
Yume no Machi Souzou Iinkai Co., Ltd.
Yushiro Chemical Industry Co., Ltd.
ZAPPALLAS, INC.

Attention: If you would like to see companies you invest in on this list, ask them to become our client, or sponsor a report yourself.

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