SymBio Pharmaceuticals / 4582

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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 November 2019, the company had obtained approval for and launched Treakisym® (anticancer agent for hematologic malignancies) for the indications of relapsed or refractory low-grade NHL and MCL, untreated (first-line treatment) and relapsed or refractory low-grade NHL and MCL, and chronic lymphocytic leukemia (CLL). Treakisym® is listed 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®, rigosertib (anticancer agent for myelodysplastic syndromes) IV and oral formulations, and the antiviral drug brincidofovir.

Earnings

- FY12/18 sales were JPY3.8bn (+11.4% YoY). Product sales totaled JPY3.8bn (+10.6% YoY) and royalty revenue totaled JPY26mn (JPY0mn in FY12/17). The operating loss totaled JPY2.7bn (loss of JPY3.9bn). The company also reported a recurring loss of JPY2.7bn (loss of JPY4.0bn). Net loss was JPY2.7bn (loss of JPY4.0bn).
- In August 2019, SymBio announced a revision to its FY12/19 earnings forecast as a result of delayed shipments of Treakisym®. SymBio now forecasts FY12/19 sales of JPY3.1bn (-19.4% YoY), an operating loss of JPY3.8bn (operating loss of JPY2.7bn in FY12/18), a recurring loss of JPY3.9bn (recurring loss of JPY2.7bn), and a net loss of JPY3.9bn (net loss of JPY3.1bn).
- In its medium-term plan, with the aims of achieving sales growth and higher profit margins, SymBio projects sales of JPY11.3–11.8bn and a net income of JPY1.7–2.1bn in FY12/22. The company is reviewing these targets in light of the revision to its FY12/19 earnings forecast announced in August 2019 and intends to announce revised plan targets once it has confirmed the figures. The company expects higher sales from increased market penetration of Treakisym® for approved indications, as well as 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 Par.	FY12/19 Est.
Sales	**1,191**	**1,450**	**1,883**	**1,955**	**1,532**	**1,955**	**1,933**	**2,368**	**3,444**	**3,836**	**3,092**
YoY	-26.9%	21.7%	29.8%	3.9%	-21.6%	27.6%	-1.1%	22.5%	45.4%	11.4%	-19.4%
Gross profit	**1,191**	**1,212**	**658**	**593**	**318**	**527**	**583**	**904**	**1,031**	**1,173**	
YoY	-26.9%	1.7%	-45.7%	-9.9%	-46.4%	65.6%	10.7%	55.1%	14.1%	13.7%	
GPM	100.0%	83.6%	35.0%	30.3%	20.8%	26.9%	30.2%	38.2%	29.9%	30.6%	
Operating profit	**-208**	**-613**	**-2,067**	**-1,700**	**-1,681**	**-1,303**	**-2,552**	**-2,127**	**-3,947**	**-2,656**	**-3,780**
YoY	-	-	-	-	-	-	-	-	-	-	-
OPM	-	-	-	-	-	-	-	-	-	-	-
Recurring profit	**-214**	**-638**	**-2,095**	**-1,729**	**-1,601**	**-1,110**	**-2,630**	**-2,317**	**-3,977**	**-2,749**	**-3,856**
YoY	-	-	-	-	-	-	-	-	-	-	-
RPM	-	-	-	-	-	-	-	-	-	-	-
Net income	**-218**	**-642**	**-2,105**	**-1,733**	**-1,605**	**-1,116**	**-2,632**	**-2,313**	**-3,978**	**-2,753**	**-3,859**
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	82,399	
EPS	-32.5	-59.3	-143.6	-90.6	-69.3	-36.3	-81.3	-58.8	-79.8	-41.4	-167.7
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	53.1	
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	4,821	
Total current assets	**4,218**	**4,213**	**7,178**	**5,421**	**7,634**	**7,290**	**4,827**	**6,685**	**4,037**	**6,038**	
Tangible fixed assets	13	22	17	14	9	49	53	75	47	57	
Investments and other assets	27	27	48	57	37	49	53	77	100	73	
Intangible fixed assets	2	1	13	11	8	66	52	42	69	71	
Total assets	**4,261**	**4,263**	**7,256**	**5,502**	**7,687**	**7,454**	**4,984**	**6,878**	**4,252**	**6,239**	
Accounts payable	-	1	309	330	-	306	320	322	604	726	
Short-term debt	-	-	-	-	-	-	-	-	-	-	
Total current liabilities	**205**	**178**	**646**	**599**	**251**	**488**	**551**	**942**	**1,011**	**1,336**	
Long-term debt	-	-	-	-	-	-	-	-	-	-	
Total fixed liabilities	**2**	**2**	**5**	**4**	**3**	**2**	**2**	**451**	**1**	**1**	
Total liabilities	**207**	**180**	**651**	**602**	**254**	**490**	**552**	**1,394**	**1,013**	**1,338**	
Net assets	**4,054**	**4,083**	**6,606**	**4,900**	**7,433**	**6,964**	**4,432**	**5,485**	**3,239**	**4,902**	
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	-2,325	
Cash flows from investing activities	-4	-116	-117	-411	-1,332	314	1,489	-44	-78	-26	
Cash flows from financing activities	2,963	663	4,611	-1	4,057	544	-3	3,658	1,164	4,272	
Financial ratios											
ROA (RP-based)	-7.6%	-15.1%	-36.5%	-27.2%	-24.3%	-14.7%	-42.3%	-39.0%	-71.5%	-52.5%	
ROE	-8.1%	-15.8%	-39.4%	-30.2%	-26.3%	-15.8%	-48.3%	-50.4%	-102.6%	-77.8%	
Equity ratio	95.1%	95.8%	91.0%	89.1%	96.7%	93.4%	88.9%	79.7%	76.2%	78.6%	

Source: Shared Research based on company data
Note: Figures may differ from company materials due to differences in rounding methods.
Note: The company conducted a four-to-one reverse stock split in July 2019. Earnings per share in the FY12/19 earnings forecast reflects the effect of the reverse stock split.

Recent updates

Highlights

On **December 2, 2019**, Shared Research updated the report following interviews with SymBio Pharmaceuticals Ltd.

On **November 12, 2019**, the company announced that it would bring forward the exercise date of its 47th stock acquisition rights and that it had concluded an amendment agreement to this effect.

The company decided to instruct the bringing forward of the exercise date of its 47th stock acquisition rights with exercise price revision clauses, which were issued in April 2018 by third-party allotment to EVO FUND, under the terms of the third-party allotment agreement between the two companies. On the same day, the company and EVO FUND also concluded an agreement to amend the third-party allotment agreement. As a result of concluding the amendment agreement, the company can specify the date on which the rights can be exercised and the start date of the full commitment period.

The company's business is progressing more or less on track to turn profitable in FY12/21, but profits in FY12/19 will likely fall short of the company forecast at the time the 47th stock acquisition rights were issued. The expected shortfall is due to delayed product shipments caused by defects discovered in lyophilized injection agents imported from Astellas Deutschland GmbH. The company must purchase and build up inventory in order to begin sales of its own products in FY12/20. It also decided that it needed additional funds to in-license (on a global license agreement) and develop brincidofovir

Name of issue: SymBio Pharmaceuticals 47th stock acquisition rights

- Number of rights issued: 15,000,000
- Number of shares issued: 3,750,000
- Date of instruction to bring forward exercise date: November 12, 2019
- Exercise start date: November 14, 2019

On **November 8, 2019**, the company announced earnings results for Q3 FY12/19; see the results section for details.

On **November 5, 2019,** the company announced that primary endpoints (response rates) were met in its phase III study of the anticancer drug Treakisym® targeting relapsed/refractory diffuse large B-cell lymphoma ("r/r DLBCL").

The company stated that the results of the phase III study, the objective of which was to confirm the efficacy and safety of Treakisym used in combination with rituximab (bendamustine-rituximab combination therapy or BR therapy) for treatment of patients with r/r DLBCL, exceeded expected primary endpoints for response rate. The company will compile the results of this study's final analyses and plans to submit an application for the treatment's approval in 1H FY12/20.

On **October 25, 2019,** the company announced an update on the global phase III INSPIRE study of the anticancer agent rigosertib, and on future clinical trial plans.

On October 24, 2019, the licensor for the anticancer agent rigosertib sodium (hereafter, rigosertib), Onconova Therapeutics, Inc. (hereafter, Onconova), provided an update on the global phase III INSPIRE study of rigosertib, and on future clinical trial plans.

The INSPIRE trial is investigating the efficacy of rigosertib in higher-risk myelodysplastic syndrome ("HR-MDS") patients who had progressed on, failed to respond to, or relapsed after previous treatment with a hypomethylating agent, the standard of care for MDS (such patients are described as "HMA-refractory"). Onconova is approaching enrollment of 90% of the required 360 patients for the INSPIRE trial, and anticipates reporting top-line data in the first half of 2020.

Regarding the development of oral rigosertib, as a result of Onconova's consultations with the FDA on SPA (Special Protocol Assessment), Onconova plans to conduct a randomized controlled phase II trial with a control arm of single agent azacitidine for the continued development of oral rigosertib plus azacitidine in untreated HR-MDS patients.

On **October 1, 2019,** the company announced the signing of an exclusive global license agreement for the highly active antiviral drug, brincidofovir (BCV).

On October 1, SymBio said it had entered into a license agreement with US-based Chimerix Inc., for the purpose of acquiring global rights for the antiviral drug, brincidofovir (BCV). Under the terms of the agreement, Chimerix has granted SymBio exclusive worldwide rights to develop, manufacture, and commercialize BCV in all human indications, excluding the prevention and treatment of smallpox. Acquiring the exclusive worldwide license to BCV will aid SymBio in its transition into a global business.

> Chimerix Inc. (NASDAQ: CMRX) is headquartered in the US state of North Carolina, and has developed two types of nucleotide compounds using its own lipid technology. Chimerix was developing brincidofovir (CMX001) as the world's first drug with strong and broad activity against viral diseases (such as AdV, BKV, EBV, and HHV-6) for which there is currently no effective treatment. In order to concentrate on businesses centering on the oncology field, however, Chimerix out-licensed a global license excluding smallpox to SymBio in September 2019.

Based on BCV's strong data, SymBio will initially target treatment of viral hemorrhagic cystitis (vHC) and HHV-6 encephalitis (HHV-6) after allogeneic hematopoietic stem cell transplantation and kidney transplantation, to address critically underserved therapeutic areas. Although other antiviral drugs are currently used for these diseases, there is a long-standing and significant medical need for a treatment that is both effective and safe.

BCV is a lipid conjugate of cidofovir (CDV), which is an antiviral drug already approved and marketed in the US and the EU, but unapproved in Japan. As BCV has not only higher antiviral activity, but also a superior safety profile in comparison with CDV, the company expects BCV to be an effective treatment against a wide spectrum of infectious diseases caused by DNA viruses, including herpes viruses (including CMV), adenovirus, BK virus, papilloma virus, and smallpox virus. BCV's innovative mechanism of action, which is based on conjugating a lipid chain of specified length to a CDV base, dramatically improves efficiency of uptake into the cells where BCV is converted into a direct-acting agent in the cell, resulting in high antiviral effect. Furthermore, BCV is easy to use due to its low risk of nephrotoxicity, which is a serious side effect of CDV. This makes BCV a novel highly active anti-multiviral drug.

On **September 26, 2019,** the company announced filing of an approval application for the RTD formulation of Treakisym®.

The company applied for approval to manufacture and market the ready-to-dilute (RTD) liquid formulation of Treakisym®. If approved, the RTD formulation can be used for the indication of relapsed or refractory diffuse large B-cell lymphoma (DLBCL), for which clinical trial is currently under way, in addition to all previously approved indications. The company plans to launch the product in Q1 FY12/21 after obtaining approval.

On **September 25, 2019**, Shared Research updated the report following interviews with the company.

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

Trends and outlook

Quarterly trends and results

Cumulative	FY12/18				FY12/19				FY12/19	
(JPYmn)	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	% of FY	FY Est.
Sales	888	1,928	3,032	3,836	1,611	2,005	2,008		64.9%	3,092
YoY	2.1%	8.0%	25.5%	11.4%	81.4%	4.0%	-33.8%			-19.4%
Gross profit	250	573	924	1,173	609	529	563			
YoY	4.4%	12.4%	37.0%	13.7%	144.0%	-7.7%	-39.1%			
GPM	28.1%	29.7%	30.5%	30.6%	37.8%	26.4%	28.0%			
SG&A expenses	964	1,898	2,832	3,829	1,205	2,545	4,099			
YoY	26.1%	8.7%	-32.3%	-23.1%	25.0%	34.1%	44.8%			
SG&A ratio	108.5%	98.4%	93.4%	99.8%	74.8%	126.9%	204.1%			
Operating profit	-715	-1,325	-1,908	-2,656	-596	-2,015	-3,536		-	-3,780
YoY	-	-	-	-	-	-	-			-
OPM	-	-	-	-	-	-	-			-
Recurring profit	-749	-1,378	-1,938	-2,749	-616	-2,069	-3,642		-	-3,856
YoY	-	-	-	-	-	-	-			-
RPM	-	-	-	-	-	-	-			-
Net income	-760	-1,389	-1,941	-2,753	-617	-2,070	-3,641		-	-3,859
YoY	-	-	-	-	-	-	-			-
Net margin	-	-	-	-	-	-	-			-

Quarterly	FY12/18				FY12/19			
(JPYmn)	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Sales	888	1,040	1,104	803	1,611	394	3	
YoY	2.1%	13.5%	75.1%	-21.8%	81.4%	-62.2%	-99.7%	
Gross profit	250	324	351	249	609	-79	33	
YoY	4.4%	19.5%	113.0%	-30.3%	144.0%	-	-90.5%	
GPM	28.1%	31.1%	31.8%	31.0%	37.8%	-	-	
SG&A expenses	964	934	934	997	1,205	1,340	1,555	
YoY	26.1%	-4.9%	-61.7%	25.4%	25.0%	43.4%	66.5%	
SG&A ratio	108.5%	89.8%	84.6%	124.2%	74.8%	340.4%	-	
Operating profit	-715	-610	-583	-749	-596	-1,419	-1,521	
YoY	-	-	-	-	-	-	-	
OPM	-	-	-	-	-	-	-	
Recurring profit	-749	-629	-560	-811	-616	-1,453	-1,573	
YoY	-	-	-	-	-	-	-	
RPM	-	-	-	-	-	-	-	
Net income	-760	-629	-552	-812	-617	-1,453	-1,571	
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	FY12/18				FY12/19			
(JPYmn)	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
SG&A expenses	964	1,898	2,832	3,829	1,205	2,545	4,099	
YoY	26.1%	8.7%	-32.3%	-23.1%	25.0%	34.1%	44.8%	
R&D expenses	416	839	1,293	1,833	472	963	1,972	
YoY	5.3%	-0.1%	-52.3%	-39.3%	13.4%	14.8%	52.5%	
SG&A expenses excl. R&D	548	1,059	1,539	1,996	733	1,582	2,127	
YoY	48.5%	16.9%	4.6%	1.8%	33.8%	49.3%	38.3%	

Quarterly	FY12/18				FY12/19			
(JPYmn)	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
SG&A expenses	964	934	934	997	1,205	1,340	1,555	
YoY	26.1%	-4.9%	-61.7%	25.4%	25.0%	43.4%	66.5%	
R&D expenses	416	423	454	540	472	491	1,009	
YoY	5.3%	-4.9%	-75.7%	76.0%	13.4%	16.2%	122.1%	
SG&A expenses excl. R&D	548	511	479	458	733	849	546	
YoY	48.5%	-4.8%	-15.2%	-6.4%	33.8%	66.0%	13.8%	

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

Q3 FY12/19 results

- Sales: JPY2.0bn (-33.8% YoY)
- Operating loss: JPY3.5bn (loss of JPY1.9bn in Q3FY12/18)
- Recurring loss: JPY3.6bn (loss of JPY1.9bn in Q3 FY12/18)
- Net loss: JPY3.6bn (loss of JPY1.9bn in Q3 FY12/18)

Cumulative Q3 sales fell YoY. By quarter, sales increased 81.4% YoY to JPY1.6bn in Q1 (Jan–Mar 2019), but fell 62.2% YoY to JPY394mn in Q2 (Apr–Jun 2019) and dropped again by 99.7% YoY to JPY3mn in Q3 (Jul–Sep 2019). As the company explained as its reason for earnings forecast revisions announced in August 2019, foreign matter contamination and appearance defects were discovered in lyophilized injection agents imported from Astellas Deutschland GmbH, a subsidiary of Astellas Pharma Inc. The extent of contamination and defects significantly exceeded limits permitted by quality standards stipulated in the supply agreement, and as a result, the initially scheduled shipment of Treakisym® 100mg vials to its domestic distributor Eisai was delayed.

Gross profit was JPY563mn (-39.1% YoY), with the GPM down 2.5pp YoY to 28.0%. By quarter, while gross profit jumped 144.0% YoY to JPY609mn and GPM rose 9.7pp YoY to 37.8% in Q1, gross profit plunged to -JPY79mn in Q2. The sharp decline in gross profit was attributed to weak sales in Q2, combined with a JPY188mn loss on valuation of inventories due to quality defects found in some batches of Treakisym® 100mg. In Q3, gross profit declined 90.5% YoY to JPY33mn.

SG&A expenses rose 44.8% YoY to JPY4.1bn and R&D expenses increased 52.5% YoY to JPY2.0bn. This included upfront payments for new antiviral drug candidate brincidofovir, and expenses for conducting clinical trials of intravenous and oral formulations of Treakisym® and rigosertib. Excluding R&D expenses, SG&A expenses increased by 38.3% YoY to JPY2.1bn.

As a result, operating loss, recurring loss, and net loss widened YoY.

Major progress in cumulative Q3 FY12/19 was as follows:

- In November 2019, the company announced that in the phase III study of the anticancer drug Treakisym® administered in combination with rituximab (BR therapy) targeting relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL), the response rate, which was the primary endpoint of the study, exceeded expectations. The company plans to compile final analysis results of the study and apply for approval during 1H FY12/20.
- In October 2019, Onconova Therapeutics, Inc. announced that it was approaching enrollment of 90% of the target 360 patients for its INSPIRE trial evaluating intravenous formulation of rigosertib in higher-risk myelodysplastic syndrome (MDS) patients who had failed to respond to or relapsed after previous treatment with a hypomethylating agent, the current standard of care for MDS, and that it planned to report primary endpoint results of the study during 1H 2020. Further, regarding the oral formulation of rigosertib, Onconova announced that based on the result of its consultation with the FDA on Special Protocol Assessment (SPA), it would consider conducting a phase II clinical trial targeting untreated higher-risk MDS patients. The purpose of the trial would be to compare the combination therapy of rigosertib and azacitidine with the azacitidine monotherapy.
- In October 2019, the company entered a global license agreement with the US-based Chimerix Inc. to acquire exclusive worldwide rights to the antiviral drug brincidofovir. Under the terms of the agreement, Chimerix will grant global exclusive rights to develop, market, and manufacture brincidofovir for all indications except smallpox to the company.
- In September 2019, the company filed for manufacturing and marketing approval of the ready-to-dilute (RTD) liquid formulation of Treakisym®. The application covers all indications for which Treakisym® has already been approved; if the RTD formulation is approved for the additional indication of r/r DLBCL, which is currently in a clinical trial stage, it can also be used to treat r/r DLBCL. Once the company obtains approval for the RTD formulation, it plans to launch the product in Q1 FY12/21.

- In August 2019, SymBio announced a revision to its FY12/19 earnings forecast. In Q2 FY12/19, impurities and appearance defects were found in Treakisym® 100mg vials imported from Astellas Deutschland, which led to the company returning the whole batch. Thus only a fraction of the batches scheduled for shipment in 2Q FY12/19 onward can be shipped by the end of the year, with shipments possibly being delayed until Q1 FY12/20. The company therefore revised down its FY12/19 earnings forecast.
- In June 2019, the US Food and Drug Administration (FDA) granted accelerated approval to polatuzumab vedotin-piiq, a CD79b-directed antibody-drug conjugate, in combination with bendamustine (product name: Treakisym®) and rituximab (BR therapy) for patients with relapsed or refractory DLBCL who are not eligible for transplant. Polatuzumab vedotin-piiq was discovered by Roche Group company Genentech and is being developed in Japan by Chugai Pharmaceutical, another member of the Roche Group.
- In 1H FY12/19, capital stock and capital surplus each increased by JPY1.3bn YoY, reflecting proceeds from the issuance of shares resulting from exercise of the 46th stock acquisition rights.
- In April 2019, the first patient was enrolled in the clinical trial of the liquid formulation of Treakisym® (rapid infusion [RI] formulation), whose primary goal was to confirm safety of the drug.
- In March 2019, the company obtained approval to partially revise the marketing approval of anticancer drug Treakisym® as a pretreatment agent in antigen-specific T cell infusion therapy. This enabled the use of Treakisym® as a pretreatment agent for the chimeric antigen receptor T-cell (CAR-T) therapy Kymriah® intravenous infusion.

Introduction of new pipeline candidate

SymBio concluded an exclusive global license agreement with Chimerix Inc. for the antiviral drug brincidofovir (SyB V-1901, hereafter BCV)*[1]. The company acquired exclusive global rights to develop, manufacture, and market BCV for all diseases except smallpox.

The company will initially develop BCV for treatment of viral hemorrhagic cystitis (vHC)*[2] and HHV-6 encephalitis*[3] occurring after hematopoietic stem cell and kidney transplantation, which have high unmet medical demand. The company also looks to expand its business in Europe, the US and Asia (including China), where organ transplant markets are large. It will also consider forming partnerships that take advantage of regional characteristics of these target diseases. The company will explore all options for maximizing business value, including the strategic utilization of wholly-owned subsidiary SymBio Pharma USA, Inc. established in May 2016.

1. Brincidofovir (BCV) has a structure in which cidofovir (CDV, an antiviral drug already approved and marketed in the US and Europe but not approved in Japan) is bound to a lipid chain (hexadecycloxypropyl, HDP). It is absorbed into the lipid bilayer membrane and transferred into cells, where the bound lipid chain (HDP) is metabolized and separated from the structure by intracellular phospholipases. This process generates an activator (CDV diphosphate [CDV-PP]) that is retained in the cells for a long period of time, raising the compound's antiviral activity. Furthermore, BCV avoids nephrotoxicity, a fundamental issue plaguing CDV, since HDP conjugation prevents the accumulation of the compound in renal tubular epithelial cells through organic anion transporter 1 (OAT 1) and CDV is released at low levels into the bloodstream.

2. Viral hemorrhagic cystitis (vHC): Among viral infections that frequently occur following hematopoietic stem cell transplantation, adenovirus infections causing hemorrhagic cystitis are particularly refractory in nature. When severe, they can cause disseminated infection and become fatal. Cases of adenovirus spreading to the kidney and causing kidney failure and ultimately death have been reported. These infections are especially likely to occur in transplantation between unrelated donors and in umbilical cord blood transplantation, which are relatively common in Japan. The infections are likely to be refractory, as they are further complicated by the length of time required for reconstruction of the immune system. Drugs currently used in treatment, including cidofovir (CDV), are either unapproved or off-label in Japan.

3. HHV-6 encephalitis: HHV-6 (Human Herpesvirus 6) is the sixth human herpesvirus to be discovered. It reactivates in 30–70% of patients after allogenic hematopoietic stem cell transplantation and can cause HHV-6 encephalitis. Most cases of HHV-6 encephalitis develop within 2–6 weeks after transplantation, most frequently in the third week after transplantation. It is characterized by the three major symptoms of impaired memory, disordered consciousness, and convulsions, which in typical cases gradually appear in the same order (convulsions occur in 30–70% of patients). In rapidly progressing cases, which are not uncommon, neurological symptoms worsen by the hour, often requiring respirator management for repeated convulsions and respiratory depression. The conditions of HHV-6 encephalitis patients often deteriorate rapidly over a short period of time, making

early treatment important. According to guidelines edited and issued by the Japan Society for Hematopoietic Cell Transplantation (February 2018), the first-line drugs are foscarnet (FOS) and ganciclovir (GCV), followed by the second-line drug cidofovir (CDV). CDV is not the preferred first-line drug due to nephrotoxicity and because it transfers poorly into cerebrospinal fluid (CSF). All three of these drugs have been found to be effective in vitro, but no trials have been conducted yet to confirm their clinical efficacy in patients with HHV-6 encephalitis.

Domestic

Preparations for in-house sales organization begin

The business alliance agreement between SymBio and Eisai Co., Ltd. under which Eisai acts as a sales agent expires in December 2020. SymBio started to build an in-house sales organization for Treakisym® in the domestic market in October 2018. Key management priority is to move into the black in FY12/21 and ongoing profit growth thereafter. The company is therefore laying the groundwork for a shift to an internal sales organization to drive future business development.

The company increased Treakisym® sales representatives and conducted training needed to form the core of its in-house marketing network. Information provision activities were started from July 2019 by the Treakisym® sales representatives dispatched to each region to promote the shift to a nationwide operation with close local ties. The company also made steady progress with preparation of infrastructure such as logistics, distribution, and information systems.

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 untreated low-grade non-Hodgkin's lymphoma and mantle cell lymphoma (marketing approval obtained in December 2016), refractory or relapsed low-grade non-Hodgkin's lymphoma and mantle cell lymphoma (October 2010), and chronic lymphocytic leukemia (August 2016).

As a result of additional indications, Treakisym® is steadily increasing its market share in the area of first-line treatment in medical settings 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, which applies to all of the approved indications. This has seen Treakisym® establish its position as a standard treatment for lymphatic cancer. According to the company, market share in the area of first-line treatment increased to 55%.

In addition to the above three approved indications, the company is conducting a phase III clinical trial for the fourth indication of relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL), and the trial is progressing well with an aim to obtain approval. In response to strong medical needs, the company began a phase III clinical trial in August 2017. With the enrollment of the first patient in January 2018, the company made steady progress and completed enrollments in April 2019. The observational period for all patients (Last Patient Last Visit, LPLV) was completed in September 2019. Results of the trial indicated that the primary endpoint of response rate exceeded initial expectations. Going forward, the company will prepare for the approval filing, projected for Q2 2020.

SymBio is targeting a transition to Treakisym® liquid formulation (RTD and RI formulations), for which it concluded an exclusive licensing agreement in Japan with Eagle Pharmaceuticals (based in New Jersey, US) in September 2017. The company has already consulted with PMDA and filed for approval of the RTD formulation in September 2019 with an eye towards commercialization by Q1 2021. SymBio launched clinical trials for the RI formulation in November 2018 primarily to confirm safety, and has made steady progress with patient enrollments since enrolling the first patient in April 2019, having enrolled 26 patients as of end October 2019. Liquid formulations of Treakisym® will offer significant value added (reduced burden) to patients and healthcare professionals, and liquid formula patent protection makes it possible to extend the product life of Treakisym® until 2031.

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 new anti-CD20 antibodies as well. This will allow combination therapy with 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. In March 2019, the company obtained approval for the partial revision to its application concerning the use of Treakisym® as a pretreatment agent in tumor-specific T cell infusion therapy. This will allow Treakisym® to be used as a pretreatment agent for Kymriah® intravenous infusion, which was approved as the first chimeric antigen receptor T-cell (CAR-T) therapy in Japan and listed on the NHI drug price list in May 2019.

To reinforce the position of Treakisym® at the core of its business to strengthen its business foundation, SymBio is looking at the possibility of developing Treakisym® for other disorders such as solid tumors and autoimmune diseases. 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 performed a preclinical study to verify the efficacy of the oral formulation of Treakisym® in treating systemic lupus erythematosus (SLE), a form of autoimmune disease. The company is currently compiling study results and after evaluating the findings will consider the next stage of this research project (including clinical trials).

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 (48 patients enrolled as of October 2019). 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. In October 2019, Onconova announced that it had reached 90% of its target of enrolling 360 patients worldwide. The company plans to report top-line (primary endpoint) results in 1H 2020. Based on these trial 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 has completed 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, enrolled the first patients in October 2017, and completed patient enrollment in June 2019. After completing the phase I trials, the company will consider phase I clinical trials for rigosertib used in combination with azacitidine, participate in global clinical trials of the drug used in combination with azacitidine as first-line treatment for higher-risk MDS currently planned by Onconova, and apply for approval of the oral formulation of the drug in Japan at the same time as in the US and Europe. In December 2018, Onconova submitted a Special Protocol Assessment (SPA) request to the US Food and Drug Administration (FDA) to speed up the approval review for the global trials. Onconova announced in October 2019 that it was considering a phase II controlled study comparing rigosertib + azacitidine to azacitidine stand-alone therapy for untreated patients with higher-risk MDS. 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 learned of an event 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 company initiated an arbitration against The Medicines Company, 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. SymBio argued that The Medicine Company's failure to provide sufficient assurance to the company regarding the performance of obligations under on the license agreement in light of its decision to suspend and withdraw from

business activities relating to SyB P-1501in the European and US markets was a material breach of the license agreement. Arbitration proceedings against The Medicines Company are still ongoing.

Overseas

The company marketed SyB L-0501 in South Korea, Taiwan, and Singapore, and product sales were in line with the company's plans.

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

Full-year company forecasts

	FY12/18			FY12/19		
(JPYmn)	1H Act.	2H Act.	FY Act.	1H Act.	2H Est.	FY Est.
Sales	1,928	1,907	3,836	2,005	1,087	3,092
Gross profit	573	600	1,173	529	450	979
GPM	29.7%	31.4%	30.6%	26.4%	41.4%	31.7%
SG&A expenses	1,898	1,931	3,829	2,545	2,214	4,759
SG&A ratio	98.4%	101.3%	99.8%	126.9%	203.7%	153.9%
R&D expenses	839	994	1,833	963	1,066	2,029
Excluding R&D expenses	1,059	937	1,996	1,582	1,148	2,730
Operating profit	-1,325	-1,331	-2,656	-2,015	-1,765	-3,780
OPM	-	-	-	-	-	-
Recurring profit	-1,378	-1,371	-2,749	-2,069	-1,787	-3,856
RPM	-	-	-	-	-	-
Net income	-1,389	-1,364	-2,753	-2,070	-1,789	-3,859
Net margin	-	-	-	-	-	-

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

Earnings outlook

- ▷ Sales: JPY3.1bn (+16.4% YoY)
- ▷ Operating loss: JPY3.8bn (loss of JPY2.7bn in FY12/18)
- ▷ Recurring loss: JPY3.9bn (loss of JPY2.7bn in FY12/18)
- ▷ Net loss: JPY3.9bn (loss of JPY2.8bn in FY12/18)

In August 2019, SymBio announced a revision to its FY12/19 earnings forecast, with downward revisions of JPY1.4bn for sales, JPY193mn for operating loss, JPY244mn for recurring loss, and JPY243mn for net loss.

Reasons for revision

SymBio imports lyophilized Treakisym® for injection from Astellas Deutschland GmBH (consolidated subsidiary of Astellas Pharma Inc.), which it supplies to the market for sale in Japan through its business partner, Eisai Co., Ltd. after quality inspection and packaging. In Q2 FY12/19, impurities and appearance defects were found in Treakisym® 100mg vials imported from Astellas Deutschland, which led to the company returning the whole batch. Thus only a fraction of the batches scheduled for shipment in 2Q FY12/19 onward can be shipped by the end of the year, with shipments possibly being delayed until Q1 FY12/20. The company therefore revised down its FY12/19 earnings forecast. Lower operating profit stems from the sales decline, but the impact on operating profit is mitigated by SG&A expenses (including R&D expenses) being revised down by JPY294mn from JPY5.1bn to JPY4.8bn.

At the start of FY12/19, SymBio set a Treakisym® sales target of JPY10.1bn on a drug price basis, amounting to YoY sales growth of 18.8%. In FY12/18, too, SymBio had anticipated full-year sales of JPY10.1bn, but sales on a drug price basis only came to JPY8.5bn, largely because Treakisym® distributor Eisai adopted a greater focus on sales of its own products. Against this backdrop, SymBio finished FY12/18 with ten highly specialized product managers for Treakisym®, up from five as of December 2017. In FY12/19 it plans to take the number of Treakisym® managers up to 20.

As noted above, SymBio revised down its FY12/19 sales forecast to call for a YoY decline, as in Q2 impurities and appearance defects were found in Treakisym® 100mg vials imported from Astellas Deutschland, which led to the company returning the whole batch. According to SymBio, though, business (including pipeline) progress otherwise has been in line with plan, so there is no change in the company's long-term outlook.

SymBio aims to further promote uptake of Treakisym® as first-line treatment of low-grade non-Hodgkin's lymphoma (NHL), with a view to raising market share to 70% as of end-FY12/20 and 75% as of end-FY12/21. Shared Research expects the following factors to contribute to market share expansion, alongside growth in Treakisym® manager numbers.

- 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 mantle cell lymphoma (MCL) in Japan prior to December 2016. In July 2018, Treakisym® was newly included as a standard treatment option for low-grade NHL and MCL 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 NHL. These findings were presented at the American Society of Hematology Annual Meeting in December 2012 (see the Business section).

SymBio forecasts SG&A expenses of JPY4.8bn (+24.3% YoY).

- The company expects R&D expenses of JPY2.0bn (+10.7% YoY). It plans to continue developing Treakisym® for relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL) and liquid formulations of Treakisym® (RTD and RI formulations), Treakisym® (oral), and oral and intravenous rigosertib products.
- The company forecasts SG&A expenses excluding R&D at JPY2.7bn (+36.8% YoY). With the increase in product managers it expects a rise in personnel expenses and higher expenses due to more activities. As indicated earlier, SymBio plans to increase the number of product managers from 10 to 20, with a view to gaining market share for Treakisym® and building an in-house sales structure in FY12/20. The company also anticipates an increase in fees and commissions paid for expert consultations.

The main pipeline development plans are as follows.

Treakisym®

- For r/r DLBCL, in FY12/19 the company plans to continue enrolling patients for phase III clinical trials already underway, with the aim of filing for approval in Q2 FY12/20
- For Treakisym® in-licensed from Eagle Pharmaceuticals, SymBio is preparing to file for approval of the RTD formulation (in Q3 FY12/19) and progressing with clinical trials of the RI formulation mainly to confirm safety (under way since November 2018, with 36 patients enrolled)
- The company has already launched phase I clinical trials for Treakisym® (oral)

Oral and intravenous rigosertib products

- SymBio is continuing to develop intravenous rigosertib formulation, and is enrolling patients in Japan as part of global phase III clinical trials
- For oral rigosertib, following confirmation of safety in domestic phase I clinical trials for single drug applications which is currently enrolling patients, SymBio is preparing for early participation in global phase III trials of rigosertib azacitidine combination therapy that Onconova Therapeutics is planning

Long-term outlook

Medium-term plan (FY12/19–FY12/22)

When it released its FY12/18 results, SymBio also announced a four-year medium-term plan for FY12/19 through FY12/22. The main goals of the medium-term plan are to build an in-house sales structure, grow sales of Treakisym® from already approved indications, expand indications for Treakisym®, and extend the product lifecycle for Treakisym®.

- Build in-house sales structure: The business alliance agreement with Eisai expires in December 2020, and the company has been making preparations to sell Treakisym® in-house from the start of 2021, after the agreement expires. To prepare for the start of in-house sales and the later launch of rigosertib IV formulation, SymBio plans to increase the number of medical representatives as necessary, build a sales and marketing organization specializing in the area of blood cancers, and set up a sophisticated and dedicated training system by 1H FY12/20.
- Grow sales of Treakisym® from already approved indications: The company seeks to increase market share to 70% by the end of FY12/20 by further promoting penetration in first-line treatment of low-grade non- Hodgkin's lymphoma.
- Expand indications for Treakisym®: SymBio aims to complete the phase III clinical trial for the indication of relapsed or refractory diffuse large B-cell lymphoma, with the aim of filing a new drug application in Q2 FY12/20 and launching in Q3 FY12/21.
- Extend the product lifecycle for Treakisym®: The company looks to launch the RTD formulation in Q1 FY12/21 and the RI formulation in 1H FY12/22, proceeding 90% of the way toward a switch from the current lyophilized powder formulation to a liquid formulation by the end of 2021 and 100% by the end of 2022. It aims to achieve an annual average switch rate of 60% in 2021.

Earnings objectives laid out in medium-term plan

Under the action plan outlined above, SymBio seeks to achieve profitability in FY12/21 and realize sustainable profit growth thereafter, with the following as earnings objectives. The company is reviewing its medium-term plan targets in light of the revised FY12/19 earnings forecast announced in August 2019, and plans to announce revised targets after confirming the figures. The below discussion of the medium-term plan only reflects the revisions made to company forecasts for FY12/19.

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®.

Medium-term plan

(JPYmn)	FY12/18 Act.	FY12/19 Est.	FY12/20 MTP	FY12/21 MTP	FY12/22 MTP
Sales	3,810	3,092	3,282	9,132	11,282–11,809
Operating profit (losses)	-2,656	-3,780	-5,180	1,225	2,084–2,464
Recurring profit (losses)	-2,749	-3,856	-5,224	1,181	2,040–2,420
Net income (losses)	-2,753	-3,859	-5,228	1,005	1,736–2,060

Source: Shared Research based on company data

Sales targets in medium-term plan (FY12/19–FY12/22)

SymBio expects product sales of Treakisym® to account for the bulk of sales. The company looks to grow Treakisym® sales by achieving greater market penetration in first-line treatment of low-grade non-Hodgkin's lymphoma, transitioning to an in-house sales structure, and expanding indications to include relapsed or refractory diffuse large B-cell lymphoma (DLBCL).

Greater market penetration in first-line treatment of low-grade non- Hodgkin's lymphoma

In December 2016, Treakisym® was approved in Japan for the additional indication of first-line treatment of low-grade non-Hodgkin's lymphoma (NHL), and in Q3 FY12/18 Treakisym® accounted for 56% of drugs used for the first-line treatment of low-grade NHL. On an NHI drug reimbursement price basis, Treakisym® sales have increased from JPY4.8bn in FY12/16 to JPY8.5bn in FY12/18. According to SymBio, the indication of first-line treatment of low-grade NHL has accounted for most of that JPY3.7bn increase.

SymBio aims to further promote uptake of Treakisym® as first-line treatment of low-grade non-Hodgkin's lymphoma, with a view to raising market share to 70% as of end-FY12/20. The following factors are seen contributing to market share expansion.

- ▷ 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 mantle cell lymphoma (MCL) in Japan prior to December 2016. In July 2018, Treakisym® was newly included as a standard treatment option for low-grade NHL and MCL 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 NHL. These findings were presented at the American Society of Hematology Annual Meeting in December 2012 (see the Business section).
- ▷ SymBio plans to increase the number of Treakisym® product managers from 10 in FY12/18 to 20 in FY12/19, and 60 in FY12/20, in doing so contributing to further market penetration for Treakisym®.

Transition to in-house sales structure

SymBio has entrusted Treakisym® sales to Eisai until end-FY12/20. During this period, product shipments to Eisai are being booked as sales. However, Eisai's exclusive sales period expires in FY12/20, and from FY12/21 SymBio will switch to selling Treakisym® in-house. Up to and including FY12/20, Shared Research assumes that the price of shipments to Eisai will be around 50% of the NHI drug price. With the transition to an in-house sales structure in FY12/21, though, Shared Research thinks the price that SymBio charges to wholesalers will rise to roughly 90% of the NHI drug price. Thus even if volume remains largely unchanged, the company expects higher selling prices to drive sharp YoY sales growth in FY12/21.

As noted, the company plans to shift to its own sales organization and switch product shipments from Eisai to pharmaceutical wholesalers in FY12/21. In the run-up to this it will be necessary to reduce Eisai's inventories toward the end of FY12/20. Sales of Treakisym® based on an NHI drug price should remain solid, reflecting actual market demand, but SymBio plans to stop shipping to Eisai with a target date of end-1H FY12/20. It expects FY12/20 sales to decline by a commensurate amount.

Additional indication of relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL)

The company plans to seek approval of Treakisym® for the additional indication of r/r DLBCL in Q2 FY12/21. It aims to commence sales of Treakisym® for this indication in Q3 FY12/21, with a view to growing Treakisym® product sales in FY12/21 onward. The company says that its sales target range for FY12/22 is based on an estimated market penetration rate due to the additional indication.

As reference for the anticipated impact of adding the indication of r/r DLBCL, 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, for a total of 16,303. For these indications, SymBio targets FY12/19 sales of JPY10.1bn on an NHI drug price basis. By comparison, the company estimates that the number of Japanese patients with r/r DLBCL is 18,672.

Gross profit under medium-term plan

Based on historical performance, Shared Research estimates a gross profit margin of about 30% for Treakisym® shipments to Eisai. As outlined earlier, from FY12/21 SymBio will conduct sales of Treakisym® in-house rather than entrusting them to Eisai. With this, the company will be shipping Treakisym® to pharmaceutical wholesalers instead of to Eisai. The gross profit earned thus far will remain, but will be augmented by the gross profit that hitherto had gone Eisai's way (difference between the procurement price

paid by Eisai and the price on shipments from Eisai to wholesalers). Shared Research believes that the transition to in-house sales will lift SymBio's gross profit margin to 60–70%.

Shared Research also sees potential for SymBio to further alter the gross profit margin by procuring Treakisym® from a different source. The company procures Treakisym® in lyophilized powder form from Astellas Deutschland GmbH, but procures the RTD and RI formulations from Eagle Pharmaceuticals. SymBio looks to launch the RTD formulation in Q1 FY12/21 and the RI formulation in 1H FY12/22, proceeding 90% of the way toward a switch from the current lyophilized powder formulation to a liquid formulation by the end of 2021 and 100% by the end of 2022.

SG&A expenses under medium-term plan

The company has broken down SG&A expenses into primarily R&D spending and other SG&A expenses.

R&D expenses

In its medium-term plan, the company has calculated R&D expenses based on the latest development plans for its existing pipeline comprising Treakisym® and rigosertib IV and oral formulations. While paying due regard to the impact on FY12/21 earnings, SymBio also will continue to search for, evaluate, and consider in-licensing rights to other promising drug candidates, in order to ensure long-term growth opportunities.

- The company forecasts R&D expenses of JPY2.0bn (+10.7% YoY) in FY12/19. It plans to continue developing Treakisym® for relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL), as well as liquid formulations of Treakisym® (RTD and RI formulations), Treakisym® (oral), and oral and intravenous rigosertib products.
- In FY12/20 the company looks for R&D expenses to increase YoY, as it expects to book clinical trial expenses for the RI formulation of Treakisym® as well as oral rigosertib. Also, SymBio aims to win approval for the RTD formulation of Treakisym® in Q4 FY12/20, at which point it expects to make a milestone payment.
- From FY12/21, the company expects R&D expenditure to decrease in comparison with FY12/20. Clinical trial expenses for the RI formulation of Treakisym® as well as oral rigosertib should decrease. For FY12/22, SymBio is targeting an operating profit range of JPY2.1–2.5bn; this is because its sales target also is a range, and there is a possibility that in-licensing drug candidates will give rise to one-time payments and higher R&D expenses.

Other SG&A expenses

Other SG&A expenses comprise primarily Treakisym® marketing, production and distribution, business development, and management related expenses. SymBio is factoring in expenses associated with building and operating its own sales organization from FY12/19 onward ahead of the expiration of Eisai's exclusive sales period at end-FY12/20 and move to sell Treakisym® in-house from FY12/21. It forecasts an increase primarily in personnel expenses due to a higher medical representative headcount and higher expenses due to more activities.

- For FY12/19, the company forecasts SG&A expenses excluding R&D of JPY2.7bn (+36.8% YoY). It forecasts an increase primarily in personnel expenses due to a higher medical representative headcount and higher expenses due to more activities. In FY12/18 the company increased the number of medical representatives to 10, and it plans a further rise to 20 in FY12/19.
- In FY12/20, Shared Research expects SG&A expenses excluding R&D to increase in comparison with FY12/19, largely because the company plans to increase the number of medical representatives to 60, from 20 in FY12/19. However, for about 30 of the 40 medical representatives that it plans to add in FY12/20, SymBio may make use of copromotion partners (collaborating with pharmaceutical company sales staff), and contract-based medical representatives specializing in oncology. The company also intends to allocate the bare minimum of necessary personnel in other parts of the organization.

Funding plans

In April 2018, the company decided to issue its 45th through 47th stock acquisition rights to secure funds needed to operate until it moves into the black in FY12/21. The proceeds were basically sufficient for its already in-licensed drug development

pipeline, creation of an in-house sales structure, and new in-licensing or M&A activity necessary to take advantage of long-term growth opportunities.

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 in-licensed new drug candidates after rigorously evaluating them.

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.

Products under development: Treakisym® (FD), Treakisym® (RTD and RI), rigosertib (IV and oral), and brincidofovir

Treakisym® (FD)

For patients that have developed resistance to other drugs, Treakisym® is safer and more efficacious than existing treatments. As outlined below, the company has gained approval in Japan for the indications of refractory or relapsed low-grade non-Hodgkin's lymphoma and mantle cell lymphoma, chronic lymphocytic leukemia, and first-line treatment of low-grade non-Hodgkin's lymphoma and mantle cell lymphoma.

- ▷ Refractory or relapsed low-grade non-Hodgkin's lymphoma and mantle cell lymphoma: After designation as an orphan drug (drug for the treatment of rare diseases), Treakisym® won marketing approval for this indication in October 2010.
- ▷ Chronic lymphocytic leukemia: SymBio received approval for this to be added as indication for Treakisym® in August 2016.
- ▷ First-line treatment of low-grade non-Hodgkin's lymphoma and mantle cell lymphoma: The company gained approval for this to be added as indication for Treakisym® in December 2016.

As of February 2019, phase III clinical trials for an additional indication of relapsed or refractory diffuse large B-cell lymphoma (DLBCL) 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. SymBio looks to gain approval for the RTD formulation in Q4 FY12/20 and win approval for and launch the RI formulation in FY12/22. With this, it aims to promote a switch in clinical settings from the current lyophilized powder formulation to RTD and RI formulations that lighten the workload for medical professionals, at the same time curtailing uptake of Treakisym® generics (filing for approval of generics will be possible from 2H 2020, although Shared Research believes that even if generics launch it will not be until around 2022). Because it has the exclusive rights to sell the RTD and RI formulations in Japan, SymBio will be able to extend the Treakisym®'s product lifecycle until 2031.

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. Based on these results, the company plans to apply for approval in Japan at the same time as in the US and Europe.

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 first-line treatment of higher-risk MDS that Onconova plans to launch.

Brincidofovir

Brincidofovir is an antiviral drug formed by conjugating a lipid chain (hexadecyloxypropyl, or HDP) of specified length to cidofovir (an antiviral drug already approved and marketed in the EU and the US, but not approved in Japan). It has a novel mechanism of action, which is attributed to its being a lipid conjugate, and can be taken up into cells with enhanced efficiency

compared to cidofovir (i.e., brincidofovir has higher cell membrane permeability). Once inside a cell, brincidofovir transforms into a direct-acting agent and inhibits viral replication, demonstrating high antiviral effect. It is also easy to use as it has a low risk of nephrotoxicity, which is a side effect of cidofovir, hence making brincidofovir a novel, highly active anti-multiviral drug. It is expected to become an effective treatment for a wide spectrum of infectious diseases caused by DNA viruses, including cytomegalovirus (CMV) and other herpes viruses, adenoviruses, BK virus, papillomaviruses, and smallpox virus.

In September 2019, SymBio entered an exclusive global license agreement with Chimerix Inc. for brincidofovir. As a result, the company acquired exclusive worldwide rights to develop, market, and manufacture brincidofovir for all indications except smallpox.

The company will initially develop brincidofovir for the indications of viral hemorrhagic cystitis (vHC) and HHV-6 encephalitis (HHV-6) after hematopoietic stem cell transplantation and kidney transplantation, areas with high unmet medical needs, with the goal of commercializing the product in Japan by mid 2020s.

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 FY12/19, the company expects a JPY3.6bn operating loss, JPY3.6bn recurring loss, and net loss of JPY3.6bn. Over the course of the medium-term plan (FY12/19–FY12/22), the company expects to post an operating loss of JPY5.2bn in FY12/20. In FY12/21, the company forecasts an operating profit of JPY1.2bn. It is targeting an operating profit of JPY2.1–2.5bn in FY12/22, and plans to remain in the black thereafter.

Business strategy

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.

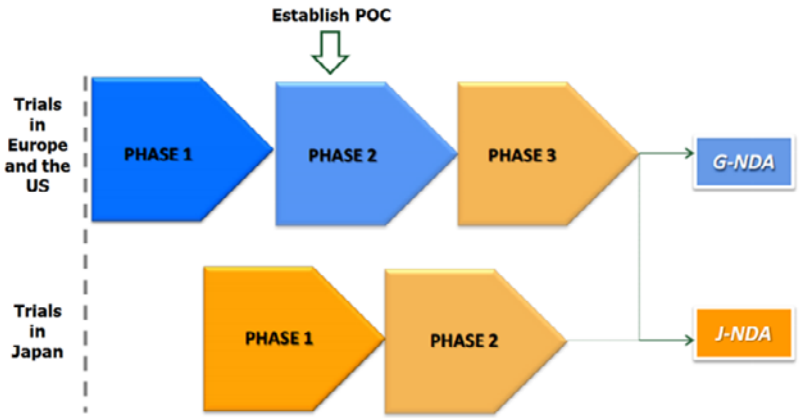
The overall aim is to reduce development risk, streamline expenses, and expand revenue opportunities. This hinges on the five strategies, namely post proof-of-concept, screening, fabless, niche market, and global expansion.

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 (confirming the efficacy and safety of a new drug candidate through clinical trials) 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

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.

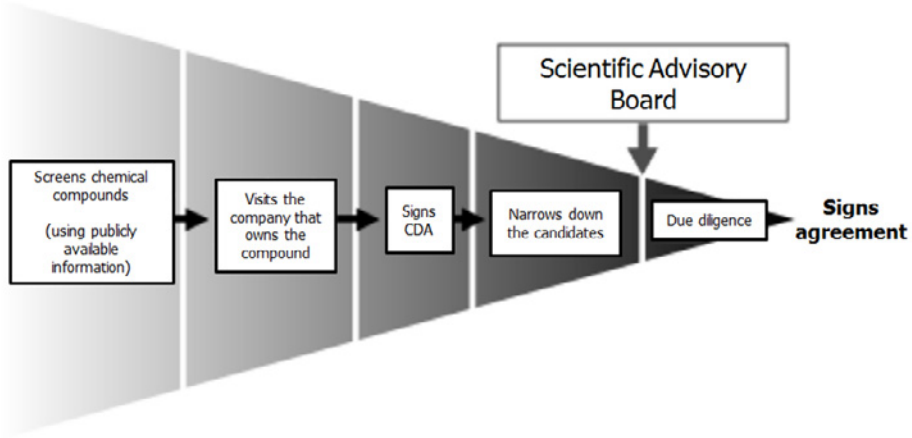
Onsite due diligence

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 a few 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) currently sells in Japan (as of February 2019). 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 anticancer 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.	Advisor and Program-Specific Research Center Professor at Center for iPS Cell Research and Application (CiRA), and Head of Drug Discovery Technology Development Office, Kyoto University Honorary member, The Japanese Society of Hematology
Toshio Suda, M.D., Ph.D.	Distinguished Professor, International Research Center for Medical Sciences, Kumamoto University Professor, Cancer Science Institute of Singapore, National University of Singapore

	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, 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 2019, 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	Licensed country	Indications	Development stage	Sales partner
Treakisym® SyB L-0501 (FD)	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	Approval granted (Jan. 2010)	Eisai Co., Ltd. (Exclusive development and sales rights granted to Eisai)
		CLL		
	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	Preparing for approval filing	—
Treakisym® SyB L-1702 (RI)	Japan	All indications	Clinical trials underway	—
Treakisym® SyB C-0501 (oral)	Japan	Systemic lupus erythematosus (SLE)	Phase I clinical trials underway	—
Rigosertib (IV) SyB L-1101	Japan	Relapsed or refractory higher-risk MDS	Global phase III clinical trials underway	—
Rigosertib (oral) SyB C-1101	Japan	Relapsed or refractory higher-risk MDS (single drug)	Phase I clinical trials underway	—
		Untreated higher-risk MDS (with azacitidine)	Preparing for phase I clinical trials Preparing for global phase III clinical trials	—
Brincidofovir SyB V-1901	Worldwide	Viral hemorrhagic cystitis (vHC) and HHV-6 encephalitis (HHV-6) after hematopoietic stem cell and kidney transplantation	—	—

Source: Shared Research based on the company website

As of November 2019, the main drugs for which SymBio was preparing filing for approval or in the development pipeline were as follows:

- Treakisym®, for the indication of relapsed or refractory DLBCL (aggressive NHL): Completed enrollment of patients for the phase III clinical trial (April 2019)
- Treakisym®, preparing to file for approval of RTD formulation and conducting clinical trials on RI formulation: Filed for approval for RTD formulation in September 2019, and clinical trials on RI formulation initiated in November 2018
- Rigosertib (intravenous formulation), for the indication of relapsed or refractory higher-risk myelodysplastic syndrome (MDS): Enrolling patients for global phase III clinical trials
- Rigosertib (oral formulation), for the indication of higher-risk MDS: Enrolling patients for the phase I clinical trial (initiated June 2017), in preparations for the phase I clinical trial of the combination therapy with azacitidine, in preparations for global clinical trials of the combination therapy with azacitidine
- Antiviral drug brincidofovir: Acquired exclusive global rights to develop, market, and manufacture brincidofovir for all indications except smallpox from Chimerix, Inc. in September 2019

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 efficacious 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 initiated phase III clinical studies of Treakisym® for an additional indication of relapsed or refractory DLBCL (aggressive NHL).

Lymphatic cancer

Lymphatic cancer a malignant growth of lymphatic corpuscles in white blood cells

Lymphatic cancer is a malignant growth of lymphatic corpuscles in white blood cells. It causes inflammation of the lymphatic nodes. The most common symptom is a painless lump or swelling in one or more lymph nodes, usually in the neck, armpit or groin. In lymphatic cancer, the lump or swelling grows persistently without decreasing in size, also spreading to other parts of the body and eventually presenting as generalized symptoms, including fever, weight loss, and night sweats. Other symptoms can include widespread itching and skin rash, as well as airway obstruction, interrupted blood flow, and numbness arising from pressure of swollen lymph nodes on the respiratory tract, blood vessels, and spinal cord.

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. According to the Japanese Association of Clinical Cancer Centers (JACCC), the five-year relative survival rates for lymphatic malignancies (among patients diagnosed between 2001 and 2005) are as outlined in the table below. In Hodgkin's lymphoma (all cases) the five-year relative survival rate was 76.0%, as compared with 68.3% for non-Hodgkin's lymphoma (all cases).

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)

Five-year relative survival rate for lymphatic malignancies (in patients diagnosed between 2001 and 2005)

Stage	Hodgkin's lymphoma		Non-Hodgkin's lymphoma	
	Number of cases	5-year relative survival rate (%)	Number of cases	5-year relative survival rate (%)
I	19	91.4	462	86.7
II	46	84.6	385	74.3
III	22	65.3	319	64.0
IV	19	44.7	535	54.6
All cases	122	76.0	1,844	68.3

Source: Survival Statistics of Japanese Association of Clinical Cancer Centers (November 2015)
Note: Covers not just patients undergoing chemotherapy, but also those undergoing radiation therapy or some other form of cancer treatment.
Note: Cancer progression is categorized into stages; in lymphatic malignancies, these are Stage I, Stage II, Stage III, and Stage IV.

Method of treatment determined by grade; separate clinical trials required for each disease subtype

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. To gain approval to manufacture and sell pharmaceuticals, companies must conduct separate clinical trials for each disease subtype. Clinical trial subjects are categorized as either treatment-naïve, or relapsed/refractory (patients who have received treatment in the past, which has proven ineffective).

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. 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 the Earnings structure section).

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 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 JPY4.5–5.0bn.

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 started 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

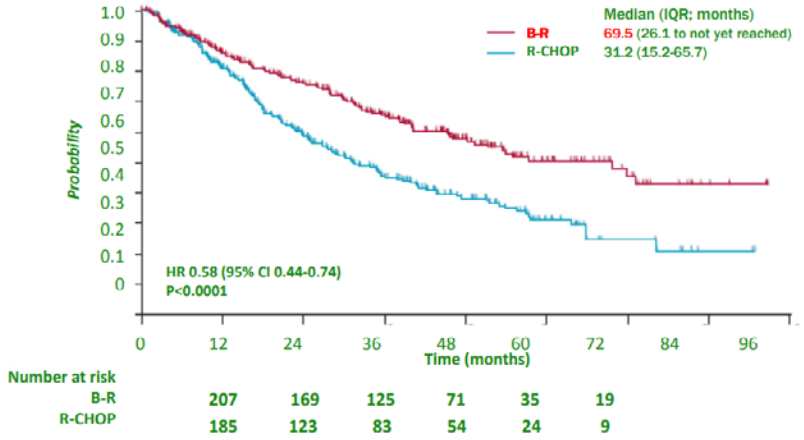
According to the company, R-CHOP therapy—a combination of rituximab with CHOP chemotherapy drugs (cyclophosphamide, doxorubicin, vincristine, and prednisolone)—was standard first-line treatment for low-grade NHL and MCL in Japan prior to December 2016. In December 2016, Treakisym® won approval for the additional indication of first-line treatment of low-grade NHL and MCL, and subsequently in July 2018, Treakisym® was newly included as a standard option for first-line treatment of low-grade NHL and MCL 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. Shared Research believes this shift will gain support from the aforementioned data demonstrating that BR therapy is more efficacious than R-CHOP therapy, and inclusion of BR therapy as a standard treatment option in the Guidelines for Tumors of Hematopoietic and Lymphoid Tissues 2018.

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 anticancer 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 efficacious 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

Phase II clinical trial data demonstrates potential for improved prognosis in patients with relapsed or refractory DLBCL (aggressive NHL)

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.

Planning to file for approval in FY12/20 for indication of relapsed or refractory DLBCL

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. SymBio aims to file for approval in Q2 FY12/20 with a view to launching in Q3 FY12/21.

Potential for use of Treakisym® as pretreatment agent for CAR-T therapy

In April 2018, Novartis Pharma K.K. applied in Japan for approval of the chimeric antigen receptor T-cell (CAR-T) therapy CTL019 (US product name: Kymriah®), for the treatment of relapsed or refractory B-cell acute lymphoblastic leukemia (ALL) in patients aged 25 years or younger and 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 (2–8°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 be manufactured and sold. 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: Aiming to obtain approval in FY12/20 for bendamustine hydrochloride RTD product

As of February 2019, the company is respectively preparing to file for approval and conducting clinical trials for the bendamustine hydrochloride RTD and RI products.

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. As of February 2019, the company has completed consultation with PMDA and is preparing to file for approval. Based on the time needed to prepare the documents required for this application, and subsequent period between filing and approval, SymBio aims to submit an application in FY12/19, obtain approval in FY12/20, and launch in Q1 FY12/21.

However, clinical trials will be required for the RI product, because the administration time is different from the FD product. In November 2018, the company began a clinical trial of the Treakisym® RI product in 36 patients. It apparently plans to launch the RI product in 1H FY12/22.

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 anticancer 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 anticancer 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, South 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 2019, 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 with

resumption of study drug supply SymBio restarted phase I clinical trials in Japan in June 2017, to verify the tolerability and safety of the oral formulation of rigosertib among Japanese patients. 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 in higher-risk MDS patients, and in combination with azacitidine.

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 2019.

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 anticancer 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 40 patients had been registered as of end December 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 50 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 2019, Onconova is making efforts toward finalizing the design for a pivotal phase III oral rigosertib/azacitidine combination trial for the first-line treatment of higher-risk MDS.

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 JPY15.6bn for FY03/18 (+11.1% YoY) and forecast to reach JPY13.6bn in FY03/19. 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.

SyB V-1901 (antiviral drug brincidofovir)

In September 2019, SymBio concluded an exclusive global license agreement with Chimerix Inc. for the antiviral drug brincidofovir (SyB V-1901). The company acquired exclusive global rights to develop, manufacture, and market brincidofovir for all diseases except smallpox. Under the terms of the agreement, the company will pay Chimerix an upfront payment of USD5mn, milestone payments on future developments of USD180mn, and royalties on the product sales. Shared Research thinks brincidofovir differs from other candidates in SymBio's pipeline in that it targets the global market and that the company had acquired not only development and marketing rights but also manufacturing rights to the drug.

According to the company, Chimerix had been developing oral formulation of brincidofovir, but suspended development due to the failure of the phase III clinical trial. SymBio determined that the failure of the oral formulation was due to its low intestinal absorption rate and side effects arising from toxicity, and thought that it could circumvent such problems if it worked on developing brincidofovir as an intravenous formulation. The company commented that one of the reasons it entered the license agreement with Chimerix was the latter's policy of focusing on cancer.

Mechanism of action and indications of brincidofovir

Brincidofovir is an antiviral drug formed by conjugating a lipid chain (hexadecyloxypropyl, or HDP) of specified length to cidofovir (antiviral drug already approved and marketed in the EU and the US, but not approved in Japan). As a lipid conjugate, it has a novel mechanism of action and can be taken up by cells at enhanced efficiency compared to cidofovir (i.e., brincidofovir has higher cell membrane permeability). Once inside a cell, brincidofovir transforms into a direct-acting agent and inhibits viral replication, demonstrating high antiviral efficacy. It is also easy to use as it has a low risk of nephrotoxicity, which is a side effect of cidofovir, hence making it a novel, highly active anti-multiviral drug. It is expected to become an effective treatment against a wide array of infectious diseases caused by DNA viruses, including cytomegalovirus (CMV) and other herpes viruses, adenoviruses, BK virus, papillomaviruses, and smallpox virus.

> Cidofovir (CDV): Approved by FDA in 1996 as a treatment for cytomegalovirus retinitis in AIDS patients. It inhibits replication of multiple families of DNA viruses other than herpes viruses, including adenoviruses, papillomaviruses, and polyomaviruses.
>
> CDV is taken up by renal tubular epithelial cells through organic anion transporter 1 (OAT1), and its accumulation in the cells cause nephrotoxicity. Brincidofovir is expected to have a low risk of nephrotoxicity as its lipid chain prevents it from being taken up by OAT1 and accumulating in renal tubular epithelial cells.

Development status

The US-based phase I clinical trial of intravenous formulation of brincidofovir has been completed. It has been reported that no serious side effects were observed in the study.

SymBio will initially develop brincidofovir toward commercialization in Japan for treatment of viral hemorrhagic cystitis (vHC)*[1] and HHV-6 encephalitis*[2] occurring after hematopoietic stem cell and kidney transplantation, which have high unmet medical demand. The company also looks to expand its business in Europe, the US, and Asia (including China), where organ transplant markets are large. It will also consider forming partnerships that take advantage of regional characteristics of these target diseases. The company will explore all options for maximizing business value, including the utilization of wholly-owned subsidiary SymBio Pharma USA, Inc. established in May 2016. It aims to commercialize the product by mid 2020s.

Hematopoietic stem cell transplantation is one of the therapies aimed at completely curing diseases such as blood cancer and immunodeficiency disorders that are difficult to treat with conventional chemotherapy. In Japan, there are about 4,000 patients who have undergone allogeneic hematopoietic stem cell transplantation, and about 60% of them have contacted viral hemorrhagic cystitis (vHC) or HHV-6 encephalitis. For vHC, cidofovir is used as first-line treatment in the EU and US. For encephalitis, foscavir and denocin are designated as the first-line drugs, and cidofovir as the second-line drug.

1. Viral hemorrhagic cystitis (vHC): Among viral infections that frequently occur following hematopoietic stem cell transplantation, adenovirus infections causing hemorrhagic cystitis are particularly refractory in nature. When severe, they can cause disseminated infection and become fatal. Cases of adenovirus spreading to the kidney and causing kidney failure and ultimately death have been reported. These infections are especially likely to occur in unrelated donor transplantation and in umbilical cord blood transplantation, which are relatively common in Japan. The infections are likely to be refractory, as they are further complicated by the length of time required for reconstruction of the immune system. Drugs currently used in treatment, including cidofovir (CDV), are either unapproved or off-label in Japan.

2. HHV-6 encephalitis: HHV-6 (Human Herpesvirus 6) is the sixth human herpesvirus to be discovered. It reactivates in 30–70% of patients after allogenic hematopoietic stem cell transplantation and can cause HHV-6 encephalitis. Most cases of HHV-6 encephalitis develop within 2–6 weeks after transplantation, most frequently in the third week after transplantation. It is characterized by the three major symptoms of impaired memory, disordered consciousness, and convulsions, which in typical cases gradually appear in the same order (convulsions occur in 30–70% of patients). In rapidly progressing cases, which are not uncommon, neurological symptoms worsen by the hour, often requiring respirator management for repeated convulsions and respiratory depression. The conditions of HHV-6 encephalitis patients often deteriorate rapidly over a short period of time, making early treatment important. According to guidelines edited and issued by the Japan Society for Hematopoietic Cell Transplantation (February 2018), the first-line drugs are foscarnet (FOS) and ganciclovir (GCV), followed by the second-line drug cidofovir (CDV). CDV is not the preferred first-line drug due to nephrotoxicity and because it transfers poorly into cerebrospinal fluid (CSF). All three of these drugs have been found to be effective in vitro, but no trials have been conducted yet to confirm their clinical efficacy in patients with HHV-6 encephalitis.

Number of patients and estimated sales

As previously mentioned, the company will initially develop brincidofovir for the indications of viral hemorrhagic cystitis (vHC) and HHV-6 encephalitis after hematopoietic stem cell and kidney transplantation toward commercialization in Japan. In Japan, there are about 4,000 patients who have received allogeneic hematopoietic stem cell transplants, and about 60% of them have contracted vHC or HHV-6 encephalitis.

In addition to vHC and HHV-6 encephalitis after hematopoietic stem cell transplantation in Japan, the company expects indications of brincidofovir to be expanded to include infectious diseases that occur after kidney transplantation (about 40% of patients suffer from infectious diseases caused by BK virus or cytomegalovirus after kidney transplantation) in China, the EU, and the US. Based on such factors, the company estimates global sales of brincidofovir, including sales from emerging markets, to reach JPY100.0bn.

Earnings structure

(JPYmn)	FY12/09	FY12/10	FY12/11	FY12/12	FY12/13	FY12/14	FY12/15	FY12/16	FY12/17	FY12/18
Sales	1,191	1,450	1,883	1,955	1,532	1,955	1,933	2,368	3,444	3,836
YoY	-26.9%	21.7%	29.8%	3.9%	-21.6%	27.6%	-1.1%	22.5%	45.4%	11.4%
Product sales	-	326	1,632	1,955	1,432	1,940	1,933	2,137	3,444	3,810
YoY	-	-	401.3%	19.8%	-26.8%	35.5%	-0.3%	10.6%	61.1%	10.6%
Treakisym sales (NHI price basis; reference)	-	644	3,390	3,940	4,230	4,320	4,760	4,720	7,600	8,500
Product sales / Sales (NHI price basis)	-	50.6%	48.2%	49.6%	33.9%	44.9%	40.6%	45.3%	45.3%	44.8%
Royalty revenue	1,191	1,124	250	-	100	15	-	231	-	26
Sales to Eisai	1,085	1,446	1,872	1,930	1,486	1,908	1,852	2,265	3,382	3,648
YoY	-32.2%	33.2%	29.5%	3.1%	-23.0%	28.4%	-2.9%	22.3%	49.4%	7.9%
Sales to other partners	106	4	10	26	46	47	81	104	62	187
CoGS	-	238	1,224	1,362	1,214	1,428	1,350	1,464	2,413	2,663
CoGS / Product sales	-	73.1%	75.0%	69.7%	84.8%	73.6%	69.8%	68.5%	70.1%	69.9%
CoGS / Sales (NHI price basis)	-	37.0%	36.1%	34.6%	28.7%	33.1%	28.4%	31.0%	31.7%	31.3%
Product procurement	-	238	1,434	1,322	1,175	1,550	1,242	1,606	2,589	2,969
Gross profit	1,191	1,212	658	593	318	527	583	904	1,031	1,173
Product gross profit	0	87	408	593	218	512	583	673	1,031	1,147
Gross profit margin	-	26.9%	25.0%	30.3%	15.2%	26.4%	30.2%	31.5%	29.9%	30.1%
Royalty revenue	1,191	1,124	250	-	100	15	-	231	-	26
SG&A expenses	1,399	1,825	2,725	2,293	1,999	1,830	3,135	3,031	4,978	3,829
Personnel expenses	323	343	365	413	441	479	488	541	554	504
R&D expenses	817	1,118	1,945	1,438	1,053	774	2,035	1,667	3,018	1,833
Other	259	364	415	442	505	577	612	823	1,406	1,492
Operating profit	-208	-613	-2,067	-1,700	-1,681	-1,303	-2,552	-2,127	-3,947	-2,656

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 anticancer agent in December 2010. ThroughFY12/16, the company booked sales of Treakisym® indicated for relapsed or refractory low-grade NHL and MCL.

In FY12/17, the company booked sales of additional indications of untreated low-grade 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 to Eisai.

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

Personnel expenses consist of directors' remuneration as well as expenses for personnel involved in such tasks as marketing, searching for in-licensing candidates and general administration. Personnel expenses have been trending upward in line with additions to the pipeline and business expansion.

R&D expenses

R&D expenses include personnel expenses for R&D staff as well as clinical trial outsourcing expenses and upfront payments accompanying product in-licensing. 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.

Eisai pays half of the development costs for the Treakisym® freeze-dried (FD) product in Japan. In its income statement, SymBio accordingly books total R&D expense less the portion of R&D expenditure borne by Eisai.

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. Eisai will be responsible for sales of Treakisym® in Japan through FY12/20. At end-FY12/20, though, the sales agreement with Eisai expires. At this point the company will switch to in-house sales, likely triggering improvement in profit margins.
- **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 JPY4.8bn at end-FY12/18. But the company expects a total net loss of JPY8.8bn over the first two years of its medium-term plan (FY12/19–FY12/22). SymBio aims to secure the funds required through its April 2018 issue of the 45th through 47th stock acquisition rights with exercise price revision clauses (Commit Issue Program) and conclusion of an unsecured loan facility agreement. The company's operations could be affected, though, if it fails to secure additional funding as planned.
- **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

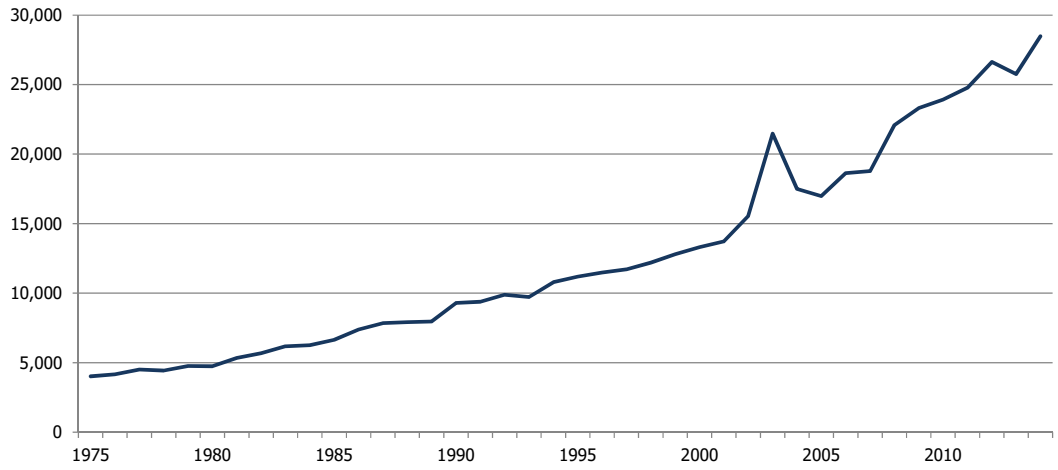
Market strategy

Lymphatic cancer: patient population, market size, drugs

Newly diagnosed patients with lymphatic cancer

In 2014, the number of people diagnosed with lymphatic cancer in Japan was 28,486 (+10.6% YoY; average annual increase in past 10 years is 5.0%), according to the Center for Cancer Control and Information Services. Of these, 22,557 (+11.0% YoY), or 79.2% (78.9% in 2013), were 60 years or older. Of the 876,713 (+1.7% YoY) people diagnosed with cancer, those diagnosed with lymphatic cancer accounted for only 3.2% (3.0% in 2013), but their number increased 62.8% between 2004 and 2014 versus a 40.7% 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. On an NHI drug reimbursement price basis, Treakisym® sales reached JPY8.5bn in FY12/18 (JPY7.6bn 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: JPY8.5bn (FY12/18)
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 JPY21.3bn (-36.2% YoY) in FY12/18.

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 efficacious 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 efficacious 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 efficacious treatment available once patients treated with Vidaza relapse. Nippon Shinyaku booked Vidaza sales of JPY15.6bn in FY03/18 (+11.1% YoY) and expects sales of JPY13.6bn in FY03/19.

Historical performance

1H FY12/19 results

- Sales: JPY2.0bn (+4.0% YoY)
- Operating loss: JPY2.0bn (loss of JPY1.3bn in 1H FY12/18)
- Recurring loss: JPY2.1bn (loss of JPY1.4bn in 1H FY12/18)
- Net loss: JPY2.1bn (loss of JPY1.4bn in 1H FY12/18)

Sales rose on domestic product sales of Treakisym®.

On a quarterly basis, sales grew 81.4% YoY to JPY1.6bn in Q1 (Jan–Mar 2019), but fell 62.2% YoY to JPY394mn in Q2 (Apr–Jun 2019). In Q2, impurities and appearance defects were found in Treakisym® 100mg vials imported from Astellas Deutschland, which led to the company returning the whole batch. For this reason, Q2 sales were low relative to Q1 as well as Q2 FY12/18. In order to resolve this problem, SymBio says that all parties involved are working to return supplies to normal; it has requested that Astellas Deutschland take steps to improve its manufacturing and quality control arrangements for Treakisym® 100mg.

Gross profit fell 7.7% YoY to JPY529mn, and the gross profit margin narrowed by 3.3pp YoY to 26.4%. On a quarterly basis, gross profit was 144.0% higher YoY at JPY609mn in Q1, for a gross profit margin of 37.8% (+9.7pp YoY), but dropped to a loss of JPY79mn in Q2. In addition to weak sales in Q2, SymBio booked a JPY188mn inventory valuation loss under CoGS, in connection with the aforementioned quality issues associated with a particular batch of Treakisym® 100mg.

SG&A expenses rose 34.1% YoY to JPY2.5bn and R&D expenses increased 14.8% YoY to JPY963mn, which included expenses for conducting clinical trials of intravenous and oral formulations of Treakisym® and rigosertib. Excluding R&D expenses, SG&A expenses increased by 49.3% YoY to JPY1.6bn. Fees and commissions paid for expert consultations rose 85.5% YoY to JPY542mn. On the other hand, personnel expenses (total for directors' remuneration and salaries) were 3.0% lower YoY at JPY248mn, as although the company hired more Treakisym® managers in the process of building an in-house sales organization, some administrative staff retired.

As a result, operating loss, recurring loss, and net loss widened YoY.

Major progress in 1H FY12/19 was as follows:

- In August 2019, SymBio announced a revision to its FY12/19 earnings forecast. In Q2 FY12/19, impurities and appearance defects were found in Treakisym® 100mg vials imported from Astellas Deutschland, which led to the company returning the whole batch. Thus only a fraction of the batches scheduled for shipment in 2Q FY12/19 onward can be shipped by the end of the year, with shipments possibly being delayed until Q1 FY12/20. The company therefore revised down its FY12/19 earnings forecast.
- Progress was made in Q2 in the company's arbitration against The Medicines Company, and SymBio expects a conclusion to be reached by the end of 2019.
- In July 2019, the company agreed upon basic terms for a new license.
- In June 2019, the US Food and Drug Administration (FDA) granted accelerated approval to polatuzumab vedotin-piiq, a CD79b-directed antibody-drug conjugate, in combination with bendamustine (product name: Treakisym®) and rituximab (BR therapy) for patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who are not eligible for transplant. Polatuzumab vedotin-piiq was discovered by Roche Group company Genentech and is being developed in Japan by Chugai Pharmaceutical, another member of the Roche Group.

- In 1H FY12/19, capital stock and capital surplus each increased by JPY1.3bn YoY, reflecting proceeds from the issuance of shares resulting from exercise of the 46th stock acquisition rights.
- In April 2019, the first patient was enrolled in the clinical trial of the liquid formulation of Treakisym® (rapid infusion [RI] formulation), whose primary goal was to confirm safety of the drug.
- In April 2019, patient enrollment was completed for the phase III clinical trial of anticancer drug Treakisym® as a treatment for relapsed or refractory diffuse large B-cell lymphoma (DLBCL). Once the follow-up period is over, the company plans to statistically analyze the efficacy and safety of the drug with an aim of filing for approval for the additional indication of relapsed or refractory DLBCL in Q2 FY12/20.
- In March 2019, the company obtained approval to partially revise the marketing approval of anticancer drug Treakisym® as a pretreatment agent in antigen-specific T cell infusion therapy. This enabled the use of Treakisym® as a pretreatment agent for the chimeric antigen receptor T-cell (CAR-T) therapy Kymriah® intravenous infusion.

Domestic

Preparations for in-house sales organization begin

The business alliance agreement between SymBio and Eisai Co., Ltd. under which Eisai acts as a sales agent expires in December 2020. SymBio started to build an in-house sales organization for Treakisym® in the domestic market in October 2018. Key management priority is to move into the black in FY12/21 and ongoing profit growth thereafter. The company is therefore laying the groundwork for a shift to an internal sales organization to drive future business development.

Twenty Treakisym® managers are to form the core of the marketing team in the internal sales organization. The company conducted the necessary recruitment and training activities, and prepared for deployment to each region of responsibility as planned by the end of 1H. In Q3, SymBio intends to deploy Treakisym® managers across Japan. The company is also making steady progress with preparation of infrastructure such as logistics, distribution, and information systems.

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 untreated low-grade non-Hodgkin's lymphoma and mantle cell lymphoma (marketing approval obtained in December 2016), refractory or relapsed low-grade non-Hodgkin's lymphoma and mantle cell lymphoma (October 2010), and chronic lymphocytic leukemia (August 2016).

As a result of additional indications, Treakisym® is steadily increasing its market share in the area of first-line treatment in medical settings 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, which applies to all of the approved indications. This has seen Treakisym® establish its position as a standard treatment for lymphatic cancer. According to the company, market share in the area of first-line treatment increased to 55% (from 52% in Q2 FY12/18). SymBio expects market share in the area of first-line treatment to grow further from 2H FY12/19, as the aforementioned Treakisym® managers become fully operational.

In addition to the above three approved indications, the company is conducting phase III clinical trials for the fourth indication of relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL) and these are progressing well 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. The company has made steady progress in enrollments following the first patient in January 2018, completing enrollments in April 2019. Going forward, after completing the follow-up period for enrolled cases, it will prepare to file an application for regulatory approval.

SymBio is targeting a transition to Treakisym® liquid formulation (RTD and RI formulations), for which it concluded an exclusive licensing agreement in Japan with Eagle Pharmaceuticals (based in New Jersey, US) in September 2017. The company has already

consulted with PMDA and is preparing to file for approval of the RTD formulation in 2H FY12/19. SymBio launched clinical trials for the RI formulation in November 2018 primarily to confirm safety, and has made steady progress with patient enrollments since enrolling the first patient in April 2019. Liquid formulations of Treakisym® will offer significant value added (reduced burden) to patients and healthcare professionals, and liquid formula patent protection makes it possible to extend the product life of Treakisym® until 2031.

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 new anti-CD20 antibodies as well. This will allow combination therapy with 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. In March 2019, the company obtained approval for the partial revision to its application concerning the use of Treakisym® as a pretreatment agent in tumor-specific T cell infusion therapy. This will allow Treakisym® to be used as a pretreatment agent for Kymriah® intravenous infusion, which was approved as the first chimeric antigen receptor T-cell (CAR-T) therapy in Japan and listed on the NHI drug price list in May 2019.

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 performed a preclinical study to verify the efficacy of the oral formulation of Treakisym® in treating systemic lupus erythematosus (SLE), a form of autoimmune disease. The company will consider the next stage of this research project (including clinical trials) after evaluating the results of the preclinical study.

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 (44 patients enrolled as of July 2019, versus a target of 50). 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. As of March 2019, the company had reached 75% of its target of enrolling 360 patients worldwide. Based on these trial 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 has completed 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, enrolled the first patients in October 2017, and completed patient enrollment in June 2019. After completing the phase I trials, the company plans to start phase I 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 currently planned by Onconova, and apply for approval of the oral formulation of the drug in Japan at the same time as in the US and Europe. In December 2018, Onconova submitted a Special Protocol Assessment (SPA) request to the US Food and Drug Administration (FDA) to speed up the approval review for the global trials, and plans to begin phase III clinical trials as soon as it receives approval from the FDA. 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 learned of an event 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.

In October 2017, SymBio initiated an arbitration against The Medicines Company, 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. According to SymBio, progress was made in Q2 in the company's arbitration against The Medicines Company, and the company expects that a conclusion will be reached by end-2019.

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. In July 2019, the company agreed upon basic terms for a new license.

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 licensing 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 South Korea, Taiwan, and Singapore, and product sales were in line with the company's plans.

Q1 FY12/19 results

- ▷ Sales: JPY1.6bn (+81.4% YoY)
- ▷ Operating loss: JPY596mn (loss of JPY715mn in Q1 FY12/18)
- ▷ Recurring loss: JPY616mn (loss of JPY749mn in Q1 FY12/18)
- ▷ Net loss: JPY617mn (loss of JPY760mn in Q1 FY12/18)

Sales rose on domestic sales of Treakisym®, whose sales based on the NHI drug price were up 11.0% YoY.

Thanks to higher sales, gross profit grew 144.0% YoY to JPY609mn and GPM was up 9.7pp YoY to 37.8%.

SG&A expenses rose 25.0% YoY to JPY1.2bn; of which, R&D expenses increased 13.4% YoY to JPY472mn, including expenses for conducting clinical trials of intravenous and oral formulations of Treakisym® and rigosertib. Excluding the climb in R&D expenses, SG&A expenses increased by 33.8% YoY to JPY733mn owing to hiring of additional Treakisym® managers in preparation for building an in-house sales structure.

As a result, operating loss, recurring loss, and net loss shrank YoY.

Major progress in Q1 FY12/19 was as follows:

- ▷ In April 2019, the first patient was enrolled in the clinical trial of the liquid formulation of Treakisym® (rapid infusion [RI] formulation), whose primary goal was to confirm safety of the drug.
- ▷ In April 2019, patient enrollment was completed for the phase III clinical trial of anticancer drug Treakisym® as a treatment for relapsed or refractory diffuse large B-cell lymphoma (DLBCL). Once the follow-up period is over, the company plans to

statistically analyze the efficacy and safety of the drug with an aim of filing for approval for the additional indication of relapsed or refractory DLBCL in Q2 FY12/20.

▷ In March 2019, the company obtained approval to partially revise the marketing approval of anticancer drug Treakisym® as a pretreatment agent in antigen-specific T cell infusion therapy. This enabled the use of Treakisym® as a pretreatment agent for the chimeric antigen receptor T-cell (CAR-T) therapy Kymriah® intravenous infusion.

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Twenty Treakisym® managers are to form the core of the marketing team in the internal sales organization. The company conducted the necessary recruitment activities as planned by the end of Q1. It also started readying the infrastructure such as logistics, distribution, and information systems.

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

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As a result of additional indications, Treakisym® is steadily increasing its market share in the area of first-line treatment in medical settings 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, which applies to all of the approved indications. This has seen Treakisym® establish its position as a standard treatment for lymphatic cancer. Sales of Treakisym® based on the National Health Insurance (NHI) drug price grew steadily by 11.0% YoY.

In addition to the above three approved indications, the company is conducting Phase III clinical trials for the fourth indication of relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL) and these are progressing well 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. The company has made steady progress in enrollments following the first patient in January 2018, completing enrollments in April 2019. Going forward, after completing the follow-up period for enrolled cases, it will prepare to file an application for regulatory approval.

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 (reduced burden) to patients and healthcare professionals, and liquid formulation patent protection extends Treakisym®'s product life until 2031. The company has already consulted with PMDA and is preparing to file for approval of the RTD formulation. SymBio launched clinical trials for the RI formulation in November 2018 primarily to confirm safety, and finished enrolling the first patient in April 2019.

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histological type of low-grade NHL, enabling the company to provide patients with a new treatment therapy. In March 2019, the company obtained approval for the partial revision to the marketing authorization allowing the use of Treakisym® as a pretreatment agent in tumor-specific T cell infusion therapy. The first chimeric antigen receptor T-cell (CAR-T) therapy CTL019 (Kymriah® intravenous infusion) was approved for use in Japan in the same month. Once this goes on sale Treakisym® will be able to be used as a pretreatment agent.

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.

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Regarding the oral formulation of rigosertib, Onconova has completed 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 making steady progress with the clinical trial after enrolling the first patients in October 2017. After completing the Phase I trials, the company plans to start Phase I 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 currently planned by Onconova, and apply for approval of the oral formulation of the drug in Japan at the same time as in the US and Europe. In December 2018, Onconova submitted a Special Protocol Assessment (SPA) request to the US Food and Drug Administration (FDA) to speed up the approval review for the global trials, and expects an outcome of the discussions in 1H 2019. 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 South Korea, Taiwan, and Singapore, and product sales were in line with the company's plans.

Full-year FY12/18 results

- Sales: JPY3.8bn (+11.4% YoY)
- Operating loss: JPY2.7bn (loss of JPY3.9bn in FY12/17)
- Recurring loss: JPY2.7bn (loss of JPY4.0bn in FY12/17)
- Net loss: JPY2.8bn (loss of JPY4.0bn in FY12/17)

Sales rose as product sales totaled JPY3.8bn (+10.6% YoY) mainly owing to domestic sales of Treakisym®.

Due to sales growth, gross profit rose 13.7% YoY to JPY1.2bn, with the gross profit margin increasing 0.7pp YoY to 30.6%.

SG&A expenses fell 23.1% YoY to JPY3.8bn, with R&D expenses dropping 39.3% YoY to JPY1.8bn. Although the company incurred expenses for conducting clinical trials of intravenous and oral formulations of Treakisym® and rigosertib, R&D expenses fell nonetheless in the absence of JPY1.4bn in-licensing expenses for liquid formulation products of Treakisym® (RTD and RI formulations) in FY12/17. Excluding the drop in R&D expenses, SG&A expenses would have risen by 1.8% YoY to JPY2.0bn.

As a result, operating loss, recurring loss, and net loss shrank YoY.

Sales fell short of full-year forecast of JPY4.2bn. On an NHI drug reimbursement price basis, SymBio had anticipated full-year sales of JPY10.1bn (+32.9% YoY), but for the two reasons outlined below, sales on a drug price basis only came to JPY8.5bn.

- Treakisym® distributor Eisai adopted a greater focus on sales of its own products, against which backdrop SymBio finished FY12/18 with ten highly specialized product managers for Treakisym®, up from five as of December 2017.
- In December 2018, a batch of Treakisym® 25mg imported from Astellas Deutschland GmbH was determined to be unsalable due to its poor external appearance, prompting a temporary halt to imports and domestic shipments of the 25mg dosage.

Progress made in the company's main businesses in 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. As of February 6, 2019, the company had enrolled 35 patients, versus its target of 60.
- 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.
- 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 (20mn units, 20mn shares), 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®.
- ▷ In November 2018, the company commenced a clinical trial of Treakisym® liquid formulation (rapid infusion [RI] formulation, intravenous administration for 10 minutes), primarily to verify the drug's safety. A total of 36 patients are enrolled in the clinical trial, and the company plans to apply for approval of the RI formulation upon completion of the trial, with plans to launch in 2022.

Domestic

Preparations for in-house sales organization begin

In October 2018, SymBio announced that it had started preparing to build an in-house sales organization for Treakisym® in the domestic market. The business alliance agreement the company reached with Eisai in 2008 regarding the sale of Treakisym® will expire in December 2020. The company considered all of its business development options including business alliances with other companies, but concluded that it was best to move to its own sales organization to better look after its patients' interests and maximize the business value. SymBio is considering the organizational structure and personnel requirements ahead of the shift to its own sales organization from early FY12/21, and planning appropriate investments in building systems and creating the necessary logistics infrastructure. These initiatives will help it engage in sophisticated marketing and enable a quality product supply structure. The company aims to move into the black in FY12/21 and post ongoing profit growth thereafter.

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 untreated low-grade non-Hodgkin's lymphoma and mantle cell lymphoma (marketing approval obtained in December 2016), refractory or relapsed low-grade non-Hodgkin's lymphoma and mantle cell lymphoma (October 2010), and chronic lymphocytic leukemia (August 2016).

As a result of additional indications, Treakisym® is steadily increasing its market share in the area of first-line treatment in medical settings 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. This has seen Treakisym® establish its position as a standard treatment for lymphatic cancer. Sales of Treakisym® based on the National Health Insurance (NHI) drug price grew steadily by 11.6% YoY.

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 (r/r 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

(reduced burden) to patients and healthcare professionals, and extend Treakisym®'s product life cycle until 2031. The company has already consulted with PMDA and is preparing to file for approval of the RTD formulation. SymBio launched clinical trials for the RI formulation in November 2018 primarily to confirm safety.

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 nearly 100 drugs for lymphatic malignancies being developed in the US and Europe combining BR (bendamustine and rituximab) or just bendamustine with anti-CD20 antibodies (20 in phase III clinical trial, 67 in phase II, and six 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. 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 (40 patients enrolled as of end December 2018). 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 international 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 South Korea, Taiwan, and Singapore, and product sales exceeded the company's plans.

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.

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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.

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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 South Korea, Taiwan, and Singapore, and sales were largely in line with plans.

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.	FY12/18 Par.
Sales	**1,191**	**1,450**	**1,883**	**1,955**	**1,532**	**1,955**	**1,933**	**2,368**	**3,444**	**3,836**
YoY	-26.9%	21.7%	29.8%	3.9%	-21.6%	27.6%	-1.1%	22.5%	45.4%	11.4%
CoGS	-	238	1,224	1,362	1,214	1,428	1,350	1,464	2,413	2,663
Gross profit	**1,191**	**1,212**	**658**	**593**	**318**	**527**	**583**	**904**	**1,031**	**1,173**
GPM	100.0%	83.6%	35.0%	30.3%	20.8%	26.9%	30.2%	38.2%	29.9%	30.6%
SG&A expenses	1,399	1,825	2,725	2,293	1,999	1,830	3,135	3,031	4,978	3,829
SG&A ratio	117.5%	125.8%	144.8%	117.3%	130.4%	93.6%	162.1%	128.0%	144.5%	99.8%
Operating profit	**-208**	**-613**	**-2,067**	**-1,700**	**-1,681**	**-1,303**	**-2,552**	**-2,127**	**-3,947**	**-2,656**
YoY	-	-	-	-	-	-	-	-	-	-
OPM	-	-	-	-	-	-	-	-	-	-
Non-operating income	20	13	56	7	114	215	17	7	5	2
Non-operating expenses	26	38	85	37	35	22	96	196	34	95
Recurring profit	**-214**	**-638**	**-2,095**	**-1,729**	**-1,601**	**-1,110**	**-2,630**	**-2,317**	**-3,977**	**-2,749**
YoY	-	-	-	-	-	-	-	-	-	-
RPM	-	-	-	-	-	-	-	-	-	-
Extraordinary gains	-	-	-	-	-	2	3	9	17	10
Extraordinary losses	-	0	5	0	-	3	1	1	15	10
Tax charges	4	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**	**-2,753**
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.	FY12/18 Par.
Sales (Initial Est.)	-	-	1,933	2,338	1,927	1,785	1,785	2,339	2,903	4,201
Sales (Results)	-	-	1,883	1,955	1,532	1,955	1,933	2,368	3,444	3,836
Results vs. Initial Est.	**-**	**-**	**-2.6%**	**-16.4%**	**-20.5%**	**9.5%**	**8.3%**	**1.2%**	**18.6%**	**-8.7%**
Operating profit (Initial Est.)	-	-	-2,351	-1,625	-1,889	-1,654	-1,654	-2,778	-3,238	-2,981
Operating profit (Results)	-	-	-2,067	-1,700	-1,681	-1,303	-2,552	-2,127	-3,947	-2,656
Results vs. Initial Est.	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Recurring profit (Initial Est.)	-	-	-2,398	-1,652	-1,922	-1,650	-1,650	-2,811	-3,303	-3,044
Recurring profit (Results)	-	-	-2,095	-1,729	-1,601	-1,110	-2,630	-2,317	-3,977	-2,749
Results vs. Initial Est.	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Net income (Initial Est.)	-	-	-2,407	-1,656	-1,926	-1,654	-1,654	-2,815	-3,306	-3,056
Net income (Results)	-	-	-2,105	-1,733	-1,605	-1,116	-2,632	-2,313	-3,978	-2,753
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.	FY12/18 Par.
Assets										
Cash and deposits	3,902	2,314	4,559	4,540	6,163	5,692	4,261	5,719	2,947	4,821
Marketable securities	219	1,701	1,953	300	1,100	899	-	-	-	-
Accounts receivable	-	6	162	148	-	273	301	487	490	412
Inventories	-	-	207	165	125	245	133	273	363	534
Other current assets	97	191	297	268	245	181	131	205	237	271
Total current assets	**4,218**	**4,213**	**7,178**	**5,421**	**7,634**	**7,290**	**4,827**	**6,685**	**4,037**	**6,038**
Buildings (net)	3	3	2	3	2	22	22	31	28	37
Tools, furniture, and fixtures (net)	11	19	15	11	6	27	31	43	18	20
Total tangible fixed assets	**13**	**22**	**17**	**14**	**9**	**49**	**53**	**75**	**47**	**57**
Total other fixed assets	**27**	**27**	**48**	**57**	**37**	**49**	**53**	**77**	**100**	**73**
Software	2	1	10	8	6	62	51	42	66	51
Other	-	-	3	3	2	4	1	-	3	20
Total intangible fixed assets	**2**	**1**	**13**	**11**	**8**	**66**	**52**	**42**	**69**	**71**
Total fixed assets	**42**	**50**	**78**	**82**	**53**	**164**	**158**	**193**	**216**	**201**
Total assets	**4,261**	**4,263**	**7,256**	**5,502**	**7,687**	**7,454**	**4,984**	**6,878**	**4,252**	**6,239**
Liabilities										
Accounts payable	-	1	309	330	-	306	320	322	604	726
Accounts payable–other	182	124	278	196	207	143	184	553	331	504
Short-term debt	-	-	-	-	-	-	-	-	-	-
Other	23	52	59	73	44	39	47	68	76	107
Total current liabilities	**205**	**178**	**646**	**599**	**251**	**488**	**551**	**942**	**1,011**	**1,336**
Long-term debt	-	-	-	-	-	-	-	-	-	-
Corporate bonds							-	450	-	-
Other fixed liabilities	2	2	5	4	3	2	2	1	1	1
Total fixed liabilities	**2**	**2**	**5**	**4**	**3**	**2**	**2**	**451**	**1**	**1**
Total interest-bearing debt	-	-	-	-	-	-	-	-	-	-
Total liabilities	**207**	**180**	**651**	**602**	**254**	**490**	**552**	**1,394**	**1,013**	**1,338**
Net assets										
Capital stock	3,378	3,711	6,025	6,025	8,059	8,331	8,331	9,948	10,762	12,973
Capital surplus	3,348	3,681	5,995	5,995	8,029	8,301	8,301	9,918	10,732	12,943
Retained earnings	-2,666	-3,309	-5,413	-7,146	-8,752	-9,868	-12,500	-14,813	-18,791	-21,543
Treasury stock	-	-	-0	-0	-0	-0	-0	-0	-0	-0
Subscription rights to shares	-	-	-	27	97	200	300	431	537	530
Total net assets	**4,054**	**4,083**	**6,606**	**4,900**	**7,433**	**6,964**	**4,432**	**5,485**	**3,239**	**4,902**
Working capital	-	5	61	-17	125	212	114	439	249	220
Total interest-bearing debt	-	-	-	-	-	-	-	-	-	-
Net debt	-3,902	-2,314	-4,559	-4,540	-6,163	-5,692	-4,261	-5,719	-2,947	-4,821

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 stock and capital surplus 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.	FY12/18 Par.
Cash flows from operating activities (1)	-211	-754	-2,074	-1,659	-1,677	-1,266	-2,272	-1,960	-3,817	-2,325
Cash flows from investing activities (2)	-4	-116	-117	-411	-1,332	314	1,489	-44	-78	-26
Free cash flow (1+2)	-215	-870	-2,191	-2,069	-3,010	-952	-783	-2,004	-3,894	-2,351
Cash flows from financing activities	2,963	663	4,611	-1	4,057	544	-3	3,658	1,164	4,272
Depreciation and good will amortization (A)	4	7	8	9	8	13	24	26	30	35
Capital expenditures (B)	-3	-14	-12	-3	-	-109	-24	-28	-57	-40
Working capital change (C)	-	5	56	-78	142	86	-98	325	-190	-29
Simple FCF (NI + A + B - C)	-217	-655	-2,165	-1,650	-1,739	-1,298	-2,534	-2,640	-3,815	-2,729
Cash and cash equivalents (year-end)	4,121	3,916	6,311	4,240	5,294	5,092	4,261	5,719	2,947	4,821

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

Outlays on the purchase 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	21,493	Exercise of stock options attached to convertible corporate bonds and other stock options
Apr. to Dec. 2018	28,349,700	82,398,924	4,422	25,915	Exercise of 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 2019, 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 anticancer 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, South Korea and Singapore.
March 2007	License Agreement finalized with Astellas Deutschland GmbH for SyB L-0501 (bendamustine) development & commercialization rights in China (HK), Taiwan, South 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 South 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 South 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 anticancer 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

September 2019

On **September 18, 2019,** the company announced achievement of LPLV in phase III clinical trials of anticancer agent Treakisym® targeting relapsed or refractory diffuse large B-cell lymphoma (DLBCL).

The company announced completion of Last Patient Last Visit (LPLV) in its phase III clinical trials of anticancer agent Treakisym® (generic name: bendamustine hydrochloride) for the additional indication of relapsed or refractory DLBCL.

The company plans to announce topline data of the drug's efficacy in Q4 FY12/19 (October–December 2019). Having received the topline results, the company will prepare to file for approval for the additional indication of relapsed or refractory DLBCL in Q2 FY12/20 (April–June 2020).

August 2019

On **August 7**, the company announced a revision to its full-year FY12/19 earnings forecast and medium-term plan.

Revised FY12/19 earnings forecast

- ▷ Sales: JPY3.1bn (previous forecast: JPY4.5bn)
- ▷ Operating loss: JPY3.8bn (JPY3.6bn)
- ▷ Recurring loss: JPY3.9bn (JPY3.6bn)
- ▷ Net loss: JPY3.9bn (JPY3.6bn)
- ▷ Loss per share: JPY167.66 (JPY175.52)

Reasons for revision

SymBio imports lyophilized Treakisym® for injection from Astellas Deutschland GmBH (consolidated subsidiary of Astellas Pharma Inc.), which it supplies to the market for sale in Japan through its business partner, Eisai Co., Ltd. after quality inspection and packaging. In Q2 FY12/19, impurities and appearance defects were found in Treakisym® 100mg vials imported from Astellas Deutschland, which led to the company returning the whole batch. Thus only a fraction of the batches scheduled for shipment in 2Q FY12/19 onward can be shipped by the end of the year, with shipments possibly being delayed until Q1 FY12/20. The company therefore revised down its FY12/19 earnings forecast. Lower operating profit stems from the sales decline, but the impact on operating profit is mitigated by SG&A expenses (including R&D expenses) being revised down by JPY294mn from JPY5.1bn to JPY4.8bn.

The company is reviewing the impact of the FY12/19 earnings forecast revision on medium-term plan targets for FY12/20, FY12/21, and FY12/22 and intends to announce revised plan targets once it has confirmed the figures.

June 2019

On **June 12, 2019**, the company announced a change of its representative director (resignation).

Details of change (resigning representative director)

Name	Current position
Kazuo Asakawa	Representative Director and Corporate Officer Executive Vice President Chief Commercial Officer

Reason for change (resignation)

Mr. Kazuo Asakawa requested to resign from the positions of representative director and corporate officer due to health reasons. His resignation will be effective as of June 30, 2019.

May 2019

On **May 22, 2019**, the company announced the launch of a regenerative medicine product that uses its anticancer drug Treakisym® as a pretreatment agent.

On the same day, Novartis Pharma K.K. announced that its chimeric antigen receptor T-cell (CAR-T) therapy Kymriah® IV Infusion (hereinafter Kymriah®) targeting CD19 positive relapsed or refractory B-cell acute lymphoblastic leukemia (B-ALL) and CD19 positive relapsed or refractory diffuse large B-cell lymphoma (DLBCL) was listed on the National Health Insurance drug price list.

In March 2019, SymBio obtained approval to make a partial revision to the marketing approval of anticancer drug Treakisym® (non-proprietary name: bendamustine hydrochloride) as a pretreatment agent for antigen-specific T-cell infusion therapy*. With the launch of Kymriah®, Treakisym® can be used as a pretreatment agent for the CAR-T therapy.

*Antigen-specific T cell infusion therapy for cancer involves the administration of T cells that recognize specific tumor antigens to patients. In most cases, patients have few such T cells in their bodies. Thus a treatment was developed in which T cells taken from patients are engineered ex vivo and administered to patients after expanding them (T cell infusion therapy). The two main T cell infusion therapies for cancer are TCR-T therapy, which entails introducing a gene coded with a T cell receptor specific to a tumor cell-derived peptide antigen into T cells, which are administered to patients by infusion after expansion; and CAR-T therapy, in which genes coding for chimeric antigen receptors (CAR) that combine intracellular signaling domains of T cell receptors and an antigen-binding site that recognizes tumor cell membrane antigens are introduced to T cells, and administered to patients by infusion after expansion. Clinical trials using CD19 expressed in B cells as the target for CAR, in which T cells engineered with CD19-targeting CAR were administered to patients with B-cell malignancies, demonstrated a high level of clinical efficacy.

April 2019

On **April 10, 2019,** the company announced the enrollment of the first patient for the clinical trial of its rapid infusion (RI) liquid formulation of Treakisym®.

SymBio enrolled its first patient for a clinical trial mainly intended to confirm the safety of Treakisym®'s RI formulation, which reduces infusion duration to 10 minutes. The clinical trial will have a total of 36 patients, and the trial results will be submitted for regulatory approval to treat relapsed or refractory diffuse large B-cell lymphoma (DLBCL) in addition to all other previously approved indications.

In September 2017, the company entered into an exclusive license agreement with Eagle Pharmaceuticals, Inc. (based in the US) for rights to develop and market ready-to-dilute (RTD) and rapid infusion (RI) liquid formulation products of Treakisym® in Japan. Obtaining the exclusive rights for these patent-protected products enables the company to extend the product lifecycle of Treakisym® until 2031. Like the RTD formulation (currently in preparation for application), the RI formulation eliminates the need to dissolve the formulation. Moreover, the RI formulation reduces the infusion duration from 60 minutes under the current freeze-dried (FD) formulation to 10 minutes, providing added-value by reducing the burden on both healthcare providers and patients.

The company aims to apply for regulatory approval of the RTD formulation in Q3 FY12/19 and release the product in 1Q FY12/21. It plans to apply for approval of the RI formulation after completing the clinical trial and release it in 1H FY12/22.

On **April 8, 2019**, the company announced the completion of patient enrollment for a phase III clinical trial of Treakisym® targeting relapsed or refractory diffuse large B-cell lymphoma (DLBCL).

The company completed patient enrollment for the ongoing phase III clinical trial of Treakisym® for relapsed or refractory diffuse large B-cell lymphoma (DLBCL). Once the follow-up period of the enrolled cases is over, it will conduct a statistical analysis to confirm the drug's efficacy and safety. It aims to apply for the additional indication of relapsed or refractory DLBCL in Q2 FY12/20.

March 2019

On **March 26, 2019**, the company announced that a partial change application had been approved for use of Treakisym® as a pretreatment agent to chimeric antigen receptor T-cell (CAR-T) therapy.

The company announced that a partial change application for marketing approval of anticancer drug Treakisym® (generic name: bendamustine hydrochloride) has been approved.

Development of novel pharmaceuticals has been progressing worldwide in the field of antigen-specific T cell infusion therapy for cancers*. The latest approval of Treakisym® gives patients a choice of pretreatments for these novel therapies. Also on March 26, 2019, Novartis Pharma K.K. received marketing approval in Japan for the first CAR-T therapy (product name: Kymriah® intravenous infusion) for the treatment of relapsed or refractory B-cell acute lymphoblastic leukemia (ALL) in patients aged 25 or younger, and relapsed or refractory diffuse large B-cell lymphoma (DLBCL) in older patients. This allows the use of Treakisym® as a pretreatment agent for CAR-T therapy in treating these diseases once Kymriah® goes on sale.

*Antigen-specific T cell infusion therapy for cancer involves the administration of T cells that recognize specific tumor antigens to patients. In most cases, patients have few such T cells in their bodies. Thus a treatment was developed in which T cells taken from patients are engineered ex vivo and administered to patients after expanding them (T cell infusion therapy). The two main T cell infusion therapies for cancer are TCR-T therapy, which entails introducing a gene coded with a T cell receptor specific to a tumor cell-derived peptide antigen into T cells, which are administered to patients by infusion after expansion; and CAR-T therapy, in which genes coding for chimeric antigen receptors (CAR) that combine intracellular signaling domains of T cell receptors and an antigen-binding site that recognizes tumor cell membrane antigens are introduced to T cells, and administered to patients by infusion after expansion. Clinical trials using CD19 expressed in B cells as the target for CAR, in which T cells engineered with CD19-targeting CAR were administered to patients with B-cell malignancies, demonstrated a high level of clinical efficacy.

February 2019

On **February 28, 2019**, the company announced a reverse stock split and partial amendment to its Articles of Incorporation.

SymBio plans to conduct a reverse stock split, subject to approval by shareholders at the Ordinary General Meeting of Shareholders scheduled for March 28, 2019. Shares held by the shareholders recorded in the final shareholder register as of June 30, 2019 (effectively, as at the end of June 28, 2019), are to be consolidated at a ratio of four to one on July 1, 2019. Before the share consolidation (as of December 31, 2018), the number of issued shares stands at 82,398,924 shares. The number of shares to be reduced upon consolidation is 61,799,193 shares, leaving 20,599,731 shares as the number of issued shares after consolidation. Although the total number of issued shares will decrease to one quarter as a result of the share consolidation, net assets will not change, and therefore book value per share will quadruple. Accordingly, excluding changes in stock market conditions and other external factors, the share consolidation will not alter the asset value of the company's stock.

The shareholder composition based on the register of shareholders as of December 31, 2018 is as follows. On this basis, as a result of the reverse stock split the 13,466 shareholders holding less than 400 shares (holding 2,234,613 shares in total) will lose shareholder status.

Reduction in number of shareholders upon reverse stock split

	Number of shareholders (%)	Number of shares held (%)
Total shareholders	31,858 persons (100.00%)	82,398,924 shares (100.00%)
Less than 400 shares	13,466 persons (42.27%)	2,234,613 shares (2.71%)
400 shares or more	18,392 persons (57.73%)	80,164,311 shares (97.29%)

On **February 7, 2019**, the company announced a medium-term plan covering FY12/19–FY12/22.

Medium-term plan targets

(JPYmn)	FY12/18 Act.	FY12/19 Est.	FY12/20 MTP	FY12/21 MTP	FY12/21 MTP
Sales	3,810	4,465	3,282	9,132	11,282–11,809
Operating profit (losses)	-2,656	-3,587	-5,180	1,225	2,084–2,464
Recurring profit (losses)	-2,749	-3,612	-5,224	1,181	2,040–2,420
Net income (losses)	-2,753	-3,616	-5,228	1,005	1,736–2,060

Source: Shared Research based on company data

Targets in medium-term plan (FY12/19–FY12/22)

Sales

SymBio expects product sales of Treakisym® to account for the bulk of sales. Product sales targets reflect the recent pace of market penetration and sales trends, which feed into the company's revised sales growth rates calculated over the medium-term plan period. Currently sales are booked based on product shipment sales to the sales distributor, Eisai. From FY12/21 onward, sales will be booked on product shipment sales to pharmaceutical wholesalers from the company's own in-house sales organization.

The company plans to shift to its own sales organization and switch product shipments from Eisai to pharmaceutical wholesalers in FY12/21. In the run-up to this it will be necessary to reduce Eisai's inventories toward the end of FY12/20. Sales of Treakisym® based on the National Health Insurance (NHI) drug price should remain solid, reflecting actual market demand, but SymBio plans to stop shipping to Eisai with a target date of end-1H FY12/20. It expects FY12/20 sales to decline by a commensurate amount.

SymBio forecasts increased product sales of Treakisym® from FY12/21 onward as it expects to gain approval of the drug as a treatment for relapsed or refractory diffuse large B-cell lymphoma (DLBCL) in Q2 FY12/21. The company said that its sales target range for FY12/22 is based on an estimated market penetration rate due to the additional indication.

SG&A expenses

The company has broken down SG&A expenses into primarily R&D spending and other SG&A expenses.

- The company calculated R&D expenses based on the latest development plans for its existing pipeline comprising Treakisym® and rigosertib IV and oral formulations
- The company has not factored in in-licensing or development costs for drug candidates outside its existing pipeline, although it will continue to evaluate and investigate them
- Other SG&A expenses comprise primarily Treakisym® marketing, production and distribution, business development, and management related costs. SymBio is factoring in costs associated with building and operating its own sales organization from FY12/19 onward ahead of the move to sell Treakisym® in-house from FY12/21. It forecasts an increase primarily in personnel costs due to a higher medical representative headcount and higher costs due to more activities

Personnel plans

SymBio assumes it will increase the number of medical representatives to as many as 60 to prepare for in-house sales from FY12/21 and subsequent launch of rigosertib IV. It plans to allocate the bare minimum of necessary personnel in other parts of the organization and is budgeting for personnel expenses accordingly.

Funding plans

In April 2018, the company decided to issue its 45th through 47th stock acquisition rights to secure funds needed to operate until it moves into the black in FY12/21. The proceeds were basically sufficient for its already in-licensed drug development pipeline, creation of an in-house sales structure, and new in-licensing or M&A activity necessary to take advantage of long-term growth opportunities.

January 2019

On **January 7, 2019**, the company announced the submission of a Special Protocol Assessment request to the US Food and Drug Administration regarding phase III clinical trial of oral rigosertib.

In December 2018, Onconova Therapeutics, Inc. (Onconova), from which the company had in-licensed the anticancer agent rigosertib in July 2011, submitted a Special Protocol Assessment (SPA) request to the US Food and Drug Administration (FDA). The subject request was regarding the phase III clinical trial of oral rigosertib combination therapy with azacitidine for the treatment of adult patients with treatment-naïve higher-risk myelodysplastic syndrome (MDS).

Special Protocol Assessment (SPA): A system under which after completion of a phase II trial and prior to the launch of phase III trial, sponsors can reach an agreement with the FDA regarding the phase III trial protocol such as target illness, purpose, trial design, primary and secondary endpoints, and method of data analysis. The agreement indicates that the FDA concurs with the adequacy of the overall protocol design and the design can be used (without changing the terms) in the approval filing process when the phase III trial is completed. The SPA is intended to shorten FDA's review period of new drug application, as it boosts the possibility of drug approval provided the trial endpoints are achieved.

According to Onconova, the discussion between the FDA and Onconova regarding this SPA submission is expected to conclude in 1H FY12/19. The phase III trial, for which the overall response rate (the percentage of complete remission and partial remission against total enrollment) has been designated as its primary endpoint, is scheduled to begin thereafter.

December 2018

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.

November 2018

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.

Major shareholders

Top shareholders	Shares held	Shareholding ratio
Fuminori Yoshida	3,451,000	4.19%
Cephalon, Inc. (Standing proxy: Teva Pharmaceutical K.K.)	2,589,000	3.14%
Matsui Securities Co Ltd	1,238,100	1.50%
Japan Securities Finance Co., Ltd.	1,224,700	1.49%
Eisai Co., Ltd.	833,400	1.01%
J.P. Morgan Securities plc (Standing proxy: J.P.Morgan Securities Japan Co., Ltd.)	695,158	0.84%
Waseda No. 1 Investment Limited Partnership	684,000	0.83%
Aizawa Securities Co., Ltd.	606,200	0.74%
BNY GCM CLIENT ACCOUNT JPRD AC ISG (FE-AC) (Standing proxy: MUFG Bank, Ltd.)	599,876	0.73%
BNP Paribas London Branch for Prime Brokerage Clearance for Third Party (Standing proxy: The Hongkong and Shanghai Banking Corporation, Limited, Tokyo branch, Custody Department)	583,000	0.71%
SUM	12,504,434	15.18%

Source: Shared Research based on company data
As of December 31, 2018
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 90 employees as of December 31, 2018.

Employees	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 Par.
No. of employees	52	56	71	76	72	69	74	77	78	90
YoY change	10	4	15	5	-4	-3	5	3	1	12

Source: Shared Research based on company data

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
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Phone	**Exchange listing**
+81-3-5472-1125	TSE JASDAQ Growth
Established	**Listed on**
March 25, 2005	October 20, 2011
Website	**Fiscal year-end**
http://www.symbiopharma.com/index_e.html	December
IR web	
http://www.symbiopharma.com/ir_e/01.html	

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CRE, Inc.
CREEK & RIVER Co., Ltd.
Daiichi Kigenso Kagaku Kogyo Co., Ltd.
Daiseki Co., Ltd.
DEMAE-CAN CO., LTD
DIC Corporation
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Digital Garage Inc.
Dream Incubator Inc.
Earth Corporation
Elecom Co., Ltd.
en-Japan Inc.
euglena Co., Ltd.
Evolable Asia Corp.
FaithNetwork Co., Ltd.
Ferrotec Holdings Corporation
FIELDS CORPORATION
Financial Products Group Co., Ltd.
FreeBit Co., Ltd.
FRONTEO, Inc.
Fujita Kanko Inc.
Gamecard-Joyco Holdings, Inc.
GameWith, Inc.
GCA Corporation
Good Com Asset Co., Ltd.
Grandy House Corporation
Hakuto Co., Ltd.
Hamee Corp.
Happinet Corporation
Harmonic Drive Systems Inc.
HOUSEDO Co., Ltd.
IDOM Inc.
IGNIS LTD.
i-mobile Co.,Ltd.
Inabata & Co., Ltd.
Infocom Corporation
Infomart Corporation
Intelligent Wave, Inc.
ipet Insurance CO., Ltd.
istyle Inc.
Itochu Enex Co., Ltd.
JSB Co., Ltd.
JTEC Corporation
J Trust Co., Ltd
Japan Best Rescue System Co., Ltd.
JINS HOLDINGS Inc.
JP-HOLDINGS, INC.
KAMEDA SEIKA CO., LTD.
Kanamic Network Co.,LTD
Kawanishi Holdings, Inc.
Kenedix, Inc.
KFC Holdings Japan, Ltd.
KI-Star Real Estate Co., Ltd.
Kondotec Inc.
Kumiai Chemical Industry Co., Ltd.
Lasertec Corporation
LUCKLAND CO., LTD.
MATSUI SECURITIES CO., LTD.
Medical System Network Co., Ltd.
MEDINET Co., Ltd.
MedPeer,Inc.
Mercuria Investment Co., Ltd.
Micronics Japan Co., Ltd.
Milbon Co., Ltd.
MIRAIT Holdings Corporation
Monex Goup Inc.
MORINAGA MILK INDUSTRY CO., LTD.
NAGASE & CO., LTD
NAIGAI TRANS LINE LTD.
NanoCarrier Co., Ltd.
Net Marketing Co., Ltd.
Net One Systems Co.,Ltd.
Nichi-Iko Pharmaceutical Co., Ltd.
Nihon Denkei Co., Ltd.
Nippon Koei Co., Ltd.
NIPPON PARKING DEVELOPMENT Co., Ltd.
NIPRO CORPORATION
Nisshinbo Holdings Inc.
NS TOOL CO., LTD.
OHIZUMI MFG. CO., LTD.
Oisix ra daichi Inc.
Oki Electric Industry Co., Ltd
ONO SOKKI Co., Ltd.
ONWARD HOLDINGS CO.,LTD.
Pan Pacific International Holdings Corporation
PARIS MIKI HOLDINGS Inc.
PIGEON CORPORATION
QB Net Holdings Co., Ltd.
RACCOON HOLDINGS, Inc.
Raysum Co., Ltd.
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.
SHIFT Inc.
SHIP HEALTHCARE HOLDINGS, INC.
SIGMAXYZ Inc.
SMS Co., Ltd.
Snow Peak, Inc.
Solasia Pharma K.K.
SOURCENEXT Corporation
Star Mica Holdings Co., Ltd.
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SymBio Pharmaceuticals Limited
Synchro Food Co., Ltd.
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Take and Give Needs Co., Ltd.
Takihyo Co., Ltd.
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3-D Matrix, Ltd.
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TKP Corporation
TOKAI Holdings Corporation
TOYOBO CO., LTD.
Toyo Ink SC Holdings Co., Ltd
Toyo Tanso Co., Ltd.
Tri-Stage Inc.
VISION INC.
VISIONARY HOLDINGS CO., LTD.
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.

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