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SymBio Pharmaceuticals

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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, conducts clinical trials, and obtains manufacture and marketing approval in order to address the underserved medical needs of patients. With its main focus on the areas of oncology, hematology, and rare diseases (mainly multiviral infections), 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 five years after in-licensing the drug. Within three years of its launch, Treakisym® captured more than 50% of the non-Hodgkin's lymphoma (NHL) and mantle cell lymphoma (MCL) market in Japan.

As of February 2022, 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, chronic lymphocytic leukemia (CLL), and relapsed or refractory diffuse large B-cell lymphoma (DLBCL). 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 first-line treatment for low-grade NHL.

The company obtained manufacturing and marketing approval for the ready-to-dilute (RTD) liquid formulation of Treakisym® and began sales in January 2021. Unlike the lyophilized (freeze-dried [FD]) powder formulation of Treakisym®, the RTD formulation eliminates the need for troublesome manual dissolution, thereby reducing burdens placed on medical personnel. In February 2022, the company received approval for Treakisym® rapid infusion (RI) administration. The RI method reduces the administration time to just 10 minutes, versus 60 minutes for the lyophilized injection and RTD formulation. This reduces the burden on patients and healthcare professionals. The re-examination term for the lyophilized formulation of Treakisym® ended in 2020, but by launching and switching to the RTD formulation and RI administration to which SymBio has exclusive rights, the company can extend the product life cycle of Treakisym® until 2031.

Drugs in the development pipeline include rigosertib (anticancer agent for myelodysplastic syndromes) IV and oral formulations, and an antiviral drug brincidofovir.

Earnings

FY12/21 sales were JPY8.3bn (+176.4% YoY). Product sales totaled JPY8.3bn (+177.4% YoY), and the company booked no royalty revenue (JPY10mn in FY12/20). Operating profit totaled JPY1.0bn (loss of JPY4.5bn in FY12/20), recurring profit JPY1.0bn (loss of JPY4.6bn), and net income JPY2.0bn (net loss of JPY4.1bn).

For FY12/22, the company forecasts sales of JPY11.0bn (+33.1% YoY), operating profit of JPY1.8bn (+74.2% YoY), recurring profit of JPY1.8bn (+74.8% YoY), and net income of JPY1.5bn (-27.2% YoY). The company expects increased product sales of Treakisym® and profit growth at all levels on the back of sales growth and higher margins.

In its medium-term plan (FY12/21–FY12/23), with the aims of achieving sales growth and higher profit margins, SymBio projects sales of JPY12.4bn and net income of JPY1.8bn in FY12/23. 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 DLBCL.

Strengths and weaknesses

Shared Research thinks SymBio's strengths include its unique drug candidate selection process, strong product development team, and business strategy focusing on niche markets. Weaknesses include its dependence on a single individual and product (see Strengths and weaknesses).

Key financial data

	FY12/12	FY12/13	FY12/14	FY12/15	FY12/16	FY12/17	FY12/18	FY12/19	FY12/20	FY12/21	FY12/22
(JPYmn)	**Par.**	**Par.**	**Par.**	**Par.**	**Par.**	**Par.**	**Par.**	**Par.**	**Par.**	**Par.**	**Est.**
Sales	**1,955**	**1,532**	**1,955**	**1,933**	**2,368**	**3,444**	**3,836**	**2,838**	**2,987**	**8,257**	**10,992**
YoY	3.9%	-21.6%	27.6%	-1.1%	22.5%	45.4%	11.4%	-26.0%	5.3%	176.4%	33.1%
Gross profit	**593**	**318**	**527**	**583**	**904**	**1,031**	**1,173**	**865**	**867**	**5,800**	
YoY	-9.9%	-46.4%	65.6%	10.7%	55.1%	14.1%	13.7%	-26.3%	0.2%	569.1%	
Gross profit margin	30.3%	20.8%	26.9%	30.2%	38.2%	29.9%	30.6%	30.5%	29.0%	70.2%	
Operating profit	**-1,700**	**-1,681**	**-1,303**	**-2,552**	**-2,127**	**-3,947**	**-2,656**	**-4,302**	**-4,506**	**1,016**	**1,770**
YoY	-	-	-	-	-	-	-	-	-	-	74.2%
Operating profit margin	-	-	-	-	-	-	-	-	-	12.3%	16.1%
Recurring profit	**-1,729**	**-1,601**	**-1,110**	**-2,630**	**-2,317**	**-3,977**	**-2,749**	**-4,377**	**-4,616**	**1,001**	**1,750**
YoY	-	-	-	-	-	-	-	-	-	-	74.8%
Recurring profit margin	-	-	-	-	-	-	-	-	-	12.1%	15.9%
Net income	**-1,733**	**-1,605**	**-1,116**	**-2,632**	**-2,313**	**-3,978**	**-2,753**	**-4,376**	**-4,090**	**2,032**	**1,480**
YoY	-	-	-	-	-	-	-	-	-	-	-27.2%
Net margin	-	-	-	-	-	-	-	-	-	24.6%	13.5%
Per-share data (split-adjusted; JPY)											
Shares issued (year-end; '000)	19,131	30,634	30,634	32,391	46,531	54,049	20,560	26,438	38,203	38,457	
EPS (JPY)	-362.4	-277.2	-145.0	-325.0	-235.3	-319.1	-165.5	-189.0	-124.1	53.0	38.6
EPS (fully diluted)	-	-	-	-	-	-	-	-	-	52.3	
Dividend per share (JPY)	-	-	-	-	-	-	-	-	-	-	-
Book value per share (JPY)	1,018.8	957.9	835.2	510.2	434.4	200.0	212.2	143.1	105.8	162.3	
Balance sheet (JPYmn)											
Cash and cash equivalents	4,840	7,264	6,591	4,261	5,719	2,947	4,821	3,911	3,849	3,860	
Total current assets	**5,421**	**7,634**	**7,290**	**4,827**	**6,685**	**4,037**	**6,038**	**4,887**	**5,815**	**6,748**	
Tangible fixed assets	14	9	49	53	75	47	57	75	77	84	
Investments and other assets	57	37	49	53	77	100	73	70	81	1,362	
Intangible assets	11	8	66	52	42	69	71	241	302	259	
Total assets	**5,502**	**7,687**	**7,454**	**4,984**	**6,878**	**4,252**	**6,239**	**5,274**	**6,275**	**8,453**	
Accounts payable	330	-	306	320	322	604	726	121	665	70	
Short-term debt	-	-	-	-	-	-	-	-	-	-	
Total current liabilities	**599**	**251**	**488**	**551**	**942**	**1,011**	**1,336**	**872**	**1,615**	**1,518**	
Long-term debt	-	-	-	-	-	-	-	-	-	-	
Total fixed liabilities	**4**	**3**	**2**	**2**	**451**	**1**	**1**	**2**	**2**	**189**	
Total liabilities	**602**	**254**	**490**	**552**	**1,394**	**1,013**	**1,338**	**874**	**1,617**	**1,707**	
Net assets	**4,900**	**7,433**	**6,964**	**4,432**	**5,485**	**3,239**	**4,902**	**4,400**	**4,657**	**6,746**	
Total interest-bearing debt	-	-	-	-	-	-	-	-	-	-	
Statement of cash flows (JPYmn)											
Cash flows from operating activities	-1,659	-1,677	-1,266	-2,272	-1,960	-3,817	-2,325	-4,351	-4,122	140	
Cash flows from investing activities	-411	-1,332	314	1,489	-44	-78	-26	-216	-160	-71	
Cash flows from financing activities	-1	4,057	544	-3	3,658	1,164	4,272	3,740	4,222	-72	
Financial ratios											
ROA (RP-based)	-27.1%	-24.3%	-14.7%	-42.3%	-39.1%	-71.5%	-52.4%	-76.0%	-79.9%	13.6%	
ROE	-30.2%	-26.3%	-15.8%	-48.3%	-50.4%	-102.6%	-77.8%	-107.4%	-104.7%	39.6%	
Equity ratio	89.1%	96.7%	93.4%	88.9%	79.7%	76.2%	78.6%	83.4%	74.2%	79.8%	

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

Announcement concerning the license agreement with Chimerix for brincidofovir

2022-05-18

On May 17, 2022, SymBio Pharmaceuticals Limited made an announcement concerning its license agreement with Chimerix for brincidofovir.

In a press release dated May 16, 2022, Chimerix Inc. announced that it has entered into an agreement with Emergent BioSolutions Inc., transferring to the latter the license for the antiviral drug brincidofovir (BCV).

In September 2019, SymBio concluded an agreement with Chimerix, acquiring the exclusive global rights to develop, manufacture, and market brincidofovir for all indications except for the prevention and treatment of smallpox. The above transfer will have no impact on the rights acquired by SymBio.

Company announces the issuance of new shares and the 58th stock acquisition rights through third-party allotment

2022-05-17

On May 16, 2022, SymBio Pharmaceuticals Limited announced that it will issue new shares and the 58th stock acquisition rights through a third-party allotment.

The company has resolved to issue new shares and the 58th stock acquisition rights through a third-party allotment.

The total number of shares after adding the new shares (1,000,000 shares) to the number of shares for delivery if all the stock acquisition rights are exercised (2,000,000 shares) is 3,000,000 shares. This corresponds to a dilution rate of 7.80%, using as a denominator the total number of SymBio's shares issued as of March 31, 2022, of 38,486,000 shares.

Funds to be raised

- Total amount to be paid in for the new shares: JPY662mn
- Total amount to be paid in for the stock acquisition rights: JPY1,584mn
- Approximate amount of various issuance-related expenses: JPY55mn
- Estimated net proceeds: JPY2,191mn

Specific use of funds to be raised

The specific uses for the funds raised through the issuance of the new shares (JPY662mn) and the expected timing of expenditure are as follows.

- Development funds for antiviral drug brincidofovir (direct expenses): JPY432mn (expected to be disbursed from July 2022 to October 2022)
- Indirect expenses (same as above): JPY190mn (from July 2022 to October 2022)

The specific uses for the funding raised through the issuance and exercise of the stock acquisition rights (JPY1,569mn) and the expected timing of expenditure are as follows.

- Development funds for antiviral drug brincidofovir (direct expenses): JPY787mn (from October 2022 to March 2023)
- Indirect expenses (same as above): JPY386mn (from October 2022 to March 2023)
- Investment funds for new in-licensing, M&A, etc.: JPY396mn (from July 2022 to March 2023)

Summary of subscription

Overview of the issuance of the new shares

Due date of payment	June 1, 2022
Number of shares to be issued	1,000,000 common shares
Issue price	JPY662 per share
Amount of funding	JPY662mn
Method for subscription or allotment	Third-party allotment
Allottee	CVI Investments, Inc.

Overview of the issuance of the stock acquisition rights

Date of allotment	June 1, 2022
Total number of stock acquisition rights	20,000 units
Issue price	Total of JPY13.8mn (JPY688 per unit)
Number of dilutive shares from the issuance	2,000,000 shares (100 shares per unit)
Amount of funding	JPY1,584mn
Exercise price	JPY785
Exercise period	From June 2, 2022 to June 1, 2027
Method for subscription or allotment	Third-party allotment
Allottee	CVI Investments, Inc.

Signing of a joint research agreement with the National Cancer Center regarding rare cancers

2022-04-01

SymBio Pharmaceuticals Ltd. announced the signing of a joint research agreement with the National Cancer Center regarding rare cancers.

The company has signed a joint research agreement with the National Cancer Center regarding the MASTER KEY Project, an industry-academia joint project led by the center and its central hospital.

Initiation of a non-clinical study in collaboration with Brown University in the US to investigate the anti-tumor efficacy of brincidofovir IV against brain tumors

2022-03-08

SymBio Pharmaceuticals Limited announced the initiation of a non-clinical study in collaboration with Brown University in the US to investigate the anti-tumor efficacy of brincidofovir IV against brain tumors.

The company has initiated a non-clinical study in collaboration with Brown University in the US to investigate the anti-tumor efficacy of brincidofovir IV (BCV) against brain tumors associated with cytomegalovirus (CMV) infections.

According to the company, many new drugs currently are being developed for the treatment of brain tumors, but only BCV, which exhibits both antiviral and anticancer activity, has a mechanism of action against cytomegalovirus infection, which accounts for about half of all brain tumors. SymBio says it will continue to pursue the development of new treatments in therapeutic areas where no effective treatments have been established.

Trends and outlook

Quarterly trends and results

Earnings (cumulative)	FY12/21				FY12/22				FY12/22	
(JPYmn)	Q1	Q1–Q2	Q1–Q3	Q1–Q4	Q1	Q1–Q2	Q1–Q3	Q1–Q4	% of Est.	FY Est.
Sales	1,420	3,147	5,553	8,257	2,316				21.1%	10,992
YoY	157.6%	131.3%	138.1%	176.4%	63.1%					33.1%
Gross profit	1,010	2,275	4,046	5,800	1,898					
YoY	690.9%	589.5%	562.4%	569.1%	87.9%					
Gross profit margin	71.1%	72.3%	72.9%	70.2%	82.0%					
SG&A expenses	1,221	2,470	3,622	4,784	1,389					
YoY	12.0%	13.8%	-3.5%	-11.0%	13.8%					
SG&A ratio	85.9%	78.5%	65.2%	57.9%	60.0%					
Operating profit	-211	-195	424	1,016	509				28.8%	1,770
YoY	-	-	-	-	-					74.2%
Operating profit margin	-	-	7.6%	12.3%	22.0%					16.1%
Recurring profit	-209	-204	414	1,001	479				27.3%	1,750
YoY	-	-	-	-	-					74.8%
Recurring profit margin	-	-	7.5%	12.1%	20.7%					15.9%
Net income	-210	-206	325	2,032	163				11.0%	1,480
YoY	-	-	-	-	-					-27.2%
Net margin	-	-	5.9%	24.6%	7.0%					13.5%

Earnings (quarterly)	FY12/21				FY12/22			
(JPYmn)	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Sales	1,420	1,726	2,406	2,704	2,316			
YoY	157.6%	113.3%	147.6%	313.1%	63.1%			
Gross profit	1,010	1,265	1,771	1,754	1,898			
YoY	690.9%	525.5%	530.6%	585.0%	87.9%			
Gross profit margin	71.1%	73.3%	73.6%	64.9%	82.0%			
SG&A expenses	1,221	1,249	1,152	1,163	1,389			
YoY	12.0%	15.6%	-27.2%	-28.2%	13.8%			
SG&A ratio	85.9%	72.4%	47.9%	43.0%	60.0%			
Operating profit	-211	16	619	592	509			
YoY	-	-	-	-	-			
Operating profit margin	-	0.9%	25.7%	21.9%	22.0%			
Recurring profit	-209	5	618	587	479			
YoY	-	-	-	-	-			
Recurring profit margin	-	0.3%	25.7%	21.7%	20.7%			
Net income	-210	4	530	1,707	163			
YoY	-	-	-	-	-			
Net margin	-	0.2%	22.0%	63.1%	7.0%			

Source: Shared Research based on company data
Note: Figures may differ from company materials due to differences in rounding methods.
"-"denotes YoY change of over 1000%.
Note: Starting from FY12/22, the company switched to preparing consolidated financial statements in connection with the commencement of full-fledged operations at SymBio Pharma USA. As data for FY12/22 are on a consolidated basis, YoY comparisons are for reference only.

Breakdown of SG&A expenses

Earnings (cumulative)	FY12/21				FY12/22			
(JPYmn)	Q1	Q1–Q2	Q1–Q3	Q1–Q4	Q1	Q1–Q2	Q1–Q3	Q1–Q4
SG&A expenses	1,221	2,470	3,622	4,784	1,389			
YoY	12.0%	13.8%	-3.5%	-11.0%	13.8%			
R&D expenses	473	912	1,286	1,736	496			
YoY	8.0%	9.4%	-26.3%	-23.4%	4.8%			
SG&A expenses excl. R&D	747	1,557	2,335	3,048	893			
YoY	14.7%	16.6%	16.3%	-1.9%	19.5%			

Earnings (quarterly)	FY12/21				FY12/22			
(JPYmn)	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
SG&A expenses	1,221	1,249	1,152	1,163	1,389			
YoY	12.0%	15.6%	-27.2%	-28.2%	13.8%			
R&D expenses	473	439	374	450	496			
YoY	8.0%	11.0%	-59.0%	-13.7%	4.8%			
SG&A expenses excl. R&D	747	810	778	713	893			
YoY	14.7%	18.3%	15.7%	-35.1%	19.5%			

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

Q1 FY12/22 results

- Sales: JPY2.3bn (+63.1% YoY)
- Operating profit: JPY509mn (loss of JPY211mn in Q1 FY12/21)
- Recurring profit: JPY479mn (loss of JPY209mn in Q1 FY12/21)
- Net income attributable to owners of the parent: JPY163mn (loss of JPY210mn in Q1 FY12/21)

SymBio has applied the Accounting Standard for Revenue Recognition (ASBJ Statement No. 29) from Q1 FY12/22. Under the previous accounting standard, the company recorded allowance for sales returns in the amount equivalent to gross profit. However, in accordance with the new accounting standard regarding variable consideration, the company no

longer recognizes revenue at the time of sale and records refund liabilities as "other" under the current liabilities section of the balance sheet.

As a result of adopting the Accounting Standard for Revenue Recognition, sales, operating profit, and recurring profit each increased by JPY42mn.

In February 2022, SymBio obtained approval for a partial change to the marketing authorization for the ready-to-dilute (RTD) intravenous formulation of TREAKISYM® 100mg/4ml, which was launched in January 2021, to add rapid infusion (RI) administration. Compared to the freeze-dried (FD) formulation, the RTD formulation reduces the time required for the complicated dissolution process. RI administration further benefits both patients and healthcare providers by reducing the infusion time from the 60 minutes required by the RTD formulation.

RI administration reduces burden on patients and healthcare providers by shortening the infusion time compared with that required for the FD and RTD formulations. Further, RI administration is diluted using only one-fifth of the amount of saline solution required for the RTD formulation, reducing the amount of salt used and hence rendering it appropriate for elderly patients.

As evidence of conversion from the FD to RTD formulation, more than 99% of medical institutions had started using the RTD formulation by end-March 2022. With over 93% of medical institutions expressing an intention to convert to RI administration as of end-April 2022, uptake of RI administration is proceeding as planned. On the quality assurance front, SymBio also has taken steps to ensure the stable supply of FD and RTD formulations of TREAKISYM®.

Despite sales activities being constrained by factors including delays in treatment and restrictions on facility visits due to the COVID-19 pandemic, sales rose 63.1% YoY to JPY2.3bn. The increase was largely due to the approval in March 2021 of TREAKISYM® for the additional indication of combination use in bendamustine-rituximab (BR) therapy and in polatuzumab vedotin plus bendamustine-rituximab (P+BR) therapy to treat recurrent/refractory diffuse large B-cell lymphoma (r/r DLBCL). The May 2021 NHI price listing of Chugai Pharmaceutical's antibody drug conjugate polatuzumab vedotin contributed to an increase in sales for the indication of r/r DLBCL.

Gross profit grew YoY on the back of higher sales and GPM. The increase in gross profit offset the rise in SG&A expenses, leading to YoY growth in all profit categories from the operating profit line down and moving the company into the black.

Gross profit was JPY1.9bn (+87.9% YoY), and GPM was 82.0% (+10.9pp YoY). The rise in GPM was attributed to the transition to in-house sales, launch of the RTD formulation of Treakisym® in January 2021, and the abovementioned switch to the liquid (RTD and RI) formulations of Treakisym®.

Reasons why in-house marketing of Treakisym® contributed to GPM improvement: Switching from marketing through Eisai (based on the marketing agreement with Eisai) to doing its own marketing meant that products are shipped to pharmaceutical wholesalers instead of to Eisai starting from December 10, 2020. This allowed the company to receive not only the gross profit it received previously (the company's sales to Eisai minus cost of sales), but also the gross profit earned by Eisai through December 9, 2020 (i.e., the difference between the shipment price from Eisai to pharmaceutical wholesalers and the price Eisai paid the company to source the product).

GPM rises due to switching from the lyophilized formulation to the liquid (RTD and RI) formulations of Treakisym®: The company sourced the lyophilized formulation of Treakisym® from Astellas Deutschland, but the liquid formulations are supplied by Eagle Pharmaceuticals. The company says that the GPM on liquid formulations of Treakisym® is higher than the GPM on the lyophilized formulation.

SG&A expenses were JPY1.4bn (+13.8% YoY).

- R&D expenses rose 4.8% YoY to JPY496mn. This included expenses for conducting clinical trials for the intravenous formulation of brincidofovir.
- Excluding R&D expenses, SG&A expenses rose 19.5% YoY to JPY893mn.

Progress in Q1 versus full-year FY12/22 company forecast

Q1 sales were 21.1% of the full-year FY12/22 company forecast while operating profit came in at 28.8%. Shared Research understands that Q1 earnings are in line with the company's expectations for the full year. Sales were slightly below plan due to delays in medical treatments and restrictions on marketing activities caused by the ongoing COVID-19 pandemic. Profits, on the other hand, were in line with expectations. Marketing activity expenses were lower than expected as the company conducted these activities online due to the pandemic.

Overview of business progress

In Q1 FY12/22, progress in main businesses was as follows:

- In May 2022, Chimerix agreed to transfer its rights to anti-viral drug brincidofovir to Emergent BioSolutions Inc. In September 2019, SymBio acquired from Chimerix exclusive worldwide rights to develop, manufacture, and market brincidofovir for all indications except for prevention and treatment of smallpox. The transfer of rights to Emergent BioSolutions will have no impact on the company's rights to brincidofovir.

- In May 2022, the company announced the issuance of new shares and the 58th series of share subscription rights through a third-party allotment. Net proceeds to be raised from the issuance are JPY2.2bn, and the dilution ratio is 7.80%. The new shares and share subscription rights will be allotted to CVI Investments, Inc. operated by Heights Capital Management, Inc. According to the company, Heights Capital Management is a member of Susquehanna International Group, a major global financial conglomerate, and has a track record of investing in over 100 biotech companies. The company intends to allocate the funds raised to development of brincidofovir.

- In February 2022, SymBio received approval for its for Treakisym® RI (rapid infusion) administration.

- In February 2022, the Ministry of Health, Labour and Welfare approved manufacture and marketing of generic drugs of the company's Treakisym® Intravenous Infusion (RTD formulation). As this could possibly infringe the company's exclusive rights to develop and commercialize the patent-protected product in Japan, the company consulted with the licensor Eagle Pharmaceuticals, and notified the four companies that had obtained the approval for generic drugs of the possibility of patent infringement, demanding they take appropriate actions.

In September 2017, the company entered into a license agreement with Eagle Pharmaceuticals, Inc., based on which Eagle granted the company exclusive rights to develop and commercialize bendamustine liquid formulation BENDEKA® (RTD and RI formulations of Treakisym®) in Japan. According to the company, some companies in the US have attempted to launch generic versions of Treakisym® liquid formulations, but they all infringed on Eagle's patents, and Eagle prevailed in lawsuits. As of May 2022, there were no generic versions of Treakisym® liquid formulations on the market.

Establishment of an in-house sales organization

The business alliance agreement between SymBio and Eisai Co., Ltd. under which Eisai acts as a sales agent expired in December 2020, and the company switched to in-house sales for domestic sales of Treakisym®.

In conducting in-house sales, SymBio established a sales organization that can cultivate needs, provide information on the company products, and plan seminars. In addition to medical representatives, the company deployed hematology experts with extensive knowledge of the field throughout Japan. Further, the company concluded basic agreements with Suzuken Co., Ltd and Toho Pharmaceutical Co., Ltd for the procurement and sale of pharmaceuticals to build a nationwide distribution network. The company has established two distribution centers, one in Eastern Japan and the other in Western Japan, under management by S.D. Collabo Co., Ltd.

Anticancer agent SyB L-0501 (FD formulation)/SyB L-1701 (RTD formulation)/SyB L-1702 (RI administration); generic name: bendamustine hydrochloride or bendamustine hydrochloride hydrate, product name: Treakisym®

In March 2021, SymBio obtained approval for the use of the FD formulation of TREAKISYM® in BR therapy to treat r/r DLBCL as an additional indication. In January 2021, the company commenced sales of the ready-to-dilute (or RTD) liquid formulation of TREAKISYM® inlicensed from US-based Eagle Pharmaceuticals, Inc., having obtained marketing approval in September 2020. In April 2021, the company obtained approval for a partial change to the marketing approval of the RTD formulation

for its use in BR and P+BR therapy for the treatment of r/r DLBCL. For the RI administration, the company completed clinical studies on safety and filed a partial change application in May 2021. This application was approved in February 2022.

SymBio will continue to explore new potential applications of TREAKISYM®, including via specified clinical research with Saitama Medical University and joint research with Kyoto University.

Anticancer agent SyB L-1101 (IV)/SyB C-1101 (oral); generic name: rigosertib sodium

Onconova Therapeutics, Inc., the drug's licensor, announced in August 2020 that INSPIRE, the pivotal phase III study in higher-risk myelodysplastic syndromes (HR-MDS) patients comparing IV rigosertib to physicians' choice of treatment, did not meet its primary endpoint. SymBio is in charge of clinical development in Japan and is collaborating with Onconova regarding the future development of rigosertib.

For rigosertib, the company is searching for new indications as well as new applications for the drugs used in combination with TREAKISYM® or with other existing drugs, through joint research with the University of Tokyo and other institutions.

Antiviral drug SyB V-1901 (generic name: brincidofovir)

In development of the intravenous and oral formulations of the antiviral drug brincidofovir (SyB V-1901; BCV IV and BCV Oral), the company is conducting joint research with top research institutions specialized in each field in Japan and overseas in light of the broad spectrum of the drug's effectiveness against dsDNA virus infections. It will consider additional global clinical trials based on the scientific findings of the research.

Earlier clinical trials in the US and Europe conducted by US-based Chimerix Inc. have demonstrated that BCV Oral has broad-spectrum antiviral effects against a variety of dsDNA viruses. BCV IV is expected to be effective and safe for the prevention and treatment of many dsDNA viruses, including adenovirus (AdV) infections after hematopoietic stem cell transplantation. In June 2021, Chimerix announced that the US FDA had granted BCV Oral approval for the treatment of smallpox.

As of May 2022, the company was conducting a phase II clinical trial of BCV in the US for treatment of adenovirus infection in children; preparing for clinical development of the drug as a treatment for BK virus infection associated with kidney transplantation; and conducting joint research on the antitumor effect of the drug on cytomegalovirus-associated glioblastoma. The company also plans to develop BCV as a treatment for diseases caused by or associated with EB virus.

- Based on a global advisory board review held in February 2020, the company has decided to prioritize the global development of BCV IV primarily in Japan, the US, and Europe, targeting disseminated AdV infections occurring after hematopoietic stem cell transplantation, a niche area with a high unmet medical need. In March 2021, the company filed an IND application with the US Food and Drug Administration (FDA) to conduct a phase II clinical trial primarily in pediatric patients suffering from AdV infections (also including adults). This development program was granted fast-track designation by the FDA in April 2021, and the investigational drug was administered to the first patient in August 2021. In January 2022, the company successfully filed a clinical trial application to the Medicines and Healthcare products Regulatory Agency (MHRA) of the UK.

- BK virus nephropathy after kidney transplantation is considered a disease with serious consequences for the recipient, the donor, the medical practitioner, and society, as it impairs the function of the transplanted kidney. SymBio has been working toward an early solution to this problem through an international framework, preparing for clinical development targeting BK virus infection after kidney transplantation. The company also has been preparing for clinical development targeting EB virus-related diseases such as the difficult-to-treat multiple sclerosis, as well as post-COVID-19 condition assumed to be associated with EB virus. Through the accumulation of clinical trial data, SymBio will examine the efficacy of BCV in humans against various dsDNA virus infections and expand target indications to include multiviral infections. By doing so, it aims to expand the target market for and maximize the business value of BCV.

- In addition to antiviral activity, the company expects BCV to have antitumor effects. Through joint research with the National Cancer Centre Singapore and University of California San Francisco Brain Tumor Center, SymBio is investigating new indications for BCV in oncology, including rare brain tumors and EB virus-positive lymphoma. In March 2022, the company commenced joint research with Brown University in the US to investigate the anti-tumor effects of BCV on cytomegalovirus-associated glioblastoma (GBM).

Overseas

With a view to accelerating global development of the antiviral drug brincidofovir, the company's US-based wholly-owned subsidiary SymBio Pharma USA, Inc. appointed Dr. Carolyn Yanavich as its Vice President and Head of Project Management and Clinical Operations in October 2021. In April 2022, SymBio Pharma USA appointed Dr. Yanavich as Chief Operating Officer and Chief Development Officer.

In-licensing of drug candidates

The company is currently focusing on unrolling global development plans for the antiviral drug brincidofovir it in-licensed in September 2019, but also constantly looking into multiple licensing deals and looking for and evaluating promising new in-licensing drug candidates.

Full-year company forecast

	FY12/21			FY12/22	
(JPYmn)	1H Act.	2H Act.	FY Act.	FY Est.	YoY
Sales	3,147	5,110	8,257	10,992	33.1%
Gross profit	2,275	3,525	5,800	8,796	51.7%
Gross profit margin	72.3%	69.0%	70.2%	80.0%	
SG&A expenses	2,470	2,314	4,784	7,026	46.9%
SG&A ratio	78.5%	45.3%	57.9%	63.9%	
R&D expenses	912	824	1,736	3,056	76.0%
SG&A expenses excl. R&D	1,557	1,491	3,048	3,970	30.3%
Operating profit	-195	1,211	1,016	1,770	74.2%
Operating profit margin	-	23.7%	12.3%	16.1%	
Recurring profit	-204	1,205	1,001	1,750	74.8%
Recurring profit margin	-	23.6%	12.1%	15.9%	
Net income	-206	2,238	2,032	1,480	-27.2%
Net margin	-	43.8%	24.6%	13.5%	

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

Earnings outlook

For FY12/22, the company forecasts sales of JPY11.0bn (+33.1% YoY), operating profit of JPY1.8bn (+74.2% YoY), recurring profit of JPY1.8bn (+74.8% YoY), and net income of JPY1.5bn (-27.2% YoY).

FY12/22 company sales forecast

The company expects the following four factors to drive sales growth in FY12/22.

- Addition of relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL) as a new indication for BR and P-BR therapy, approved in March 2021.
- Addition of Chugai Pharmaceutical's genetically engineered polatuzumab vedotin in the NHI drug price list in May 2021, which will contribute to Treakisym® sales for the indication of r/r DLBCL for the full year. Chugai Pharmaceutical forecasts FY12/22 sales of POLIVY (generic name: polatuzumab vedotin) at JPY9.4bn (+38.2% YoY).
- Progress in the switch from the current multi-drug combination therapy for the indication of r/r DLBCL to Treakisym®
- Increased use of Treakisym® for first line treatment for the indication of low-grade non-Hodgkin's lymphoma (progress in switch from R-CHOP therapy [refer to Business section for discussion of R-CHOP therapy])

According to the company, in FY12/21 the clearance in February–May 2021 of Eisai's market inventory distributed prior to the switch to its own sales force reduced sales by about JPY450mn, and delayed medical care due to the COVID-19 pandemic reduced sales by roughly JPY400mn. Clearance of Eisai's inventory will not be a factor in FY12/22, and Shared Research believes that the backlog of delayed medical treatment will be cleared as the COVID-19 vaccine rollout progresses.

In February 2022, Japan's MHLW approved manufacture and marketing of generic drugs of the company's Treakisym® Intravenous Infusion (RTD formulation). As this could infringe the company's exclusive rights to develop and commercialize the patent-protected product in Japan, the company consulted with the licensor Eagle Pharmaceuticals, and notified the four companies that had obtained the approval for generic drugs of the possibility of patent infringement, demanding they take appropriate actions. The company was considering the potential impact of the approval of the generic RTD formulation, but has not factored this into its FY12/22 forecast.

FY12/22 company operating profit forecast

FY12/22 company gross profit forecast

The company forecasts gross profit of JPY8.8bn (+51.7% YoY) and GPM of 80.0% (+9.8pp YoY). The company expects higher GPM as the valuation loss of JPY332mn on inventories of Treakisym® FD formulation drops out and the switchover from Treakisym® FD formulation to the RTD formulation and RI administration progresses.

Higher margins accompanying switch from lyophilized formulation to RTD formulation of Treakisym®: The company sourced the lyophilized formulation of Treakisym® from Astellas Deutschland, but the liquid (RTD and RI) formulations are supplied by Eagle Pharmaceuticals. The company says that the GPM on liquid formulations of Treakisym® is higher than that on the lyophilized formulation.

FY12/22 company SG&A expenses forecast

SymBio forecasts SG&A expenses of JPY7.0bn (+46.9% YoY).

- The company forecasts R&D expenses of JPY3.1bn (+76.0% YoY). It plans to accelerate the global development of antiviral drug brincidofovir for multiple indications. It will also search for new indications through joint research with academia and step up efforts to investigate in-licensing candidates, with an eye on forming partnerships as well.

- SG&A expenses excluding R&D are estimated at JPY4.0bn (+30.3% YoY). The company plans to increase headcount at subsidiary SymBio Pharma USA. The forecast includes one-time costs such as milestone payments.

Key pipeline development plans for FY12/22

The main pipeline development plans are as follows.

Treakisym®

In February 2022, the company obtained approval for a partial change to the marketing authorization of Treakisym® RI liquid formulation. In 1H FY12/22, it plans to press ahead with the switch to the RI formulation.

The RI method reduces the administration time to just 10 minutes, versus 60 minutes for the lyophilized injection and RTD formulation. This lessens the burden on patients and healthcare professionals. The volume of diluted saline solution is one-fifth that of the RTD formulation, with the lower salt content making it suitable for elderly patients. According to the company, as of February 2022, all of the Treakisym® used in the US was the liquid formulation administered using the RI technique.

Rigosertib injection and oral rigosertib

In August 2020, rigosertib licensor Onconova announced that its global phase III trial (INSPIRE study) of intravenous rigosertib formulation in patients with higher-risk myelodysplastic syndromes (higher-risk MDS) intolerant of treatment with hypomethylating agents failed to meet its primary endpoints. SymBio is in charge of clinical development in Japan, and plans to use the knowledge obtained from genomic analysis of the INSPIRE study in future development of rigosertib.

Antiviral drug brincidofovir

Regarding the intravenous formulation of brincidofovir (BCV IV), after a global advisory board review in February 2020, the company decided to prioritize global development of BCV IV (mainly in Japan, the US, and Europe) to treat adenovirus (AdV) infections in patients receiving hematopoietic stem cell transplantation to address an unmet medical need. In August 2021, the investigational drug was administered to the first patient enrolled in the phase II clinical trial for the indication of adenovirus infections for children (as well as adults).

The company is preparing to investigate the development of BCV IV in other transplant areas, cancer, and neuro-infectious diseases (see Business description for details).

- In transplants, the company is preparing to launch a global phase II clinical trial to treat adenovirus (AdV) infections in patients following hematopoietic stem cell transplants. It is also preparing to launch a clinical trial targeting BK virus infections following kidney transplants.

- In the field of cancer, in March 2022 the company launched a joint non-clinical study with Brown University of the US to investigate the antitumor effect of BCV IV on brain tumors associated with cytomegalovirus infection.

- In neuro-infectious diseases, the company plans to look into the efficacy of BCV IV on multiple sclerosis (MS).

Long-term outlook

Medium-term plan (FY12/21–FY12/23)

SymBio announced a three-year medium-term plan for FY12/21 through FY12/23 along with the FY12/20 results announcement.

Medium-term plan targets

	FY12/20	FY12/21	FY12/22	FY12/23
(JPYmn)	Act.	Est.	Targets	Targets
Sales	2,987	9,151	10,985	12,369
YoY	5.3%	206.4%	20.0%	12.6%
Operating profit	-4,506	1,361	1,738	2,099
YoY	-	-	27.7%	20.8%
Operating profit margin	-	14.9%	15.8%	17.0%
Recurring profit	-4,616	1,350	1,727	2,088
YoY	-	-	27.9%	20.9%
Recurring profit margin	-	14.8%	15.7%	16.9%
Net income	-4,090	1,149	1,470	1,778
YoY	-	-	27.9%	21.0%
Net margin	-	12.6%	13.4%	14.4%

Source: Shared Research based on company data

Targets in medium-term plan (FY12/21–FY12/23)

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.

- Sales through FY12/20 were 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.

- In estimating sales from FY12/21 onward, SymBio disclosed targets assuming increased product sales of Treakisym® 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.

Transition to in-house sales structure

SymBio entrusted Treakisym® sales to Eisai until end-FY12/20. During this period, product shipments to Eisai were booked as sales. However, Eisai's exclusive sales period expired in FY12/20, and from FY12/21 SymBio switched to selling Treakisym® in-house. Up to and including FY12/20, Shared Research assumed that the price of shipments to Eisai would be around 50% of the NHI drug price. Following the transition to an in-house sales structure in FY12/21, Shared Research thinks the price that SymBio charges to wholesalers is roughly 90% of the NHI drug price. Thus even if volume remains largely unchanged, the company expected higher selling prices to drive sharp YoY sales growth in FY12/21.

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

The company planned to seek approval of the additional indication of r/r DLBCL for Treakisym® in Q2 FY12/21 (gained in March 2021). It aimed 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's FY12/19 sales target was 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.

Treakisym® indicated for DLBCL will begin contributing to earnings in FY12/21. The full-year contribution of this product (indicated for DLBCL) in FY12/22 and FY12/23, as well as its higher market penetration rate will likely boost overall sales.

Gross profit under the medium-term plan

The FY12/21 full-year forecast called for a rise in GPM to 76.0% (+47pp YoY; came in at 70.2%), due to starting in-house marketing of Treakisym® and switching to the RTD formulation of the product. The company assumes that progress in switching to liquid formulations of Treakisym® during the medium-term plan period will gradually raise the GPM.

Based on historical performance, Shared Research understands that the gross profit margin was about 30% for Treakisym® shipments to Eisai prior to December 10, 2020. As outlined earlier, on December 10, 2020, SymBio transitioned to in-house sales of Treakisym®, rather than entrusting them to Eisai. The company now ships Treakisym® to pharmaceutical wholesalers instead of to Eisai. The gross profit earned prior to the transition remains, but is augmented by the gross profit that had previously gone Eisai's way (difference between the procurement price paid by Eisai and the price on shipments from Eisai to wholesalers). Shared Research estimates that the transition to in-house sales will lift SymBio's gross profit margin to around 70%.

SymBio is likely to further boost the gross profit margin by procuring Treakisym® from a different source. The company procures lyophilized Treakisym® from Astellas Deutschland, but procures the liquid formulations (RTD and RI formulations) from Eagle Pharmaceuticals.

SG&A expenses under the medium-term plan

The company expects a gradual increase in SG&A expenses, including milestone payments and clinical trial expenses. SG&A expenses are largely broken down to 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®, rigosertib, and antiviral drug brincidofovir.
  - The company plans milestone payments for Treakisym® RTD formulation and antiviral drug brincidofovir in FY12/22 and FY12/23. It also expects an increase in clinical trial expenses for brincidofovir in FY12/22 onward.
  - The company does not assume any upfront payments for in-licensing drug candidates outside its existing pipeline after brincidofovir, an antiviral drug, although it will continue to evaluate and investigate them.
- Other SG&A expenses comprise primarily Treakisym® sales and marketing, production and distribution, business development, and management related costs. From FY12/21, SymBio assumes costs associated with operating its own sales organization for sales of Treakisym®. It forecasts an increase primarily in personnel expenses due to a higher medical representative headcount and higher expenses due to more activities.

Net income

In the previous medium-term plan announced in February 2020, the company forecast net income exceeding recurring profit in FY12/21 and FY20/22 to reflect the reduction in loss carried forward from FY12/21 onward on tax effect accounting. Heeding the advice of accounting auditors, the new medium-term plan was formulated by removing income taxes adjustment factors for FY12/21 onward.

Personnel plans

SymBio completed the formation of its 62-member nationwide sales structure in FY12/20. It plans to allocate the bare minimum of necessary personnel in other parts of the organization and is budgeting for personnel expenses accordingly. The company plans to increase personnel expenses for global expansion of brincidofovir, an antiviral drug, and reflected this in personnel expenses.

Funding plans

Regarding funding plans, the company will work toward strengthening its financial base so that it can respond in a flexible and nimble way to the need for funds according to business developments.

Shared Research thinks that once the company has turned profitable at net income level in FY12/21, there will be no need to raise funds through the issue of shares. In December 2020, SymBio concluded a JPY3.0bn syndicated loan (committed credit line) agreement with MUFG Bank, Ltd. as the arranger and agent to have a flexible funding structure in place.

Business

Business description

SymBio obtains rights to develop and market new drug candidates from biotech companies in the US and EU

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)

- **Post 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.
- **Niche market:** 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 rare diseases—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**: The company identifies and capitalizes on opportunities to grow sales by acquiring the right to develop drug candidates in Japan and other international markets.

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%.

Products under development: Treakisym® (RTD formulation and RI administration), brincidofovir, and rigosertib (injection and oral)

Additional indications for Treakisym®

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, mantle cell lymphoma, and relapsed or refractory diffuse large B-cell lymphoma (DLBCL).

- 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 untreated 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.
- Relapsed or refractory diffuse large B-cell lymphoma (DLBCL): Approved as additional indication in March 2021.

Treakisym® (RTD formulation and RI administration)

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) formulation and rapid infusion (RI) administration products in Japan. Securing products to replace freeze-dried (FD) product (whose exclusive sales rights in Japan expired in 2H 2020) had been a priority for the company. SymBio obtained approval for the RTD formulation in September 2020, and launched the product in January 2021. The company obtained approval for the RI administration in February 2022.

With this, it aims to promote a switch in clinical settings from lyophilized powder formulation to RTD and RI formulations that lighten the workload for medical professionals, at the same time curtailing uptake of Treakisym® generics. Because it has exclusive rights to sell the RTD and RI formulations in Japan, SymBio will be able to extend 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 of rigosertib (injection) 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.

In August 2015, Onconova initiated global phase III clinical trials for patients with higher-risk MDS who had failed to respond to the standard therapy with hypomethylating agents (HMAs) or relapsed in more than 20 countries, and announced in August 2020 that they had failed to meet the primary endpoints in comparison with physician's choice. In Japan, the company conducted joint global phase III clinical trials in cooperation with Onconova. SymBio says it will utilize the knowledge obtained from additional analysis of the global phase III clinical trials in future development of rigosertib.

For the oral form of the drug, Onconova completed phase I/II clinical trials targeting first-line treatment of higher-risk MDS, which suggested efficacy and safety of rigosertib-azacitidine combination therapy. SymBio initiated the phase I clinical trial of rigosertib monotherapy for higher-risk MDS in Japan in June 2017 and completed patient enrollments in June 2019.

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. In August 2021, the company launched phase II clinical trials in the US targeting adenovirus infection in children.

Revenue source: Treakisym® sales

Revenue mainly comes from product sales of Treakisym®. Operating losses had persisted since the company's founding with the exception of FY12/08 when the company booked operating profit due to a one-time contract payment from Eisai for an exclusive domestic right to sell Treakisym®.

In FY12/21, the company turned profitable from the operating profit line down. SymBio began in-house sales of Treakisym® in December 2020 and sales of the RTD formulation in January 2021, and in March 2021 it obtained approval for the additional indication of relapsed or refractory DLBCL in FY12/21, which all contributed to sales growth and GPM improvement.

Over the course of the medium-term plan (FY12/21–FY12/23), the company targets operating profit of JPY2.1bn in FY12/23 and expects to continue posting operating profit over the medium term 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. It can obtain approval 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.

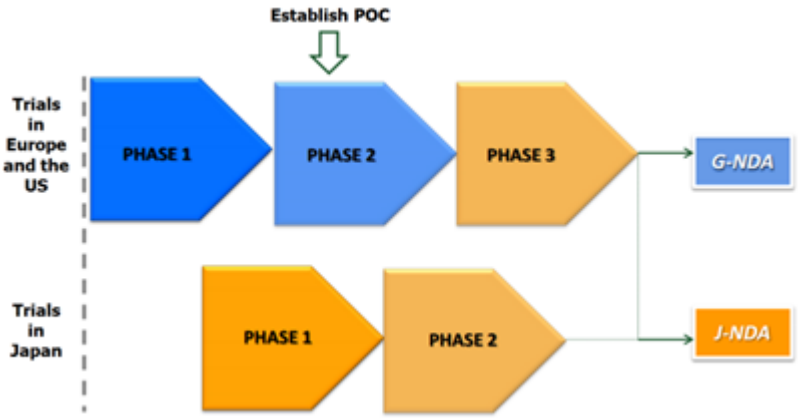
The overall aim is to reduce development risk, streamline expenses, and expand revenue opportunities. This hinges on the following five strategies, namely post proof-of-concept, screening, fabless, niche market, and global expansion.

Post-POC strategy: 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 efficacy and safety of a new drug candidate through administration to animals or humans) 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 strategy: independent search network plus evaluation experience

Identify candidate drugs by utilizing independent search network and 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.

Evaluation by a panel of pharmaceutical experts

The final in-licensing candidate will be determined by the Scientific Advisory Board after rigorous evaluation by external experts involved in therapeutic research in related fields.

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

The company has in-licensed only a few new drug candidates that have met its stringent criteria. The first was Treakisym®, which the company currently sells in Japan (as of February 2022). The company is also developing intravenous and oral formulations of rigosertib and antiviral drug brincidofovir.

Scientific Advisory Board

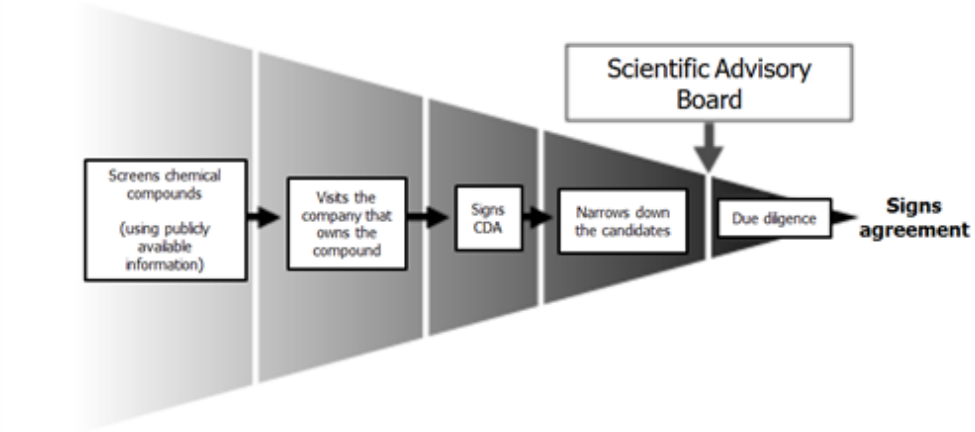
The Scientific Advisory Board is comprised of former directors of pharmaceutical companies, researchers, and doctors, and meets three times a year. Typically, the SAB panel evaluates two to three drug candidates that have been selected via the company's in-house screening process. This in-house screening 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

Drug candidate selection process



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

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 began in-house sales in Japan of Treakisym® on December 10, 2020, taking over from Eisai, which marketed the product until December 9, 2020.

Niche markets: oncology, hematology, and rare diseases

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 rare diseases.

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. In July 2018, Treakisym® was newly included as a standard option for first-line treatment of low-grade NHL and mantle cell lymphoma in the Guidelines for Hematological Malignancies 2018 issued by the Japan Society of Hematology in July 2018.

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. Also, it acquired exclusive worldwide rights to develop, manufacture, and market brincidofovir.

Pipeline

Pipeline

Name/Code	Licensed country	Indications	Development stage	Sales partner
Treakisym® SyB L-0501 (FD)	Japan	Relapsed or refractory low-grade NHL and MCL	Approved (Oct. 2010)	In-house sales
		Relapsed or refractory DLBCL (aggressive NHL)	Approved (Mar. 2021)	
		Untreated low-grade NHL and MCL	Approved (Dec. 2016)	
		CLL	Approved (Aug. 2016)	
	Singapore	Low-grade B-cell NHL	Approved (Jan. 2010)	Eisai Co., Ltd. (Exclusive development and sales rights granted to Eisai)
		CLL		
	South Korea	CLL MM	Approved (May 2011)	Eisai Co., Ltd. (Exclusive development and sales rights granted to Eisai)
		Relapsed or refractory low-grade NHL	Approved (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	Approved (Dec. 2009)	
		CLL		
	Taiwan	Low-grade NHL	Approved (Oct. 2011)	InnoPharmax, Inc. (Taiwan) (Exclusive development and sales rights granted to Eisai)
		CLL		
Treakisym® SyB L-1701 (RTD)	Japan	All indications	Approved (Sep 2020)	In-house sales
Treakisym® SyB L-1702 (RI)	Japan	All indications	Approved (Feb. 2022)	In-house sales
Rigosertib (IV) SyB L-1101	Japan	Relapsed or refractory higher-risk MDS	Global phase III clinical trials Additional analysis underway	—
Rigosertib (oral) SyB C-1101	Japan	Relapsed or refractory higher-risk MDS (monotherapy)	Phase I clinical trials underway	—
		Untreated higher-risk MDS (with azacitidine)	Global phase I/II clinical trials completed	—
Brincidofovir (IV) SyB V-1901	Worldwide	Adenovirus infection after hematopoietic stem cell and kidney transplantation	Phase II clinical trials underway	—

Source: Shared Research based on the company website

As of February 2022, the main drugs for which SymBio was preparing to file for approval or in the development pipeline were as follows:

- Rigosertib (intravenous formulation), for the indication of relapsed or refractory higher-risk MDS: Conducting additional analysis of global phase III clinical trial results
- Rigosertib (oral formulation), for the indication of higher-risk MDS: Completed patient enrollment for the phase I clinical trial in June 2019, and completed global phase I/II clinical trials of the combination therapy with azacitidine. Preparing for phase I clinical trial of the combination therapy with azacytidine.
- Antiviral drug brincidofovir: Phase II clinical trials of brincidofovir (liquid formulation) targeting adenovirus infection in children are underway.

SyB L-0501 (generic name: 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 March 2021, the company gained approval of Treakisym® for the additional indication of relapsed or refractory DLBCL (aggressive NHL).

Lymphatic cancer

Lymphatic cancer, a malignant growth of lymphocytes in white blood cells

Lymphatic cancer is a malignant growth of lymphocytes 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

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

Source: Shared Research based on materials from 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; developed jointly with Eisai in Japan; sold in-house from December 2020

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). The marketing agreement with Eisai expired in December 2020, after which SymBio began to independently market Treakisym® in Japan.

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.

Approved 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. The domestic launch of the drug was in December 2010.

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 and RI formulations

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

In December 2016, Treakisym® was approved in Japan as the first-line treatment for low-grade NHL/MCL. It was approved for CLL in August 2016.

The company received approval of Treakisym® for the additional indication of relapsed or refractory DLBCL (aggressive NHL) in March 2021.

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	Obtained approval (Dec. 2016)	-	Obtained approval (Aug. 2016)
Relapsed and refractory	Number of patients	9,336	18,672	
	Approval	Obtained	Completed patient enrollment for phase III clinical trials in Japan	
	Development status	Obtained approval in Japan (Oct. 2010)	Applied approval (May 2020)	

Source: Shared Research based on company data

Treakisym® indicated for untreated low-grade NHL and MCL

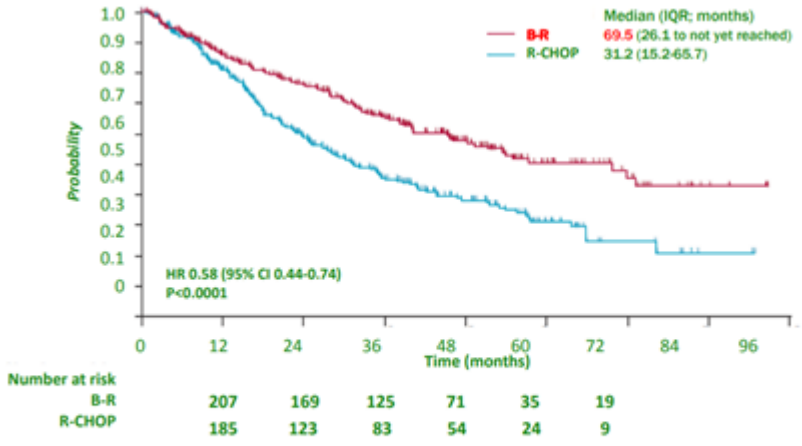
According to the company, R-CHOP therapy—a combination of rituximab with CHOP chemotherapy drugs (cyclophosphamide, doxorubicin (hydroxydaunomycin), vincristine (oncovin), and prednisolone)—was standard first-line treatment for low-grade NHL and MCL in Japan prior to December 2016. In December 2016, 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.

In Phase III clinical trials conducted overseas, rituximab in combination with Treakisym® (bendamustine hydrochloride; BR therapy) demonstrated safety and efficacy superior to those of the 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.

These comparative studies were conducted at 81 facilities in Germany, in patients who were newly diagnosed between September 2003 and August 2008 with stage III or IV low-grade NHL or MCL. The studies compared R-CHOP therapy with the combination therapy of bendamustine-rituximab (BR) (bendamustine is marketed as Levact®, Ribomustin®, or Ribovact® in Europe). A total of 275 patients underwent R-CHOP therapy, while 274 underwent the BR therapy. The median observation period was 45 months. Clinical results showed that the median progression-free survival was 69.5 months for the BR group and 31.2 months ($p<0.0001$) for the R-CHOP group, demonstrating greater statistical significance for 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 comparative study of BR and R-CHOP therapies in patients with untreated 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 untreated low-grade NHL and MCL

In December 2016, SymBio received marketing approval of Treakisym® in Japan, for untreated low-grade NHL and MCL. 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 and estimated sales

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® indicated for chronic lymphocytic leukemia (CLL)

Additional indication of CLL approved in August 2016

In Japan, SymBio obtained approval for the additional indication of CLL for Treakisym® in August 2016.

Potential patient population, estimated 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 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 was a need for a safer, more efficacious method of treatment such as Treakisym®.

In March 2021, the company obtained approval for a partial change to the marketing authorization of Treakisym® for use in bendamustine-rituximab combination therapy to treat r/r DLBCL. In April 2021, it obtained approval for a partial change to the marketing authorization of Treakisym® RTD formulation for use in BR and P-BR therapy as a treatment for r/r DLBCL.

Results of phase III clinical trials in patients with relapsed or refractory DLBCL

Following consultations with the Pharmaceuticals and Medical Devices Agency (PMDA), the company commenced phase III clinical trials of Treakisym® in combination with rituximab (BR therapy) for relapsed or refractory DLBCL. The objective of the study was to examine the efficacy and safety of BR therapy, with the overall response rate (ORR; antitumor effect) as the primary endpoint. Enrollment of 60 patients was completed in April 2019. The following results of the clinical trial (main efficacy evaluation results in 38 cases) were presented at the Japanese Society of Medical Oncology Annual Meeting 2021 held in February 2021.

- Response rate (CR+PR): 76.3%
- Complete response (CR): 47.4%
- Median overall survival: 29.2 months

* CR (complete response) = disappearance of all signs of cancer in response to treatment. Also known as complete remission.
* PR (partial response) = the cancer partly responded to treatment, but has not disappeared. Also known as partial remission.

Patient population, estimated sales

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.

The treatment for relapsed or refractory diffuse large B-cell lymphoma (DLBCL) involves administering 120mg once daily for two consecutive days (one cycle), repeated over a maximum of six cycles. A 100mg vial of Treakisym® for intravenous infusion costs JPY95,764 (NHI drug price).

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 Pharmaceuticals' bendamustine hydrochloride ready-to-dilute (RTD) and rapid infusion (RI) formulations (marketed in the US by Teva Pharmaceutical Industries as BENDEKA®) in Japan. Under the terms of this agreement, SymBio will pay Eagle Pharmaceuticals 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 formulation 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 reduce the workload of healthcare professionals. RI formulation also does 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. The volume of diluted saline solution is one-fifth that of the RTD formulation, with the lower salt content making it suitable for elderly patients.

Comparison of RTD/RI formulations and freeze-dried formulation

RTD formulation		RI formulation	FD powder injection product
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
Specifications	100mg/4mL		100mg/vial 25mg/vial
Storage	Refrigerated storage (2–8°C)		Room temperature

Life cycle of Treakisym® can be extended until 2031

The re-examination term for the FD formulation of Treakisym® ended in 2020, after which generics can be manufactured and sold. SymBio believes that by selling the RTD and RI formulations of the product that offer the advantages of reducing healthcare professionals' workload and stress on patients after 2020, it can extend the exclusive sales period until 2031 if these penetrate the market. The company aims to prolong the life cycle of Treakisym® and limit the spread of generics.

Profits of a company that develops a brand-name product are protected by patents and re-examination. After a drug is developed, other companies cannot manufacture products using the same active ingredient until the patent expires (usually 20 years, up to a maximum of 25 years). Brand-name products have a re-examination period, usually of six years up to a maximum of 10 years, and during this period, even if the patent has expired, other companies cannot apply to manufacture generic versions of the drug.

Bendamustine hydrochloride RTD and RI injection products are marketed in the US by Eagle Pharmaceuticals as BENDEKA®, which captured a 97% share of the US bendamustine market within two years after its launch. According to the company, some companies in the US have attempted to launch generic versions of Treakisym® liquid formulations, but they all infringed on Eagle Pharmaceuticals' patents, and Eagle prevailed in lawsuits. As of May 2022, there were no generic versions of Treakisym® liquid formulations on the market.

R&D status: obtained approval in September 2020 for RTD formulation and RI formulation in February 2022

The company obtained approval for the bendamustine hydrochloride RTD formulation in September 2020 and rapid infusion (RI) administration in February 2022.

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

In March 2019, Novartis Pharma K.K. received approval in Japan for 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. Shared Research understands that Novartis Pharma's CTL019 is limited to adult patients for whom two or more lines of therapy have proved ineffective, and is thus different from SymBio's Treakisym® used to treat DLBCL, so the two do not compete.

In March 2019, the company obtained approval for a partial change to the marketing authorization for Treakisym® as a pretreatment agent prior to CTL019 for relapsed or refractory B-cell acute lymphoblastic leukemia (ALL) and relapsed or refractory DLBCL in adults.

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 facility. 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 (injection)/ SyB C-1101 (oral) (generic name: rigosertib)

Rigosertib is an anti-cancer agent under development by Onconova Therapeutics, Inc. in the US and EU for the treatment of myelodysplastic syndromes (MDS) and solid tumors. According to SymBio, rigosertib has high safety profile and can be used in combination with other anticancer drugs. It is provided in injection and oral formulations.

Rigosertib inhibits the action of multiple kinases such as phosphatidyl inositol 3-kinase (PI3K) by blocking the action of the Ras gene, a cancer-related gene product. It is a small molecule anticancer agent with a new mechanism of action that kills cells by suppressing transmission of intracellular signals required for cancer survival and growth.

The PI3K pathway is activated by various gene mutations in cancer, and is thought to be deeply involved in cancer survival, differentiation, and proliferation.

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 market rigosertib in Japan, South Korea

In July 2011 SymBio bought exclusive rights to develop and sell the intravenous (IV) and oral forms of rigosertib in Japan and Korea following completion of Onconova's phase II US clinical trial for the IV form (upfront payment of JPY800mn, Shared Research estimate).

In September 2012, Baxter International Inc. acquired exclusive rights to develop and sell rigosertib in Europe. It paid an upfront payment of USD50mn, for a total licensing fee including milestone payments of USD565mn.

Development status of rigosertib

Licensor Onconova conducted joint global phase III clinical trials in over 20 countries starting in August 2015 for the intravenous form of rigosertib in higher-risk MDS patients who had failed to respond to or relapsed after therapy with hypomethylating agents (HMAs). In the Japanese market, the company conducted joint global phase III clinical trials starting in December 2015. As a result, in August 2020, Onconova announced that the global phase III trial of rigosertib (IV) failed to meet its primary endpoints. Onconova is performing additional analysis of the results. The company commented that it is looking to apply the knowledge gleaned from additional analysis of the study to rigosertib development going forward.

Onconova completed phase I/II clinical trials in the US for the oral form of rigosertib as first-line treatment for higher-risk MDS (in combination with azacitidine), which demonstrated safety and efficacy of the combination therapy. SymBio restarted phase I clinical trials of the oral formulation of rigosertib monotherapy in Japan in June 2017 and completed patient enrollment in June 2019, to verify the tolerability and safety of the study drug in Japanese patients.

Market for rigosertib (oral form) and number of patients

		Low-risk MDS	High risk MDS	
		First-line	First-line	Relapsed and refractory
Intravenous	Number of patients	-	-	3,200
	Approval	-	- TBD	
	Development status	-	- Global phase III trials underway	
Oral	Number of patients	7,800	3,200	-
	Approval	TBD	TBD	-
	Development status	Phase II trials underway in the US	Global clinical trials being reviewed by Onconova	-
			Phase I clinical trials underway in Japan	

Source: Shared Research based on company data

Rigosertib injection in patients with higher-risk refractory or relapsed 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 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.

R&D status: global phase III studies underway in patients with relapsed higher-risk MDS following HMA therapy

Phase III clinical trials in patients with relapsed or refractory higher-risk MDS

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.

Phase III clinical trials in patients with higher-risk MDS for whom HMA therapy was ineffective or who relapsed after treatment

In August 2015, Onconova submitted plans to US Food and Drug Administration (FDA) and regulatory agencies in England, Germany, and Australia and launched 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.

In August 2020, Onconova announced that the primary endpoint (overall survival compared with physician's choice [PC] treatment) was not met in the phase III clinical trial. More specifically, the primary endpoint of the trial was overall survival, comparing IV rigosertib plus best supportive care to PC plus best supportive care. Onconova also analyzed a pre-specified subgroup of very high risk (VHR-MDS) patients. Results of the trial demonstrated that in the intent-to-treat analysis patients

given IV rigosertib achieved overall survival of 6.4 months, versus 6.3 months for PC (p=0.33) in the overall HR-MDS population. There was also no significant difference in overall survival between the two study arms in the VHR-MDS subgroup.

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

The company conducted global phase III clinical trials in Japan from December 2015. The first patient was registered in July 2016 and 48 patients had been registered as of end December 2019 versus the target of 50. Regarding Onconova's August 2020 announcement regarding not meeting primary endpoints of its phase III clinical trial, SymBio commented that it is looking to apply the knowledge gleaned from additional analysis of the study to rigosertib development going forward.

Oral rigosertib in patients with higher-risk MDS

R&D status: phase I/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 among 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.

Phase I clinical trials in Japan

The company began the domestic phase I clinical trial of oral rigosertib to confirm the safety of the drug at high doses (a requirement for phase II clinical trials conducted by Onconova in the US for the indication of first-line treatment for relapsed or refractory higher-risk MDS). The patient enrollment for the study was completed in June 2019.

Exploring new indications

In January 2021, the company entered into a joint research agreement with the Institute of Medical Science, the University of Tokyo (IMSUT) to explore potential new indications for bendamustine and rigosertib.

Under this agreement, SymBio will undertake joint research with Professor Toshio Kitamura, from the Division of Cellular Therapy within IMSUT's Advanced Clinical Research Center, using bendamustine and rigosertib in combination or with other approved drugs to explore efficacy and new indications. The joint research will analyze the epigenetic control of various tumor cells to explore as-yet-unknown pharmacological effects of bendamustine and rigosertib, analyzing their effects when used in combination and with other approved drugs.

Professor Kitamura is an accomplished researcher and has a large network of researchers and physicians in the areas of hematopoietic stem cell differentiation and hematopoietic tumors such as leukemia.

He is also studying molecular mechanisms in the development of hematopoietic tumors caused by epigenetic abnormalities, looking to develop novel therapies using hematopoietic tumor models. SymBio will leverage its experience in winning early approval for proprietary anticancer drugs in collaborating with IMSUT to search for new indications for bendamustine and rigosertib.

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 JPY15.4bn in FY03/21 (-1.9% YoY) and forecast to reach JPY18.0bn in FY03/22.

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. 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.

In June 2021, Chimerix received FDA approval for the use of the oral BCV formulation as a medical defense against smallpox.

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 target 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 for the treatment of 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 of IV formulation of brincidofovir

The US-based phase I clinical trial of intravenous formulation of brincidofovir was completed. No serious side effects were observed in the study.

Phase II clinical trials targeting adenovirus diseases in children

In March 2021, the company filed an indicative new drug (IND) application with the US FDA, so it could start a phase II clinical trial for the indication of adenovirus diseases in children (including adults). The development program received fast-track designation from the FDA in April 2021, and the investigational drug was administered to the first patient enrolled in the clinical trial in August 2021. In January 2022, the company submitted a Clinical Trial Application (CTA) to the Medicines and Healthcare products Regulatory Agency (MHRA) of the UK, which was accepted.

The company is preparing to investigate the development of the intravenous formulation of brincidofovir in other transplant areas, cancer, and neuro-infectious diseases.

Transplants

Proceeding with development targeting AdV infections following hematopoietic stem cell transplants

After a review at the global advisory board held in February 2020, the company concluded that it would prioritize global development of brincidofovir (mainly in Japan, the US, and Europe) to treat adenovirus (AdV) infections in patients receiving hematopoietic stem cell transplantation to address an unmet medical need. As of February 2022, the company was preparing for the launch of a global phase II study targeting ADV infections following hematopoietic stem cell transplants. Based on safety and efficacy data acquired from its study, the company plans to review the drug's efficacy against dsDNA viral infections in patients receiving hematopoietic stem cell transplantation and extend its target indications to include multiviral infections.

Clinical trials by Chimerix have demonstrated superior, broad-spectrum antivirus activity of the oral formulation of brincidofovir, raising expectations for the potential of the liquid formulation as a safe and effective therapy to prevent and treat a range of viral infections in patients receiving hematopoietic stem cell transplantation.

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.

Expanding target disease areas to cover organ transplants

In a bid to grow the market for brincidofovir and maximize its business value, the company is exploring the potential for expanding target disease areas to viral infections related to kidney and other organ transplants, in addition to ADV infections following hematopoietic stem cell transplants. As of February 2022, it was also preparing to launch a clinical trial targeting BK virus infections following kidney transplants.

dsDNA viruses: Includes families of herpesviridae, adenoviridae, polyomaviridae, papillomaviridae, and poxviridae, such as cytomegaloviruses (CMV), adenoviruses (AdV), human herpesvirus 6 (HHV-6), BK virus, herpes simplex virus HSV-1 and -2, varicella-zoster virus (VZV), human papillovirus (HPV), JC virus (JCV), and smallpox (variola virus).

Viral hemorrhagic cystitis (vHC): Among viral infections that frequently occur following hematopoietic stem cell transplantation, adenovirus infections causing hemorrhagic cystitis are particularly refractory. 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 after unrelated donor and umbilical cord blood transplants, 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.

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 of transplantation, most frequently in the third week. 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 common, neurological symptoms worsen by the hour, often requiring ventilator management for repeated convulsions and respiratory depression.

The condition of HHV-6 encephalitis patients frequently deteriorates rapidly, making early treatment important. According to guidelines from the Japan Society for Hematopoietic Cell Transplantation (February 2018), the first-line drugs are foscarnet (FOS) or 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 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.

Cancer

In addition to antiviral activity, the company thinks BCV may have antitumor effects. Through joint research with the National Cancer Centre Singapore and University of California San Francisco Brain Tumor Center, SymBio is investigating new indications for BCV in oncology, including refractory brain tumors and EB virus-positive lymphoma.

As of February 2022, the company was conducting a nonclinical study targeting glioblastoma multiforme (GBM), brain tumors associated with cytomegalovirus infection. According to the company, roughly 50% of GBM patients have cytomegalovirus infections, and it is possible that cytomegalovirus promotes tumorigenesis. Further, while many GBM therapies are being developed, none of them target cytomegalovirus and GBM (other than brincidofovir). In March 2022, the company launched a joint nonclinical study with Brown University of the US to investigate the antitumor effect of BCV IV on brain tumors associated with cytomegalovirus infection.

Glioblastoma multiforme: A malignant brain tumor of the glial cells that support the brain's nerve cells. Survival is 15–20 months, with a five-year survival rate of under 5%.

Neuro-infectious diseases

According to Science magazine (January 2022), a Harvard University team found that Epstein-Barr virus (EBV) infections are a major pathogenic factor in multiple sclerosis (MS). Analysis of a sample of over 10mn US military personnel showed that a history of EBV infection increased the risk of MS by 32 times. A January 2022 story in Nature magazine said that a research team from Stanford University elucidated the mechanism of action whereby the EBV causes MS. The magazine says that this suggests eradication of the EBV from the body after the onset of MS could hinder its progression.

BCV has strong antiviral activity on the EBV, so the company plans to investigate whether it could be an effective treatment for MS.

Multiple sclerosis (MS): A disease in which lesions form throughout the brain, spinal cord, and optic nerves, causing a variety of symptoms. MS often features repeated relapses of symptoms and remissions (symptoms subside). Symptoms vary widely depending on the location of the lesions, and include loss of vision, double vision, and motor paralysis. There are roughly 3mn MS patients worldwide, and treatment sales were over JPY1.5tn (2020).

Earnings structure

(JPYmn)	FY12/12	FY12/13	FY12/14	FY12/15	FY12/16	FY12/17	FY12/18	FY12/19	FY12/20	FY12/21
Sales	1,955	1,532	1,955	1,933	2,368	3,444	3,836	2,838	2,987	8,257
YoY	3.9%	-21.6%	27.6%	-1.1%	22.5%	45.4%	11.4%	-26.0%	5.3%	176.4%
Product sales	1,955	1,432	1,940	1,933	2,137	3,444	3,810	2,811	2,977	8,257
YoY	19.8%	-26.8%	35.5%	-0.3%	10.6%	61.1%	10.6%	-26.2%	5.9%	177.4%
Treakisym sales (NHI price basis; reference)	3,940	4,230	4,320	4,760	4,720	7,600	8,500	-	-	-
Product sales / Sales (NHI price basis)	49.6%	33.9%	44.9%	40.6%	45.3%	45.3%	44.8%	-	-	-
Royalty revenue	-	100	15	-	231	-	26	26	10	-
Sales to Eisai	1,930	1,486	1,908	1,852	2,265	3,382	3,648	2,831	2,546	-
YoY	3.1%	-23.0%	28.4%	-2.9%	22.3%	49.4%	7.9%	-22.4%	-10.1%	-
Sales to other partners	26	46	47	81	104	62	187	6	441	8,257
CoGS	1,362	1,214	1,428	1,350	1,464	2,413	2,663	1,973	2,120	2,452
CoGS / Product sales	69.7%	84.8%	73.6%	69.8%	68.5%	70.1%	69.9%	70.2%	71.2%	29.7%
CoGS / Sales (NHI price basis)	34.6%	28.7%	33.1%	28.4%	31.0%	31.7%	31.3%	-	-	-
Product procurement	1,322	1,175	1,550	1,242	1,606	2,589	2,969	1,684	3,163	2,145
Gross profit	593	318	527	583	904	1,031	1,173	865	867	5,800
Product gross profit	593	218	512	583	673	1,031	1,147	838	857	5,800
Gross profit margin	30.3%	15.2%	26.4%	30.2%	31.5%	29.9%	30.1%	29.8%	28.8%	70.2%
Royalty revenue	-	100	15	-	231	-	26	26	10	-
SG&A expenses	2,293	1,999	1,830	3,135	3,031	4,978	3,829	5,166	5,373	4,784
Personnel	413	441	479	488	541	554	504	506	530	574
R&D expenses	1,438	1,053	774	2,035	1,667	3,018	1,833	2,442	2,267	1,736
Other	442	505	577	612	823	1,406	1,492	2,219	2,576	2,474
Operating profit	-1,700	-1,681	-1,303	-2,552	-2,127	-3,947	-2,656	-4,302	-4,506	1,016

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 through FY12/19 have originated from Eisai. The company began own sales of Treakisym® from December 10, 2020 and recorded sales to non-Eisai partners (i.e., wholesalers) of JPY441mn in FY12/20. In FY12/21, all sales were to non-Eisai partners.

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. Through FY12/16, 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 sales growth YoY.

FY12/19 product sales declined YoY. A lyophilized injection formulation of Treakisym® imported from Astellas Deutschland GmbH, a consolidated subsidiary of Astellas Pharma, was found to contain impurities and appearance defects, and as a result, shipments of Treakisym® 100mg to Japan distributor Eisai were postponed. Consequently, booking of some product sales was delayed until the following fiscal year, resulting in a YoY decline in sales.

Sales increased YoY in FY12/21, largely due to the transfer of sales from Eisai to the company's own sales force. The business alliance agreement with Eisai for Treakisym® expired on December 9, 2020, and SymBio began independently marketing Treakisym® in Japan on December 10. This enabled the company to earn not only its previous gross profit (sales to Eisai minus cost of sales), but also the gross profit earned by Eisai through December 9, 2020 (the difference between the shipment price from Eisai to pharmaceutical wholesalers and the price Eisai paid SymBio to supply Treakisym®).

Royalty revenue

Royalty revenue includes one-time contract payments and milestone payments.

CoGS

CoGS refers to procurement costs for drugs. SymBio purchases lyophilized Treakisym® from Astellas Deutschland GmbH. Before December 2019, Astellas supplied Treakisym® to the company for about 70% of SymBio's wholesale price to Eisai. As noted above, the company began own sales of Treakisym® on December 10, 2020. This allowed the company to receive not only the gross profit it received previously, but also the gross profit earned by Eisai through December 9, 2020 (i.e., the difference between the shipment price from Eisai to pharmaceutical wholesalers and the price Eisai paid the company to source the product), boosting GPM.

SymBio sources the liquid (RTD and RI) formulations of Treakisym® from US company Eagle Pharmaceuticals. According to the company, its GPM on the liquid formulations is higher than for lyophilized Treakisym®.

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 paid half of the development costs for the Treakisym® freeze-dried (FD) formulation in Japan.

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, hematologic, and multiviral infectious diseases and rare diseases. 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

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.

Dependence on a single product: As of February 2022, Treakisym® accounted for all product sales of the company. SymBio is a biotech startup whose strength lies in having brought a pharmaceutical product to market, but its dependence on a single product raises the risk of earnings volatility. Sales and gross profit declined in FY12/19 and FY12/20 due to contamination and irregular appearance of lyophilized Treakisym® imported from Astellas Deutschland GmbH, which led to a temporary slump in product sales.

Market overview

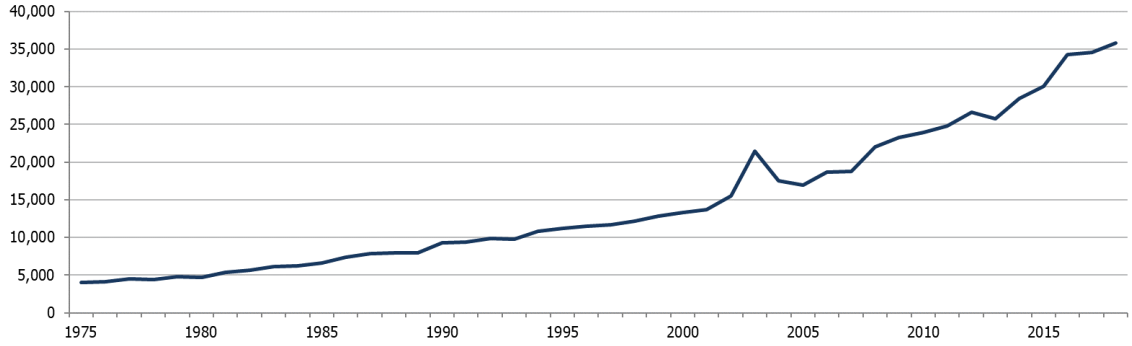
Lymphatic cancer: patient population, market size, treatment drugs

Morbidity of lymphatic cancer

In 2018, the number of people diagnosed with lymphatic cancer in Japan was 35,782 (+3.5% YoY; average annual increase in past 10 years is 4.9%), according to "Cancer statistics and cancer registration in Japan" complied by the Center for Cancer Control and Information Services. Of these, 29,156 (+4.6% YoY), or 81.5% (80.7% in the previous year), were 60 years or older.

Of the 980,856 (+0.4% YoY) people diagnosed with cancer, those diagnosed with lymphatic cancer accounted for only 3.6% (3.5% in the previous year), but their number increased 62.1% between 2008 and 2018, versus a 30.8% increase in the number of people newly diagnosed with cancer.

Morbidity of lymphatic malignancy



	1,975	1,980	1,985	1,990	1,995	2,000	2,005	2,010	2,015
Number of patients	4,013	4,741	6,635	9,297	11,195	13,307	16,991	23,919	30,103
Incidence rate (per 100,000)	3.6	4.1	5.5	7.5	8.9	10.5	13.3	18.7	23.7

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

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 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	Approved	Sales: JPY8.5bn (FY12/18)
Untreated low-grade NHL, and untreated MCL	6,967	Approved	
CLL	656	Approved	
Relapsed or refractory NHL	18,672	Clinical trials underway	

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 JPY5.1bn (-29.2% YoY) in FY12/21.

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 Toyama Chemical Co., Ltd., a subsidiary of Fujifilm Holdings Corporation.

Patient population, treatment drugs for MDS

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	Number of patients
Low-risk MDS	7,800
High-risk MDS	3,200

Source: Shared Research based on company data

Drugs competing with rigosertib

Nippon Shinyaku Co., Ltd.'s Vidaza is an 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 JPY15.4bn (-1.9% YoY) in FY03/21 and expects sales of JPY18.0bn in FY03/22.

Historical performance

Full-year FY12/21 results

- Sales: JPY8.3bn (+176.4% YoY)
- Operating profit: JPY1.0bn (loss of JPY4.5bn in FY12/20)
- Recurring profit: JPY1.0bn (loss of JPY4.6bn in FY12/20)
- Net income: JPY2.0bn (loss of JPY4.1bn in FY12/20)

Sales increased YoY in FY12/21, largely due to the transfer of sales from Eisai Co., Ltd. to the company's own sales force. The business alliance agreement with Eisai for Treakisym® expired on December 9, 2020, and SymBio began independently marketing Treakisym® in Japan on December 10. This allows the company to receive not only the gross profit it received previously (the company's sales to Eisai minus cost of sales), but also the gross profit earned by Eisai through December 9, 2020 (i.e., the difference between the shipment price from Eisai to pharmaceutical wholesalers and the price Eisai paid the company to source the product).

However, there were headwinds such as the clearance of market inventory of the FD formulation sold by Eisai prior to the switch to the company's own sales force in December 2020, delays in medical care due to the COVID-19 outbreak from late 2020, and constraints on sales activities due to tighter restrictions on facilities visits.

In 2H, sales of Treakisym® for the indication of relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL) accelerated. This was partially because the backlog of delayed medical treatments cleared on progress in COVID-19 countermeasures, including vaccinations for the elderly. Other factors included the March 2021 approval of BR-therapy and P-BR therapy to treat r/r DLBCL, and Chugai Pharmaceutical's genetically engineered polatuzumab vedotin being added to the NHI drug list in May 2021.

Gross profit came to JPY5.8bn (+569.1% YoY), on the back of sales growth and an increase in gross profit margin driven by the switch from the FD formulation to the RTD formulation of Treakisym®. Meanwhile, due to the switch in Q4, the company booked a valuation loss of JPY332mn on inventories of Treakisym® FD formulation.

Reasons why in-house marketing of Treakisym® contributed to GPM improvement: Switching from marketing through Eisai (based the marketing agreement with Eisai) to doing its own marketing meant that products are shipped to pharmaceutical wholesalers instead of to Eisai starting from December 10, 2020. This allows the company to receive not only the gross profit it received previously (the company's sales to Eisai minus cost of sales), but also the gross profit earned by Eisai through December 9, 2020 (i.e., the difference between the shipment price from Eisai to pharmaceutical wholesalers and the price Eisai paid the company to source the product).

GPM rises due to switching from the lyophilized formulation to the RTD formulation of Treakisym®: The company sourced the lyophilized formulation of Treakisym® from Astellas Deutschland, but the liquid formulations (RTD and RI formulations) are supplied by Eagle Pharmaceuticals. The company says that the GPM on liquid formulations of Treakisym® is higher than the GPM on the lyophilized formulation.

Profits grew at all levels owed to reductions in SG&A expenses and sales growth, and the company achieved profitability. SG&A expenses decreased 11.0% YoY to JPY4.8bn.

- R&D expenses were JPY1.7bn (-23.4% YoY). This included expenses for conducting clinical trials of intravenous formulations of Treakisym®, rigosertib, and brincidofovir.
- Excluding R&D expenses, SG&A expenses fell 1.9% YoY to JPY3.0bn, despite the transition to in-house sales pushing up selling costs.

Growth in net income was driven by an increase in recurring profit and income taxes deferred of JPY1.3bn.

Q4 FY12/21 (October–December 2021) results

In Q4 FY12/21 (October–December 2021), sales were JPY2.7bn (+313.1% YoY), gross profit was JPY1.8bn (+585.0% YoY), the GPM was 64.9% (+25.8pp YoY), and operating profit was JPY592mn (JPY1.4bn loss in Q4 FY12/20). The company turned profitable at the OP level in Q2 and kept the OPM above 20% from Q3 onward.

Versus Q3 FY12/21, sales were up JPY297mn, gross profit down JPY17mn, the GPM down 8.7pp, and operating profit down JPY27mn.

Factors that contributed to sales growth were as follows. In Q4, the backlog of delayed medical treatments was being cleared due to progress in measures against COVID-19 compared with Q3. In March 2021, BR therapy was approved for r/r DLBCL while Chugai Pharmaceutical received approval for the combination of polatuzumab vedotin + BR therapy (P-BR therapy). In Q4, sales of Treakisym® used in BR and P-BR therapies for the r/r DLBCL treatment increased.

The GPM fell QoQ, as the company booked a valuation loss of JPY332mn on inventories of Treakisym® FD formulation. Excluding this impact, GPM was 77.2% (up 3.6pp QoQ). The switch from the lyophilized formulation to the RTD formulation of Treakisym® progressed faster in Q4 than in Q3.

Variations between full-year FY12/21 results and company forecast

FY12/21 sales came in at 90.2% of the full-year company forecast, and operating profit 74.7%. Sales were JPY894mn below the forecast and operating profit JPY345mn below.

The clearance in February–May of Eisai's market inventory distributed prior to the switch to the company's own sales force resulted in sales falling short of the company forecast by about JPY450mn. Delayed medical care due to the COVID-19 pandemic saw sales fall short by roughly JPY400mn.

The GPM came in at 70.2% versus the company forecast of 76%. The valuation loss of JPY332mn on inventories of Treakisym® FD formulation reduced the GPM by 4.0pp versus the company forecast. In addition, delays in shifting from Treakisym® FD formulation to the RTD formulation reduced the GPM by 2.0pp.

While sales and GPM fell short of the company forecast, SG&A expenses came in JPY811mn below expectations, so operating profit was just JPY345mn below forecast.

Overview of business progress

In FY12/21, progress in main businesses was as follows:

- In February 2022, SymBio received approval for its for Treakisym® rapid infusion (RI) liquid formulation.
- In February 2022, the Ministry of Health, Labour and Welfare approved manufacture and marketing of generic drugs of the company's Treakisym® Intravenous Infusion (RTD formulation). As this could possibly infringe the company's exclusive rights to develop and commercialize the patent-protected product in Japan, the company consulted with the licensor Eagle Pharmaceuticals, and notified the four companies that had obtained the approval for generic drugs of the possibility of patent infringement, demanding they take appropriate actions.
- In October 2021, Dr. Carolyn Yanavich was appointed Vice President, and Head of Project Management and Clinical Operations of SymBio Pharma USA.
- In September 2021, results of the domestic phase III trial evaluating TREAKISYM in combination with Rituximab for treatment of relapsed and refractory diffuse large B-cell lymphoma were disclosed. The phase III and follow-up studies demonstrated a response rate (complete response and partial response [CR+PR]) of 76.3%, complete response rate (CR) of 47.4%, and median overall survival of 29.2 months.
- In September 2021, the company announced plans to adjust shipments of lyophilized TREAKISYM. As of September 2021, SymBio manufactures and markets both the RTD and FD formulations while it looks to switch FD to RTD. Adjustments to FD shipments are being made because of potential stockout.
- In September 2021, the company initiated a pre-clinical study to investigate the anti-tumor effect of brincidofovir IV on brain tumors at the Brain Tumor Center, Department Neurological Surgery, University of California, San Francisco.

- In September 2021, the company concluded a joint research agreement with the National Cancer Centre Singapore to explore the anti-tumor effects of brincidofovir IV in Epstein-Barr (EB) virus positive lymphoma and its mechanism of action.

- In August 2021, the company announced it had started administration to the first patient enrolled (FPI) in the Phase II clinical trial of antiviral drug brincidofovir (IV forumulation).

- In June 2021, Chimerix, Inc. (licensor of brincidofovir) obtained FDA approval of brincidofovir tablets and oral suspensions as antiviral formulations for the treatment of smallpox.

- In April 2021, the company obtained approval of Treakisym® ready-to-dilute (RTD) liquid formulation for use in combination with rituximab and in combination with rituximab and polatuzumab vedotin for the treatment of refractory or relapsed diffuse large B-cell lymphoma (r/r DLBCL).

- In March 2021, the company obtained approval of Treakisym® for use in combination with rituximab, and in combination with rituximab and polatuzumab vedotin for the treatment of r/r DLBCL.

- In January 2021, the company launched Treakisym® RTD liquid formulation.

Domestic

Establishment of an in-house sales organization

The business alliance agreement between SymBio and Eisai Co., Ltd. under which Eisai acts as a sales agent expired in December 2020, and the company switched to in-house sales for domestic sales of Treakisym®.

In conducting in-house sales, SymBio established a sales organization that can cultivate needs, provide information on the company products, and plan seminars. In addition to medical representatives, the company deployed hematology experts with extensive knowledge of the field throughout Japan. Further, the company concluded basic agreements with Suzuken Co., Ltd and Toho Pharmaceutical Co., Ltd for the procurement and sale of pharmaceuticals to build a nationwide distribution network. The company has established two distribution centers, one in Eastern Japan and the other in Western Japan, under management by S.D. Collabo Co., Ltd.

During FY12/21, in January 2021, the company began sales of the ready-to-dilute (RTD) formulation of Treakisym®, for which it obtained manufacturing and marketing approval in September 2020. Since then, the company has promoted the shift from the existing FD formulation to the newly approved formulation.

In March 2021, the company obtained approval for a partial change to the marketing authorization of Treakisym® for use in bendamustine-rituximab combination therapy (BR therapy) and bendamustine-rituximab-polatuzumab vedotin combination therapy (P-BR therapy) to treat r/r DLBCL. This promptly enabled the FD formulation of Treakisym® to be used in BR therapy, and the company promoted the switch from the current multi-drug combination therapy to Treakisym® for treating r/r DLBCL.

In April 2021, the company obtained approval for a partial change to the marketing authorization of Treakisym® RTD formulation for use in BR therapy and P-BR therapy for the treatment of r/r DLBCL.

In May 2021, Chugai Pharmaceutical's polatuzumab vedotin was added to the NHI drug price list, enabling Treakisym® to be used in P-BR therapy.

Stable product supply

With the start of sales of Treakisym® RTD formulation in January 2021, the company has been promoting the switch from the FD formulation to the RTD formulation.

SymBio imports FD formulation Treakisym® for injection from Astellas Deutschland (consolidated subsidiary of Astellas Pharma) and Treakisym® RTD formulation from Eagle Pharmaceuticals Inc.

On the quality control front, the company conducts secondary packaging and quality screening on imported batches of both the FD and RTD formulations of TREAKISYM® to maintain stable quality.

On the supply front, the company had been striving to replace the FD formulation of TREAKISYM® with the RTD formulation in the market, but progress in this front was behind plan. Due to the possibility of the FD formulation going out of stock, SymBio began controlling shipments of the FD formulation from September 21, 2021, but since then, the switch to the RTD formulation has made progress. The company has secured sufficient quantities of the RTD formulation to ensure stable supply.

Treakisym® (SyB L-0501[FD formulation]/SyB L-1701 [RTD formulation]/SyB L-1702 [RI administration]; generic name: bendamustine hydrochloride or bendamustine hydrochloride hydrate, product name: Treakisym®)

The anticancer agent Treakisym® is used to treat malignant lymphomas, indicated for untreated low-grade non-Hodgkin's lymphoma and mantle cell lymphoma (marketing approval obtained in December 2016), refractory or relapsed low-grade NHL and MCL (October 2010), and chronic lymphocytic leukemia (August 2016).

The combination therapy of Treakisym® and rituximab (BR therapy) was newly included in the Practical Guidelines for Hematological Malignancies 2018 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.

Also, SymBio obtained approval for a partial change to the marketing authorization of Treakisym® in July 2018. With the approval, Treakisym® can be used in combination with new anti-CD20 antibodies and not just with rituximab for the treatment of CD20-positive follicular lymphoma, the most common histological type of low-grade NHL. This has allowed the company to provide patients a new treatment option: combination therapy with obinutuzumab. In March 2019, SymBio obtained approval for a partial change to its marketing authorization to use Treakisym® as a pretreatment agent in tumor-specific T cell infusion therapy. This has allowed Treakisym® to be used as a pretreatment agent for Kymriah® intravenous infusion, which was the first chimeric antigen receptor T-cell (CAR-T) therapy approved in Japan. Growing use of Treakisym® as a pretreatment agent in regenerative medicine has solidified its positioning as standard therapy for malignant lymphomas.

In the phase III clinical study of Treakisym® used in BR therapy targeting r/r DLBCL, the company filed a partial change application in May 2020 and obtained approval in March 2021. In April 2021, it obtained approval for a partial change to the marketing authorization of Treakisym® RTD formulation for use in BR and P-BR therapy as a treatment for r/r DLBCL. The company has conducted a follow-up study with overall survival as the primary endpoint, because evaluating the survival data (e.g., overall survival and progression-free survival) for Treakisym® used in BR therapy is crucial for establishing the drug as a treatment for DLBCL. The company is making preparations to present the results of the study at an annual meeting of the Japanese Society of Hematology and other academic conferences, and to publish the results in academic journals. Further, after Chugai Pharmaceutical Co., Ltd. applied for manufacture and marketing approval of polatuzumab vedotin (genetically engineered) used in combination with BR therapy to treat r/r DLBCL in June 2020, the company applied for approval of a partial change to the marketing authorization of Treakisym® for the drug to be used in P-BR therapy in July 2020 and obtained approval in March 2021. Polatuzumab vedotin (genetically engineered) was added to the NHI drug price list in May 2021, enabling Treakisym® to be used in P-BR therapy. Previously there was no effective treatment for r/r DLBCL, which was usually treated by a combination of anticancer agents as salvage chemotherapy, so development of a highly effective but safe new drug was much needed. Since BR therapy is already being used in Western countries to treat r/r DLBCL, patient organizations and related academic societies petitioned MHLW so that it could also be used in Japan as soon as possible.

The company concluded an exclusive licensing agreement in Japan with Eagle Pharmaceuticals (based in New Jersey, US) in September 2017 for the RTD formulation and rapid infusion (RI) injection of Treakisym® (the RI formulation reduces administration time). Manufacturing and marketing approval of the RTD formulation was obtained in September 2020, and the company launched the drug in January 2021. The company concluded clinical trials to confirm safety of the RI injection and submitted a partial change application in May 2021. For the RTD formulation, in November 2021 the company filed a partial change application to extend the effective date of the drug to 30 months based on the results of long-term stability tests. Unlike the current FD formulation, the RTD formulation reduces the workload of medical professionals, because it eliminates the need for troublesome manual dissolution. The RI injection can be administered in just 10 minutes, versus 60 minutes for the current FD and RTD formulation. This reduces the burden on patients and healthcare professionals, providing value-added.

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

Onconova Therapeutics, Inc., the licensor, conducted a global phase III trial (INSPIRE study) across more than 20 countries addressing higher-risk myelodysplastic syndromes (higher-risk MDS) with overall survival as the primary endpoint. The target is patients who do not respond to the current standard treatment with hypomethylating agents, relapse after treatment under the current standard of care, or are intolerant to hypomethylating agents. In August 2020, Onconova announced a

comparator trial to physicians' choice of treatment failed to achieve the primary endpoint. The company leads clinical trials conducted in Japan and is looking to apply the knowledge gleaned from additional analysis of the INSPIRE study to rigosertib development going forward.

Regarding the oral formulation of rigosertib, Onconova completed a phase I/II clinical trial for the drug used in combination with azacytidine, with the results suggesting the efficacy and safety of the combination therapy. To verify the tolerability and safety among Japanese patients, SymBio began a phase I clinical trial in Japan in June 2017 and completed patient enrollment in June 2019.

The company said it would conduct joint research into Treakisym® and rigosertib with the University of Tokyo's Institute of Medical Science and Gunma University regarding efficacy of using the two compounds in combination or with existing drugs and also explore new indications.

Antiviral drug SyB V-1901 (generic name: brincidofovir)

In September 2019, SymBio concluded an exclusive global license agreement with Chimerix Inc. (hereafter Chimerix) for brincidofovir (SyB V-1901, hereafter BCV IV and BCV Oral), an antiviral drug in intravenous and oral forms). The company acquired exclusive global rights to develop, manufacture, and market BCV for all diseases except smallpox.

The company has concluded that it would prioritize global development of BCV IV (mainly in Japan, the US, and Europe) to treat adenovirus (AdV) infections in patients receiving hematopoietic stem cell transplantation to address an unmet medical need. In March 2021, the company submitted of an investigational new drug (IND) application to the Food and Drug Administration (FDA) of the US with the goal of obtaining permission for the launch of a phase II clinical trial for a phase II clinical trial of BCV IV as a treatment for adenovirus infections that primarily occur in children (although also in adults). In April 2021, the company received granted fast track designation from the FDA and in August 2021, the investigational drug was administered to the first patient enrolled (first patient in [FPI]) in the clinical trial. In January 2022, the company submitted a Clinical Trial Application (CTA) to the Medicines and Healthcare products Regulatory Agency (MHRA) of the UK, and the application was accepted.

Based on safety and efficacy data acquired from its study, the company plans to review the drug's efficacy against dsDNA viral infections in patients receiving hematopoietic stem cell transplantation and extend its target indications to include multiviral infections. By exploring the potential for expanding target disease areas to viral infections related to organ transplants (including kidney transplants), the company aims to grow the market for and maximize the business value of BCV. Clinical trials by Chimerix have demonstrated superior, broad-spectrum antivirus activity of BCV Oral against dsDNA viruses, raising expectations for its potential as a safe and effective therapy to prevent and treat a range of viral infections in patients receiving hematopoietic stem cell transplantation.

In addition to antiviral activity, the company expects BCV to have antitumor effects. Through joint research with the National Cancer Centre Singapore and University of California San Francisco Brain Tumor Center, SymBio is investigating new indications for BCV in oncology, including rare brain tumors and EB virus-positive lymphoma.

Chimerix announced in December 2020 that the FDA had accepted its new drug application (NDA) for BCV as a medical defense against smallpox; Chimerix obtained approval in June 2021.

Overseas

The company's US-based wholly-owned subsidiary SymBio Pharma USA, Inc. appointed Dr. Carolyn Yanavich as its Vice President, and Head of Project Management and Clinical Operations on October 11, 2021, and launched full-scale operations aimed at accelerating global development of antiviral drug brincidofovir toward commercialization.

In-licensing of drug candidates

The company is currently focusing on unrolling global development plans for the antiviral drug brincidofovir it in-licensed in September 2019, but also constantly looking into multiple licensing deals and looking for and evaluating promising new in-licensing drug candidates.

Cumulative Q3 FY12/21 results

- Sales: JPY5.6bn (+138.1% YoY)

- Operating profit: JPY424mn (loss of JPY3.1bn in cumulative Q3 FY12/20)
- Recurring profit: JPY414mn (loss of JPY3.2bn in cumulative Q3 FY12/20)
- Net income: JPY325mn (loss of JPY2.7bn in cumulative Q3 FY12/20)

Sales increased YoY in cumulative Q3 (January–September) FY12/21, largely due to the transfer of sales from Eisai Co., Ltd. to the company's own sales force. The business alliance agreement with Eisai for Treakisym® expired on December 9, 2020, and SymBio began independently marketing Treakisym® in Japan on December 10. This allows the company to receive not only the gross profit it received previously (the company's sales to Eisai minus cost of sales), but also the gross profit earned by Eisai through December 9, 2020 (i.e., the difference between the shipment price from Eisai to pharmaceutical wholesalers and the price Eisai paid the company to source the product).

However, there were headwinds such as the clearance of market inventory of the FD formulation sold by Eisai prior to the switch to the company's own sales force in December 2020, delays in medical care due to the COVID-19 outbreak from late 2020, and constraints on sales activities due to tighter restrictions on facilities visits.

In Q3, sales of Treakisym® for the indication of relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL) accelerated. This was partially because the backlog of delayed medical treatments cleared on COVID-19 measures, including vaccinations for the elderly. Other factors included the March 2021 approval of BR-therapy and P-BR therapy to treat r/r DLBCL, and Chugai Pharmaceutical's polatuzumab vedotin being added to the NHI drug list in May 2021.

Gross profit was JPY4.0bn (+562.4% YoY), and GPM was 72.9% (+46.7pp YoY). The company attributes the GPM rise to the shift to its own marketing system and the launch of Treakisym® Ready-to-dilute (RTD) formulation in January 2021. In cumulative Q3, sales of Treakisym® lyophilized formulations surpassed those of Treakisym® RTD formulations.

Reasons why in-house marketing of Treakisym® contributed to GPM improvement: Switching from marketing through Eisai (based the marketing agreement with Eisai) to doing its own marketing meant that products are shipped to pharmaceutical wholesalers instead of to Eisai starting from December 10, 2020. This allows the company to receive not only the gross profit it received previously (the company's sales to Eisai minus cost of sales), but also the gross profit earned by Eisai through December 9, 2020 (i.e., the difference between the shipment price from Eisai to pharmaceutical wholesalers and the price Eisai paid the company to source the product).

GPM rises due to switching from the lyophilized formulation to the RTD formulation of Treakisym®: The company sourced the lyophilized formulation of Treakisym® from Astellas Deutschland, but the liquid formulations (RTD and RI formulations) are supplied by Eagle Pharmaceuticals. The company says that the GPM on liquid formulations of Treakisym® is higher than the GPM on the lyophilized formulation.

Profits at the operating profit level down grew on reduced SG&A expenses and sales growth, and the company achieved profitability in cumulative Q3. SG&A expenses decreased 3.5% YoY to JPY3.6bn

- R&D expenses decreased 26.3% YoY to JPY1.3bn. This included expenses for conducting clinical trials of intravenous formulations of Treakisym® and brincidofovir.

- Excluding R&D expenses, SG&A expenses rose 16.3% YoY to JPY2.3bn. The switch to in-house sales drove up the cost of sales.

Q3 FY12/21 (July–September 2021) results

In Q3 FY12/21 (July–September 2021), sales were JPY2.4bn (+147.6% YoY), gross profit was JPY1.8bn (+530.6% YoY), the GPM was 73.6% (+44.7pp YoY), and operating profit was JPY619mn (JPY1.3bn loss in Q3 FY12/20). The company turned profitable at OP level in Q2 and further increased OP in Q3.

Versus Q2 FY12/21, sales were up JPY680mn, gross profit up JPY506mn, the GPM up 0.3pp, and operating profit up JPY603mn.

Factors that contributed to sales growth were as follows. In Q2, sales were impacted by clearance of unsold inventory of lyophilized formulations sold by Eisai prior to December 2020, but this was no longer a factor in Q3. In March 2021, BR

therapy was approved for r/r DLBCL while Chugai Pharmaceutical received approval for the combination of polatuzumab vedotin + BR therapy (P-BR therapy). In Q3, sales of Treakisym® used in BR and P-BR therapies for the for the r/r DLBCL treatment increased.

The GPM rose QoQ, because the switch from the lyophilized formulation to the RTD formulation of Treakisym® progressed faster in Q3 than in Q2.

Progress in cumulative Q3 versus full-year FY12/21 company forecast

When reporting Q2 FY12/21 results, 1H sales fell short of the company forecast, but the company left its full-year forecast unchanged, because it expects higher sales in 2H than in 1H, and thinks the full-year forecast is achievable. Reasons for the company's expectation of profit growth in 2H versus 1H are as follows.

- In 1H FY12/21, the impact of the clearance of unsold inventory of the lyophilized formulation of Treakisym® sold by Eisai totaled around JPY400mn. The clearance was completed in 1H and will have no impact on 2H results.
- Patients cut back on hospital visits in 1H because of COVID-19, but the company expects this pattern to change in 2H as more seniors are vaccinated and likely to resume hospital visits.
- The company received approval for BR therapy indicated for r/r DLBCL in March 2021, while Chugai Pharmaceutical received approval for polatuzumab vedotin + BR therapy indicated for r/r DLBCL. These approvals were granted about three months earlier than the company expected at the beginning of FY12/21. The company targets JPY2.6bn in sales of Treakisym® indicated for r/r DLBCL on a NHI drug reimbursement price basis, but Shared Research understands that sales may exceed this target because of the earlier-than-expected approval timing. The company recorded sales of Treakisym® indicated for r/r DLBCL in the second half of Q2 and expects this sales to increase in 2H.
- The company forecasts a higher GPM in 2H as the switch from the lyophilized formulation to the RTD formulation of Treakisym® progresses.

Cumulative Q3 sales were 60.7% of full-year FY12/21 company forecasts while operating profit came in at 31.2%. It is our understanding that Q3 earnings are in line with company expectations for 2H. Q4 sales and operating profit are projected to exceed Q3 levels as higher vaccination rates help reduce patient hesitancy for doctor consultations, progress is made switching to the higher-margin RTD formulation, and increases in SG&A expenses are curbed.

Overview of business progress

In FY12/21, progress in main businesses are as follows:

- In October 2021, Dr. Carolyn Yanavich was appointed Vice President, and Head of Project Management and Clinical Operations of SymBio Pharma USA.
- In September 2021, results of the domestic phase III trial evaluating TREAKISYM in combination with Rituximab for treatment of relapsed and refractory diffuse large B-cell lymphoma were disclosed. The phase III and follow-up studies demonstrated a response rate (complete response and partial response [CR+PR]) of 76.3%, complete response rate (CR) of 47.4%, and median overall survival of 29.2 months.
- In September 2021, the company announced plans to adjust shipments of lyophilized TREAKISYM. As of September 2021, SymBio manufactures and markets both the RTD and FD formulations while it looks to switch FD to RTD. Adjustments to FD shipments are being made because of potential stockout.
- In September 2021, the company initiated a pre-clinical study to investigate the anti-tumor effect of brincidofovir IV on brain tumors at the Brain Tumor Center, Department Neurological Surgery, University of California, San Francisco.
- In September 2021, the company concluded a joint research agreement with the National Cancer Centre Singapore to explore the anti-tumor effects of brincidofovir IV in Epstein-Barr (EB) virus positive lymphoma and its mechanism of action.
- In August 2021, the company announced it had started administration to the first patient enrolled (FPI) in the Phase II clinical trial of antiviral drug brincidofovir (IV forumulation).

- Also in August 2021, the company concluded a joint research agreement with Kyoto University regarding the mechanism of effect of bendamustine, under development as an anticancer agent indicated for DLBCL.

- In July 2021, the company concluded a joint research agreement with the General Surgical Science Department, Gunma University Graduate School of Medicine regarding the exploration of new indications for bendamustine and rigosertib, which are under development as anticancer agents.

- In June 2021, Chimerix, Inc. (licensor of brincidofovir) obtained FDA approval of brincidofovir tablets and oral suspensions as antiviral formulations for the treatment of smallpox.

- In May 2021, SymBio submitted approval application for Treakisym® rapid infusion (RI) liquid formulation.

- In April 2021, the company obtained approval of Treakisym® ready-to-dilute (RTD) liquid formulation for use in combination with rituximab and in combination with rituximab and polatuzumab vedotin for the treatment of refractory or relapsed diffuse large B-cell lymphoma (r/r DLBCL).

- In March 2021, the company obtained approval of Treakisym® for use in combination with rituximab, and in combination with rituximab and polatuzumab vedotin for the treatment of r/r DLBCL.

- In January 2021, the company launched Treakisym® RTD liquid formulation.

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 expired in December 2020, and the company switched to in-house sales for domestic sales of Treakisym®.

The company has thus far deployed a nationwide network of marketing representatives as well as hematology experts to cover each region to establish a highly productive internal sales organization capable of making proposals that fit the needs of each region. With the termination of its alliance agreement with Eisai, in September 2020, the company concluded a basic agreement with Suzuken Co., Ltd and Toho Pharmaceutical Co., Ltd for the procurement and sale of pharmaceuticals to achieve nationwide distribution. The company has established two distribution centers, one in Eastern Japan and the other in Western Japan, under management by S.D. Collabo Co., Ltd.

During cumulative Q3, in January 2021, the company launched sales of the ready-to-dilute (RTD) formulation of Treakisym®, for which it obtained manufacturing and marketing approval in September 2020.

On March 23, 2021, the company obtained approval of a partial change to the manufacturing and marketing authorization for bendamustine-rituximab combination therapy (BR therapy) and bendamustine-rituximab-polatuzumab vedotin combination therapy (P-BR therapy) to treat r/r DLBCL patients. This enabled conventional lyophilized (freeze-dried [FD]) powder formulation of Treakisym® to be used in BR therapy right away. In April 2021, the company obtained approval of Treakisym® ready-to-dilute (RTD) liquid formulation for use in BR therapy and P-BR therapy for the treatment of r/r DLBCL. In May 2021, Chugai Pharmaceutical's polatuzumab vedotin was added to the NHI drug price list, enabling Treakisym® to be used in P-BR therapy.

Stable product supply

With the launch of sales of Treakisym® RTD formulation in January 2021, the company now markets both Treakisym® in both RTD formulation and FD formulation.

SymBio imports FD formulation Treakisym® for injection from Astellas Deutschland (consolidated subsidiary of Astellas Pharma) and Treakisym® RTD formulation from Eagle Pharmaceuticals Inc.

On the quality control front, the company conducts secondary packaging and quality screening on imported batches of both the FD and RTD formulations of TREAKISYM® to maintain stable quality.

On the supply front, the company is striving to replace the FD formulation of TREAKISYM® with RTD formulation in the market, but the current conversion rate is behind plan. Due to the possibility of the FD formulation being out of stock,

SymBio began controlling shipments of FD from September 21, 2021. The company has secured sufficient quantities of the RTD formulation to ensure stable supply.

Treakisym® (SyB L-0501[FD formulation]/SyB L-1701 [RTD formulation]/SyB L-1702 [RI administration]; generic name: bendamustine hydrochloride or bendamustine hydrochloride hydrate, product name: Treakisym®)

The anticancer agent Treakisym® is used to treat malignant lymphomas, indicated for untreated low-grade non-Hodgkin's lymphoma and mantle cell lymphoma (marketing approval obtained in December 2016), refractory or relapsed low-grade NHL and MCL (October 2010), and chronic lymphocytic leukemia (August 2016).

The combination therapy of Treakisym® and rituximab (BR therapy) was newly included in the Practical Guidelines for Hematological Malignancies 2018 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.

Also, SymBio obtained approval for the partial revision to the marketing authorization of Treakisym® in July 2018. Treakisym® can now be used in combination with new anti-CD20 antibodies and not just rituximab for the treatment of CD20-positive follicular lymphoma, the most common histological type of low-grade NHL. This allows the company to provide patients a new treatment option: combination therapy with obinutuzumab. In March 2019, SymBio obtained approval for the partial revision to its application to use Treakisym® as a pretreatment agent in tumor-specific T cell infusion therapy. This allows Treakisym® to be used as a pretreatment agent for Kymriah® intravenous infusion, which was the first chimeric antigen receptor T-cell (CAR-T) therapy approved in Japan. Growing use of Treakisym® as a pretreatment agent in regenerative medicine has solidified its positioning as standard therapy for malignant lymphomas.

In the phase III clinical study of Treakisym® administered in BR therapy targeting r/r DLBCL, the company filed for approval for partial revision to manufacturing and marketing authorization in May 2020 and obtained that approval in March 2021. In April 2021, it obtained approval for partial revision to manufacturing and marketing authorization of Treakisym® RTD liquid formulation for use in BR and P-BR therapy as treatment for r/r DLBCL. The company has conducted a follow-up study with overall survival as the primary endpoint, because evaluating the survival data (e.g., overall survival and progression-free survival) for Treakisym® administered in BR therapy is crucial for establishing Treakisym® as a treatment for DLBCL. It is now making preparations to publicize the results of that study.

In response to Chugai's June 2020 filing for manufacturing and marketing approval of combination therapy of polatuzumab vedotin + BR therapy (P-BR therapy) to treat r/r DLBCL, SymBio submitted a filing for Treakisym® + polatuzumab vedotin + rituximab in July 2020 and received approval in March 2021. Polatuzumab vedotin was included in the NHI price list from May 2021, at which time it became possible to use Treakisym® in P-BR therapy. Prior to this, there were no effective treatments for this indication so multi-drug regimens comprised of different anticancer agents were used as rescue chemotherapy. Accordingly, there was strong demand for development of an effective and safe treatment option. As BR therapy was already used to treat r/r DLBCL in Europe and the US, patient groups and related academic societies submitted a request to MHLW for an accelerated approval in Japan.

The company concluded an exclusive licensing agreement in Japan with Eagle Pharmaceuticals (based in New Jersey, US) in September 2017 for the RTD and rapid infusion (RI) formulations of Treakisym® (the RI formulation reduces administration time). Manufacturing and marketing approval of the RTD formulation was obtained in September 2020, and the company launched it in January 2021. The company has concluded clinical trials to confirm safety of the RI formulation and applied for approval in May 2021. Unlike the current FD formulation, the RTD formulation reduces the workload of medical professionals, because it eliminates the need for troublesome manual dissolution. The RI formulation can be administered in just 10 minutes, versus 60 minutes for the current FD and RTD formulation. This reduces the burden on patients and healthcare professionals, providing significant value added.

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

Onconova Therapeutics, Inc., the licensor, conducted a global phase III trial (INSPIRE study) across more than 20 countries addressing higher-risk myelodysplastic syndromes (higher-risk MDS) with overall survival as the primary endpoint. The target is patients who do not respond to the current standard treatment with hypomethylating agents, relapse after treatment under the current standard of care, or are intolerant to hypomethylating agents. In August 2020, Onconova announced a comparator trial to physicians' choice of treatment failed to achieve the primary endpoint. The company leads clinical trials conducted in Japan and is looking to apply the knowledge gleaned from additional analysis of the INSPIRE study to rigosertib development going forward.

Regarding the oral formulation of rigosertib, Onconova completed a phase I/II clinical trial for the drug used in combination with azacytidine, whose results suggested the efficacy and safety of the combination therapy. To verify the tolerability and safety among Japanese patients, SymBio began a phase I clinical trial in Japan in June 2017 and completed patient enrollment in June 2019.

The company said it would conduct joint research into Treakisym® and rigosertib with the University of Tokyo's Institute of Medical Science and Gunma University regarding efficacy of using the two compounds in combination or with existing drugs and also explore new indications.

Antiviral drug SyB V-1901 (generic name: brincidofovir)

In September 2019, SymBio concluded an exclusive global license agreement with Chimerix Inc. (hereafter Chimerix) for brincidofovir (SyB V-1901, hereafter BCV IV and BCV Oral), an antiviral drug in intravenous and oral forms). The company acquired exclusive global rights to develop, manufacture, and market BCV for all diseases except smallpox.

The company has concluded that it would prioritize global development of BCV IV (mainly in Japan, the US, and Europe) to treat adenovirus (AdV) infections in patients receiving hematopoietic stem cell transplantation to address an unmet medical need. In March 2021, the company submitted of an investigational new drug (IND) application to the Food and Drug Administration (FDA) of the US with the goal of obtaining permission for the launch of a phase II clinical trial for a phase II clinical trial of BCV IV as a treatment for adenovirus infections that primarily occur in children (although also in adults). In April 2021, the company received granted fast track designation from the FDA and on August 16, 2021, the investigational drug was administered to the first patient enrolled (first patient in [FPI]) in the clinical trial.

Based on safety and efficacy data acquired from its study, the company plans to review the drug's efficacy against dsDNA viral infections in patients receiving hematopoietic stem cell transplantation and extend its target indications to include multiviral infections. By exploring the potential for expanding target disease areas to viral infections related to organ transplants (including kidney transplants), the company aims to grow the market for and maximize the business value of BCV. Clinical trials by Chimerix have demonstrated superior, broad-spectrum antivirus activity of BCV Oral against dsDNA viruses, raising expectations for its potential as a safe and effective therapy to prevent and treat a range of viral infections in patients receiving hematopoietic stem cell transplantation.

Chimerix announced in December 2020 that the FDA had accepted its new drug application (NDA) for BCV as a medical defense against smallpox and that it had received FDA approval in June 2021. Further, through joint research with the National Cancer Centre Singapore and University of California San Francisco Brain Tumor Center, SymBio is investigating new indications for BCV.

Overseas

The company's US-based wholly-owned subsidiary SymBio Pharma USA, Inc. appointed Dr. Carolyn Yanavich as its Vice President, and Head of Project Management and Clinical Operations on October 11, 2021, and launched full-scale operations aimed at accelerating global development of antiviral drug brincidofovir toward commercialization.

In-licensing of drug candidates

The company is currently focusing on unrolling global development plans for the antiviral drug brincidofovir it in-licensed in September 2019, but also constantly looking into multiple licensing deals and looking for and evaluating promising new in-licensing drug candidates.

1H FY12/21 results

- Sales: JPY3.1bn (+131.3% YoY)
- Operating loss: JPY195mn (loss of JPY1.8bn in 1H FY12/20)
- Recurring loss: JPY204mn (loss of JPY1.9bn in 1H FY12/20)
- Net loss: JPY206mn (loss of JPY1.9bn in 1H FY12/20)

Sales increased YoY in 1H, largely due to the transfer of sales from Eisai Co., Ltd. to the company's own sales force. The business alliance agreement with Eisai concerning the marketing of Treakisym® expired on December 9, 2021, and the company began its own marketing in Japan on December 10, 2021, starting shipments to pharmaceutical wholesalers instead of Eisai. This allowed the company to receive not only the gross profit it received previously (the company's sales to Eisai

minus cost of sales), but also the gross profit earned by Eisai through December 9, 2020 (i.e., the difference between the shipment price from Eisai to pharmaceutical wholesalers and the price Eisai paid the company to source the product).

However, there were negative factors for Treakisym® sales, such as the impact of clearance of unsold inventory of lyophilized formulations sold by Eisai prior to December 2020, delays in treating patients after the COVID-19 outbreak starting in late 2020, and tightened restrictions on visiting facilities limiting sales activities.

From Q3 onward, the company says that it expects sales of drugs targeting relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL) to accelerate. The backlog of delayed medical treatments should clear as measures to combat COVID-19, including vaccinations for the elderly, progress. Other factors include the March 2021 approval of BR-therapy and Pola-BR therapy to treat r/r DLBCL, and Chugai Pharmaceutical's polatuzumab vedotin being added to the NHI drug list in May 2021.

Gross profit was JPY2.3bn (+589.5% YoY), and GPM was 72.3% (+48.0pp YoY). The company attributes the GPM rise to the shift to its own marketing system and the launch of Treakisym® Ready-to-dilute (RTD) formulation in January 2021. In 1H, sales of Treakisym® lyophilized formulations surpassed those of Treakisym® RTD formulations.

Reasons why in-house marketing of Treakisym® contributed to GPM improvement: Switching from marketing through Eisai to doing its own marketing meant that products are shipped to pharmaceutical wholesalers instead of to Eisai starting from December 10, 2020. This allows the company to receive not only the gross profit it received previously (the company's sales to Eisai minus cost of sales), but also the gross profit earned by Eisai through December 9, 2020 (i.e., the difference between the shipment price from Eisai to pharmaceutical wholesalers and the price Eisai paid the company to source the product).

GPM rises due to switching from the lyophilized formulation to the RTD formulation of Treakisym®: The company sourced the lyophilized formulation of Treakisym® from Astellas Deutschland, but the liquid formulations (RTD and RI formulations) are supplied by Eagle Pharmaceuticals. The company says that the GPM on liquid formulations of Treakisym® is higher than the GPM on the lyophilized formulation.

Although SG&A expenses increased in 1H, losses at the operating profit/losses level down narrowed thanks to the effect of sales growth, and the company recorded operating profit in Q2 (April–June 2021). SG&A expenses increased 13.8% YoY to JPY2.5bn and R&D expenses increased 9.4% YoY to JPY912mn.

- R&D expenses were JPY912mn (+9.4% YoY). The company incurred clinical trial expenses for the IV formulations of Treakisym® and brincidofovir.
- SG&A expenses other than R&D expenses were JPY1.6bn (+16.6% YoY). Sales expenses associated with the transition to its own sales system increased.

Q2 FY12/21 (April-June 2021) results

In Q2 FY12/21, sales were JPY1.7bn (+113/3% YoY), gross profit was JPY1.3bn (+525.5% YoY), the GPM was 73.3% (+48.3pp YoY), and operating profit was JPY16mn (JPY878mn loss in Q2 FY12/20). The company turned profitable at OP level.

Versus Q1 FY12/21, sales were up JPY306mn, gross profit up JPY255mn, the GPM up 2.2pp, and operating profit up JPY226mn.

Factors that contributed to sales growth were as follows. In Q1, sales were impacted by clearance of unsold inventory of lyophilized formulations sold by Eisai prior to December 2020, but this effect faded in Q2. In March 2021, approval was granted for Treakisym® in combination with rituximab for the indication of r/r DLBCL (BR therapy). In Q2, the company recorded sales of Treakisym® for the indication of r/r DLBCL.

The GPM rose QoQ, because the switch from the lyophilized formulation to the RTD formulation of Treakisym® progressed faster in Q2 than in Q1.

June 2021 results

The company commented that it turned profitable on a monthly basis in June 2021. Sales were JPY706mn (+298.3% YoY), gross profit was JPY523mn (+881.6% YoY), the GPM was 74.1% (+44.1pp YoY), and operating profit was JPY85mn (JPY324mn loss in June 2020).

Sales in June 2021 surpassed the average monthly sales in Q2 FY12/21 and the GPM was also higher than the monthly average in Q2. Sales were higher in June than in April and May, because the company recorded sales of Treakisym® targeting r/r DLBCL. GPM rose especially in the latter half of Q2 thanks to the switch to the RTD formulation.

Progress in 1H versus full-year FY12/21 company forecast

In 1H FY12/21, sales were 34.4% of the full-year forecast, while the company posted a JPY195mn operating loss versus the full-year forecast of JPY1.4bn profit. Although 1H sales fell short of the company forecast, the company left its full-year forecast unchanged, because it expects higher sales in 2H than in 1H, and thinks the full-year forecast is achievable. Reasons for the company's expectation of profit growth in 2H versus 1H are as follows.

- In 1H FY12/21, the impact of the clearance of unsold inventory of the lyophilized formulation of Treakisym® sold by Eisai totaled around JPY400mn. The clearance was completed in 1H and will have no impact on 2H results.
- Patients cut back on hospital visits in 1H because of COVID-19, but the company expects this pattern to change in 2H as more seniors are vaccinated and likely to resume hospital visits.
- The company received approval for BR therapy indicated for r/r DLBCL in March 2021, while Chugai Pharmaceutical received approval for polatuzumab vedotin + BR therapy indicated for r/r DLBCL. These approvals were granted about three months earlier than the company expected at the beginning of FY12/21. The company targets JPY2.6bn in sales of Treakisym® indicated for r/r DLBCL on a NHI drug reimbursement price basis, but Shared Research understands that sales may exceed this target because of the earlier-than-expected approval timing. The company recorded sales of Treakisym® indicated for r/r DLBCL in the second half of Q2 and expects this sales to increase in 2H.
- The company forecasts a higher GPM in 2H as the switch from the lyophilized formulation to the RTD formulation of Treakisym® progresses.

Business progress

- In August 2021, the company announced it had started administration to the first patient enrolled (FPI) in the Phase II clinical trial of antiviral drug brincidofovir (IV forumulation).
- Also in August 2021, the company concluded a joint research agreement with Kyoto University regarding the mechanism of effect of bendamustine, under development as an anticancer agent indicated for DLBCL.
- In July 2021, the company concluded a joint research agreement with the General Surgical Science Department, Gunma University Graduate School of Medicine regarding the exploration of new indications for bendamustine and rigosertib, which are under development as anticancer agents.
- Chimerix Inc., the licensor of antiviral drug brincidofovir, obtained approval from the US Food and Drug Administration (FDA) in June 2021 for antiviral drug brincidofovir tablets and oral formulation as a treatment for smallpox.
- In May 2021, the company filed for approval of of Treakisym® Rapid Infusion (RI) formulation.
- In April 2021, the company received approval for the RTD formulation of Treakisym® in combination with rituximab, and for the RTD formulation of Treakisym® in combination with rituximab and polatuzumab vedotin for the indication of r/r DLBCL.
- In March 2021, the company received approval for Treakisym® in combination with rituximab, and for Treakisym® in combination with rituximab and polatuzumab vedotin for the indication of r/r DLBCL.
- In March 2021, the company filed an Investigational New Drug (IND) application of brincidofovir IV formulation for a Phase II clinical trial targeting adenovirus infection in children.

- In January 2021, the company began sales of the read-to-dilute (RTD) liquid formulation of Treakisym®.

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 expired in December 2020, and the company switched to in-house sales for domestic sales of Treakisym®.

The company has thus far deployed a nationwide network of marketing representatives as well as hematology experts to cover each region to establish a highly productive internal sales organization capable of making proposals that fit the needs of each region. With the termination of its alliance agreement with Eisai, in September 2020, the company concluded a basic agreement with Suzuken Co., Ltd and Toho Pharmaceutical Co., Ltd for the procurement and sale of pharmaceuticals to achieve nationwide distribution. The company has established two distribution centers, one in Eastern Japan and the other in Western Japan, under management by S.D. Collabo Co., Ltd.

During 1H, in January 2021, the company launched sales of the ready-to-dilute (RTD) formulation of Treakisym®, for which it obtained manufacturing and marketing approval in September 2020.

On March 23, 2021, the company obtained approval of a partial change to the manufacturing and marketing authorization for bendamustine-rituximab combination therapy (BR therapy) and bendamustine-rituximab-polatuzumab vedotin combination therapy (Pola-BR therapy) to treat r/r DLBCL patients. This enabled conventional lyophilized (freeze-dried [FD]) powder formulation of Treakisym® to be used in BR therapy right away. In April 2021, the company obtained approval of Treakisym® ready-to-dilute (RTD) liquid formulation for use in BR therapy and Pola-BR therapy for the treatment of r/r DLBCL. In May 2021, Chugai Pharmaceutical's polatuzumab vedotin was added to the NHI drug price list, enabling Treakisym® to be used in Pola-BR therapy.

Stable product supply

With the launch of sales of Treakisym® RTD formulation in January 2021, the company now markets both Treakisym® in both RTD formulation and FD formulation.

SymBio imports FD formulation Treakisym® for injection from Astellas Deutschland (consolidated subsidiary of Astellas Pharma) and Treakisym® RTD formulation from Eagle Pharmaceuticals Inc. In 1H, secondary packaging and quality tests were applied to imported batches, resulting in stable quality, and as of May 2021, inventories had maintained proper levels to enable stable product supply.

On the supply front, the company is aiming for 91% completion of the switchover from the FD formulation to the RTD formulation of Treakisym®.

Treakisym® (SyB L-0501[FD formulation]/SyB L-1701 [RTD formulation]/SyB L-1702 [RI formulation]; generic name: bendamustine hydrochloride or bendamustine hydrochloride hydrate, product name: Treakisym®)

The anticancer agent Treakisym® is used to treat malignant lymphomas, indicated for untreated low-grade non-Hodgkin's lymphoma and mantle cell lymphoma (marketing approval obtained in December 2016), refractory or relapsed low-grade NHL and MCL (October 2010), and chronic lymphocytic leukemia (August 2016).

The combination therapy of Treakisym® and rituximab (BR therapy) was newly included in the Practical Guidelines for Hematological Malignancies 2018 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.

Also, SymBio obtained approval for the partial revision to the marketing authorization of Treakisym® in July 2018. Treakisym® can now be used in combination with new anti-CD20 antibodies and not just rituximab for the treatment of CD20-positive follicular lymphoma, the most common histological type of low-grade NHL. This allows the company to provide patients a new treatment option: combination therapy with obinutuzumab. In March 2019, SymBio obtained approval for the partial revision to its application to use Treakisym® as a pretreatment agent in tumor-specific T cell infusion therapy. This allows Treakisym® to be used as a pretreatment agent for Kymriah® intravenous infusion, which was the first chimeric antigen receptor T-cell (CAR-T) therapy approved in Japan. Growing use of Treakisym® as a pretreatment agent in regenerative medicine has solidified its positioning as standard therapy for malignant lymphomas.

In the phase III clinical study of Treakisym® administered in BR therapy targeting r/r DLBCL, the company filed for approval for partial revision to manufacturing and marketing authorization in May 2020 and obtained that approval in March 2021. In April 2021, it obtained approval for partial revision to manufacturing and marketing authorization of Treakisym® RTD liquid formulation for use in BR and Pola-BR therapy as treatment for r/r DLBCL. The company has conducted a follow-up study with overall survival as the primary endpoint, because evaluating the survival data (e.g., overall survival and progression-free survival) for Treakisym® administered in BR therapy is crucial for establishing Treakisym® as a treatment for DLBCL. It is now making preparations to publicize the results of that study. Also, after Chugai Pharmaceutical Co., Ltd. applied for manufacture and marketing approval for polatuzumab vedotin in combination with BR therapy to treat r/r DLBCL in June 2020, the company applied for approval for partial revision to manufacturing and marketing authorization for Treakisym® in Pola-BR therapy and obtained approval in March 2021. Polatuzumab vedotin was added to the NHI drug price list in May 2021, and now Treakisym® may be used in Pola-BR therapy. Previously there were no effective treatments for the additional indication of r/r DLBCL, which was usually treated by a combination of anticancer agents as salvage chemotherapy, so development of a highly effective but safe new drug was sought after. Since BR therapy is already being used in the West to treat r/r DLBCL, patient organizations and related academic societies petitioned MHLW so that it could be used in Japan as soon as possible.

The company concluded an exclusive licensing agreement in Japan with Eagle Pharmaceuticals (based in New Jersey, US) in September 2017 for the RTD and rapid infusion (RI) formulations of Treakisym® (the RI formulation reduces administration time). Manufacturing and marketing approval of the RTD formulation was obtained in September 2020, and the company launched it in January 2021. The company has concluded clinical trials to confirm safety of the RI formulation and applied for approval in May 2021. Unlike the current FD formulation, the RTD formulation reduces the workload of medical professionals, because it eliminates the need for troublesome manual dissolution. The RI formulation can be administered in just 10 minutes, versus 60 minutes for the current FD and RTD formulation. This reduces the burden on patients and healthcare professionals, providing significant value added. Multiple patent protections in the form of a liquid product license will enable the extension of the product life of Treakisym® to 2031.

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

Onconova Therapeutics, Inc., the licensor, conducted a global phase III trial (INSPIRE study) across more than 20 countries addressing higher-risk myelodysplastic syndromes (higher-risk MDS) with overall survival as the primary endpoint. The target is patients who do not respond to the current standard treatment with hypomethylating agents, relapse after treatment under the current standard of care, or are intolerant to hypomethylating agents. In August 2020, Onconova announced a comparator trial to physicians' choice of treatment failed to achieve the primary endpoint. The company leads clinical trials conducted in Japan and is looking to apply the knowledge gleaned from additional analysis of the INSPIRE study to rigosertib development going forward.

Regarding the oral formulation of rigosertib, Onconova completed a phase I/II clinical trial for the drug used in combination with azacytidine, whose results suggested the efficacy and safety of the combination therapy. To verify the tolerability and safety among Japanese patients, SymBio began a phase I clinical trial in Japan in June 2017 and completed patient enrollment in June 2019.

The company said it would conduct joint research into Treakisym® and rigosertib with the University of Tokyo's Institute of Medical Science regarding efficacy of using the two compounds in combination or with existing drugs and also explore new indications.

Antiviral drug SyB V-1901 (generic name: brincidofovir)

In September 2019, SymBio concluded an exclusive global license agreement with Chimerix Inc. (hereafter Chimerix) for brincidofovir (SyB V-1901, hereafter BCV IV and BCV Oral), an antiviral drug in intravenous and oral forms). The company acquired exclusive global rights to develop, manufacture, and market BCV for all diseases except smallpox.

The company has concluded that it would prioritize global development of BCV IV (mainly in Japan, the US, and Europe) to treat adenovirus (AdV) infections in patients receiving hematopoietic stem cell transplantation to address an unmet medical need. In March 2021, the company submitted of an investigational new drug (IND) application to the Food and Drug Administration (FDA) of the US with the goal of obtaining permission for the launch of a phase II clinical trial for a phase II clinical trial of BCV IV as a treatment for adenovirus infections that primarily occur in children (although also in adults). In April 2021, the company received granted fast track designation from the FDA.

Based on safety and efficacy data acquired from its study, the company plans to review the drug's efficacy against dsDNA viral infections in patients receiving hematopoietic stem cell transplantation and extend its target indications to include multiviral infections. By exploring the potential for expanding target disease areas to viral infections related to organ transplants

(including kidney transplants), the company aims to grow the market for and maximize the business value of BCV. Clinical trials by Chimerix have demonstrated superior, broad-spectrum antivirus activity of BCV Oral against dsDNA viruses, raising expectations for its potential as a safe and effective therapy to prevent and treat a range of viral infections in patients receiving hematopoietic stem cell transplantation.

Chimerix announced in December 2020 that the FDA had accepted its new drug application (NDA) for BCV as a medical defense against smallpox and that it had received FDA approval in June 2021.

Overseas

The company marketed SyB L-0501 in China and Hong Kong, and product sales were in line with the company's plans.

In-licensing of drug candidates

The company is currently focusing on unrolling global development plans for antiviral drug brincidofovir it in-licensed in September 2019. It is constantly looking into multiple licensing deals and looking for and evaluating promising in-licensing drug candidates.

Q1 FY12/21 results

- Sales: JPY1.4bn (+157.6% YoY)
- Operating loss: JPY211mn (loss of JPY962mn in Q1 FY12/19)
- Recurring loss: JPY4.6bn (loss of JPY991mn in Q1 FY12/19)
- Net loss: JPY4.1bn (loss of JPY992mn in Q1 FY12/19)

Sales increased 157.6% YoY to JPY1.4bn, largely due to the transfer of sales from Eisai Co., Ltd. to the company's own sales force. The business alliance agreement for Treakisym® concluded with Eisai expired on December 9, 2020, and SymBio started independently marketing Treakisym® in Japan on December 10, 2020. With this change, the product is shipped to pharmaceutical wholesalers instead of to Eisai. This allows the company to receive not only the gross profit it received previously (the company's sales to Eisai minus cost of sales), but also the gross profit earned by Eisai through December 9, 2020 (i.e., the difference between the shipment price from Eisai to pharmaceutical wholesalers and the price Eisai paid the company to source the product).

Earnings were partially hindered by medical care delays due to the COVID-19 outbreak since late 2020 and constraints on sales activities due to tighter restrictions on facilities visitations, but considering the clearance of market inventory of the lyophilized (freeze-dried [FD]) powder formulation of Treakisym® sold by Eisai prior to the switch to the company's own sales force in December 2020, demand for Treakisym® was strong in Q1.

For Q2, although there are lingering impacts of the clearance of market inventory distributed prior to the switch to the company' own sales force, there will be minimal impact on sales overall, and the company says that it anticipates sales growth on the additional indications for relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL) that were approved on March 23, 2020.

Gross profit was JPY1.0bn (+690.9% YoY), and GPM was 71.1% (+47.9pp YoY). The company attributes GPM growth to the shift to its own marketing system and the launch of Treakisym® Ready-To-Dilute (RTD) formulation in January 2021. In Q1, sales of Treakisym® lyophilized formulations surpassed those of Treakisym® RTD formulations

Reasons why in-house marketing of Treakisym® contributed to GPM improvement: Switching from marketing through Eisai (based the marketing agreement with Eisai) to doing its own marketing meant that products are shipped to pharmaceutical wholesalers instead of to Eisai starting from December 10, 2020. This allows the company to receive not only the gross profit it received previously (the company's sales to Eisai minus cost of sales), but also the gross profit earned by Eisai through December 9, 2020 (i.e., the difference between the shipment price from Eisai to pharmaceutical wholesalers and the price Eisai paid the company to source the product).

GPM rises due to switching from the lyophilized formulation to the RTD formulation of Treakisym®: The company sourced the lyophilized formulation of Treakisym® from Astellas Deutschland, but the liquid formulations (RTD and RI formulations) are supplied by Eagle Pharmaceuticals. The company says that the GPM on liquid formulations of Treakisym® is higher than the GPM on the lyophilized formulation.

Although SG&A expenses increased, losses at the operating profit level on down shrank thanks to the effect of sales growth. SG&A expenses increased 12.0% YoY to JPY1.2bn.

- R&D expenses increased 8.0% YoY to JPY473mn. This included expenses for conducting clinical trials of Treakisym® and brincidofovir injections.
- Excluding R&D expenses, SG&A expenses rose 14.7% YoY to JPY747mn. The switch to in-house sales drove up the cost of sales. Yet, the results were below the company's forecast for SG&A expenses (excluding R&D expenses) of JPY3.6bn (+15.1% YoY), as the shift to online sales activities and other factors curbed the expenses.

Overview of business progress

In FY12/21, progress in main businesses are as follows:

- In June 2021, Chimerix, Inc. (licensor of brincidofovir) obtained FDA approval of brincidofovir tablets and oral suspensions as antiviral formulations for the treatment of smallpox.
- In May 2021, SymBio submitted approval application for Treakisym® rapid infusion (RI) liquid formulation.
- In April 2021, the company obtained approval of Treakisym® ready-to-dilute (RTD) liquid formulation for use in combination with rituximab and in combination with rituximab and polatuzumab vedotin for the treatment of refractory or relapsed diffuse large B-cell lymphoma (r/r DLBCL).
- In March 2021, the company obtained approval of Treakisym® for use in combination with rituximab, and in combination with rituximab and polatuzumab vedotin for the treatment of r/r DLBCL.
- In March 2021, the company submitted an Investigational New Drug (IND) application for phase II clinical study of brincidofovir injection in pediatric patients with adenovirus infections.
- In January 2021, the company launched Treakisym® RTD liquid formulation.

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 expired in December 2020, and the company switched to in-house sales for domestic sales of Treakisym®.

The company has thus far deployed a nationwide network of marketing representatives as well as hematology experts to cover each region to establish a highly productive internal sales organization capable of making proposals that fit the needs of each region. With the termination of its alliance agreement with Eisai, in September 2020, the company concluded a basic agreement with Suzuken Co., Ltd and Toho Pharmaceutical Co., Ltd for the procurement and sale of pharmaceuticals to achieve nationwide distribution. The company has established two distribution centers, one in Eastern Japan and the other in Western Japan, under management by S.D. Collabo Co., Ltd.

During Q1, in January 2021, the company launched sales of the ready-to-dilute (RTD) formulation of Treakisym®, for which it obtained manufacturing and marketing approval in September 2020.

On March 23, 2021, the company obtained approval of a partial change to the approved matters of the lyophilized (freeze-dried) powder formulation of Treakisym® for use in bendamustine-rituximab combination therapy (BR therapy) and in bendamustine-rituximab-polatuzumab vedotin combination therapy (Pola-BR therapy) to treat r/r DLBCL patients. The lyophilized powder formulation of Treakisym® can be used in BR therapy (120mg/sqm as bendamustine hydrochloride) right

away, and it can also be used in Pola-BR therapy (90mg/sqm as bendamustine hydrochloride) once polatuzumab vedotin is added to the NHI drug price list (listed in May 2021) .

On April 28, 2021, the company obtained approval of a partial change to the approved matters of Treakisym® RTD liquid formulation for use in BR and Pola-BR therapy as treatment for r/r DLBCL.

Stable product supply

With the launch of sales of Treakisym® RTD formulation in January 2021, the company now markets both Treakisym® in both RTD formulation and lyophilized powder formulation.

SymBio imports lyophilized Treakisym® for injection from Astellas Deutschland (consolidated subsidiary of Astellas Pharma) and Treakisym® RTD formulation from Eagle Pharmaceuticals Inc. In Q1, secondary packaging and quality tests were applied to imported batches, resulting in stable quality, and as of May 2021, inventories had maintained proper levels to enable stable product supply.

On the supply front, the company is aiming for 91% completion of the switchover from the lyophilized formulation to the RTD formulation of Treakisym®.

Anticancer agents: (SyB L-0501[lyophilized injection]/SyB L-1701 [RTD]/SyB L-1702 [RI] (generic name: bendamustine hydrochloride, product name: Treakisym®)

The anticancer agent Treakisym® is used in malignant lymphomas, indicated for untreated low-grade non-Hodgkin's lymphoma and mantle cell lymphoma (marketing approval obtained in December 2016), refractory or relapsed low-grade NHL and MCL (October 2010), and chronic lymphocytic leukemia (August 2016).

The combination therapy of Treakisym® and rituximab (BR therapy) was newly included in the Practical Guidelines for Hematological Malignancies 2018 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.

Also, SymBio obtained approval for partial change to the approved matters of Treakisym® in July 2018. Treakisym® can now be used in combination with new anti-CD20 antibodies and not just rituximab for the treatment of CD20-positive follicular lymphoma, the most common histological type of low-grade NHL. This allows the company to provide patients a new treatment option: combination therapy with obinutuzumab. In March 2019, SymBio obtained approval for partial change to the approved matters of Treakisym® to enable its use as a pretreatment agent in tumor-specific T cell infusion therapy. This allows Treakisym® to be used as a pretreatment agent for Kymriah® intravenous infusion, which was the first chimeric antigen receptor T-cell (CAR-T) therapy approved in Japan. Growing use of Treakisym® as a pretreatment agent in regenerative medicine has solidified its positioning as standard therapy for malignant lymphomas.

In the phase III clinical study of Treakisym® administered in BR therapy for the treatment of r/r DLBCL, the company submitted an application for partial change to approved matters in May 2020 and obtained approval in March 2021. In April 2021, it obtained approval for a partial change to the approved matters of Treakisym® RTD liquid formulation for use in BR and Pola-BR therapy as treatment for r/r DLBCL. The company has conducted a follow-up study with overall survival as the primary endpoint, because evaluating the survival data (e.g., overall survival and progression-free survival) for Treakisym® administered in BR therapy is crucial for establishing Treakisym® as a treatment for DLBCL. It is now making preparations to publicize the results of that study. Also, after Chugai Pharmaceutical Co., Ltd. applied for manufacture and marketing approval for polatuzumab vedotin in combination with BR therapy to treat r/r DLBCL in June 2020, the company applied for approval for a partial change to the approved matters of Treakisym® for use in Pola-BR therapy and obtained approval in March 2021. With the approvals obtained by Chugai and SymBio, once polatuzumab vedotin is added to the NHI drug price list, Treakisym® will be able to be used in Pola-BR therapy. At present there are no effective treatments for the additional indication of r/r DLBCL, which is usually treated by a combination of anticancer agents as salvage chemotherapy, so development of a highly effective but safe new drug would be ideal. Since BR therapy is already being used in the West to treat r/r DLBCL, patient organizations and related academic societies have petitioned MHLW so that it can be used in Japan as soon as possible.

The company concluded an exclusive licensing agreement in Japan with Eagle Pharmaceuticals (based in New Jersey, US) in September 2017 for the RTD and rapid infusion (RI) formulations of Treakisym® (the RI formulation reduces administration time). Manufacturing and marketing approval of the RTD formulation was obtained in September 2020, and the company launched it in January 2021. The company has concluded clinical trials to confirm safety of the RI formulation and applies for

approval in May 2021. Unlike the current lyophilized powder formulation, the RTD formulation reduces the workload of medical professionals, because it eliminates the need for troublesome manual dissolution. The RI formulation can be administered in just 10 minutes versus 60 minutes for the current lyophilized injection and RTD formulation. This reduces the burden on patients and healthcare professionals, providing significant value added. Multiple patent protections in the form of a liquid product license will enable the extension of the product life of Treakisym® to 2031.

Anticancer agents: SyB L-1101 [IV]/SyB C-1101 [oral] (generic name: rigosertib sodium)

Onconova Therapeutics, Inc., the licensor, conducted a global phase III trial (INSPIRE study) across more than 20 countries addressing higher-risk myelodysplastic syndromes (higher-risk MDS) with overall survival as the primary endpoint. The target is patients who do not respond to the current standard treatment with hypomethylating agents, relapse after treatment under the current standard of care, or are intolerant to hypomethylating agents. In August 2020, Onconova announced a comparator trial to physicians' choice of treatment failed to achieve the primary endpoint. The company leads clinical trials conducted in Japan and is looking to apply the knowledge gleaned from additional analysis of the INSPIRE study to rigosertib development going forward.

Regarding the oral formulation of rigosertib, Onconova completed a phase I/II clinical trial for the drug used in combination with azacytidine, whose results suggested the efficacy and safety of the combination therapy. To verify the tolerability and safety of the high-dose oral formulation of rigosertib as an initial treatment for higher-risk MDS among Japanese patients, SymBio began a phase I clinical trial in Japan in June 2017 and completed patient enrollment in June 2019.

Antiviral drug: SyB V-1901 (generic name: brincidofovir)

In September 2019, SymBio concluded an exclusive global license agreement with Chimerix Inc. (hereafter Chimerix) for brincidofovir (SyB V-1901, hereafter BCV IV and BCV Oral), an antiviral drug in intravenous and oral forms). The company acquired exclusive global rights to develop, manufacture, and market BCV for all diseases except smallpox.

The company has concluded that it would prioritize global development of BCV IV (mainly in Japan, the US, and Europe) to treat adenovirus (AdV) infections in patients receiving hematopoietic stem cell transplantation to address an unmet medical need. In March 2021, the company submitted of an investigational new drug (IND) application to the Food and Drug Administration (FDA) of the US with the goal of obtaining permission for the launch of a phase II clinical trial for a phase II clinical trial of BCV IV as a treatment for adenovirus infections that primarily occur in children (although also in adults). In April 2021, the company received granted fast track designation from the FDA.

Based on safety and efficacy data acquired from its study, the company plans to review the drug's efficacy against dsDNA viral infections in patients receiving hematopoietic stem cell transplantation and extend its target indications to include multiviral infections. By exploring the potential for expanding target disease areas to viral infections related to organ transplants (including kidney transplants), the company aims to grow the market for and maximize the business value of BCV. Clinical trials by Chimerix have demonstrated superior, broad-spectrum antivirus activity of BCV Oral against dsDNA viruses, raising expectations for its potential as a safe and effective therapy to prevent and treat a range of viral infections in patients receiving hematopoietic stem cell transplantation.

Chimerix announced in June 2021 that the FDA approved BCV tablets and oral suspensions in adult and pediatric patients including neonates for the treatment of smallpox.

Overseas

company marketed SyB L-0501 in China and Hong Kong, and product sales were in line with the company's plans.

In-licensing of drug candidates

The company is currently focusing on unrolling global development plans for antiviral drug brincidofovir it in-licensed in September 2019. It is constantly looking into multiple licensing deals and looking for and evaluating promising in-licensing drug candidates.

Income statement

Income statement	FY12/12	FY12/13	FY12/14	FY12/15	FY12/16	FY12/17	FY12/18	FY12/19	FY12/20	FY12/21
(JPYmn)	Par.	Par.	Par.	Par.	Par.	Par.	Par.	Par.	Par.	Par.
Sales	**1,955**	**1,532**	**1,955**	**1,933**	**2,368**	**3,444**	**3,836**	**2,838**	**2,987**	**8,257**
YoY	3.9%	-21.6%	27.6%	-1.1%	22.5%	45.4%	11.4%	-26.0%	5.3%	176.4%
CoGS	1,362	1,214	1,428	1,350	1,464	2,413	2,663	1,973	2,120	2,452
Gross profit	**593**	**318**	**527**	**583**	**904**	**1,031**	**1,173**	**865**	**867**	**5,800**
Gross profit margin	30.3%	20.8%	26.9%	30.2%	38.2%	29.9%	30.6%	30.5%	29.0%	70.2%
SG&A expenses	2,293	1,999	1,830	3,135	3,031	4,978	3,829	5,166	5,373	4,784
SG&A ratio	117.3%	130.4%	93.6%	162.1%	128.0%	144.5%	99.8%	182.1%	179.9%	57.9%
Operating profit	**-1,700**	**-1,681**	**-1,303**	**-2,552**	**-2,127**	**-3,947**	**-2,656**	**-4,302**	**-4,506**	**1,016**
YoY	-	-	-	-	-	-	-	-	-	-
Operating profit margin	-	-	-	-	-	-	-	-	-	12.3%
Non-operating income	7	114	215	17	7	5	2	4	3	17
Non-operating expenses	37	35	22	96	196	34	95	79	112	32
Recurring profit	**-1,729**	**-1,601**	**-1,110**	**-2,630**	**-2,317**	**-3,977**	**-2,749**	**-4,377**	**-4,616**	**1,001**
YoY	-	-	-	-	-	-	-	-	-	-
Recurring profit margin	-	-	-	-	-	-	-	-	-	12.1%
Extraordinary gains	-	-	2	3	9	17	10	4	529	0
Extraordinary losses	0	-	3	1	1	15	10	-	-	-
Income taxes	4	4	4	4	4	4	4	4	4	-1,031
Implied tax rate	-	-	-	-	-	-	-	-	-	-
Net income	**-1,733**	**-1,605**	**-1,116**	**-2,632**	**-2,313**	**-3,978**	**-2,753**	**-4,376**	**-4,090**	**2,032**
YoY	-	-	-	-	-	-	-	-	-	-
Net margin	-	-	-	-	-	-	-	-	-	24.6%

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. Regarding non-operating profit/loss, extraordinary gain/loss, corporate income tax, etc., extraordinary gain of JPY529mn in FY12/20 mainly comes from the booking of JPY525mn in settlement payment. Income taxes of -JPY1.0bn in FY12/21 were due to the booking of JPY1.3bn in deferred tax assets.

Historical forecast accuracy

Results vs. Initial Est.	FY12/12	FY12/13	FY12/14	FY12/15	FY12/16	FY12/17	FY12/18	FY12/19	FY12/20	FY12/21
(JPYmn)	Par.	Par.	Par.	Par.	Par.	Par.	Par.	Par.	Par.	Par.
Sales (Initial Est.)	2,338	1,927	1,785	1,785	2,339	2,903	4,201	4,465	3,404	9,151
Sales (Results)	1,955	1,532	1,955	1,933	2,368	3,444	3,836	2,838	2,987	8,257
Results vs. Initial Est.	**-16.4%**	**-20.5%**	**9.5%**	**8.3%**	**1.2%**	**18.6%**	**-8.7%**	**-36.4%**	**-12.2%**	**-9.8%**
Operating profit (Initial Est.)	-1,625	-1,889	-1,654	-1,654	-2,778	-3,238	-2,981	-3,587	-5,090	1,361
Operating profit (Results)	-1,700	-1,681	-1,303	-2,552	-2,127	-3,947	-2,656	-4,302	-4,506	1,016
Results vs. Initial Est.	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-25.3%**
Recurring profit (Initial Est.)	-1,652	-1,922	-1,650	-1,650	-2,811	-3,303	-3,044	-3,612	-5,134	1,350
Recurring profit (Results)	-1,729	-1,601	-1,110	-2,630	-2,317	-3,977	-2,749	-4,377	-4,616	1,001
Results vs. Initial Est.	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-25.8%**
Net income (Initial Est.)	-1,656	-1,926	-1,654	-1,654	-2,815	-3,306	-3,056	-3,612	-4,803	1,149
Net income (Results)	-1,733	-1,605	-1,116	-2,632	-2,313	-3,978	-2,753	-4,376	-4,090	2,032
Results vs. Initial Est.	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**76.9%**

Source: Shared Research based on company data

Note: Figures may differ from company materials due to differences in rounding methods.

Balance sheet

Balance sheet (JPYmn)	FY12/12	FY12/13	FY12/14	FY12/15	FY12/16	FY12/17	FY12/18	FY12/19	FY12/20	FY12/21
	Par.	Par.	Par.	Par.	Par.	Par.	Par.	Par.	Par.	Par.
Assets										
Cash and deposits	4,540	6,163	5,692	4,261	5,719	2,947	4,821	3,911	3,849	3,860
Marketable securities	300	1,100	899	-	-	-	-	-	-	-
Accounts receivable	148	-	273	301	487	490	412	549	407	2,148
Inventories	165	125	245	133	273	363	534	1	945	386
Other current assets	268	245	181	131	205	237	271	427	615	355
Total current assets	**5,421**	**7,634**	**7,290**	**4,827**	**6,685**	**4,037**	**6,038**	**4,887**	**5,815**	**6,748**
Buildings (net)	3	2	22	22	31	28	37	47	43	45
Tools, furniture, and fixtures (net)	11	6	27	31	43	18	20	19	34	39
Total tangible assets	**14**	**9**	**49**	**53**	**75**	**47**	**57**	**75**	**77**	**84**
Investments and other assets	**57**	**37**	**49**	**53**	**77**	**100**	**73**	**70**	**81**	**1,362**
Software	8	6	62	51	42	66	51	95	296	255
Other	3	2	4	1	-	3	20	146	6	4
Total intangible assets	**11**	**8**	**66**	**52**	**42**	**69**	**71**	**241**	**302**	**259**
Total fixed assets	**82**	**53**	**164**	**158**	**193**	**216**	**201**	**386**	**459**	**1,705**
Total assets	**5,502**	**7,687**	**7,454**	**4,984**	**6,878**	**4,252**	**6,239**	**5,274**	**6,275**	**8,453**
Liabilities										
Accounts payable	330	-	306	320	322	604	726	121	665	70
Unearned revenue	-	-	-	-	-	-	-	-	193	-
Accounts payable–other	196	207	143	184	553	331	504	639	646	515
Short-term debt	-	-	-	-	-	-	-	-	-	-
Other	73	44	39	47	68	76	107	112	111	933
Total current liabilities	**599**	**251**	**488**	**551**	**942**	**1,011**	**1,336**	**872**	**1,615**	**1,518**
Long-term debt	-	-	-	-	-	-	-	-	-	-
Corporate bonds				-	450	-	-	-	-	-
Other fixed liabilities	4	3	2	2	1	1	1	2	2	189
Total fixed liabilities	**4**	**3**	**2**	**2**	**451**	**1**	**1**	**2**	**2**	**189**
Total interest-bearing debt	-	-	-	-	-	-	-	-	-	-
Total liabilities	**602**	**254**	**490**	**552**	**1,394**	**1,013**	**1,338**	**874**	**1,617**	**1,707**
Net assets										
Capital stock	6,025	8,059	8,331	8,331	9,948	10,762	12,973	14,871	17,045	17,158
Capital surplus	5,995	8,029	8,301	8,301	9,918	10,732	12,943	14,841	17,019	17,133
Retained earnings	-7,146	-8,752	-9,868	-12,500	-14,813	-18,791	-21,543	-25,919	-30,010	-27,978
Treasury stock	-0	-0	-0	-0	-0	-0	-0	-15	-18	-86
Share subscription rights	27	97	200	300	431	537	530	621	620	519
Net assets	**4,900**	**7,433**	**6,964**	**4,432**	**5,485**	**3,239**	**4,902**	**4,400**	**4,657**	**6,746**
Working capital	-17	125	212	114	439	249	220	429	686	2,464
Total interest-bearing debt	-	-	-	-	-	-	-	-	-	-
Net debt	-4,540	-6,163	-5,692	-4,261	-5,719	-2,947	-4,821	-3,911	-3,849	-3,860

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

Assets

SymBio outsources manufacturing and clinical development. Therefore, most of the company's assets are cash and deposits.

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

Liabilities

As of FY12/21, the company did 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, there is a deficit in retained earnings as the company continued to post losses.

Cash flow statement

Cash flow statement	FY12/12	FY12/13	FY12/14	FY12/15	FY12/16	FY12/17	FY12/18	FY12/19	FY12/20	FY12/21
(JPYmn)	Par.	Par.	Par.	Par.	Par.	Par.	Par.	Par.	Par.	Par.
Cash flows from operating activities (1)	-1,659	-1,677	-1,266	-2,272	-1,960	-3,817	-2,325	-4,351	-4,122	140
Cash flows from investing activities (2)	-411	-1,332	314	1,489	-44	-78	-26	-216	-160	-71
FCF (1+2)	-2,069	-3,010	-952	-783	-2,004	-3,894	-2,351	-4,567	-4,283	69
Cash flows from financing activities	-1	4,057	544	-3	3,658	1,164	4,272	3,740	4,222	-72
Depreciation and good will amortization (A)	9	8	13	24	26	30	35	38	64	94
Capital expenditures (B)	-3	-	-109	-24	-28	-57	-40	-217	-149	-64
Change in working capital (C)	-78	142	86	-98	325	-190	-29	209	257	1,777
Simple FCF (NI + A + B - C)	-1,650	-1,739	-1,298	-2,534	-2,640	-3,815	-2,729	-4,764	-4,433	285
Cash and cash equivalents (year-end)	4,240	5,294	5,092	4,261	5,719	2,947	4,821	3,911	3,849	3,860

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 net income before income tax.
In FY12/21, accounts receivable increased as the company started in-house sales, giving rise to a gap between cash flows from operating activities and net income before income tax.

Cash flows from investing activities

Outlays on the purchase of tangible fixed assets and intangible assets are limited as SymBio outsources clinical trials and manufacturing. 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 historically often reported inflows from financing activities.

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)	
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
Jan. to Dec. 2019	1,726,800	26,437,681	3,796	29,711	Exercise of stock options
Jan. to Dec. 2020	11,765,275	38,202,956	4,349	34,064	Exercise of stock options

Source: Shared Research based on company data
Note: In July 2019, the company conducted a 4:1 reverse stock split, reducing the number of shares outstanding by 73,088,043.

Other information

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 more than 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 2021, 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® indications, RI formulation of Treakisym®, and anticancer drug rigosertib for myelodysplastic syndromes.

In addition, after acquiring exclusive worldwide rights from Chimerix in September 2019 to develop, manufacture, and market brincidofovir for all indications except smallpox, SymBio looks to commercialize it by the mid-2020s.

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	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 concluded 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 multiple myeloma.
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.
August 2016	Received approval for the additional indication of chronic lymphocytic leukemia for Treakisym®.
December 2016	Obtained approval for the additional indication of untreated low-grade non-Hodgkin's lymphoma and mantle cell lymphoma for the anticancer drug Treakisym®
September 2017	Concluded an exclusive license agreement with Eagle Pharmaceuticals, Inc. (US) on rights to develop, market, and sell Eagle's bendamustine hydrochloride RTD and RI formulations in Japan.
September 2019	Concluded an exclusive global license agreement with Chimerix Inc. (US) on rights to develop, manufacture, and market antiviral brincidofovir for all indications except smallpox.
December 2020	Began in-house sales of anticancer drug Treakisym®
January 2021	Launched Treakisym® liquid formulation (RTD)
March 2021	Obtained approval for use of Treakisym® in bendamustine-rituximab combination therapy to treat r/r DLBCL
February 2022	Received approval for Treakisym® rapid infusion (RI) administration

Major shareholders

Top shareholders	Shares held (shares)	Shareholding ratio
Rakuten Securities, Inc.	1,345,100	3.5%
Fuminori Yoshida	1,074,700	2.8%
Matsui Securities Co., Ltd.	738,500	1.9%
SMBC Nikko Securities Inc.	727,300	1.9%
Nomura Securities Co., Ltd. self-deposit account	550,000	1.4%
SBI Securities Co., Ltd.	403,608	1.1%
NOMURA PB NOMINEES LIMITED OMUNIBUS-MARGIN	303,650	0.8%
Sukenori Ito	302,000	0.8%
Hitoshi Imamura	225,700	0.6%
Nomura Securities Co., Ltd.	207,731	0.5%
Total	5,878,289	15.3%

Source: Shared Research based on company data
As of December 31, 2020
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 141 employees as of December 31, 2021.

Number of employees	FY12/12	FY12/13	FY12/14	FY12/15	FY12/16	FY12/17	FY12/18	FY12/19	FY12/20	FY12/21
	Par.	Par.	Par.	Par.	Par.	Par.	Par.	Par.	Par.	Par.
Number of employees	76	72	69	74	77	78	90	107	127	141
Change	5	-4	-3	5	3	1	12	17	20	14

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.

Glossary

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.

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.

Overall Survival (OS)

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

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.

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.

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.

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.

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.

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.

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.

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).

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.

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.

Chronic Lymphocytic Leukemia (CLL)

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

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.

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.

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.

News and topics

Approval for TREAKISYM® liquid formulation for rapid infusion (RI) administration

2022-03-01

On February 28, 2022, SymBio Pharmaceuticals Limited announced approval for its TREAKISYM® liquid formulation for rapid infusion (RI) administration.

SymBio Pharmaceuticals announced that it had received approval for a partial change to its manufacture and marketing authorization for TREAKISYM® 100mg/4ml ready-to-dilute (RTD) liquid formulation to add rapid RI administration.

Response to manufacture and marketing approval of generic drugs

2022-02-28

On February 25, 2022, SymBio Pharmaceuticals Ltd. announced its response to the manufacture and marketing approval of generic drugs.

In February 2022, the Ministry of Health, Labour and Welfare approved manufacture and marketing of generic drugs of the company's Treakisym® Intravenous Infusion (RTD formulation). As this approval could possibly infringe the company's exclusive rights to develop and commercialize the patent-protected product in Japan, the company consulted with the licensor Eagle Pharmaceuticals, Inc. ("Eagle") and notified the four companies that had obtained the approval for generic drugs of the possibility of patent infringement, demanding they take appropriate actions.

The company entered into an agreement with Eagle in September 2017 for exclusive rights to develop and commercialize the liquid formulations of Treakiysm® (RTD and RI formulations) in Japan.

If an infringement becomes apparent, the company, in cooperation with Eagle, will take appropriate legal actions against the companies that have obtained manufacture and marketing approval for generic drugs.

Commencement of phase II study for treatment of diffuse large B-cell lymphoma

2022-01-31

On January 31, 2022, SymBio Pharmaceuticals Ltd. announced the commencement of a phase II study of bendamustine-rituximab combination therapy in patients with diffuse large B-cell lymphoma (DLBCL) who are eligible for autologous hematopoietic stem cell transplantation (AHSCT).

The company entered into a joint clinical research agreement with Saitama Medical University regarding a phase II clinical study of bendamustine-rituximab combination therapy, and the two parties commenced the study on January 26, 2022. The study, classified as specified clinical research, is initiated by Professor Yasuhito Terui of Department of Hematology, Saitama Medical University Hospital, and in it, patients suffering from relapsed or refractory DLBCL who are eligible for AHSCT will be treated with the bendamustine (Treakisym®)-rituximab combination therapy before undergoing AHSCT.

Filed a CTA in the UK for phase II study of antiviral drug brincidofovir injection targeting adenovirus infection in children

2022-01-18

On January 18, 2022, SymBio Pharmaceuticals Ltd. announced that it had filed a Clinical Trial Application (CTA) in the UK for a phase II study of antiviral drug brincidofovir injection in children with adenovirus infection.

The company filed a CTA with the Medicines and Healthcare products Regulatory Agency of the UK, aimed at obtaining approval to conduct the global Phase II clinical trial of antiviral drug brincidofovir injection targeting adenovirus infection primarily in children in the UK, following the study's US counterpart currently ongoing.

Obtained approval to extend the expiration date of Treakisym® Injection (RTD formulation)

2021-11-24

On November 24, 2021, SymBio Pharmaceuticals Ltd. announced that it obtained approval to extend the expiration date of Treakisym® Injection (RTD formulation).

The company obtained approval to make a partial change to the approved matters of Treakisym® Injection 100mg/4ml (ready-to-dilute [RTD] formulation), aimed at extending the expiration date of the drug to 30 months based on the results of long-term stability tests.

SymBio announced final results of phase III trial in Japan for Treakisym® used in combination with rituximab as treatment for r/r DLBCL

2021-09-29

SymBio Pharmaceuticals Ltd. announced the final results of the phase III trial in Japan for Treakisym® used in combination with rituximab (BR therapy) as treatment for relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL).

The company announced the final results of a phase III trial in Japan for its anticancer agent Treakisym® used in BR therapy to treat r/r DLBCL.

The company conducted the phase III trial and its long-term follow-up study to obtain approval for use of Treakisym® in BR therapy for r/r DLBCL, and the final results were presented at the 83rd Annual Meeting of the Japanese Society of Hematology in September 2021. The phase III trial confirmed the efficacy of BR therapy as demonstrated in the phase II trial (conducted in Japan and Korea), and the regulatory approval was granted in March 2021.

Final main efficacy evaluation results of phase III trial and long-term follow-up study (38 cases)

- Response rate (complete or partial response [CR+PR]): 76.3%
- Complete response (CR): 47.4%
- Median overall survival: 29.2 months

Initiation of controls on shipments of Treakisym® lyophilized injection formulation

2021-09-21

SymBio Pharmaceuticals Ltd. announced that it will initiate controls on shipments of Treakisym® lyophilized injection formulation.

In January 2021, SymBio commenced manufacture and sale of a ready-to-dilute (RTD) formulation of Treakisym® intravenous fluid in quantities of 100mg/4ml, as a successor to the lyophilized (freeze-dried [FD]) powder formulation of Treakisym® 100mg. Although the company is still manufacturing and selling both the RTD and FD formulations as of September 2021, it is actively converting the market from FD to RTD.

However, SymBio has announced that it will initiate controls on shipments of the FD formulation, to avoid a potential stockout arising from delays in the migration from FD to RTD.

The company has sufficient inventory to ensure stable supply of RTD. In addition, in May 2021 SymBio submitted a partial change application with respect to its marketing authorization for the RTD liquid formulation to add rapid infusion (RI)

administration.

As of September 2021, there is no change to the company's full-year FY12/21 earnings forecast in relation to the controls on shipments.

UCSF Brain Tumor Center initiates studies to investigate new indications for brincidofovir IV

2021-09-08

SymBio Pharmaceuticals Ltd. announced that the University of California San Francisco (UCSF) Brain Tumor Center initiated studies to investigate new indications for brincidofovir IV.

The company announced that the Brain Tumor Center, Department of Neurological Surgery, UCSF, initiated preclinical studies to investigate antitumor effects of brincidofovir IV against brain tumor.

Collaborative research agreement with the National Cancer Centre Singapore (NCCS) concerning the injectable formulation of antiviral drug brincidofovir

2021-09-01

SymBio Pharmaceuticals Limited announced that it has concluded a collaborative research agreement with the National Cancer Centre Singapore (NCCS) concerning the injectable formulation of antiviral drug brincidofovir.

The company has entered a collaborative research agreement with the National Cancer Centre Singapore (NCCS) under which both parties will explore anti-tumor effects produced by brincidofovir IV in cases of Epstein-Barr (EB) virus positive lymphoma and the mechanism of action.

Epstein-Barr (EB) virus: The EB virus is a tumor-causing virus that belongs to the Herpesviridae family of DNA viruses. It was first discovered during 1964 in Burkitt lymphoma, a type of pediatric tumor primarily seen in Africa. Many infants who contract the virus often display no symptoms. However, patients who contract the virus during puberty or later exhibit temporary symptoms such as glandular fever (infectious mononucleosis), sore throat, and swollen lymph nodes. This virus is also linked with the development of some types of malignant lymphoma and epipharyngeal cancer.

First patient dosed in Phase II clinical trial for antiviral agent brincidofovir IV formulation (FPI milestone)

2021-08-17

SymBio Pharmaceuticals Limited announced dose administration for the first patient in the Phase II clinical trial for the intravenous formulation of antiviral agent brincidofovir (First-Patient-In [FPI] milestone).

The company made progress in connection with the ongoing international joint Phase II clinical trial for the intravenous formulation of antiviral agent brincidofovir as a treatment for adenovirus infections in children, achieving the First-Patient-In (FPI) milestone on August 16, 2021 (United States Pacific Daylight Time).

Conclusion of an agreement with Gunma University concerning joint research into possible new indications for bendamustine and rigosertib

2021-07-15

SymBio Pharmaceuticals Ltd. announced the conclusion of an agreement with Gunma University concerning joint research into possible new indications for bendamustine and rigosertib.

The company has concluded an agreement with the General Surgical Science Department of the Graduate School of Medicine at Gunma University concerning joint research into possible new indications for pipeline anticancer agents bendamustine and rigosertib.

Chimerix, Inc. obtained FDA approval of brincidofovir as a medical countermeasure

2021-06-07

SymBio Pharmaceuticals Ltd. announced that Chimerix, Inc. obtained FDA approval of brincidofovir as a medical countermeasure for the treatment of smallpox.

Chimerix announced in its press release dated June 4, 2021 that FDA approved brincidofovir (generic name; BCV) tablets and oral suspensions, antiviral formulations for the treatment of smallpox for adult and pediatric patients including neonates.

As part of bioterrorism countermeasures, Chimerix developed oral BCV formulations as medical countermeasures for the treatment of smallpox, with continued funding and support from the Biomedical Advanced Research and Development Authority (BARDA) within the U.S. Department of Health and Human Services (HHS). With this FDA approval, Chimerix intends to proceed with negotiations with BARDA toward a procurement agreement to support national preparedness.

SymBio obtained global exclusive development, manufacturing, and marketing rights for BCV from Chimerix in September 2019 regarding all indications except for the prevention and treatment of smallpox. Global development of BCV intravenous injection is underway in patients with adenovirus (AdV) infections developed after hematopoietic stem cell transplantation.

Profile

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2005-03-25

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Exchange Listing

2011-10-20

Fiscal Year-End

Dec

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