SymBio Pharmaceuticals / 4582

COVERAGE INITIATED ON: 2014.10.31
LAST UPDATE: 2021.06.16

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INDEX

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

Executive summary

SymBio in-licenses drugs for development and sale

- SymBio Pharmaceuticals Ltd. is a specialty pharmaceutical company that buys the right to develop and commercialize drug candidates, 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, 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 2021, the company had obtained approval for and launched Treakisym® (anticancer agent for hematologic malignancies) for the indications of relapsed or refractory low-grade NHL and MCL, untreated (first-line treatment) and relapsed or refractory low-grade NHL and MCL, and chronic lymphocytic leukemia (CLL). Treakisym® is listed in the Practical Guidelines for Hematological Malignancies 2018 edited and published by Japanese Society of Hematology as the standard treatment for relapsed or refractory low-grade B-cell NHL, MCL, and CLL, and as 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. The re-examination term for the lyophilized formulation of Treakisym® ends in 2020, but by launching the RTD formulation to which SymBio has exclusive rights, the company can extend the product life cycle of Treakisym® until 2031.
- Drugs in the development pipeline include Treakisym® for the indication of relapsed or refractory diffuse large B-cell lymphoma (DLBCL), rapid infusion (RI) liquid formulation of Treakisym®, rigosertib (anticancer agent for myelodysplastic syndromes) IV and oral formulations, and the antiviral drug brincidofovir. With regard to Treakisym® indicated for refractory or relapsed DLBCL, in March 2021 the company obtained approval for the combination therapies of Treakisym® with rituximab, and with rituximab and polatuzumab vedotin.

Earnings

- FY12/20 sales were JPY3.0bn (+5.3% YoY). Product sales totaled JPY3.0bn (+5.9% YoY) and royalty revenue totaled JPY10mn (JPY26mn in FY12/19). The operating loss totaled JPY4.5bn (operating loss of JPY4.3bn). The company also reported a recurring loss of JPY4.6bn (recurring loss of JPY4.4bn) and a net loss of JPY4.1bn (net loss of JPY4.4bn).
- The company's FY12/21 forecast calls for sales of JPY9.2bn (+206.4% YoY), operating profit of JPY1.4bn (operating loss of JPY4.5bn in FY12/20), recurring profit of JPY1.4bn (recurring loss of JPY4.6bn), and net income of JPY1.1bn (net loss of JPY4.1bn). The company expects increased product sales in Japan due to the move to sell Treakisym® in-house, and to turn profitable at all levels on the back of sales growth and improved profit 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.

- SymBio aims to turn profitable in FY12/21. To this end, the company intends to build its own sales structure, obtain approval for and switch to Treakisym® liquid formulations, and obtain approval for the additional indication of Treakisym® for relapsed or refractory DLBCL. Shared Research understands that the first two of these measures (own sales structure and approval/switch to Treakisym® liquid formulations) are key to improvement in gross profit and GPM, which in turn will help the company achieve profitability in FY12/21. As of February 2021, the company was on track to moving into the black, having established its own sales structure and commenced sales of Treakisym® liquid formulations. SymBio also filed for approval of the additional indication of Treakisym® for relapsed or refractory DLBCL in May 2020.

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

Income statement (JPYmn)	FY12/11 Par.	FY12/12 Par.	FY12/13 Par.	FY12/14 Par.	FY12/15 Par.	FY12/16 Par.	FY12/17 Par.	FY12/18 Par.	FY12/19 Par.	FY12/20 Par.	FY12/21 Est.
Sales	**1,883**	**1,955**	**1,532**	**1,955**	**1,933**	**2,368**	**3,444**	**3,836**	**2,838**	**2,987**	**9,151**
YoY	29.8%	3.9%	-21.6%	27.6%	-1.1%	22.5%	45.4%	11.4%	-26.0%	5.3%	206.4%
Gross profit	**658**	**593**	**318**	**527**	**583**	**904**	**1,031**	**1,173**	**865**	**867**	
YoY	-45.7%	-9.9%	-46.4%	65.6%	10.7%	55.1%	14.1%	13.7%	-26.3%	0.2%	
GPM	35.0%	30.3%	20.8%	26.9%	30.2%	38.2%	29.9%	30.6%	30.5%	29.0%	
Operating profit	**-2,067**	**-1,700**	**-1,681**	**-1,303**	**-2,552**	**-2,127**	**-3,947**	**-2,656**	**-4,302**	**-4,506**	**1,361**
YoY	-	-	-	-	-	-	-	-	-	-	-
OPM	-	-	-	-	-	-	-	-	-	-	14.9%
Recurring profit	**-2,095**	**-1,729**	**-1,601**	**-1,110**	**-2,630**	**-2,317**	**-3,977**	**-2,749**	**-4,377**	**-4,616**	**1,350**
YoY	-	-	-	-	-	-	-	-	-	-	-
RPM	-	-	-	-	-	-	-	-	-	-	14.8%
Net income	**-2,105**	**-1,733**	**-1,605**	**-1,116**	**-2,632**	**-2,313**	**-3,978**	**-2,753**	**-4,376**	**-4,090**	**1,149**
YoY	-	-	-	-	-	-	-	-	-	-	-
Net margin	-	-	-	-	-	-	-	-	-	-	12.6%
Per share data (JPY)											
Shares issued (year-end; '000)	19,131	19,131	30,634	30,634	32,391	46,531	54,049	20,560	26,438	38,203	
EPS	-574.4	-362.4	-277.2	-145.0	-325.0	-235.3	-319.1	-165.5	-189.0	-124.1	30.1
EPS (fully diluted)	-	-	-	-	-	-	-	-	-	-	
Dividend per share	-	-	-	-	-	-	-	-	-	-	-
Book value per share	1,381.1	1,018.8	957.9	835.2	510.2	434.4	200.0	212.2	143.1	105.8	
Balance sheet (JPYmn)											
Cash and cash equivalents	6,511	4,840	7,264	6,591	4,261	5,719	2,947	4,821	3,911	3,849	
Total current assets	**7,178**	**5,421**	**7,634**	**7,290**	**4,827**	**6,685**	**4,037**	**6,038**	**4,887**	**5,815**	
Tangible fixed assets	17	14	9	49	53	75	47	57	75	77	
Investments and other assets	48	57	37	49	53	77	100	73	70	81	
Intangible fixed assets	13	11	8	66	52	42	69	71	241	302	
Total assets	**7,256**	**5,502**	**7,687**	**7,454**	**4,984**	**6,878**	**4,252**	**6,239**	**5,274**	**6,275**	
Accounts payable	309	330	-	306	320	322	604	726	121	665	
Short-term debt	-	-	-	-	-	-	-	-	-	-	
Total current liabilities	**646**	**599**	**251**	**488**	**551**	**942**	**1,011**	**1,336**	**872**	**1,615**	
Long-term debt	-	-	-	-	-	-	-	-	-	-	
Total fixed liabilities	**5**	**4**	**3**	**2**	**2**	**451**	**1**	**1**	**2**	**2**	
Total liabilities	**651**	**602**	**254**	**490**	**552**	**1,394**	**1,013**	**1,338**	**874**	**1,617**	
Net assets	**6,606**	**4,900**	**7,433**	**6,964**	**4,432**	**5,485**	**3,239**	**4,902**	**4,400**	**4,657**	
Total interest-bearing debt	-	-	-	-	-	-	-	-	-	-	
Statement of cash flows (JPYmn)											
Cash flows from operating activities	-2,074	-1,659	-1,677	-1,266	-2,272	-1,960	-3,817	-2,325	-4,351	-4,122	
Cash flows from investing activities	-117	-411	-1,332	314	1,489	-44	-78	-26	-216	-160	
Cash flows from financing activities	4,611	-1	4,057	544	-3	3,658	1,164	4,272	3,740	4,222	
Financial ratios											
ROA (RP-based)	#REF!	-27.2%	-24.3%	-14.7%	-42.3%	-39.0%	-71.5%	-52.5%	-76.0%	-70.8%	
ROE	-39.4%	-30.2%	-26.3%	-15.8%	-48.3%	-50.4%	-102.6%	-77.8%	-107.4%	-104.7%	
Equity ratio	91.0%	89.1%	96.7%	93.4%	88.9%	79.7%	76.2%	78.6%	83.4%	74.2%	

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

Recent updates

Highlights

On June 16, 2021, Shared Research updated the report following interviews with SymBio Pharmaceuticals Ltd.

On June 7, 2021, the company 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.

On May 19, 2021, the company announced that polatuzumab vedotin has been added to the NHI drug price list.

Chugai Pharmaceutical Co., Ltd. announced that its genetically engineered polatuzumab vedotin indicated for the treatment of relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL) has been added to the NHI drug price list and that it began selling the drug. Accordingly, Treakisym® can now be used in the combination therapy of genetically engineered polatuzumab vedotin, bendamustine, and genetically engineered rituximab (the combination therapy of the latter two also referred to as BR therapy).

On May 13, 2021, the company announced earnings results for Q1 FY12/21; see the results section for details.

On May 10, 2021, the company announced that it has filed for approval of the rapid infusion (RI) method for Treakisym® intravenous formulation.

The company has submitted an application for partial change to the approved matters of Treakisym® ready-to-dilute (RTD) intravenous formulation 100mg/4ml to allow its use with the rapid infusion (RI) method.

On April 28, 2021, the company announced that it has obtained approval for the use of Treakisym® RTD liquid formulation in combination with rituximab and polatuzumab vedotin as treatment for r/r DLBCL.

The company has obtained approval of a partial change to the approved matters of its anticancer agent Treakisym® ready-to-dilute (RTD) intravenous formulation (non-proprietary name: bendamustine hydrochloride) pertaining to the drug's efficacy/effectiveness, administration, and additional dosage (90mg/sqm of bendamustine hydrochloride) for use in combination with genetically engineered rituximab and genetically engineered polatuzumab vedotin ("Pola-BR therapy") as treatment for relapsed or refractory diffuse large B-cell lymphoma ("r/r DLBCL").

On the same day, the company announced that it has obtained approval for the use of Treakisym® RTD liquid formulation in combination with rituximab as treatment for r/r DLBCL.

The company has obtained approval of a partial change to the approved matters of its anticancer agent Treakisym® ready-to-dilute (RTD) intravenous formulation (non-proprietary name: bendamustine hydrochloride) pertaining to the drug's efficacy/effectiveness, administration, and additional dosage (120mg/sqm of bendamustine hydrochloride) for use in combination with rituximab ("BR therapy") as treatment for r/r DLBCL.

On April 26, 2021, the company announced that the US Food and Drug Administration has granted fast track designation to intravenous formulation of antiviral agent brincidofovir.

The company announced that it has received fast track designation from the US Food and Drug Administration (FDA) for its development program for intravenous formulation of antiviral agent brincidofovir (BCV IV) for the treatment of adenovirus (AdV) infections in pediatric patients.

The FDA's fast track designation is a process intended to expedite the review of new drugs that are expected to be effective in treating serious or potentially life-threatening diseases as well as diseases with high unmet medical needs, with the goal of accelerating the process from development to review. Receiving this designation provides more opportunities for consultation with the FDA including clinical trial consultations, and if clinical trials show positive efficacy and safety results, accelerated approval through priority reviews may be obtained.

SymBio has begun a global phase II clinical trial in the US and the UK for disseminated AdV infection and AdV infection in immunocompromised patients, an area with high unmet medical needs as there currently exists no effective treatment. This study will confirm the appropriate dosage and administration for pediatric patients. The company plans to conduct a global study as the next phase for approval applications.

On the same day, the company announced that Onconova Therapeutics, Inc. has dosed the first patient in an investigator-initiated phase II study of rigosertib in recessive dystrophic epidermolysis bullosa-associated squamous cell carcinoma.

According the company's statement, its US licensor of anticancer drug rigosertib, Onconova Therapeutics, Inc., announced on April 22, 2021 (US EST) that the first patient has been dosed in an investigator-initiated phase II study to assess the efficacy and safety of rigosertib in patients with recessive dystrophic epidermolysis bullosa (RDEB)-associated locally advanced/metastatic squamous cell carcinoma (SCC).

On March 29, 2021, the company announced that it has applied for approval to extend the shelf life of Treakisym® RTD liquid formulation.

The company submitted an application for partial change to the approved matters of the RTD formulation (ready-to dilute-formulation; only requires diluting the drug before use, no dissolution required) of Treakisym® intravenous fluid with the aim of extending its shelf life.

On March 25, 2021, the company announced that it has filed for approval of the RTD liquid formulation of Treakisym® used in combination with rituximab and with rituximab and polatuzumab vedotin, for the treatment of relapsed or refractory diffuse large B-cell lymphoma.

The company submitted an application for partial change to the approved matters of the RTD formulation (ready-to-dilute formulation that only requires diluting the drug before use [no dissolution required]) of Treakisym® intravenous injection used in bendamustine-rituximab combination therapy (BR therapy) in patients with relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL). At the same time, the company also submitted an application for partial change to the approved matters of the RTD formulation for use in bendamustine-rituximab-polatuzumab vedotin combination therapy targeting r/r DLBCL.

On March 23, 2021, the company announced that it had obtained approval for Treakisym® used in combination with rituximab and polatuzumab vedotin to treat patients with relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL).

The company obtained approval of a partial change to the approved matters of anticancer agent Treakisym® 25mg and 100mg vials (lyophilized powder for intravenous infusion; generic name: bendamustine hydrochloride) for use in combination with rituximab and polatuzumab vedotin to treat r/r DLBCL.

On the same day, based on results of clinical trials in Japan and overseas to evaluate combination therapy of Treakisym® and rituximab (BR therapy) with polatuzumab vedotin, Chugai Pharmaceutical Co., Ltd. obtained manufacturing and marketing approval for polatuzumab vedotin targeting r/r DLBCL.

As noted below, the phase III clinical trial of BR therapy targeting r/r DLBCL obtained favorable results in the response rate (primary endpoint), which exceeded expectations. On March 23, 2021, the company obtained approval of a partial change to the approved matters. Once polatuzumab vedotin is added to the NHI drug price list and goes on sale, Treakisym® can be used in the combination therapy of polatuzumab vedotin and BR therapy.

The latest approval is for the lyophilized formulation of Treakisym® to treat r/r DLBCL. SymBio commented that it plans to apply this week for a partial change to the approved matters of the RTD formulation of Treakisym® to treat r/r DLBCL.

On the same day, the company announced that it had obtained approval for Treakisym® used in combination with rituximab to treat patients with r/r DLBCL.

The company obtained approval of a partial change to the approved matters of anticancer agent Treakisym® 25mg and 100mg vials (lyophilized powder for intravenous infusion; generic name: bendamustine hydrochloride) for use in combination with rituximab (BR therapy) to treat r/r DLBCL, relating to indication and additional dosage regimen (bendamustine hydrochloride 120mg/m^2).

The latest approval is based on results of the phase III clinical trial targeting r/r DLBCL, which demonstrated favorable results in primary endpoints, with response rates exceeding expectations.

This approval is for the lyophilized formulation of Treakisym® for r/r DLBCL. The company plans to apply for a partial change to the approved matters of the RTD formulation of Treakisym® for r/r DLBCL by March 27, 2021.

On March 11, 2021, the company announced its submission of an investigational new drug (IND) application for a phase II clinical trial of the injectable antiviral agent brincidofovir as a treatment for adenovirus infections in children.

The company has submitted an IND application to the Food and Drug Administration of the US to start a phase II study of the antiviral injection brincidofovir, primarily in pediatric patients with adenovirus infections.

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

Trends and outlook

Quarterly trends and results

Cumulative	FY12/20				FY12/21				FY12/21	
(JPYmn)	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	% of Est.	FY Est.
Sales	551	1,361	2,333	2,987	1,420				15.5%	9,151
YoY	-65.8%	-32.1%	16.2%	5.3%	157.6%					206.4%
Gross profit	128	330	611	867	1,010					
YoY	-79.0%	-37.7%	8.5%	0.2%	690.9%					
GPM	23.2%	24.2%	26.2%	29.0%	71.1%					
SG&A expenses	1,090	2,170	3,753	5,373	1,221					
YoY	-9.6%	-14.7%	-8.4%	4.0%	12.0%					
SG&A ratio	197.6%	159.5%	160.9%	179.9%	85.9%					
Operating profit	-962	-1,840	-3,142	-4,506	-211				-	1,361
YoY	-	-	-	-	-					-
OPM	-	-	-	-	-					14.9%
Recurring profit	-991	-1,883	-3,221	-4,616	-209				-	1,350
YoY	-	-	-	-	-					-
RPM	-	-	-	-	-					14.8%
Net income	-992	-1,885	-2,694	-4,090	-210				-	1,149
YoY	-	-	-	-	-					-
Net margin	-	-	-	-	-					12.6%
Quarterly	**FY12/20**				**FY12/21**					
(JPYmn)	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**		
Sales	551	809	972	654	1,420					
YoY	-65.8%	105.7%	-	-21.1%	157.6%					
Gross profit	128	202	281	256	1,010					
YoY	-79.0%	-	738.4%	-15.2%	690.9%					
GPM	23.2%	25.0%	28.9%	39.1%	71.1%					
SG&A expenses	1,090	1,080	1,583	1,620	1,221					
YoY	-9.6%	-19.4%	1.8%	51.8%	12.0%					
SG&A ratio	197.6%	133.5%	162.9%	247.5%	85.9%					
Operating profit	-962	-878	-1,302	-1,364	-211					
YoY	-	-	-	-	-					
OPM	-	-	-	-	-					
Recurring profit	-991	-892	-1,338	-1,395	-209					
YoY	-	-	-	-	-					
RPM	-	-	-	-	-					
Net income	-992	-893	-809	-1,396	-210					
YoY	-	-	-	-	-					
Net margin	-	-	-	-	-					

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%.

Breakdown of SG&A expenses

Cumulative	FY12/20				FY12/21			
(JPYmn)	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
SG&A expenses	1,090	2,170	3,753	5,373	1,221			
YoY	-9.6%	-14.7%	-8.4%	4.0%	12.0%			
R&D expenses	438	834	1,745	2,267	473			
YoY	-7.1%	-13.4%	-11.5%	-7.2%	8.0%			
SG&A expenses excl. R&D	651	1,336	2,008	3,107	747			
YoY	-11.1%	-15.5%	-5.6%	14.0%	14.7%			
Quarterly	**FY12/20**				**FY12/21**			
(JPYmn)	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**
SG&A expenses	1,090	1,080	1,583	1,620	1,221			
YoY	-9.6%	-19.4%	1.8%	51.8%	12.0%			
R&D expenses	438	396	911	522	473			
YoY	-7.1%	-19.4%	-9.7%	11.0%	8.0%			
SG&A expenses excl. R&D	651	685	672	1,098	747			
YoY	-11.1%	-19.3%	23.2%	83.9%	14.7%			

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

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

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.

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

Full-year company forecast

	FY12/20			FY12/21
(JPYmn)	1H Act.	2H Act.	FY Act.	FY Est.
Sales	1,361	1,626	2,987	9,151
Gross profit	330	537	867	6,957
Gross profit margin	24.2%	33.0%	29.0%	76.0%
SG&A expenses	2,170	3,203	5,373	5,596
SG&A ratio	159.5%	197.0%	179.9%	61.2%
R&D expenses	834	1,433	2,267	2,019
Excluding R&D expenses	1,336	1,770	3,107	3,577
Operating profit	-1,840	-2,666	-4,506	1,361
Operating profit margin	-	-	-	14.9%
Recurring profit	-1,883	-2,733	-4,616	1,350
Recurring profit margin	-	-	-	14.8%
Net income	-1,885	-2,205	-4,090	1,149
Net margin	-	-	-	12.6%

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

Earnings outlook

The company's FY12/21 forecast calls for sales of JPY9.2bn (+206.4% YoY), operating profit of JPY1.4bn (operating loss of JPY4.5bn in FY12/20), recurring profit of JPY1.4bn (recurring loss of JPY4.6bn), and a net income of JPY1.1bn (net loss of JPY4.1bn).

▷ The company expects increased product sales in Japan due to the move to sell Treakisym® in-house and obtaining approval for, and beginning sales of Treakisym® for the additional indication of relapsed or refractory diffuse large B-cell lymphoma (DLBCL).

- Sales increase resulting from move to sell Treakisym® in-house: The business alliance agreement with Eisai for Treakisym® expired on December 9, 2020, and SymBio began independently marketing Treakisym® in Japan on December 10. 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. 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).
- Obtaining approval for, and beginning sales of Treakisym® for the additional indication of relapsed or refractory DLBCL: The company targets sales of JPY2.6bn on an NHI drug reimbursement price basis for Treakisym® indicated for DLBCL.

▷ The company expects to turn profitable at all profit levels on the back of sales growth.

▷ It forecasts gross profit of JPY7.0bn (+702.6% YoY) with a GPM of 76.0% (+47pp YoY). The increase in gross profit is due to higher sales and GPM. The GPM rise is due to starting in-house sales of Treakisym® and switching to the RTD formulation of the product.

- GPM rise due to starting in-house sales of Treakisym®: As noted above, 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. 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). Before December 9, 2020, the company was selling the lyophilized formulation of Treakisym® to Eisai at a GPM of around 30%. Shared Research understands that from December 10 onward, by doing its own marketing, the GPM on Treakisym® would go up to around 70%.
- GPM rise 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 commented that the GPM on liquid formulations of Treakisym® will

be higher than the GPM on the lyophilized formulation. By the end of 2021, the company targets an RTD product sales share of 91% of total Treakisym® sales.

▷ SymBio expects SG&A expenses of JPY5.6bn (+4.1% YoY).

- The company plans R&D expenses of JPY2.0bn (-10.9% YoY). It will proceed with development of Treakisym® for the indication of relapsed or refractory DLBCL, Treakisym® liquid formulations, and rigosertib, as well as antiviral drug brincidofovir. The company made a milestone payment on obtaining approval of the RTD formulation of Treakisym® in FY12/20, but no milestone payments are expected in FY12/21.
- SG&A expenses excluding R&D expenses are estimated to be JPY3.6bn (+15.1% YoY). The company will reinforce its in-house sales structure and prepare to expand its business overseas so that it can turn profitable in FY12/21 and sustain earnings expansion thereafter.

The main pipeline development plans are as follows.

Treakisym®

The company targets Treakisym® sales of JPY11.3bn in FY12/21 on an NHI drug reimbursement price basis (JPY8.0bn in FY12/20).

▷ Sales growth of Treakisym® for approved indications: The company targets Treakisym® sales of JPY4.1bn as first-line therapy for low-grade non-Hodgkin's lymphoma and JPY4.6bn for other indications (NHI reimbursement price basis) in FY12/21.

▷ Sales growth of Treakisym® for added indication: SymBio applied for approval of the additional indication of relapsed or refractory DLBCL for Treakisym® in May 2020, and expects to obtain approval and launch in Q2 FY12/21. The company targets Treakisym® sales of JPY2.6bn for the indication of DLBCL.

▷ Extended product life cycle: The company began sales of the RTD formulation of Treakisym® in Q1 FY12/21. By the end of 2021, the company targets a 91% sales share of the RTD formulation of total Treakisym® sales. It plans to begin sales of the RI formulation in 1H FY12/22.

Oral rigosertib and rigosertib injection

▷ SymBio is continuing to develop intravenous rigosertib formulation. Onconova, the licensor of anticancer drug rigosertib, announced in August 2020 that its global phase III trial (INSPIRE study) in patients with higher-risk myelodysplastic syndromes (higher-risk MDS) intolerant of treatment with hypomethylating agents failed to meet its primary endpoints. SymBio engages in clinical development of rigosertib 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 review at the global advisory board held in February 2020, the company 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. As of February 2021, the company was preparing to begin clinical trials of the liquid formulation of BCV for dose determination in children.

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.

Medium-term plan targets

(JPYmn)	FY12/20 Act.	FY12/21 Est.	FY12/22 Target	FY12/23 Target
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 has entrusted Treakisym® sales to Eisai until end-FY12/20. During this period, product shipments to Eisai are being booked as sales. However, Eisai's exclusive sales period expires in FY12/20, and from FY12/21 SymBio will switch to selling Treakisym® in-house. Up to and including FY12/20, Shared Research assumes that the price of shipments to Eisai will be around 50% of the NHI drug price. With the transition to an in-house sales structure in FY12/21, though, Shared Research thinks the price that SymBio charges to wholesalers will rise to roughly 90% of the NHI drug price. Thus even if volume remains largely unchanged, the company expects higher selling prices to drive sharp YoY sales growth in FY12/21.

Based on data supplied by Eisai, sales of Treakisym® were JPY7.7bn (+6.3% YoY) in FY03/20. In contrast, SymBio's product sales stood at JPY2.8bn in FY12/19. The fiscal year ends of the two companies differ by three months, SymBio's product sales include overseas sales, and at Eisai, there is a time lag between product procurement and sales. Broadly speaking, however, we can infer that Eisai's gross profit is roughly Eisai's sales minus SymBio's sales, so once SymBio begins its own sales of Treakisym®, it is our understanding that the company will be gaining the equivalent of Eisai's portion of gross profit.

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

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

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

As reference for the anticipated impact of adding the indication of r/r DLBCL, the company estimates that the number of patients being treated for relapsed or refractory low-grade NHL and MCL in Japan is 9,336 and the number of patients with untreated low-grade NHL and MCL is 6,967, for a total of 16,303. For these indications, SymBio'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.

In FY12/21, the company targets Treakisym® sales (on an NHI drug reimbursement price basis; same below) of JPY11.3bn (JPY8.0bn in FY12/20), breaking down into JPY8.7bn for approved indications and JPY2.6bn for the DLBCL indication.

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 calls for a rise in GPM to 76.0% (+47pp YoY), which is 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. The company expects GPM to be higher for the liquid formulations than for the lyophilized product. The company targets 91% sales share of the RTD formulation of total Treakisym® sales at end-FY12/21 and 95% at end-FY12/22.

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 forecasts R&D expenses of JPY2.0bn (-10.9% YoY) in FY12/21. It made a milestone payment of around JPY500mn for the RTD formulation of Treakisym® in FY12/20 after obtaining approval, but plans no milestone payment in FY12/21.
  - ➢ 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. The company forecasts JPY3.6bn (+15.1% YoY) in SG&A expenses other than for R&D in FY12/21, assuming an increase in sales promotion and other expenses. It does not anticipate a large increase in expenses in FY12/22 onward, having established its own sales structure.

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%.

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

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

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 and mantle cell lymphoma.

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

As of February 2021, phase III clinical trials for the fourth indication of relapsed or refractory DLBCL had been completed, with the trial confirming a positive overall response rate (the primary endpoint of the study) exceeding expectations (November 2019). The company filed for manufacture and marketing approval in May 2020 and expects to obtain approval in 1H FY12/21.

Treakisym® (RTD and RI formulations)

In September 2017, Eagle Pharmaceuticals and SymBio concluded a license agreement that licenses to SymBio rights to develop, market, and sell Eagle's bendamustine hydrochloride ready-to-dilute (RTD) and rapid infusion (RI) products in Japan. Securing products to replace existing freeze-dried (FD) product (whose exclusive sales rights in Japan expire in 2H 2020) had been a priority for the company. SymBio obtained approval for the RTD formulation in September 2020 and launched it in January 2021.

With this, it aims to promote a switch in clinical settings from the current lyophilized powder formulation to RTD and RI formulations that lighten the workload for medical professionals, at the same time curtailing uptake of Treakisym® generics (filing for approval of generics will be possible from 2H 2020, although Shared Research believes that even if generics launch it will not be until around 2022). Because it has 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. As of February 2021, the company was preparing for dose determination trials of brincidofovir liquid formulation targeting adenovirus infection in children.

Revenue source: Treakisym® sales

Revenue mainly comes from product sales of Treakisym®. Operating losses have 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®.

For FY12/21, the company expects JPY1.4bn operating profit (versus a JPY4.5bn operating loss in FY12/20) and JPY1.1bn net income (net loss of JPY4.1bn in FY12/20). The company began in-house sales of Treakisym® in December 2020 and sales of the RTD formulation in January 2021. It also expects to obtain approval for the additional indication of relapsed or refractory DLBCL in FY12/21, which are all factors expected to contribute toward sales growth and GPM improvement. The company therefore forecasts a turn to profitability at operating profit level in FY12/21.

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. Because the company does not conduct basic research, the company 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.

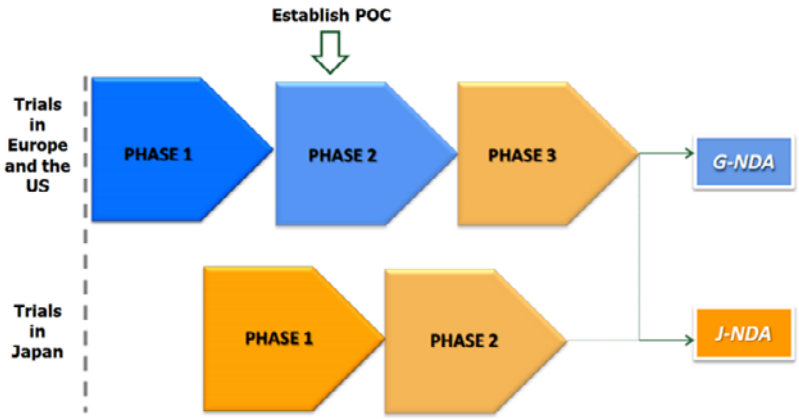
The overall aim is to reduce development risk, streamline expenses, and expand revenue opportunities. This hinges on the following five strategies, namely post proof-of-concept, screening, fabless, niche market, and global expansion.

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

The company identifies quality chemical compounds owned by pharmaceutical and biotech companies in the US or EU using a proprietary "search engine" and rigorous evaluation process. These candidates are first screened in-house by the search and evaluation team, whose members have extensive product development experience working at various pharmaceutical and biotech companies.

Onsite due diligence

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

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

The company 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 2021). Clinical trials for additional Treakisym® indications are underway, as are preparations to file for approval of the RI formulation of the drug. The company is also developing intravenous and oral formulations of rigosertib and antiviral drug brincidofovir.

Scientific Advisory Board

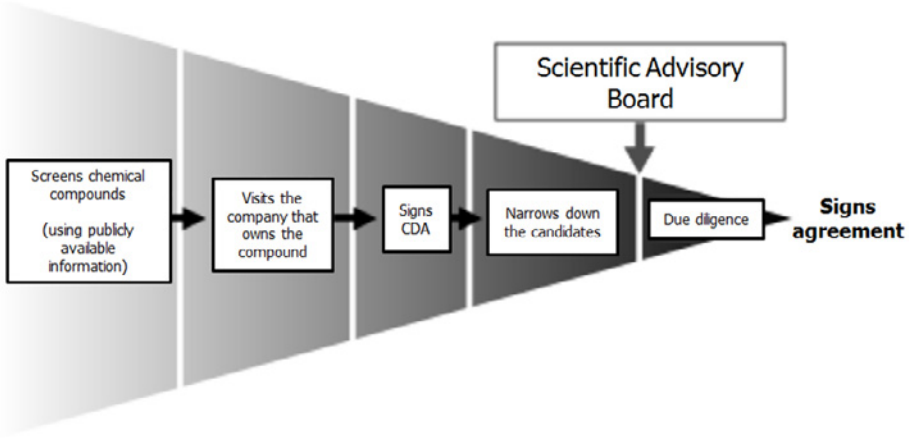
The Scientific Advisory Board is comprised of former directors of pharmaceutical companies, researchers, and doctors, and meets three times a year. Typically, the SAB panel evaluates two to three drug candidates that have been selected via the company's in-house screening process. This in-house screening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

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)	Approval application in review	
		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	Clinical trials underway	—
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	Preparations for phase II clinical trials underway	—

Source: Shared Research based on the company website

As of February 2021, the main drugs for which SymBio was preparing to file for approval or in the development pipeline were as follows:

▷ Treakisym®, for the indication of relapsed or refractory DLBCL (aggressive NHL): Completed enrollment of patients for the phase III clinical trial (April 2019). Filed for approval in May2020. Expects to obtain approval and begin sales in FY12/21.

▷ Treakisym®, clinical trials of the RI formulation: Initiated clinical trials in November 2018. Plans to file for approval in FY12/21 and begin sales in FY12/22

- 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: Preparing to begin phase II clinical trials of brincidofovir (liquid formulation) targeting adenovirus infection in children

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. As of February 2021, the company had filed for approval of Treakisym® for the additional indication of relapsed or refractory DLBCL (aggressive NHL; May 2020).

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

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

Source: Japanese Society for Lymphoreticular Tissue Research (JSLTR)

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

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

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

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

Physicians examine tissue and determine the method of treatment depending on the type of cancerous cells observed: they look at the grade (high, intermediate, or low, depending on the aggressiveness of the disease) and clinical staging, which shows to what extent the cancer has spread. To gain approval to manufacture and sell pharmaceuticals, companies must conduct separate clinical trials for each disease subtype. Clinical trial subjects are categorized as either treatment-naïve, or relapsed/refractory (patients who have received treatment in the past, which has proven ineffective).

Treakisym® in-licensed from Astellas; 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. In FY12/16—six years after the domestic launch of the drug in December 2010—Treakisym® sales reached JPY4.7bn on an NHI drug price basis.

According to the company, Japan has about 4,700 patients who suffer from relapsed or refractory NHL and MCL. SymBio thinks annual Treakisym® sales could reach JPY4.5–5.0bn.

Treakisym®: additional indications, RTD, RI, and oral 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 filed for the approval of Treakisym® for the additional indication of relapsed or refractory DLBCL (aggressive NHL) in May 2020.

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

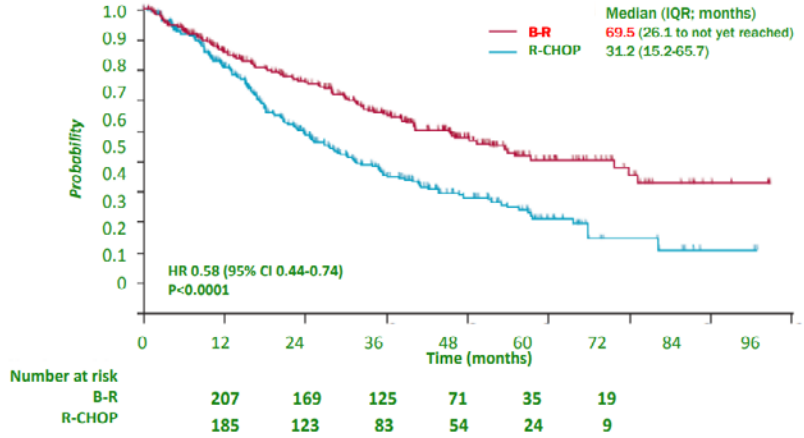
According to the company, R-CHOP therapy—a combination of rituximab with CHOP chemotherapy drugs (cyclophosphamide, doxorubicin (hydroxydaunomycin), vincristine (oncovin), and prednisolone)—was standard first-line treatment for low-grade NHL and MCL in Japan prior to December 2016. In December 2016,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

R&D status: approval application of Treakisym® for the indication of relapsed or refractory 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.

Based on these results the company filed for approval of Treakisym® to make BR therapy possible for the treatment of relapsed or refractory DLBCL. The company expects to obtain approval for this indication and begin sales in FY12/21.

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

In April 2018, Novartis Pharma K.K. applied in Japan for approval of the chimeric antigen receptor T-cell (CAR-T) therapy CTL019 (US product name: Kymriah®), for the treatment of relapsed or refractory B-cell acute lymphoblastic leukemia (ALL) in patients aged 25 years or younger and relapsed or refractory DLBCL. In May 2018, Novartis obtained approval in the US for use of CTL019 to treat adult patients with relapsed or refractory DLBCL after two or more lines of systemic therapy. Since the use of CTL019 is limited to adult patients for whom two or more lines of therapy have proved ineffective, Shared Research understands that CTL019 is different from Treakisym® and that the two companies do not compete in this area. In September 2018, the company applied for a partial change to the approved matters of Treakisym® to enable its use as a pretreatment agent for CTL019 targeting relapsed or refractory B-cell acute lymphoblastic leukemia (ALL) and relapsed or refractory diffuse large B-cell lymphoma (DLBCL) in adults.

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.

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) products (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 product can be administered in one sixth of the time as FD product

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

Comparison of RTD/RI formulations and current (freeze-dried) formulation

	RTD products	RI products	Currently available products
Generic name	bendamustine hydrochloride		
Dosage form	Liquid		Freeze-dried powder injection
Reconstitution	Not required		Required (manual reconstitution)
Dilution	Dilute with 250ml physiological saline	Dilute with 50ml physiological saline	Dilute with 250ml physiological saline
Administration time	60 minutes	10 minutes	60 minutes
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® ends 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. This increases the possibility of prolonging the life cycle of Treakisym® and limiting 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 Teva Pharmaceutical Industries as BENDEKA®, which has 97% share of the US bendamustine market within two years after its sales.

R&D status: obtained approval in September 2020 for RTD formulation and preparing for approval application of RI formulation

The company obtained approval for the bendamustine hydrochloride RTD formulation in September 2020. As of February 2021, it was preparing to file for approval of the RI formulation.

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

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

In September 2018, the company applied for a partial change to the approved matters of anticancer drug Treakisym® to enable its use as a pretreatment agent for regenerative medical products.

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

> CAR-T cell therapy genetically modifies T-cells collected from patients' blood samples to express chimeric antigen receptors (CARs) on their surface at a cell processing 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

As of February 2021, SymBio was developing the IV form of rigosertib for the indication of relapsed or refractory higher-risk MDS, and the oral form for higher-risk MDS.

Onconova has been conducting joint global phase III clinical trials in over 20 countries since August 2015 for the intravenous form of rigosertib in higher-risk MDS patients who had failed to respond to or relapsed after prior therapy with hypomethylating agents (HMAs). In the Japanese market, the company has been conducting the joint global phase III clinical trials in cooperation with Onconova since December 2015. 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. After establishing safety in phase I clinical trials, the company plans to resume the trial of rigosertib in combination with azacitidine and participate in global clinical trials of the combination therapy planned by Onconova in higher-risk MDS 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			TBC
	Development status			Global phase III trials underway
Oral	Number of patients	7,800	3,200	
	Approval	TBC	TBC	
	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 most advanced research being conducted for rigosertib was for the treatment of patients with higher-risk MDS who had progressed on, failed or relapsed after prior therapy with HMAs. According to the company, no drugs had been approved for the treatment of post-HMA higher-risk MDS patients as of February 2021.

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 for global phase III comparative trials of rigosertib for patients who did not see results from low

methylation, or experienced higher-risk refractory or relapsed MDS following HMA treatment. These global trials are currently ongoing.

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. Onconova is conducting further analysis.

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

The company has been conducting the global phase III clinical trials in Japan since 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.

As of February 2021, Onconova was making efforts toward finalizing the design for a pivotal phase III oral rigosertib/azacitidine combination trial for the first-line treatment of higher-risk MDS.

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. After establishing safety in the phase I clinical trial, the company plans to resume the trial of the drug in combination with azacitidine and participate in global clinical trials conducted by Onconova. In December 2019, Onconova issued a press release announcing it was considering a phase II/III adaptive trial for untreated high-risk MDS patients based on data presented at the 61st American Society of Hematology Annual Meeting and Exposition held in December 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 JPY15.7bn in FY03/20 (+8.3% YoY) and forecast to reach JPY16.0bn in FY03/21. Shared Research thinks that sales of the intravenous and oral forms of rigosertib could match or exceed sales of Vidaza, used for patients who have not received treatment with Vidaza or in combination therapy with Vidaza.

SyB V-1901 (antiviral drug, brincidofovir)

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

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

Mechanism of action and 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: preparing to begin phase II clinical trials in the US and Europe

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

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. 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 brincidofovir. As of February 2021, the company was in preparation to initiate a dose-finding study of the liquid formulation of brincidofovir in pediatric patients.

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.

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

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

Earnings structure

(JPYmn)	FY12/11	FY12/12	FY12/13	FY12/14	FY12/15	FY12/16	FY12/17	FY12/18	FY12/19	FY12/20
Sales	1,883	1,955	1,532	1,955	1,933	2,368	3,444	3,836	2,838	2,987
YoY	29.8%	3.9%	-21.6%	27.6%	-1.1%	22.5%	45.4%	11.4%	-26.0%	5.3%
Product sales	1,632	1,955	1,432	1,940	1,933	2,137	3,444	3,810	2,811	2,977
YoY	401.3%	19.8%	-26.8%	35.5%	-0.3%	10.6%	61.1%	10.6%	-26.2%	5.9%
Treakisym sales (NHI price basis; reference)	3,390	3,940	4,230	4,320	4,760	4,720	7,600	8,500	-	-
Product sales / Sales (NHI price basis)	48.2%	49.6%	33.9%	44.9%	40.6%	45.3%	45.3%	44.8%	-	-
Royalty revenue	250	-	100	15	-	231	-	26	26	10
Sales to Eisai	1,872	1,930	1,486	1,908	1,852	2,265	3,382	3,648	2,831	2,546
YoY	29.5%	3.1%	-23.0%	28.4%	-2.9%	22.3%	49.4%	7.9%	-22.4%	-10.1%
Sales to other partners	10	26	46	47	81	104	62	187	6	441
CoGS	1,224	1,362	1,214	1,428	1,350	1,464	2,413	2,663	1,973	2,120
CoGS / Product sales	75.0%	69.7%	84.8%	73.6%	69.8%	68.5%	70.1%	69.9%	70.2%	71.2%
CoGS / Sales (NHI price basis)	36.1%	34.6%	28.7%	33.1%	28.4%	31.0%	31.7%	31.3%	-	
Product procurement	1,434	1,322	1,175	1,550	1,242	1,606	2,589	2,969	1,684	3,163
Gross profit	658	593	318	527	583	904	1,031	1,173	865	867
Product gross profit	408	593	218	512	583	673	1,031	1,147	838	857
Gross profit margin	25.0%	30.3%	15.2%	26.4%	30.2%	31.5%	29.9%	30.1%	29.8%	28.8%
Royalty revenue	250	-	100	15	-	231	-	26	26	10
SG&A expenses	2,725	2,293	1,999	1,830	3,135	3,031	4,978	3,829	5,166	5,373
Personnel expenses	365	413	441	479	488	541	554	504	506	530
R&D expenses	1,945	1,438	1,053	774	2,035	1,667	3,018	1,833	2,442	2,267
Other	415	442	505	577	612	823	1,406	1,492	2,219	2,576
Operating profit	-2,067	-1,700	-1,681	-1,303	-2,552	-2,127	-3,947	-2,656	-4,302	-4,506

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 of JPY441mn in FY12/20.

Product sales

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

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

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.

Royalty revenue

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

CoGS

Cost of goods sold 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 allows 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). Shared Research understands that this is a factor that contributes to higher GPM.

SymBio sources the RTD formulation of Treakisym® from US company Eagle Pharmaceuticals. According to the company, its GPM on the RTD formulation 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 and hematologic 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 2021, 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 and value chain

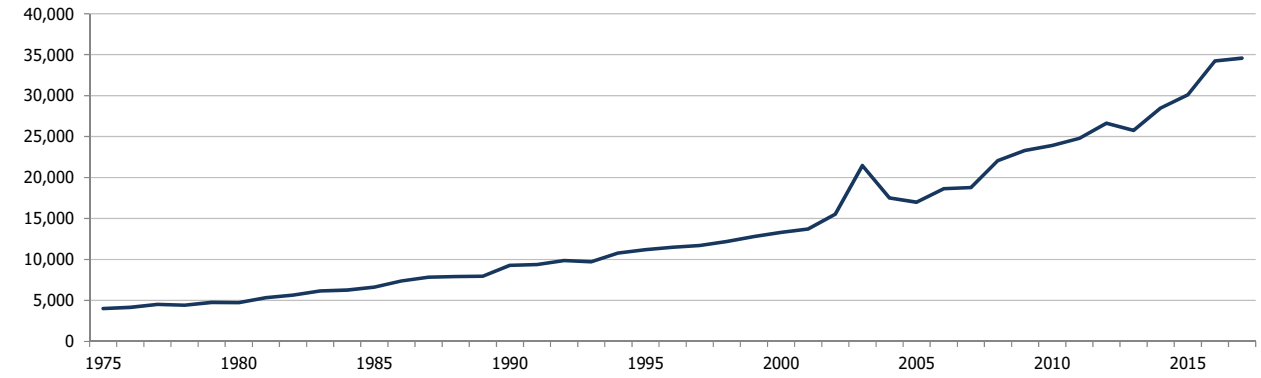
Market overview

Lymphatic cancer: patient population, market size, treatment drugs

Morbidity of lymphatic cancer

In 2017, the number of people diagnosed with lymphatic cancer in Japan was 34,571 (+1.0% YoY; average annual increase in past 10 years is 6.3%), according to "Cancer statistics and cancer registration in Japan" complied by the Center for Cancer Control and Information Services. Of these, 27,887 (+1.3% YoY), or 80.7% (80.4% in the previous year), were 60 years or older. Of the 977,393 (-1.8% YoY) people diagnosed with cancer, those diagnosed with lymphatic cancer accounted for only 3.5% (3.4% in the previous year), but their number increased 84.1% between 2007 and 2017 versus a 38.8% increase in the number of people newly diagnosed with cancer.

Morbidity of lymphatic malignancy



	1975	1980	1985	1990	1995	2000	2005	2010	2015
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 for which the company is considering application for approval of an additional indication is 18,672.

Treakisym® indications and number of patients

Indications	Patients	Progress	Notes
Relapsed or refractory low-grade NHL and relapsed or refractory MCL	9,336	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	

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

Drugs competing with Treakisym®

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

Rituximab (product name: Rituxan)

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

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

In Japan, Zenyaku Kogyo and Chugai have been jointly selling the drug since September 2001. Chugai's Rituxan sales were JPY7.2bn (-39.5% YoY) in FY12/20.

Ibritumomab tiuxetan (product name: Zevalin)

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

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

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

Source: Shared Research based on company data

Drugs competing with rigosertib

According to the company, as of February 2021, Nippon Shinyaku Co., Ltd.'s Vidaza was the only IV drug approved in Japan for the main indication of MDS.

Azacitidine (product name: Vidaza)

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

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

According to Nippon Shinyaku, Vidaza is the only approved drug in Japan for the first-line treatment of higher-risk MDS, with no efficacious treatment available once patients treated with Vidaza relapse. Nippon Shinyaku booked Vidaza sales of JPY15.7bn (+8.3% YoY) in FY03/20 and expects sales of JPY16.0bn in FY03/21.

Historical performance

Full-year FY12/20 results

- Sales: JPY3.0bn (+5.3% YoY)
- Operating loss: JPY4.5bn (loss of JPY4.3bn in FY12/19)
- Recurring loss: JPY4.6bn (loss of JPY4.4bn in FY12/19)
- Net loss: JPY4.1bn (loss of JPY4.4bn in FY12/19)

Sales increased YoY, as the company booked sales of Treakisym®. Sales declined 32.1% YoY to JPY1.4bn in 1H (January–June 2020), but were up 95.3% YoY to JPY1.6bn in 2H (July–December 2020). Through 1H, there was a high defect rate and unreliable delivery of multiple batches of lyophilized formulations of Treakisym® (supplied by Astellas Deutschland), reflected in the YoY sales decline. Sales recovered sharply YoY in 2H, because the defect rate improved and the company sold inspected products.

The business alliance agreement with Eisai for Treakisym® expired on December 9, 2020, and SymBio began independently marketing Treakisym® in Japan on December 10. Sales broke down by customer were as follows: Eisai, JPY2.5bn (-10.1% YoY); Suzuken Group, JPY126mn (JPY0mn in FY12/19); and Toho Pharmaceutical JPY120mn (JPY0mn in FY12/19).

Based on Treakisym® sales data from Eisai, which marketed the product until December 9, 2020, revenue from Treakisym® was JPY7.7bn (+6.3% YoY) in FY03/20. Total sales from Q4 FY03/20 through Q3 FY03/21 (January–December 2020) came to JPY6.9bn (JPY7.5bn for the same period a year earlier).

Gross profit was JPY867mn (+0.2% YoY) and GPM on product sales was 28.8% (-1.0pp YoY). The CoGS ratio rose in 1H due to strengthened inspection procedures for lyophilized formulation of Treakisym® (two visual inspections), valuation loss on inventories (JPY69mn versus JPY188mn a year earlier), and higher transportation costs. The inventory valuation loss was related to quality defects of Treakisym®.

The GPM improved from 24.2% in 1H to 33.0% in 2H. The company booked a valuation loss on inventories in 1H, but none in 2H. Shared Research understands that beginning its own marketing of Treakisym® in Q4 also contributed to the GPM improvement.

> 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).

SG&A expenses increased 4.0% YoY to JPY5.4bn. Although the company reduced R&D and administrative expenses by JPY900mn, SG&A expenses increased overall due to upfront spending to establish its own sales structure.

- R&D expenses declined 7.2% YoY to JPY2.3bn. This included expenses for conducting clinical trials of intravenous formulations of Treakisym® and rigosertib. The company also recorded a milestone payment of roughly JPY500mn on obtaining marketing approval for the RTD formulation of Treakisym®.
- Excluding R&D expenses, SG&A expenses rose 14.0% YoY to JPY3.1bn. The company incurred upfront expenses to establish its own sales organization.

Losses expanded across the board despite higher sales due to an increase in SG&A expenses. The difference between recurring loss and net loss is attributable to a JPY525mn settlement payment booked as extraordinary gains.

Business progress updates

Major business developments in FY12/20 were as follows.

- The business alliance agreement with Eisai for Treakisym® expired on December 9, 2020, and SymBio began independently marketing Treakisym® in Japan on December 10.
- In September 2020, the company obtained approval for the RTD formulation of Treakisym®. It began sales in January 2021.
- Also in September 2020, the company completed observation of all patients enrolled in a clinical trial of the RI formulation of Treakisym®. The company plans to apply for approval on completion of the clinical trial, targeting approval in 2H FY12/22.
- In August 2020, Onconova, the licensor of anticancer drug rigosertib, announced that its global phase III trial (INSPIRE study) addressing higher-risk myelodysplastic syndromes (higher-risk MDS) intolerant of treatment using hypomethylating agents failed to meet its primary endpoints. SymBio engages in clinical development of rigosertib in Japan, and plans to use the knowledge obtained from genomic analysis of the INSPIRE study in future development of rigosertib.
- In August 2020, the company decided to develop intravenous formulation of antiviral drug brincidofovir (SyB V-1901, BCV IV) globally (mainly in Japan, the US, and Europe) for adenovirus (AdV) infections occurring after hematopoietic stem cell transplantation. Shared Research understands this is the first time the company has conducted global new drug development independently.
- In July 2020, the Court of Arbitration delivered a ruling in The Medicines Company (MDCO) arbitration case. The court did not grant damage claims made against MDCO but ordered MDCO to pay 50% of costs incurred by SymBio (USD4.95mn) in the arbitration proceedings, including attorney fees.
- In July 2020, the company applied for a partial change to the approved matters of Treakisym® for use in combination with polatuzumab vedotin and rituximab targeting patients with relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL).
- In May 2020, the company submitted an application for partial change to the approved matters of BR therapy (combination of anticancer agents Treakisym® and rituximab) to enable its use for r/r DLBCL.

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. The company therefore began preparations to build an in-house sales organization for domestic sales of Treakisym®.

In FY12/21, the company has deployed a nationwide network of 53 marketing representatives as well as nine 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.

To establish a nationwide distribution structure, in September 2020, the company concluded a basic agreement with Suzuken Co., Ltd (Suzuken Group) and Toho Pharmaceutical Co., Ltd (a consolidated subsidiary of Toho Holdings Co., Ltd.; Kyoso Mirai Group) for the procurement and sale of pharmaceuticals. SymBio is using Suzuken Group and Kyoso Mirai Group as its sole distributors after the marketing agreement with Eisai expired. 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.

SymBio has thus completed building its in-house sales organization, and transitioned to in-house sales of Treakisym® in December 2020 after expiry of the business alliance agreement with Eisai.

Stable product supply

SymBio imports lyophilized Treakisym® for injection from Astellas Deutschland (consolidated subsidiary of Astellas Pharma). Treakisym® inventories were substantially depleted in 1H relative to year-ago levels, but inventory levels recovered in 2H as secondary packaging and quality tests were applied to some batches of Treakisym® 100mg vials imported from Astellas Deutschland.

In September 2020, the company obtained manufacturing and marketing approval for liquid formulations of Treakisym® (RTD formulation) under license from Eagle Pharmaceuticals with plans to begin sales in January 2021. Import and shipments to the sole distributors of the Treakisym® (RTD formulation) began in Q4 FY12/20 (October–December 2020).

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 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 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 the 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 and on the NHI drug price list from May 2019. 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® in BR therapy conducted in patients with relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL), an additional indication following the above approved ones, results showed that the response rate (primary endpoint) was better than expected. Based on this, the company submitted an application for partial change to approved matters in May 2020. It is currently conducting 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 combination with rituximab is crucial for establishing Treakisym® as a treatment for DLBCL. 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 submitted an application for partial change to the approved matters of Treakisym® for use in combination with polatuzumab vedotin and rituximab. If the new drug applications by Chugai and SymBio are approved and polatuzumab vedotin is added to the NHI drug price list, Treakisym® can be used with polatuzumab vedotin in combination with 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 RI formulations of Treakisym®. Manufacturing and marketing approval of the RTD formulation was obtained in September 2020, and the company plans to launch it in January 2021. The company is conducting clinical trials to confirm safety of the RI formulation and plans to apply for approval in FY12/21. 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 [injection]/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 azacitidine, 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), an antiviral drug in intravenous and oral forms). The company acquired exclusive global rights to develop, manufacture, and market brincidofovir for all diseases except smallpox.

After a review at the global advisory board held in February 2020, the company concluded that it would prioritize global development of brincidofovir 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. 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 brincidofovir. The company is presently in preparation to initiate a dose-finding study of the liquid formulation of brincidofovir in pediatric patients slated to begin in December 2021.

Clinical trials by Chimerix have demonstrated superior, broad-spectrum antivirus activity of brincidofovir oral against dsDNA viruses. Brincidofovir IV is also expected to become 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 brincidofovir as a medical defense against smallpox. The FDA has approved priority review for BCV under the Prescription Drug User Fee Act (PDUFA) and set the date for completing the review (PDUFA date) at April 7, 2021.

SyB P-1501, transdermal pain management system
Regarding SyB P-1501 licensed by The Medicines Company (marketed as IONSYS in the US), the company initiated an arbitration against The Medicines Company (MDCO), under the rules of the International Chamber of Commerce, seeking damages of USD82mn arising from MDCO's repudiation of the license agreement. SymBio argued that MDCO's failure to provide sufficient assurance to the company regarding the performance of obligations under the license agreement in light of its decision to withdraw from business activities relating to SyB P-1501 in the European and US markets was a material breach of the license agreement. In September 2020, SymBio announced it had received the arbitration judgment and although the Court of Arbitration did not award damages sought by the company, it did order MDCO to pay 50% of legal costs (about USD5mn) sought by the company.

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

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.

Cumulative Q3 FY12/20 results

- ▷ Sales: JPY2.3bn (+16.2% YoY)
- ▷ Operating loss: JPY3.1bn (loss of JPY3.5bn in Q3 FY12/19)
- ▷ Recurring loss: JPY3.2bn (loss of JPY3.6bn in Q3 FY12/19)
- ▷ Net loss: JPY2.7bn (loss of JPY3.6bn in Q3 FY12/19)

Overview

In cumulative Q3 FY12/20, sales increased YoY, as the company booked sales of Treakisym®. Sales were JPY1.4bn (-32.1% YoY) in 1H and JPY972mn in Q3 (versus sales of JPY3mn in Q3 FY12/19), representing YoY growth on a cumulative Q3 basis. A large defect ratio in multiple batches of lyophilized Treakisym® formulations imported from Astellas Deutschland and unstable deliveries continued in 1H, resulting in lower YoY sales. The defect ratio improved and selling inspected products led to higher YoY sales in Q3.

Based on data supplied by Treakisym® distributor Eisai, sales of Treakisym® were JPY7.7bn (+6.3% YoY) in FY03/20. Sales were solid on a quarterly basis at JPY1.6bn in Q4 FY03/20 (January–March 2020) versus JPY1.4bn in Q4 FY03/19, JPY1.9bn in Q1 FY03/21 (April–June 2020) versus JPY2.0bn in Q1 FY03/20, and JPY1.7bn in Q2 FY03/21 (July–September 2020) versus JPY2.1bn in Q2 FY03/20.

Gross profit was JPY611mn (+8.5% YoY) and the GPM on product sales was 26.2% (-1.8pp YoY). The cost ratio increased due to strengthened inspection procedures for lyophilized formulation of Treakisym® (two visual inspections), valuation loss on inventories (JPY69mn versus JPY188mn a year earlier), and higher transportation costs. The inventory valuation loss was related to quality defects of Treakisym®. However, GPM was 28.9% in Q3, an improvement over 24.2% in 1H. Although the company booked an inventory valuation loss in 1H, it did not book a loss in Q3, leading to an improved cost ratio.

SG&A expenses declined 8.4% YoY to JPY3.8bn.

- ▷ R&D expenses declined 11.5% YoY to JPY1.7bn. This included expenses for conducting clinical trials of intravenous formulations of Treakisym® and rigosertib.
- ▷ Excluding R&D expenses, SG&A expenses fell by 5.6% YoY to JPY2.0bn. The company incurred development costs for its in-house sales organization.

Losses narrowed across the board on higher sales and lower SG&A expenses. The difference between recurring and net losses is attributable to a JPY525mn settlement payment booked as extraordinary gains.

Business progress updates

Major business developments in cumulative Q3 FY12/20 were as follows.

- ▷ In September 2020, the company obtained approval for the RTD formulation of Treakisym®. It plans to begin sales in January 2021.
- ▷ Also in September 2020, the company completed observation of all patients enrolled in a clinical trial of the RI formulation of Treakisym®. The company plans to apply for approval on completion of the clinical trial, targeting approval in 2H FY12/22.

- In August 2020, Onconova, the licensor of anticancer drug rigosertib, announced that its global phase III trial (INSPIRE study) addressing higher-risk myelodysplastic syndromes (higher-risk MDS) intolerant of treatment using hypomethylating agents failed to meet its primary endpoints. SymBio engages in clinical development of rigosertib in Japan, and plans to use the knowledge obtained from genomic analysis of the INSPIRE study in future development of rigosertib.
- In August 2020, the company decided to develop intravenous formulation of antiviral drug brincidofovir (SyB V-1901, BCV IV) globally (mainly in Japan, the US, and Europe) for adenovirus (AdV) infections occurring after hematopoietic stem cell transplantation. Shared Research understands this is the first time the company has conducted global new drug development independently.
- In July 2020, the Court of Arbitration delivered a ruling in The Medicines Company (MDCO) arbitration case. The court did not grant damage claims made against MDCO but ordered MDCO to pay 50% of costs incurred by SymBio (USD4.95mn) in the arbitration proceedings, including attorney fees.
- In July 2020, the company applied for a partial change to the approved matters of Treakisym® for use in combination with polatuzumab vedotin and rituximab targeting patients with relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL).
- In May 2020, the company applied for a partial change to the approved matters of BR therapy (combination of anticancer agents Treakisym® and rituximab) to enable its use for r/r DLBCL.
- In May 2020, an abstract on analysis of phase III BR therapy (combination of anticancer agents Treakisym® and rituximab) results for treatment of relapsed or refractory diffuse large B-cell lymphoma was adopted for the 25th Congress of the European Hematology Association scheduled to be held in June 2020.

Domestic

Preparations for in-house sales organization begin

The business alliance agreement between SymBio and Eisai Co., Ltd. under which Eisai acts as a sales agent expires in December 2020. The company plans to transition to its in-house sales organization for domestic sales of Treakisym® in January 2021. This should facilitate a move into the black from FY12/21 and ongoing profit growth thereafter and lay the groundwork for future business development.

In Q3, the company has started work on transferring marketing operations from Eisai, and as planned, has deployed a nationwide network of 51 marketing representatives as well as six hematology experts to cover each region.

In September 2020, the company concluded a basic agreement with Suzuken Co., Ltd (hereafter, Suzuken Group) and Toho Pharmaceutical Co., Ltd (a consolidated subsidiary of Toho Holdings Co., Ltd., hereafter Kyoso Mirai Group) for the procurement and sale of pharmaceuticals. SymBio will use Suzuken Group and Kyoso Mirai Group as its sole distributors once the marketing agreement with Eisai expires. The company will have two distribution centers, one in Eastern Japan and the other in Western Japan, under management by S.D. Collabo Co., Ltd.

Stable product supply

SymBio imports lyophilized Treakisym® for injection from Astellas Deutschland (consolidated subsidiary of Astellas Pharma), which is marketed in Japan by sales agent Eisai. Treakisym® inventories were substantially depleted in 1H relative to year-ago levels, but inventory levels were recovering as of Q3 as secondary packaging and quality tests were applied to some batches of Treakisym® 100mg vials imported from Astellas Deutschland while shipments to Eisai were on track with plan.

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

Approved indications

The anticancer agent Treakisym® is used for the indications of untreated low-grade non-Hodgkin's lymphoma and mantle cell lymphoma (marketing approval obtained in December 2016), refractory or relapsed low-grade 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 edited and published by Japanese Society of Hematology as a standard treatment option, which applies to all of the approved indications. This has seen Treakisym® establish its position as a standard treatment for lymphatic cancer.

Also, SymBio obtained approval for the 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 the 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 and on the NHI drug price list from May 2019.

Relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL)

In the phase III clinical study of Treakisym® administered in combination with rituximab (BR therapy) targeting relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL), an additional indication following the above approved ones, results showed that the response rate (primary endpoint) was better than expected. Based on this, the company applied for a partial change to approved matters in May 2020. It is currently conducting 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 combination with rituximab is crucial for establishing Treakisym® as a treatment for DLBCL.

In May 2020, an abstract on analysis of phase III BR therapy (combination of anticancer agents Treakisym® and rituximab) results for treatment of relapsed or refractory diffuse large B-cell lymphoma was adopted for the 25th Congress of the European Hematology Association scheduled to be held in June 2020. The company noted the main results of the phase III (38 patients) trial analysis were as follows:

Overall response rate (ORR) was 76% and complete response (CR) rate was 47%.

<By gene activity pattern>

- ▷ GCB type: ORR of 83%, CR rate of 67%
- ▷ Non-GCB type: ORR of 78%, CR rate of 39%

Divided into GCB or non-GCB type DLBCL GCB type: Geminal center B-cell type Non-GCB type: non Geminal center B-cell type

<By age group>

- ▷ Under 65 years of age: ORR of 86%, CR rate of 71%
- ▷ 65 to 75 years old: ORR of 75%, CR rate of 45%
- ▷ Over 75 years of age: ORR of 73%, CR rate of 36%

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, distributor Eisai booked sales of JPY8.0bn in FY03/20. By comparison, the company estimates that the number of Japanese patients with r/r DLBCL is 18,672.

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 a partial change to the approved matters of Treakisym® for use in combination with polatuzumab vedotin and rituximab. If the new drug applications by Chugai and SymBio are approved and polatuzumab vedotin is added to the NHI drug price list, Treakisym® can be used with polatuzumab vedotin in combination with 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.

Treakisym® liquid formulations (RTD/RI)

The company concluded an exclusive licensing agreement in Japan with Eagle Pharmaceuticals (based in New Jersey, US) in September 2017 for the RTD and RI formulations of Treakisym®. Manufacturing and marketing approval of the RTD formulation was obtained in September 2020, and the company plans to launch it in Q1 FY12/21. SymBio commenced a clinical trial for the RI formulation in November 2018 primarily to confirm safety, and the follow-up period for all patients enrolled in the trial was completed in September 2020 (LPLV: Last Patient Last Visit). The company will apply for approval without delay after the end of the clinical trial of the RI formulation and aims to begin sales in 2H FY12/22. 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 (for RTD and RI formulations) will enable the extension of the product life of Treakisym® to 2031. The RTD and RI formulations were launched in the US market from January 2016 and had captured a 40% share of the bendamustine market within four months of commercialization, rising to over 90% within 12 months. The company looks for an even more rapid switch from the lyophilized powder to liquid formulations in Japan.

Treakisym® lifecycle management strategy

As noted above, SymBio anticipates Treakisym® sales will expand on the back of increased sales for already approved indications and contributions from the new indication of r/r DLBCL. Treakisym® is designated as a treatment for rare diseases and the re-examination period ends in 2020, so the launch of liquid Treakisym® (RTD and RI formulations) will extend the product life until 2031.

In addition, SymBio is slated to take over domestic marketing of Treakisym® in January 2021. Shared Research thinks this could lead to higher profit margins for SymBio as it may be able to pocket gross profits booked by Eisai (difference between Eisai's procurement price and delivery price to drug wholesalers). We further believe gross profit margins could rise following transition to liquid Treakisym® owing to a change in suppliers. The lyophilized powder formulation of Treakisym® is supplied by Astellas Deutschland whereas the RTD and RI formulations are supplied by Eagle Pharmaceuticals. The company is also considering in-house production of liquid Treakisym® as a future possibility.

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

Rigosertib injection

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 genomic analysis of the INSPIRE study to rigosertib development going forward.

Oral rigosertib

Regarding the oral formulation of rigosertib, Onconova completed a phase I/II clinical trial for the drug used in combination with azacitidine, 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 to treat infections: 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 for the treatment of infections in intravenous and oral forms). The company acquired exclusive global rights to develop, manufacture, and market BCV for all diseases except smallpox.

After a review at the global advisory board held in February 2020, the company 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. 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. The company is presently in preparation to initiate a dose-finding study of the liquid formulation of BCV in pediatric patients slated to begin in December 2021.

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.

SyB P-1501, transdermal pain management system

Regarding SyB P-1501 licensed by The Medicines Company, the company initiated an arbitration against The Medicines Company (MDCO), under the rules of the International Chamber of Commerce, seeking damages of USD82mn arising from MDCO's repudiation of the license agreement. SymBio argued that MDCO's failure to provide sufficient assurance to the company regarding the performance of obligations under the license agreement in light of its decision to withdraw from business activities relating to SyB P-1501 in the European and US markets was a material breach of the license agreement. In September 2020, SymBio announced it had received the arbitration judgment and although the Court of Arbitration did not award damages sought by the company, it did order MDCO to pay 50% of legal costs (USD4.95mn) sought by the company.

Overseas

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

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.

1H FY12/20 results

- ▷ Sales: JPY1.4bn (-32.1% YoY)
- ▷ Operating loss: JPY1.8bn (loss of JPY2.0bn in 1H FY12/19)
- ▷ Recurring loss: JPY1.9bn (loss of JPY2.1bn in 1H FY12/19)

▷ Net loss: JPY1.9bn (loss of JPY2.1bn in 1H FY12/19)

Earnings summary

Sales fell YoY. The company booked sales of Treakisym®. As discussed later, lyophilized Treakisym® for injection imported from Astellas Deutschland continued to have high defect ratios and deliveries were irregular in 1H FY12/20. Consequently, supply problems persisted, and sales declined YoY.

According to materials disclosed by Treakisym® distributor Eisai, FY03/20 product sales increased 6.3% YoY to JPY7.7bn. Even on a quarterly basis, Treakisym® sales were flat YoY, at JPY1.6bn in Q4 FY03/20 (JPY1.4bn in Q4 FY03/19) and JPY1.9bn in Q1 FY03/21 (JPY2.0bn in Q1 FY03/20).

Gross profit totaled JPY330mn (-37.7% YoY) while GPM dropped 2.2pp YoY to 24.2%. The cost ratio increased due to strengthened inspection procedures for lyophilized formulation of Treakisym® (two visual inspections), valuation losses on inventories, and higher transportation costs. Valuation losses on inventories was JPY69mn in 1H (versus JPY188mn in 1H FY12/19) and attributable to quality defects of Treakisym® products.

SG&A expenses fell 14.7% YoY to JPY2.2bn.

▷ R&D expenses declined 13.4% YoY to JPY834mn. This included expenses for conducting clinical trials of intravenous and oral formulations of Treakisym® and rigosertib.

▷ Excluding R&D expenses, SG&A expenses fell by 15.5% YoY to JPY1.3bn. The company incurred development expenses for its in-house sales organization. Among expense items, salaries and promotion expenses increased YoY while fee expenses declined from JPY542mn in 1H FY12/19 to JPY35mn.

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

Progress versus company full-year forecast

SymBio left its FY12/20 full-year forecast unchanged even though 1H sales reached only 40.0% of target. Heading into 2H, the company looks for sales of Treakisym® to increase on higher overseas sales and a boost from its nationwide marketing operation. On the supply side, the company aims to alleviate the Treakisym® substandard problems by maintaining high inventories and thus make up for the 1H shortfall in 2H.

Also, as discussed later, the Court of Arbitration in August 2020 ordered The Medicines Company (MDCO) to pay SymBio 50% of costs incurred in the arbitration proceedings, including attorney fees. The company plans to thoroughly review the related costs and later estimate the impact on FY12/20 earnings forecast.

Business progress updates

New major business developments in 1H FY12/20 were as follows.

▷ In August 2020, the company decided to develop intravenous formation of antiviral drug brincidofovir (SyB V-1901, BCV IV) globally (mainly in Japan, the US, and Europe) for adenovirus (AdV) infections occurring after hematopoietic stem cell transplantation. Shared Research understands this is the first time the company has conducted global new drug development independently.

▷ In July 2020, the Court of Arbitration delivered a ruling in The Medicines Company (MDCO) arbitration case. The court did not grant damage claims made against MDCO but ordered MDCO to pay 50% of costs incurred by SymBio in the arbitration proceedings, including attorney fees.

▷ In July 2020, the company applied for a partial change to the approved matters of Treakisym® for use with polatuzumab vedotin and rituximab targeting patients with relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL).

- In May 2020, the company applied for a partial change to the approved matters of BR therapy (combination of anticancer agents Treakisym® and rituximab) to enable its use for r/r DLBCL.
- In May 2020, an abstract on analysis of phase III BR therapy (combination of anticancer agents Treakisym® and rituximab) results for treatment of relapsed or refractory diffuse large B-cell lymphoma was adopted for the 25th Congress of the European Hematology Association scheduled to be held in June 2020.
- In March 2020, Onconova, the licensor of anticancer drug rigosertib, announced it had completed enrollment of the target 360 patients for the international joint phase III (INSPIRE) study, 48 of whom were enrolled in Japan.
- In March 2020, enrollment of trial subjects for the study to confirm safety of Treakisym® liquid formulation (rapid infusion, RI) was completed.

Domestic

Preparations for in-house sales organization begin

The business alliance agreement between SymBio and Eisai Co., Ltd. under which Eisai acts as a sales agent expires in December 2020. The company plans to transition to its in-house sales organization for domestic sales of Treakisym® in January 2021. This should facilitate a move into the black from FY12/21 and ongoing profit growth thereafter and lay the groundwork for future business development.

In Q2, the company completed setting up its nationwide internal sales organization as planned, hiring and training additional Treakisym® medical representatives (MRs) and regional sales managers. The nationwide in-house marketing team consists of 51 MRs, six regional managers, one key account manager (KAM) of key opinion leaders, and four hematology experts, for a total of 62. In addition, SymBio continued building its distribution and logistics capabilities with logistics centers in East and West Japan and in-house infrastructure including a new IT system with ERP, which is also now in the final stages.

Substandard products

SymBio imports lyophilized Treakisym® for injection from Astellas Deutschland (consolidated subsidiary of Astellas Pharma). Some batches of Treakisym® 100mg vials imported from Astellas Deutschland for domestic sales in FY12/19 had impurities and appearance defects in a significantly higher percentage than stipulated in the supply agreement. In order to prevent a recurrence of such product quality issues, the company objected to Astellas Deutschland, and demanded steps such as corrective and preventive action (CAPA) processes to fulfil its responsibilities as the supplier.

Nonetheless, there was no improvement in 1H, with persistent supply issues. Several batches from Astellas Deutschland had high defect ratios and deliveries were irregular. Q2 sales fell YoY as Treakisym® inventory levels were low compared with Q2 FY12/19.

In Q3, the company is persisting with its efforts to restore Treakisym® inventory levels by continuing discussions with Astellas Deutschland to reduce defect rates, and stabilize supply.

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

Approved indications

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

The combination therapy of Treakisym® and rituximab (BR therapy) was newly included in the Practical Guidelines for Hematological Malignancies 2018 edited and published by Japanese Society of Hematology as a standard treatment option, which applies to all of the approved indications. This has seen Treakisym® establish its position as a standard treatment for lymphatic cancer.

Also, SymBio obtained approval for the 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 (launched in August 2018). In March 2019, SymBio obtained approval for the 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 and on the NHI drug price list from May 2019.

Relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL)

Following on from the above approved indications, the company conducted a phase III clinical study for the fourth indication of relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL), with Treakisym® administered in combination with rituximab (BR therapy). The response rate (primary endpoint) in the test results released in November 2019 was better than expected. In May 2020, the company applied for a partial change to approved matters.

In May 2020, an abstract on analysis of phase III BR therapy (combination of anticancer agents Treakisym® and rituximab) results for treatment of relapsed or refractory diffuse large B-cell lymphoma was adopted for the 25th Congress of the European Hematology Association scheduled to be held in June 2020. The company noted the main results of the phase III (38 patients) trial analysis were as follows:

Overall response rate (ORR) was 76% and complete response (CR) rate was 47%.

<By gene activity pattern>

- ▷ GCB type: ORR of 83%, CR rate of 67%
- ▷ Non-GCB type: ORR of 78%, CR rate of 39%

Divided into GCB or non-GCB type DLBCL GCB type: Geminal center B-cell type Non-GCB type: non Geminal center B-cell type

<By age group>

- ▷ Under 65 years of age: ORR of 86%, CR rate of 71%
- ▷ 65 to 75 years old: ORR of 75%, CR rate of 45%
- ▷ Over 75 years of age: ORR of 73%, CR rate of 36%

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, distributor Eisai booked sales of JPY8.0bn in FY03/20. By comparison, the company estimates that the number of Japanese patients with r/r DLBCL is 18,672.

After Chugai Pharmaceutical Co., Ltd. applied for manufacture and marketing approval of polatuzumab vedotin in combination with BR therapy to treat r/r DLBCL in June 2020, the company applied for a partial change to the approved matters of Treakisym® for use in combination with polatuzumab vedotin and rituximab therapy. If the new drug applications by Chugai and SymBio are approved and polatuzumab vedotin is added to the NHI drug price list, Treakisym® can be used with polatuzumab vedotin in combination with 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. An effective new drug with few side effects is sought, however, because salvage chemotherapy produces severe adverse effects. 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.

Treakisym® liquid formulations (RTD and RI)

The company concluded an exclusive licensing agreement in Japan with Eagle Pharmaceuticals (based in New Jersey, US) in September 2017 for the RTD and RI formulations of Treakisym®.

- The company applied for approval of the RTD formulation in September 2019, and plans to launch it in Q1 FY12/21.
- SymBio started clinical trials for the RI formulation in November 2018 with the main objective of confirming safety and completed patient enrollment in March 2020. The company will apply for approval without delay upon completion of the clinical trials of the RI formulation and aims to begin sales in 2H FY12/22. 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 of the product in liquid formulations (RTD and RI) with product licenses will enable the extension of the product life of Treakisym® to 2031. The RTD and RI formulations were launched in the US market from January 2016 and had captured a 40% share of the bendamustine market within four months of commercialization, rising to over 90% within 12 months. The company looks for an even more rapid switch from the lyophilized powder to liquid formulations in Japan.

Treakisym® lifecycle management strategy

As noted above, SymBio anticipates Treakisym® sales will expand on the back of increased sales for already approved indications and contributions from the new indication of r/r DLBCL. Treakisym® is designated as a treatment for rare diseases and the re-examination period ends in 2020, so the launch of liquid Treakisym® (RTD and RI formulations) will extend the product life until 2031.

In addition, SymBio is slated to take over domestic marketing of Treakisym® in January 2021. Shared Research thinks this could lead to higher profit margins for SymBio as it may be able to pocket gross profits booked by Eisai (difference between Eisai's procurement price and delivery price to drug wholesalers). We further believe gross profit margins could rise following transition to liquid Treakisym® owing to a change in suppliers. The lyophilized powder formulation of Treakisym® is supplied by Astellas Deutschland whereas the RTD and RI formulations are supplied by Eagle Pharmaceuticals. The company is also considering in-house production of liquid Treakisym® as a future possibility.

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

Rigosertib injection

Onconova Therapeutics, Inc., the licensor, is currently conducting a global phase III trial (INSPIRE trial), with SymBio performing the Japan trial. The global phase III trial addresses higher-risk myelodysplastic syndromes (higher-risk MDS), which do not respond to the current standard treatment with hypomethylating agents, which relapse after treatment under the current standard of care, or which are intolerant to hypomethylating agents, and is under way at clinical trial sites in more than 20 countries worldwide. Onconova announced that it had reached its target of enrolling 360 patients worldwide as of March 2020 and achieved the required number of survival events in July 2020. Onconova said the primary endpoint results would become clear in Q3 2020, and that it planned to announce trial results at an academic conference by the end of the year. Based on these trial results, the company plans to apply for approval in Japan at the same time as in the US and Europe.

Oral rigosertib

Regarding the oral formulation of rigosertib, Onconova completed phase I/II clinical trials for the drug used in combination with azacitidine, whose results suggested the efficacy and safety of the combination therapy. To verify the tolerability and safety of the oral formulation of rigosertib among Japanese patients, SymBio began phase I clinical trials in Japan in June 2017 and completed patient enrollment in June 2019. After completing the phase I trials, the company will participate in global clinical trials of the drug used in combination with azacitidine as first-line treatment for higher-risk MDS currently planned by Onconova. In December 2019, Onconova announced that it was considering the design of a Phase II/III adaptive trial with untreated higher- risk

MDS patients based on the data presented at the 61st American Society of Hematology (ASH) Annual Meeting in December 2019.

Antiviral drug to treat infections 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 for the treatment of infections in intravenous and oral forms). The company acquired exclusive global rights to develop, manufacture, and market BCV for all diseases except smallpox.

After concluding the exclusive global license agreement, SymBio held discussions with Japanese and overseas infectious disease experts to examine the scientific and medical validity of BCV and progress its feasibility study. The company concluded in August 2020 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. Based on safety and efficacy data acquired from its study, the company plans to extend its target disease area to multiviral infections in patients receiving hematopoietic stem cell transplantation. By exploring the potential for expanding target disease areas to organ transplants (including kidney transplants) to grow the market for, and maximize the business value of BCV, the company aims to transform itself into a global specialty pharmaceutical company with an integrated structure to supply quality pharmaceutical products.

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.

SyB P-1501, transdermal pain management system

Regarding SyB P-1501 licensed by The Medicines Company, the company initiated an arbitration against The Medicines Company (MDCO), under the rules of the International Chamber of Commerce, seeking damages of USD82mn (approximately JPY9.0bn) arising from MDCO's repudiation of the license agreement. SymBio argued that MDCO's failure to provide sufficient assurance to the company regarding the performance of obligations under on the license agreement in light of its decision to suspend and withdraw from business activities relating to SyB P-1501in the European and US markets was a material breach of the license agreement. In August 2020, SymBio announced that it had received the arbitration judgment. The Court of Arbitration did not award damages sought by the company, but ordered MDCO to pay 50% of all arbitration costs as sought by the company. Counterclaims and claims for costs by MDCO were rejected. The above costs are under close examination and expected to take several weeks to finalize. The company commented that it would examine the arbitration judgment in detail to assess carefully its impact on FY12/20 earnings forecast.

For reference, Shared Research understands expenses associated with the arbitration proceeding, including attorney fees, were booked as fee expenses under SG&A expenses. The arbitration petition against MDCO was initiated in December 2017, and the company booked fee expenses of JPY137mn in FY12/16, JPY567mn in FY12/17, JPY444mn in FY12/18, and JPY712mn in FY12/19. Shared Research believes expenses associated with the arbitration were a major factor boosting fee expenses from FY12/17.

Overseas

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

In-licensing of drug candidates

The company is currently focusing on producing and unrolling 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 FY12/20 results

- Sales: JPY551mn (-65.8% YoY)
- Operating loss: JPY962mn (loss of JPY596mn in Q1 FY12/19)
- Recurring loss: JPY991mn (loss of JPY616mn in Q1 FY12/19)
- Net loss: JPY992mn (loss of JPY617mn in Q1 FY12/19)

Sales fell YoY. The company booked sales of Treakisym®. As will be described later, high product defect rates and unstable deliveries persisted in Q1 for multiple batches of Treakisym® lyophilized injections supplied by Astellas Deutschland so sales declined YoY due to continued supply problems.

According to disclosure by Eisai, the sales agent for Treakisym®, FY03/20 sales of the product increased 6.2% YoY to JPY8.0bn. On a quarterly basis, Q4 (January–March 2020) Treakisym® sales were JPY1.6bn, up from JPY1.5bn in Q1 FY12/19.

Gross profit totaled JPY128mn (-79.0% YoY) while GPM was 23.2% (-14.6pp YoY). Increased inspections boosted the cost ratio for Treakisym® lyophilized injection.

SG&A expenses fell 9.6% YoY to JPY1.1bn and R&D expenses declined 7.1% YoY to JPY438mn. This included expenses for conducting clinical trials of intravenous and oral formulations of Treakisym® and rigosertib. Excluding R&D expenses, SG&A expenses declined 11.1% YoY to JPY651mn. The company incurred development expenses building its in-house sales structure, but it seems fee and other expenses declined YoY.

As a result, operating loss, recurring loss, and net loss widened YoY. The difference between operating loss and recurring loss was accounted for largely by JPY30mn in non-operating expenses: mainly JPY16mn in forex losses and JPY13mn in stock issuance costs.

Although Q1 sales reached only 16.2% of the company's full-year target, SymBio left full-year forecast unchanged, likely because it anticipates the supply issues concerning Treakisym® lyophilized injection formulation to be resolved in 2H.

Major pipeline progress in Q1 FY12/20 is shown below.

- May 2020: submitted an application for partial change to the approved matters of BR therapy (combination use of anticancer agents Treakisym® and rituximab) to enable its use for relapsed or refractory diffuse large B-cell lymphoma (DLBCL).
- May 2020: an abstract on analysis of phase III BR therapy (combination of anticancer agents Treakisym® and rituximab) results for treatment of relapsed or refractory diffuse large B-cell lymphoma was adopted for the 25th Congress of the European Hematology Association scheduled to be held in June 2020.
- March 2020: Onconova, the licensor of anticancer drug rigosertib, announced it had completed enrollment of the target 360 patients for the international joint phase III (INSPIRE) study, 48 of whom were enrolled in Japan.
- March 2020: Enrollment of trial subjects for the study to confirm safety of Treakisym® liquid formulation (rapid infusion, RI) was completed.

Domestic

Preparations for in-house sales organization begin

The business alliance agreement between SymBio and Eisai Co., Ltd. under which Eisai acts as a sales agent expires in December 2020. The company plans to transition to its in-house sales organization in January 2021. This should facilitate a move into the black from FY12/21 and ongoing profit growth thereafter and lay the groundwork for future business development.

In Q1, the company hired and trained additional Treakisym® sales representatives and regional sales managers who will form the core of its in-house marketing network. This set the stage to complete the nationwide sales structure in 1H FY12/20. SymBio continued building its distribution and logistics capabilities with logistics centers in East and West Japan and in-house infrastructure including a new IT system with ERP.

Substandard products

SymBio imports lyophilized Treakisym® for injection from Astellas Deutschland (consolidated subsidiary of Astellas Pharma). Some batches of Treakisym® 100mg vials imported from Astellas Deutschland for domestic sales in FY12/19 had impurities and appearance defects in a significantly higher percentage than stipulated in the supply agreement. In order to prevent a recurrence of such product quality issues, the company objected to Astellas Deutschland, and demanded steps such as corrective and preventive action (CAPA) processes to fulfil its responsibilities as the supplier. Nonetheless, there was no improvement in Q1, with persistent supply issues. Several batches from Astellas Deutschland had high defect ratios and deliveries were irregular. Sales fell YoY as Treakisym® inventory levels were low compared with Q1 FY12/19.

The problems with defective products and irregular deliveries are likely to persist through the rest of 1H, and SymBio expects sales from shipments to its Treakisym® sales agent, Eisai, to be down YoY. The company is persisting with its efforts to restore Treakisym® inventory levels, reduce defect rates, and stabilize supply through discussions with its supplier.

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

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

The combination therapy of Treakisym® and rituximab (BR therapy) was newly included in the Practical Guidelines for Hematological Malignancies 2018 edited and published by Japanese Society of Hematology as a standard treatment option, which applies to all of the approved indications. This has seen Treakisym® establish its position as a standard treatment for lymphatic cancer.

Also, SymBio obtained approval for the 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 (launched in August 2018). In March 2019, SymBio obtained approval for the 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 and on the NHI drug price list from May 2019.

Following on from the above approved indications, the company conducted a phase III clinical study for the fourth indication of relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL), with Treakisym® administered in combination with rituximab (BR therapy). The response rate (primary endpoint) in the test results released in November 2019 was better than expected. In May 2020, the company applied for a partial change to approved matters.

In May 2020, an abstract on analysis of phase III BR therapy (combination of anticancer agents Treakisym® and rituximab) results for treatment of relapsed or refractory diffuse large B-cell lymphoma was adopted for the 25th Congress of the European Hematology Association scheduled to be held in June 2020. The company noted the main results of the phase III (38 patients) trial analysis were as follows:

<By gene activity pattern>

▷ GCB type: Overall response rate (ORR) of 83%, complete response (CR) rate of 67%

▷ Non-GCB type: ORR of 78%, CR rate of 39%

Divided into GCB or non-GCB type DLBCL
GCB type: Geminal center B-cell type
Non-GCB type: non Geminal center B-cell type

<By age group>

▷ Under 65 years of age: ORR of 86%, CR rate of 71%

▷ 65 to 75 years old: ORR of 75%, CR rate of 45%

▷ Over 75 years of age: ORR of 73%, CR rate of 36%

The company concluded an exclusive licensing agreement in Japan with Eagle Pharmaceuticals (based in New Jersey, US) in September 2017. Following consultations with the PMDA, the company filed for approval of the RTD formulation in September 2019, and plans to launch it in Q1 FY12/21. SymBio launched clinical trials for the RI formulation in November 2018 primarily to confirm safety and completed patient enrollment in March 2020. The company will apply for approval without delay after the end of the clinical trials of the RI formulation and aims to begin sales in 2H FY12/22. 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 extended the product life of Treakisym® to 2031.

Anticancer agents: rigosertib sodium (SyB L-1101 [IV]/SyB C-1101 [oral] (generic name: rigosertib sodium)
Onconova Therapeutics, Inc., the licensor, is currently conducting a global phase III trial and SymBio Pharmaceuticals started the Japan trial in December 2015 (50 patients enrolled as of April 2020). The global phase III trial addresses higher-risk myelodysplastic syndromes (higher-risk MDS), which do not respond to the current standard treatment with hypomethylating agents, which relapse after treatment under the current standard of care, or which are intolerant to hypomethylating agents, and is under way at clinical trial sites in more than 20 countries worldwide. Onconova announced that it had reached its target of enrolling 360 patients worldwide as of March 2020. Onconova said the primary endpoint results would become clear in 2H 2020, and that it planned to announce trial results at an academic conference by the end of the year. Based on these trial results, the company plans to apply for approval in Japan at the same time as in the US and Europe.

Regarding the oral formulation of rigosertib, Onconova completed phase I/II clinical trials for the drug used in combination with azacitidine, whose results suggested the efficacy and safety of the combination therapy. To verify the tolerability and safety of the oral formulation of rigosertib among Japanese patients, SymBio began phase I clinical trials in Japan in June 2017 and completed patient enrollment in June 2019. After completing the phase I trials, the company will participate in global phase III clinical trials of the drug used in combination with azacitidine as first-line treatment for higher-risk MDS currently planned by Onconova. In December 2019, Onconova announced that it was considering the design of a Phase II/III adaptive trial with untreated higher risk MDS patients based on the data presented at the 61st American Society of Hematology (ASH) Annual Meeting in December 2019.

Antiviral drug to treat infections 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 for the treatment of infections in intravenous and oral forms). The company acquired exclusive global rights to develop, manufacture, and market BCV for all diseases except smallpox.

BCV Oral has demonstrated a strong, broad-spectrum antiviral effect in clinical trials in Europe and the US by Chimerix. The company will design a global clinical trial based on these findings.

The company will initially develop BCV-IV for treatment of viral hemorrhagic cystitis (vHC) occurring after hematopoietic stem cell transplantation for the domestic market, which has high unmet medical needs. It plans to conduct clinical studies and gain approval in Japan first so it can offer it to patients there. It also plans to market BCV IV globally after conducting international joint clinical trials in countries including the US and Europe. As well, the company plans clinical development of BCV IV as an antiviral treatment of infections after kidney transplants, because it is likely to be effective for transplants other than hematopoietic stem cell transplants, including organ transplants. The company looks to expand its business in Europe, the US and Asia (including China), where organ transplant markets are larger than Japan's. It is also looking for partnerships that take advantage of regional characteristics of these target diseases.

SyB P-1501, transdermal pain management system

Regarding SyB P-1501 licensed by The Medicines Company, the company initiated an arbitration against The Medicines Company, under the rules of the International Chamber of Commerce, seeking damages of USD82mn (approximately JPY9.0bn) arising from The Medicines Company's repudiation of the license agreement. SymBio argued that The Medicine Company's failure to provide sufficient assurance to the company regarding the performance of obligations under on the license agreement in light of its decision to suspend and withdraw from business activities relating to SyB P-1501in the European and US markets was a material breach of the license agreement. On November 30, 2017, the license agreement was terminated as the breach was not corrected within the contract period and development of the product ceased in February 2018. Arbitration proceedings against The Medicines Company are still ongoing. In January 2020, Swiss company Novartis AG announced that it had acquired The Medicines Company. SymBio expects an arbitration judgment in 1H 2020.

Overseas

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

In-licensing of drug candidates

The company is currently focusing on producing and unrolling 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 (JPYmn)	FY12/11 Par.	FY12/12 Par.	FY12/13 Par.	FY12/14 Par.	FY12/15 Par.	FY12/16 Par.	FY12/17 Par.	FY12/18 Par.	FY12/19 Par.	FY12/20 Par.
Sales	**1,883**	**1,955**	**1,532**	**1,955**	**1,933**	**2,368**	**3,444**	**3,836**	**2,838**	**2,987**
YoY	29.8%	3.9%	-21.6%	27.6%	-1.1%	22.5%	45.4%	11.4%	-26.0%	5.3%
CoGS	1,224	1,362	1,214	1,428	1,350	1,464	2,413	2,663	1,973	2,120
Gross profit	**658**	**593**	**318**	**527**	**583**	**904**	**1,031**	**1,173**	**865**	**867**
Gross profit margin	35.0%	30.3%	20.8%	26.9%	30.2%	38.2%	29.9%	30.6%	30.5%	29.0%
SG&A expenses	2,725	2,293	1,999	1,830	3,135	3,031	4,978	3,829	5,166	5,373
SG&A ratio	144.8%	117.3%	130.4%	93.6%	162.1%	128.0%	144.5%	99.8%	182.1%	179.9%
Operating profit	**-2,067**	**-1,700**	**-1,681**	**-1,303**	**-2,552**	**-2,127**	**-3,947**	**-2,656**	**-4,302**	**-4,506**
YoY	-	-	-	-	-	-	-	-	-	-
Operating profit margin	-	-	-	-	-	-	-	-	-	-
Non-operating income	56	7	114	215	17	7	5	2	4	3
Non-operating expenses	85	37	35	22	96	196	34	95	79	112
Recurring profit	**-2,095**	**-1,729**	**-1,601**	**-1,110**	**-2,630**	**-2,317**	**-3,977**	**-2,749**	**-4,377**	**-4,616**
YoY	-	-	-	-	-	-	-	-	-	-
Recurring profit margin	-	-	-	-	-	-	-	-	-	-
Extraordinary gains	-	-	-	2	3	9	17	10	4	529
Extraordinary losses	5	0	-	3	1	1	15	10	-	-
Income taxes	4	4	4	4	4	4	4	4	4	4
Implied tax rate	-	-	-	-	-	-	-	-	-	-
Net income	**-2,105**	**-1,733**	**-1,605**	**-1,116**	**-2,632**	**-2,313**	**-3,978**	**-2,753**	**-4,376**	**-4,090**
YoY	-	-	-	-	-	-	-	-	-	-
Net margin	-	-	-	-	-	-	-	-	-	-

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

See the Earnings Structure section for more information about specific items (from total sales to recurring profit) on the company's income statement. 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.

Historical forecast accuracy

Results vs. Initial Est. (JPYmn)	FY12/11 Par.	FY12/12 Par.	FY12/13 Par.	FY12/14 Par.	FY12/15 Par.	FY12/16 Par.	FY12/17 Par.	FY12/18 Par.	FY12/19 Par.	FY12/20 Par.
Sales (Initial Est.)	1,933	2,338	1,927	1,785	1,785	2,339	2,903	4,201	4,465	3,404
Sales (Results)	1,883	1,955	1,532	1,955	1,933	2,368	3,444	3,836	2,838	2,987
Results vs. Initial Est.	**-2.6%**	**-16.4%**	**-20.5%**	**9.5%**	**8.3%**	**1.2%**	**18.6%**	**-8.7%**	**-36.4%**	**-12.2%**
Operating profit (Initial Est.)	-2,351	-1,625	-1,889	-1,654	-1,654	-2,778	-3,238	-2,981	-3,587	-5,090
Operating profit (Results)	-2,067	-1,700	-1,681	-1,303	-2,552	-2,127	-3,947	-2,656	-4,302	-4,506
Results vs. Initial Est.	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Recurring profit (Initial Est.)	-2,398	-1,652	-1,922	-1,650	-1,650	-2,811	-3,303	-3,044	-3,612	-5,134
Recurring profit (Results)	-2,095	-1,729	-1,601	-1,110	-2,630	-2,317	-3,977	-2,749	-4,377	-4,616
Results vs. Initial Est.	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Net income (Initial Est.)	-2,407	-1,656	-1,926	-1,654	-1,654	-2,815	-3,306	-3,056	-3,612	-4,803
Net income (Results)	-2,105	-1,733	-1,605	-1,116	-2,632	-2,313	-3,978	-2,753	-4,376	-4,090
Results vs. Initial Est.	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**

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)	FY12/11 Par.	FY12/12 Par.	FY12/13 Par.	FY12/14 Par.	FY12/15 Par.	FY12/16 Par.	FY12/17 Par.	FY12/18 Par.	FY12/19 Par.	FY12/20 Par.
ASSETS										
Cash and deposits	4,559	4,540	6,163	5,692	4,261	5,719	2,947	4,821	3,911	3,849
Marketable securities	1,953	300	1,100	899	-	-	-	-	-	-
Accounts receivable	162	148	-	273	301	487	490	412	549	407
Inventories	207	165	125	245	133	273	363	534	1	945
Other current assets	297	268	245	181	131	205	237	271	427	615
Total current assets	**7,178**	**5,421**	**7,634**	**7,290**	**4,827**	**6,685**	**4,037**	**6,038**	**4,887**	**5,815**
Buildings (net)	2	3	2	22	22	31	28	37	47	43
Tools, furniture, and fixtures (net)	15	11	6	27	31	43	18	20	19	34
Total tangible fixed assets	**17**	**14**	**9**	**49**	**53**	**75**	**47**	**57**	**75**	**77**
Total other fixed assets	**48**	**57**	**37**	**49**	**53**	**77**	**100**	**73**	**70**	**81**
Software	10	8	6	62	51	42	66	51	95	296
Other	3	3	2	4	1	-	3	20	146	6
Total intangible fixed assets	**13**	**11**	**8**	**66**	**52**	**42**	**69**	**71**	**241**	**302**
Total fixed assets	**78**	**82**	**53**	**164**	**158**	**193**	**216**	**201**	**386**	**459**
Total assets	**7,256**	**5,502**	**7,687**	**7,454**	**4,984**	**6,878**	**4,252**	**6,239**	**5,274**	**6,275**
LIABILITIES										
Accounts payable	309	330	-	306	320	322	604	726	121	665
Unearned revenue	-	-	-	-	-	-	-	-	-	193
Accounts payable–other	278	196	207	143	184	553	331	504	639	646
Short-term debt	-	-	-	-	-	-	-	-	-	-
Other	59	73	44	39	47	68	76	107	112	111
Total current liabilities	**646**	**599**	**251**	**488**	**551**	**942**	**1,011**	**1,336**	**872**	**1,615**
Long-term debt	-	-	-	-	-	-	-	-	-	-
Corporate bonds					-	450	-	-	-	-
Other fixed liabilities	5	4	3	2	2	1	1	1	2	2
Total fixed liabilities	**5**	**4**	**3**	**2**	**2**	**451**	**1**	**1**	**2**	**2**
Total interest-bearing debt	-	-	-	-	-	-	-	-	-	-
Total liabilities	**651**	**602**	**254**	**490**	**552**	**1,394**	**1,013**	**1,338**	**874**	**1,617**
NET ASSETS										
Capital stock	6,025	6,025	8,059	8,331	8,331	9,948	10,762	12,973	14,871	17,045
Capital surplus	5,995	5,995	8,029	8,301	8,301	9,918	10,732	12,943	14,841	17,019
Retained earnings	-5,413	-7,146	-8,752	-9,868	-12,500	-14,813	-18,791	-21,543	-25,919	-30,010
Treasury stock	-0	-0	-0	-0	-0	-0	-0	-0	-15	-18
Share subscription rights	-	27	97	200	300	431	537	530	621	620
Total net assets	**6,606**	**4,900**	**7,433**	**6,964**	**4,432**	**5,485**	**3,239**	**4,902**	**4,400**	**4,657**
Working capital	61	-17	125	212	114	439	249	220	429	686
Total interest-bearing debt	-	-	-	-	-	-	-	-	-	-
Net debt	-4,559	-4,540	-6,163	-5,692	-4,261	-5,719	-2,947	-4,821	-3,911	-3,849

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 FY12/20, 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, the deficit in retained earnings is expanding as the company continued to post losses.

Cash flow statement

Cash flow statement (JPYmn)	FY12/11 Par.	FY12/12 Par.	FY12/13 Par.	FY12/14 Par.	FY12/15 Par.	FY12/16 Par.	FY12/17 Par.	FY12/18 Par.	FY12/19 Par.	FY12/20 Par.
Cash flows from operating activities (1)	-2,074	-1,659	-1,677	-1,266	-2,272	-1,960	-3,817	-2,325	-4,351	-4,122
Cash flows from investing activities (2)	-117	-411	-1,332	314	1,489	-44	-78	-26	-216	-160
Free cash flow (1+2)	-2,191	-2,069	-3,010	-952	-783	-2,004	-3,894	-2,351	-4,567	-4,283
Cash flows from financing activities	4,611	-1	4,057	544	-3	3,658	1,164	4,272	3,740	4,222
Depreciation and good will amortization (A)	8	9	8	13	24	26	30	35	38	64
Capital expenditures (B)	-12	-3	-	-109	-24	-28	-57	-40	-217	-149
Change in working capital (C)	56	-78	142	86	-98	325	-190	-29	209	257
Simple FCF (NI + A + B - C)	-2,165	-1,650	-1,739	-1,298	-2,534	-2,640	-3,815	-2,729	-4,764	-4,433
Cash and cash equivalents (year-end)	6,311	4,240	5,294	5,092	4,261	5,719	2,947	4,821	3,911	3,849

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

Cash flows from operating activities

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

Cash flows from investing activities

Outlays on the purchase of tangible fixed assets and intangible assets are limited as SymBio outsources 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 reported a series of 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	Abeille Pharmaceuticals licensed SyB D-0701 (granisetron patch) to SymBio Pharmaceuticals for development & commercialization in Japan, China (HK), Taiwan, South Korea and Singapore.
March 2007	License Agreement finalized with Astellas Deutschland GmbH for SyB L-0501 (bendamustine) development & commercialization rights in China (HK), Taiwan, South Korea and Singapore.
August 2008	License Agreement finalized with Eisai Co., Ltd. for co-development and commercialization rights of SyB L-0501 (bendamustine) in Japan.
March 2009	SymBio Pharmaceuticals concluded Sublicense Agreement with Cephalon, Inc. for development and commercialization rights of bendamustine hydrochloride in China (HK).
May 2009	License Agreement finalized with Eisai Co., Ltd. for co-development and commercialization rights of SyB L-0501 (bendamustine) in South Korea and Singapore.
September 2010	SymBio Pharmaceuticals and Eisai launch SYMBENDA® (bendamustine) in Singapore for the treatment of Low-grade Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukemia.
October 2010	Announced NDA Approval of Treakisym® (bendamustine) in Japan.

December 2010	Launched Treakisym® in Japan.
July 2011	Onconova and SymBio Pharmaceuticals 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.
October 2015	Concluded a license agreement with The Medicines Company (US) on exclusive development and marketing rights to Ionsys (transdermal pain management system) in Japan.
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)

News and topics

February 2021

On February 22, 2021, the company announced the results of phase III clinical trial for Treakisym® as a treatment for relapsed or refractory diffuse large B-cell lymphoma.

At the 2021 Annual Meeting of the Japanese Society of Medical Oncology held on February 20, 2021, the company announced results of phase III clinical trial of anticancer agent Treakisym® (generic name: bendamustine hydrochloride) administered in combination with rituximab (BR therapy) in patients with relapsed or refractory diffuse large B-cell lymphoma.

Primary phase III clinical trial results concerning efficacy (38 patients)

- ▷ Response rate (complete and partial response): 76.3%
- ▷ Complete response rate: 47.4%
- ▷ Median overall survival (29.2 months)

On February 4, 2021, the company announced a three-year medium-term plan covering FY12/21–FY12/23.

Medium-term plan targets

(JPYmn)	FY12/21 Est.	FY12/22 Target	FY12/23 Target
Sales	9,151	10,985	12,369
YoY	206.4%	20.0%	12.6%
Operating profit	1,361	1,738	2,099
YoY	-	27.7%	20.8%
Operating profit margin	14.9%	15.8%	17.0%
Recurring profit	1,350	1,727	2,088
YoY	-	27.9%	20.9%
Recurring profit margin	14.8%	15.7%	16.9%
Net income	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.

SG&A expenses

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

- ▷ The company calculated R&D expenses based on the latest development plans for its existing pipeline comprising Treakisym®, rigosertib, and brincidofovir, an antiviral drug.
- ▷ 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 costs due to a higher medical representative headcount and higher costs 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.

January 2021

On January 28, 2021, the company announced that it had entered into a joint research agreement with the University of Tokyo's Institute of Medical Science to explore potential new indications for bendamustine and rigosertib.

The company has entered into a joint research agreement with the Institute of Medical Science, the University of Tokyo (IMSUT), to explore potential new indications for two anticancer agents it has in development: 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.

On January 12, 2021, the company announced the sales launch of the ready-to-dilute (RTD) liquid formulation of Treakisym®.

On the same day, the company began selling its ready-to-dilute (RTD) formulation of Treakisym® intravenous fluid in quantities of 100mg/4mL.

In September 2017, the company concluded an exclusive license agreement with Eagle Pharmaceuticals, Inc. covering both the RTD and rapid infusion (RI) liquid formulations of Treakisym® in Japan. With multiple patent protections obtained using

pharmaceutical licenses for both of these formulations of Treakisym®, the company will be able to extend the life of the product through 2031.

Unlike the lyophilized formulation of Treakisym® that is currently on the market, the RTD formulation eliminates the need for troublesome manual dissolution, reducing the required dissolving time. This advantage provides value-added by reducing burdens placed on medical personnel. Meanwhile, the RI formulation of Treakisym® is currently undergoing clinical trials to determine its safety, and the company plans to apply for its approval in FY12/21.

In the US market, the company has received FDA approval for the RI formulation of its Bendeka® intravenous fluid and is marketing it through Teva Pharmaceutical Industries Ltd. This formulation reduces the required administration time to 10 minutes, lightening burdens placed on patients and medical personnel.

December 2020

On December 22, 2020, the company announced the conclusion of a syndicated loan agreement.

The company entered into a syndicated loan (committed credit line) agreement with a view to building a stable and agile fundraising structure to undergird business expansion.

Overview of the syndicated loan agreement

- Credit line amount: JPY3.0bn
- Date of agreement: December 22, 2020
- Commitment period: December 25, 2020 to June 24, 2022
- Use of funds: Working capital
- Interest rate: Base rate + spread
- Security: Unsecured
- Arranger and agent: MUFG Bank, Ltd.
- Participating financial institutions: MUFG Bank, Ltd., The Bank of Yokohama, Ltd.

On December 10, 2020, the company announced that it began in-house sales of the anticancer drug Treakisym®.

With the expiration of its business alliance agreement with Eisai Co., Ltd. regarding the anticancer drug Treakisym® on December 9, 2020, the company began selling the drug in Japan through its own sales organization from December 10.

SymBio allocated a total of 62 medical representatives and others with expert knowledge and extensive sales experience in hematology to major regions nationwide, and established the Regulatory Affairs & Quality Assurance Division to enhance stable supply of the product and quality assurance. Further, the company built a nationwide distribution system with Suzuken Group and Kyoso Mirai Group as its sole distributors. It has two logistics centers, one in Eastern and the other in Western Japan, and in collaboration with S.D. Collabo Co., Ltd., the company said it has established an optimal nationwide distribution and logistics system.

September 2020

On September 23, 2020, the company announced the acquisition of approval for the RTD formulation of Treakisym®.

The company has obtained approval for manufacturing and marketing the ready-to-dilute (RTD) liquid formulation of Treakisym®.

In September 2017, the company entered into an exclusive licensing agreement in Japan with Eagle Pharmaceuticals, Inc. for Treakisym® liquid formulations (RTD and RI formulations), extending the product life of Treakisym® under patent protection to 2031. Compared to lyophilized Treakisym® (FD formulation), liquid Treakisym® (RTD and RI formulations) does not require any

complex and time-consuming manual reconstitution. This substantially reduces the burden on patients and healthcare professionals, providing significant value added. The company plans to start selling the RTD formulation in January 2021.

On September 17, 2020, the company announced revisions to its earnings forecast and medium-term plan.

Revisions to earnings forecast

Revised full-year FY12/20 forecast

- ▷ Sales: JPY3.0bn (previous forecast: JPY3.4bn)
- ▷ Operating loss: JPY4.6bn (JPY5.1bn)
- ▷ Recurring loss: JPY4.7bn (JPY5.1bn)
- ▷ Net loss: JPY3.8bn (JPY4.8bn)
- ▷ Loss per share: JPY116.16 (JPY146.98)

Reasoning behind revisions

With regard to sales in FY12/20, the outlook for the business environment is becoming more uncertain due to the impact from the novel coronavirus pandemic, and while the company forecasts sales to grow YoY over the full-year, it has downgraded its initial forecast in consideration of 1H results (sales fell 32.1% YoY to JPY1.4bn). In 2H, SymBio forecasts sales to increase from JPY1.4bn in 1H to JPY1.7bn, mainly because demand tends to be stronger in 2H than in 1H in the domestic market for Treakisym®, and because planned overseas sales in 2H are expected to push up sales.

SymBio is prioritizing necessary investments for the planned FY12/20 launch of its in-house sales structure, for achieving profitability in FY12/21, and for making preparations for the planned launch of global phase II trials of brincidofovir in 1H FY12/21. Otherwise, it plans to rein in spending by reviewing all other expenses. In this way, it plans to significantly reduce SG&A expenses so as to minimize the impact from lower sales, and it has revised its forecast for operating profit (loss) in order to reflect this.

SymBio has also revised its net income (loss) forecast to reflect the arbitration judgment announced in September 2020 for The Medicines Company to pay SymBio USD5.0bn.

Revisions to the medium-term plan

SymBio has also revised its FY12/20 targets in its medium-term plan for the three years from FY12/20 to FY12/22 in accordance with the above revisions to its earnings forecast. It is currently assessing the impact on FY12/21 and FY12/22.

On September 9, 2020, the company announced progress (LPLV) in clinical study of Treakisym® rapid infusion (RI) liquid formulation.

In the clinical trial of Treakisym® RI liquid formulation (infusion time: 10 minutes) with the primary endpoint of confirming safety, the company completed observation periods for all patients (last patient last visit, or LPLV) after it enrolled the target number of patients.

The company completed filing for approval of the ready-to-dilute (RTD) formulation of the drug in Q3 FY12/19, and is making preparations with the aim of launching the product in Q1 FY12/21. For the RI formulation, the company plans to apply for approval upon completion of the clinical trial, with the approval expected to be granted in 2H FY12/22.

On September 7, 2020, the company announced the transfer of the sale of Treakisym® to an in-house organization.

The business alliance agreement that the company entered into in August 2008 with Eisai Co., Ltd., granting the latter exclusive marketing rights to bendamustine (Treakisym® 100mg and 25mg vials for intravenous infusion), will expire on December 9, 2020.

As part of its preparations for transfer of the sales of anticancer drug Treakisym® in Japan to its in-house organization, the company has begun preparations with Eisai for the inheritance of this business.

In addition, the company has entered into agreements in regard to the sale and purchase of Treakisym® with Suzuken Co., Ltd. (hereafter "Suzuken Group"), and Toho Pharmaceutical Co., Ltd. (a consolidated subsidiary of Toho Holdings Co., Ltd., hereafter "Kyoso Mirai Group") as part of the preparations to build its own distribution and logistics system.

Establishment of the sales organization

The company has already completed the assignment of 51 sales representatives across Japan, and will begin to distribute relevant information from this point onward, in cooperation with Eisai. At the same time, the company will newly designate highly specialized hematology experts responsible for the development and implementation of plans meeting the needs of each region.

Establishment of the distribution and logistics system

The two aforementioned companies (Suzuken Group and Kyoso Mirai Group) will serve as the sole nationwide agents. Two distribution centers, located in Eastern and Western Japan, will commence operations under the management of Suzuken Group subsidiary S.D. Collabo Co., Ltd.

On September 1, 2020, the company announced that a resolution had been reached in its arbitration against The Medicines Company, from which the company had in-licensed the patient-controlled pain management drug SyB P-1501.

The arbitral tribunal constituted under the rules of the International Chamber of Commerce (ICC) reached a final decision with respect to the company's arbitration against The Medicines Company (MDCO).

The arbitral tribunal dismissed the company's claim for damages, dismissing the company's claim that MDCO had failed to provide adequate assurances of its performance under the license agreement. However, the arbitral tribunal determined that MDCO is to pay the company USD4.95mn corresponding to 50% of the company's legal fees and expenses. The arbitral tribunal also dismissed MDCO's counterclaim.

In terms of future outlook, the company states that it will undertake a thorough examination of the impact of the final decision of the arbitration on FY12/20 company forecasts.

August 2020

On August 25, 2020, the company announced that Onconova Therapeutics, Inc. had released topline results of its phase III INSPIRE trial targeting patients with higher-risk myelodysplastic syndromes (HR-MDS).

On August 24, 2020, Onconova, the licensor for rigosertib, an anticancer agent the company is developing, announced the results of its phase III (INSPIRE) trial assessing the safety and efficacy of intravenous injection of rigosertib in patients with higher-risk myelodysplastic syndromes (HR-MDS). Compared with physician's choice (PC) treatment, it did not meet its primary endpoint.

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 INSPIRE 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. Onconova is conducting further analysis.

Safety analysis indicates that IV rigosertib was generally well tolerated, with reported adverse events similar to those observed in previous clinical studies with IV rigosertib in MDS patients. Serious adverse events were relatively uncommon, with a similar profile of SAEs in both study arms.

On August 5, 2020, the company announced the arbitration judgment in proceedings against The Medicines Company, the licensor of SyB P-1501, a patient-controlled post-operative analgesia.

The company received the arbitration judgment against The Medicines Company (MDCO) on July 23, 2020. On October 11, 2017, the company initiated arbitration against MDCO, under the rules of the International Chamber of Commerce, seeking damages of USD82mn arising from a material breach of the license agreement by MDCO. A judgment was issued on July 21 and received by the company through lawyers on July 23.

Summary of arbitration judgment

The Court of Arbitration did not award damages sought by the company, but ordered MDCO to pay 50% of all arbitration costs as sought by the company. Counterclaims and claims for costs by MDCO were rejected. The above costs are under close examination and expected to take several weeks to finalize.

July 2020

On July 13, 2020, the company announced that it had applied for a partial change to the approved matters of Treakisym® for use in combination with polatuzumab vedotin and rituximab to treat relapsed or refractory diffuse large B-cell lymphoma.

The company applied for a partial change to the approved matters of its anticancer drug Treakisym® (generic name: bendamustine hydrochloride) for use in combination with polatuzumab vedotin and rituximab to treat relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL).

Major shareholders

Top shareholders	Shares held	Shareholding ratio
Kyoichi Kageyama	1,020,000	2.7%
Fuminori Yoshida	900,000	2.4%
SBI Securities Co., Ltd.	744,310	1.9%
Cephalon, Inc.	647,250	1.7%
Arata Takahashi	534,000	1.4%
Norihiro Kuroda	447,500	1.2%
Matsui Securities Co., Ltd.	310,600	0.8%
Fumishige Ehira	270,200	0.7%
Hitochi Imamura	239,300	0.6%
Eisai Co., Ltd.	208,350	0.5%
SUM	5,321,510	13.9%

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 127 employees as of December 31, 2020.

Employees	FY12/11 Par.	FY12/12 Par.	FY12/13 Par.	FY12/14 Par.	FY12/15 Par.	FY12/16 Par.	FY12/17 Par.	FY12/18 Par.	FY12/19 Par.	FY12/20 Par.
No. of employees	71	76	72	69	74	77	78	90	107	127
YoY change	15	5	-4	-3	5	3	1	12	17	20

Source: Shared Research based on company data

Other

Overview of clinical trials

Development of a new drug takes between 10 and 17 years

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

Ordinary process and periods of developing new drugs

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

Source: Shared Research based on company data

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

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

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

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

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

Ethnic factors in the acceptability of foreign clinical data

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

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

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

Glossary

Antigen

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

Bridging Data

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

Chronic Lymphocytic Leukemia (CLL)

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

Contract Research Organization (CRO)

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

Dose-Responsiveness

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

First-line Drug

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

Immunoglobulin G (IgG)

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

Mantle-Cell Lymphoma (MCL)

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

Monoclonal Antibody

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

Multikinase Inhibitor

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

Myelodysplastic Syndromes

Myelodysplastic Syndrome leads to abnormalities in hematopoietic stem cells that produce blood cells, resulting in a lack of blood. Blood cells produced this way are abnormally shaped. This change in the cells is called dysplasia. The disease typically

leads to frequent anemia with some patients dying from infection or bleeding due to the reduction in blood cells. The disease is most common among the elderly. 10 to 20% of MDS patients progress to acute leukemia.

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

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

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

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

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

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

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

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

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

Company name

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

Company profile

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

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

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AVANT CORPORATION
Axell Corporation
Azbil Corporation
AZIA CO., LTD.
AZoom, Co., Ltd.
Base Co., Ltd
BEENOS Inc.
Bell-Park Co., Ltd.
Benefit One Inc.
B-lot Co.,Ltd.
Broadleaf Co., Ltd.
CanBas Co., Ltd.
Canon Marketing Japan Inc.
Career Design Center Co., Ltd.
Carna Biosciences, Inc.
CARTA HOLDINGS, INC
CERES INC.
Chiyoda Co., Ltd.
Chori Co., Ltd.
Chugoku Marine Paints, Ltd.
cocokara fine Inc.
COMSYS Holdings Corporation
COTA CO.,LTD.
CRE, Inc.
CREEK & RIVER Co., Ltd.
Daiichi Kigenso Kagaku Kogyo Co., Ltd.
Daiki Axis Co.,Ltd.
Daiseki Co., Ltd.
Daiwabo Holdings Co.,Ltd.
Demae-Can CO., LTD
DIC Corporation
Digital Arts Inc.
Digital Garage Inc.
Doshisha Corporation
Dream Incubator Inc.
Earth Corporation
Edion Corporation
Elecom Co., Ltd.
en Japan Inc.
Estore Corporation.
euglena Co., Ltd.
FaithNetwork Co., Ltd.
Ferrotec Holdings Corporation
FIELDS CORPORATION
Financial Products Group Co., Ltd.
First Brothers Col, Ltd.
FreeBit Co., Ltd.
Gamecard-Joyco Holdings, Inc.
GameWith, Inc.
GCA Corporation
Good Com Asset Co., Ltd.
Grandy House Corporation
GiG Works Inc.
Hakuto Co., Ltd.
Hamee Corp.
Happinet Corporation
Harmonic Drive Systems Inc.
HENNGE K.K.
Hosokawa Micron Corporation
Hope, Inc.
HOUSEDO Co., Ltd.
H2O Retailing Corporation
IDOM Inc.
IGNIS LTD.
i-mobile Co.,Ltd.
Inabata & Co., Ltd.
Infocom Corporation
Infomart Corporation
Intelligent Wave, Inc.
ipet Insurance CO., Ltd.
Itochu Enex Co., Ltd.
ItoKuro Inc.
JAFCO Co.,Ltd.
JMDC Inc.
JSB Co., Ltd.
JTEC Corporation
J Trust Co., Ltd
Japan Best Rescue System Co., Ltd.
JINS HOLDINGS Inc.
JP-HOLDINGS, INC.
KAMEDA SEIKA CO., LTD.
Kanamic Network Co.,LTD
KANEMATSU CORPORATION
kaonavi, inc.
KFC Holdings Japan, Ltd.
KI-Star Real Estate Co., Ltd.
KLab Inc.
Kondotec Inc.
Kumiai Chemical Industry Co., Ltd.
Lasertec Corporation
Locondo, Inc.
LUCKLAND CO., LTD.
Marumae Co., Ltd.
MATSUI SECURITIES CO., LTD.
Media Do Co., Ltd.
Medical System Network Co., Ltd.
MEDINET Co., Ltd.
MedPeer,Inc.
Mercuria Investment Co., Ltd.
Metaps Inc.
Micronics Japan Co., Ltd.
MIRAIT Holdings Corporation
Monex Goup Inc.
MORINAGA MILK INDUSTRY CO., LTD.
Mortgage Service Japan Limited.
MRT Inc.
NAGASE & CO., LTD
NAIGAI TRANS LINE LTD.
NanoCarrier Co., Ltd.
Net Marketing Co., Ltd.
Net One Systems Co.,Ltd.
Nichi-Iko Pharmaceutical Co., Ltd.
NIHON CHOUZAI Co.,Ltd.
Nihon Denkei Co., Ltd.
Nippon Commercial Development Co., Ltd.
Nippon Koei Co., Ltd.
NIPPON PARKING DEVELOPMENT Co., Ltd.
NIPRO CORPORATION
Nisshinbo Holdings Inc.
Nisso Corporation
NS TOOL CO., LTD.
OLBA HEALTHCARE HOLDINGS,Inc.
OHIZUMI MFG. CO., LTD.
Oisix ra daichi Inc.
Oki Electric Industry Co., Ltd
ONO SOKKI Co., Ltd.
ONWARD HOLDINGS CO.,LTD.
Pan Pacific International Holdings Corporation
PARIS MIKI HOLDINGS Inc.
PCA CORPORATION
PIGEON CORPORATION
P3, inc.
QB Net Holdings Co., Ltd.
RACCOON HOLDINGS, Inc.
Raysum Co., Ltd.
RESORTTRUST, INC.
ROUND ONE Corporation
RYOHIN KEIKAKU CO., LTD.
SanBio Company Limited
SANIX INCORPORATED
Sanrio Company, Ltd.
SATO HOLDINGS CORPORATION
SBS Holdings, Inc.
Seikagaku Corporation
Seria Co.,Ltd.
Serverworks Co.,Ltd.
SHIFT Inc.
Shikigaku Co., Ltd
SHIP HEALTHCARE HOLDINGS, INC.
SIGMAXYZ Inc.
SMS Co., Ltd.
Snow Peak, Inc.
Solasia Pharma K.K.
SOURCENEXT Corporation
Space Value Holdings CO., LTD
Star Mica Holdings Co., Ltd.
Strike Co., Ltd.
Sunnexta Group Inc.
SymBio Pharmaceuticals Limited
Synchro Food Co., Ltd.
TAIYO HOLDINGS CO., LTD.
Takashimaya Company, Limited
Take and Give Needs Co., Ltd.
TEAR Corporation
Tenpo Innovation Inc.
3-D Matrix, Ltd.
The Hokkoku Bank,Ltd.
TKC Corporation
TKP Corporation
Tsuzuki Denki Co., Ltd.
TOCALO Co., Ltd.
TOKAI Holdings Corporation
Tokyu Construction Co., Ltd.
TOYOBO CO., LTD.
Toyo Ink SC Holdings Co., Ltd
Toyo Tanso Co., Ltd.
Tri-Stage Inc.
TSURUHA Holdings
VISION INC.
VISIONARY HOLDINGS CO., LTD.
V-cube,Inc.
World Holdings Co., Ltd.
YELLOW HAT LTD.
YOSHINOYA HOLDINGS CO., LTD.
ZAPPALLAS, INC.

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

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