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4582

SymBio Pharmaceuticals

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INDEX

Executive summary

SymBio in-licenses drugs for development and sale

SymBio Pharmaceuticals Ltd. is a specialty pharmaceutical company that acquires development and marketing rights to drug candidates for rare diseases. The main target areas are cancer, blood disorders, and multiple viral infections. The company primarily acquires rights from European and US biotech and pharmaceutical companies. Once the company secures these rights, it conducts clinical trials to obtain manufacturing and sales rights, aiming to generate revenues from product sales.

The company does not conduct basic research but instead focuses on developing novel drug candidates that have already undergone basic research in humans and have established proof of concept (POC). In addition to sourcing potential drug candidates through independent information gathering conducted by internal experts, the company holds a Scientific Advisory Board (SAB) meeting three times a year to evaluate and select candidates with a high probability of approval. The company is also pursuing a lab-less strategy to increase cost efficiency, focusing on unmet medical needs to increase profitability, and seeking to expand revenue opportunities through a global expansion strategy.

Normally, drug development takes 10–17 years from basic research to manufacturing and approval for sale. However, the company obtained domestic manufacturing and sales approval for its first development product, Treakisym®, within five years of in-licensing, and gained a market share of over 50% three years after its launch.

The company had obtained approval for and launched Treakisym® (anticancer agent for hematologic malignancies) for the indications of relapsed or refractory low-grade non-Hodgkin's lymphoma (NHL) and mantle cell lymphoma (MCL), untreated (first-line treatment) low-grade NHL and MCL, chronic lymphocytic leukemia (CLL), and relapsed or refractory diffuse large B-cell lymphoma (DLBCL). Treakisym® is listed in the Practical Guidelines for Hematological Malignancies 2018 edited and published by Japanese Society of Hematology as the standard treatment for relapsed or refractory low-grade B-cell NHL, MCL, and CLL, and as first-line treatment for low-grade NHL.

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

Drugs in the development pipeline include rigosertib (anticancer agent for myelodysplastic syndromes) IV and oral formulations, and antiviral drug brincidofovir (BCV). All planned development for Treakisym® has been completed and management is shifting development resources to BCV, which has potential to treat various diseases. In May 2023, the company successfully established the human proof of concept (POC) in the Phase II clinical trial of BCV targeting adenovirus (AdV) infections.

Earnings

In FY12/23, SymBio reported sales of JPY5.6bn (-44.1% YoY), an operating loss of JPY812mn (compared to an operating profit of JPY2.0bn in the previous year), a recurring loss of JPY736mn (compared to a recurring profit of JPY2.0bn), and a net loss attributable to owners of the parent of JPY2.0bn (compared to a net income of JPY1.2bn). Sales declined as the impact of generic sales of Treakisym® (bendamustine) became apparent. In addition, the ongoing impact of the COVID-19 pandemic in the oncology sector led to reduced overall use of bendamustine, including its generics.

The company's forecast for FY12/24 calls for sales of JPY3.6bn (-34.9% YoY), an operating loss of JPY2.8bn (compared to an operating loss of JPY812mn in the previous year), a recurring loss of JPY2.9bn (compared to a recurring loss of JPY736mn), and a net loss attributable to owners of the parent of JPY2.9bn (compared to a net loss of JPY2.0bn). SymBio expects sales to decline due to a substantial cut in the price of Treakisym® and the impact of sales of generic drugs. The company also anticipates an increase in R&D expenses as it progresses with the global development of the antiviral drug BCV.

The medium-term plan unveiled in February 2020 forecasted FY12/23 sales to reach JPY12.4bn. However, actual results did not meet these projections, primarily due to the commercialization of generic Treakisym® by two companies, which occurred despite SymBio's patent infringement warnings. As of February 2024, the company has yet to announce a new medium-term management plan.

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 of the company include its dependence on a single individual and product (see Strengths and weaknesses).

Key financial data

	FY12/14	FY12/15	FY12/16	FY12/17	FY12/18	FY12/19	FY12/20	FY12/21	FY12/22	FY12/23	FY12/24
(JPYmn)	Parent	Parent	Parent	Parent	Parent	Parent	Parent	Parent	Cons.	Cons.	Company forecast
Sales	**1,955**	**1,933**	**2,368**	**3,444**	**3,836**	**2,838**	**2,987**	**8,257**	**10,008**	**5,590**	**3,641**
YoY	27.6%	-1.1%	22.5%	45.4%	11.4%	-26.0%	5.3%	176.4%	21.2%	-44.1%	-34.9%
Gross profit	**527**	**583**	**904**	**1,031**	**1,173**	**865**	**867**	**5,800**	**7,600**	**4,411**	
YoY	65.6%	10.7%	55.1%	14.1%	13.7%	-26.3%	0.2%	569.1%	31.0%	-42.0%	
Gross profit margin	26.9%	30.2%	38.2%	29.9%	30.6%	30.5%	29.0%	70.2%	75.9%	78.9%	
Operating profit	**-1,303**	**-2,552**	**-2,127**	**-3,947**	**-2,656**	**-4,302**	**-4,506**	**1,016**	**1,964**	**-812**	**-2,837**
YoY	-	-	-	-	-	-	-	-	93.3%	-	-
Operating profit margin	-	-	-	-	-	-	-	12.3%	19.6%	-	-
Recurring profit	**-1,110**	**-2,630**	**-2,317**	**-3,977**	**-2,749**	**-4,377**	**-4,616**	**1,001**	**2,000**	**-736**	**-2,867**
YoY	-	-	-	-	-	-	-	-	99.8%	-	-
Recurring profit margin	-	-	-	-	-	-	-	12.1%	20.0%	-	-
Net income	**-1,116**	**-2,632**	**-2,313**	**-3,978**	**-2,753**	**-4,376**	**-4,090**	**2,032**	**1,179**	**-1,963**	**-2,870**
YoY	-	-	-	-	-	-	-	-	-42.0%	-	-
Net margin	-	-	-	-	-	-	-	24.6%	11.8%	-	-
Per-share data (split-adjusted; JPY)											
Shares issued at year-end (000 shares)	30,634	32,391	46,531	54,049	20,560	26,438	38,203	38,457	39,604	42,278	
EPS (JPY)	-145.0	-325.0	-235.3	-319.1	-165.5	-189.0	-124.1	53.0	30.2	-49.2	-71.9
EPS (fully diluted)	-	-	-	-	-	-	-	52.3	29.8	-	-
Dividend per share (JPY)	-	-	-	-	-	-	-	-	-	-	
Book value per share (JPY)	835.2	510.2	434.4	200.0	212.2	143.1	105.8	162.3	204.8	164.3	
Balance sheet (JPYmn)											
Cash and cash equivalents	6,591	4,261	5,719	2,947	4,821	3,911	3,849	3,860	6,283	6,517	
Total current assets	**7,290**	**4,827**	**6,685**	**4,037**	**6,038**	**4,887**	**5,815**	**6,748**	**9,313**	**8,083**	
Tangible fixed assets	49	53	75	47	57	75	77	84	69	-	
Investments and other assets	49	53	77	100	73	70	81	1,362	829	88	
Intangible assets	66	52	42	69	71	241	302	259	222	-	
Total assets	**7,454**	**4,984**	**6,878**	**4,252**	**6,239**	**5,274**	**6,275**	**8,453**	**10,433**	**8,170**	
Accounts payable	306	320	322	604	726	121	665	70	47	-	
Short-term debt	-	-	-	-	-	-	-	-	-	-	
Total current liabilities	**488**	**551**	**942**	**1,011**	**1,336**	**872**	**1,615**	**1,518**	**1,924**	**957**	
Long-term debt	-	-	-	-	-	-	-	-	-	-	
Total fixed liabilities	**2**	**2**	**451**	**1**	**1**	**2**	**2**	**189**	**3**	**4**	
Total liabilities	**490**	**552**	**1,394**	**1,013**	**1,338**	**874**	**1,617**	**1,707**	**1,927**	**960**	
Net assets	**6,964**	**4,432**	**5,485**	**3,239**	**4,902**	**4,400**	**4,657**	**6,746**	**8,506**	**7,210**	
Total interest-bearing debt	-	-	-	-	-	-	-	-	-	-	
Cash flow statement (JPYmn)											
Cash flows from operating activities	-1,266	-2,272	-1,960	-3,817	-2,325	-4,351	-4,122	140	1,614	-195	
Cash flows from investing activities	314	1,489	-44	-78	-26	-216	-160	-71	-47	-377	
Cash flows from financing activities	544	-3	3,658	1,164	4,272	3,740	4,222	-72	628	680	
Financial ratios											
ROA (RP-based)	-14.7%	-42.3%	-39.1%	-71.5%	-52.4%	-76.0%	-79.9%	13.6%	21.2%	-7.9%	
ROE	-15.8%	-48.3%	-50.4%	-102.6%	-77.8%	-107.4%	-104.7%	39.6%	16.5%	-26.1%	
Equity ratio	93.4%	88.9%	79.7%	76.2%	78.6%	83.4%	74.2%	79.8%	81.5%	88.2%	

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.

Note: The company moved to consolidated reporting from FY12/22 as SymBio Pharma USA, Inc. started operations. Figures for FY12/22 are consolidated, and YoY figures are provided for reference purposes only.

Recent updates

BCV selected for oral session at EBMT Annual Meeting

2024-02-14

SymBio Pharmaceuticals Limited announced that an abstract demonstrating the anti-adenovirus (AdV) effects of brincidofovir (BCV) has been selected for an oral session at the Annual Meeting of the European Society for Blood and Marrow Transplantation (EBMT).

The 50th Annual Meeting of the EBMT, where this presentation is scheduled, will be held in Glasgow, UK, in April 2024. This marks the third oral presentation at a prominent conference about the antiviral activity of BCV against AdV infection.

Additional brincidofovir Phase IIa data to be presented at 2024 Tandem Meetings in US

2024-01-23

SymBio Pharmaceuticals Limited announced that its antiviral drug under development, brincidofovir (BCV), has been selected as a presentation topic for the Pediatric Best Abstracts session at the 2024 Tandem Meetings in the US.

This event, jointly hosted by the American Society for Transplantation and Cellular Therapy (ASTCT) and the Center for International Blood and Marrow Transplant Research (CIBMTR), is scheduled for February 2024. The presentation will build on the content shared at a previous academic conference in December 2023, introducing new findings on BCV's effectiveness against adenovirus (AdV) in stool samples.

Because adenovirus (AdV) in stool samples often tests positive before the onset of AdV viremia in children, it is monitored internationally as an early indicator of the infection. The upcoming presentation will include the following new content:

- A dose-dependent reduction of AdV in stool samples was observed, with levels falling below the detection threshold in PCR tests.
- Intravenous BCV demonstrated a dose-dependent effect in lowering AdV quantities in the blood. Short-term treatment effectively cleared AdV from both blood and stool samples, indicating a prolonged anti-AdV effect.

SymBio granted patent in Japan for use of BCV to treat ADV infections

2024-01-19

SymBio Pharmaceutical Limited announced that it has obtained a patent in Japan covering the use of brincidofovir (BCV) injection as a treatment for adenovirus (AdV) infections.

The company has successfully registered a use patent for BCV injection as a treatment for AdV infections in Japan. The details of the patent are as follows:

- Drug covered by the patent: BCV liquid formulation
- Indication: Infectious diseases caused by AdV infection
- Dosage and administration: Administer a fixed amount of BCV liquid formulation intravenously at regular intervals, based on the patient's weight. Continue administration for a specified period and discontinue according to the discontinuation criteria.

The company plans to proceed with filing patent applications for the same drug and indication in Europe, the US, and other regions.

Results from a Phase II clinical trial of brincidofovir (BCV) for adenovirus (AdV) infection

2023-12-11

SymBio Pharmaceuticals Limited announced results from a Phase II clinical trial of brincidofovir (BCV) for adenovirus (AdV) infection.

The results of a Phase IIa clinical trial of BCV in patients with AdV infection were presented at the 65th American Society of Hematology Annual Meeting and Exposition in San Diego, US, in December 2023.

In this study, 27 immunocompromised patients with AdV infection received intravenous (IV) BCV twice a week. In the group receiving 0.4mg/kg IV BCV twice a week (Cohort 3), AdV clearance was confirmed in 100% of patients, and 90% of these patients achieved viral clearance within four weeks of treatment. No serious adverse events were observed.

Based on the data from this trial, the company plans to consider a Phase III trial for BCV.

Revision of FY12/23 earnings forecast

2023-11-14

SymBio Pharmaceuticals Limited announced a revision to its full-year earnings forecast for FY12/23.

Revision of full-year earnings forecast for FY12/23

In November 2023, the company announced a revision to its full-year company forecast for FY12/23. The revised company forecast is as follows:

- Sales: JPY5.6bn (previous forecast: JPY6.5bn)
- Operating loss: JPY680mn (previous forecast: operating loss of JPY331mn)
- Recurring loss: JPY549mn (previous forecast: recurring loss of JPY219mn)
- Net loss attributable to owners of the parent: JPY1.3bn (previous forecast: net loss of JPY370mn)

Reasons for revision

- In comparison to the previous forecast, the company has downwardly revised its sales forecast by JPY874mn to JPY5.6bn. Although the impact of bendamustine generics generally met the company's expectations, the decline in drug usage per case of malignant lymphoma treatment, coupled with treatment delays, persisted due to the influence of seasonal flu and COVID-19.

- The company has revised its operating loss forecast to a loss of JPY680mn, a decrease of JPY349mn from the previous forecast. While prioritizing R&D investments for the global development of brincidofovir (BCV), the company has been reviewing expenses to reduce SG&A expenses. However, this was not sufficient to compensate for the decrease in sales. The company has also revised its recurring loss forecast to JPY549mn, a decrease of JPY330mn from the previous forecast, despite forex valuation gains on foreign currency-denominated assets.

- As a result of evaluating the recoverability of deferred tax assets in the future, the company has decided to reverse JPY642mn of deferred tax assets and record deferred income taxes at the end of FY12/23. As a result, the company has reduced its forecast for net loss attributable to owners of the parent by JPY921mn from the previous forecast to JPY1.3bn.

Trends and outlook

Quarterly trends and results

Earnings (cumulative)	FY12/22				FY12/23				FY12/23	
(JPYmn)	Q1	Q1-Q2	Q1-Q3	Q1-Q4	Q1	Q1-Q2	Q1-Q3	Q1-Q4	% of forecast	FY forecast
Sales	2,316	4,874	7,356	10,008	1,545	3,179	4,421	5,590	99.8%	5,603
YoY	63.1%	54.9%	32.5%	21.2%	-33.3%	-34.8%	-39.9%	-44.1%		-44.0%
Gross profit	1,898	4,010	5,467	7,600	1,243	2,473	3,476	4,411		
YoY	87.9%	76.3%	35.1%	31.0%	-34.5%	-38.3%	-36.4%	-42.0%		
Gross profit margin	82.0%	82.3%	74.3%	75.9%	80.5%	77.8%	78.6%	78.9%		
SG&A expenses	1,389	2,638	3,878	5,636	1,192	2,523	3,759	5,223		
YoY	13.8%	6.8%	7.1%	17.8%	-14.2%	-4.4%	-3.1%	-7.3%		
SG&A ratio	60.0%	54.1%	52.7%	56.3%	77.2%	79.4%	85.0%	93.4%		
Operating profit	509	1,372	1,589	1,964	51	-50	-283	-812	-	-680
YoY	-	-	274.5%	93.3%	-89.9%	-	-	-		-
Operating profit margin	22.0%	28.2%	21.6%	19.6%	3.3%	-	-	-		-
Recurring profit	479	1,447	1,843	2,000	48	67	-156	-736	-	-549
YoY	-	-	344.8%	99.8%	-89.9%	-95.4%	-	-		-
Recurring profit margin	20.7%	29.7%	25.1%	20.0%	3.1%	2.1%	-	-		-
Net income	163	1,108	1,556	1,179	4	-80	-789	-1,963	-	-1,291
YoY	-	-	378.9%	-42.0%	-97.3%	-	-	-		-
Net margin	7.0%	22.7%	21.2%	11.8%	0.3%	-	-	-		-
Earnings (quarterly)	**FY12/22**				**FY12/23**					
(JPYmn)	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**		
Sales	2,316	2,558	2,482	2,653	1,545	1,634	1,242	1,169		
YoY	63.1%	48.2%	3.1%	-1.9%	-33.3%	-36.1%	-49.9%	-55.9%		
Gross profit	1,898	2,112	1,456	2,133	1,243	1,230	1,003	935		
YoY	87.9%	67.0%	-17.8%	21.6%	-34.5%	-41.8%	-31.1%	-56.2%		
Gross profit margin	82.0%	82.6%	58.7%	80.4%	80.5%	75.3%	80.7%	80.0%		
SG&A expenses	1,389	1,249	1,240	1,759	1,192	1,331	1,237	1,463		
YoY	13.8%	0.0%	7.6%	51.3%	-14.2%	6.5%	-0.3%	-16.8%		
SG&A ratio	60.0%	48.8%	50.0%	66.3%	77.2%	81.5%	99.5%	125.2%		
Operating profit	509	863	216	375	51	-101	-233	-528		
YoY	-	-	-65.0%	-36.7%	-89.9%	-	-	-		
Operating profit margin	22.0%	33.8%	8.7%	14.1%	3.3%	-	-	-		
Recurring profit	479	969	396	156	48	19	-223	-580		
YoY	-	-	-35.9%	-73.3%	-89.9%	-	-	-		
Recurring profit margin	20.7%	37.9%	16.0%	5.9%	3.1%	1.1%	-	-		
Net income	163	945	448	-377	4	-84	-709	-1,174		
YoY	-	-	-15.6%	-	-97.3%	-	-	-		
Net margin	7.0%	36.9%	18.0%	-	0.3%	-	-	-		

Source: Shared Research based on company data

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

Note: "-" denotes YoY change of over 1,000%.

Note: Starting from FY12/22, the company switched to preparing consolidated financial statements in connection with the commencement of full- fledged operations at SymBio Pharma USA. As data for FY12/22 are on a consolidated basis, YoY comparisons are for reference only.

Breakdown of SG&A expenses

Earnings (cumulative)	FY12/22				FY12/23			
(JPYmn)	Q1	Q1-Q2	Q1-Q3	Q1-Q4	Q1	Q1-Q2	Q1-Q3	Q1-Q4
SG&A expenses	1,389	2,638	3,878	5,636	1,192	2,523	3,759	5,223
YoY	13.8%	6.8%	7.1%	17.8%	-14.2%	-4.4%	-3.1%	-7.3%
R&D expenses	496	1,009	1,564	2,555	550	1,204	1,824	2,638
YoY	4.8%	10.6%	21.6%	47.2%	10.8%	19.3%	16.6%	3.3%
SG&A expenses excl. R&D	893	1,629	2,314	3,081	642	1,319	1,936	2,584
YoY	19.5%	4.6%	-0.9%	1.1%	-28.1%	-19.0%	-16.4%	-16.1%
Earnings (quarterly)	**FY12/22**				**FY12/23**			
(JPYmn)	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**
SG&A expenses	1,389	1,249	1,240	1,759	1,192	1,331	1,237	1,463
YoY	13.8%	0.0%	7.6%	51.3%	-14.2%	6.5%	-0.3%	-16.8%
R&D expenses	496	513	554	991	550	654	620	815
YoY	4.8%	16.9%	48.2%	120.3%	10.8%	27.4%	11.8%	-17.8%
SG&A expenses excl. R&D	893	736	686	767	642	677	617	649
YoY	19.5%	-9.2%	-11.9%	7.7%	-28.1%	-8.0%	-10.0%	-15.5%

Source: Shared Research based on company data

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

Full-year FY12/23 results (out February 8, 2024)

- Sales: JPY5.6bn (-44.1% YoY)
- Operating loss: JPY812mn (compared to an operating profit of JPY2.0bn in the previous year)
- Recurring loss: JPY736mn (compared to a recurring profit of JPY2.0bn)
- Net loss attributable to owners of the parent: JPY2.0bn (compared to a net income of JPY1.2bn)

In February 2022, SymBio obtained approval for a partial change to the marketing authorization for the ready-to-dilute (RTD) intravenous formulation of TREAKISYM® 100mg/4ml, which was launched in January 2021, to add rapid infusion (RI) administration. Compared to the freeze-dried (FD) formulation, the RTD formulation reduces the time required for the

complicated dissolution process. RI administration further benefits both patients and healthcare providers by reducing the infusion time from the 60 minutes required by the RTD formulation. In addition, the RI administration uses less saline solution and accordingly less salt (sodium chloride).

The switch from the FD to RTD formulation is almost complete. With over 90% of medical institutions administering the RI formulation to patients as of end-December 2023, progress was made in the switch to the RI formulation. On the quality assurance front, SymBio also has taken steps to ensure the stable supply of the RTD formulation of TREAKISYM®.

Sales decreased by 44.1% YoY to JPY5.6bn. This decline can be attributed to several factors: first, the reduced usage of drugs per patient due to COVID-19's impact; second, the introduction of generic drugs in June 2022, affecting SymBio's product sales. Additionally, a temporary sales spike occurred in the previous year due to the transition from the FD formulation to the RTD formulation, impacting this year's sales. Concerns over the increased risk of infection for patients with blood cancers, especially those with malignant lymphoma, and the possibility of prolonged or severe infections during or after treatment with bendamustine have led to a decrease in bendamustine prescriptions, including generics.

Gross profit was JPY4.4bn (-42.0% YoY), and the gross profit margin reached 78.9% (+3.0pp YoY). SG&A expenses were JPY5.2bn (-7.3% YoY), of which R&D expenses amounted to JPY2.6bn (+3.3% YoY). As a result, the operating loss was JPY812mn (compared to an operating profit of JPY2.0bn in the previous year).

Establishment of an in-house sales organization

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

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

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

In March 2021, SymBio obtained approval for the use of the FD formulation of TREAKISYM® in BR therapy to treat r/r DLBCL as an additional indication. In February 2022, the company secured approval for a partial amendment to the marketing authorization for the ready-to-dilute (RTD) formulation of TREAKISYM® (in-licensed from US-based Eagle Pharmaceuticals, Inc.), enabling the use of RI administration for all approved indications of the RTD formulation.

SymBio will continue to explore new potential applications of TREAKISYM®, including via joint research with the University of Tokyo and Kyoto University.

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

For rigosertib and TREAKISYM®, the company is searching for new indications as well as new applications for the drugs used in combination with each other or with other existing drugs, through joint research and the offering of academia-industry collaborative courses with the University of Tokyo.

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

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

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

In September 2022, Chimerix announced that it had completed procedures to transfer the rights to brincidofovir to Emergent BioSolutions Inc. (headquarters: Maryland, US). The agreement, however, has no impact on the company's exclusive rights to develop, manufacture, and sell brincidofovir globally for all indications except orthopoxvirus diseases including smallpox and monkeypox.

Based on a global advisory board review held in February 2020, the company has decided to prioritize the global development of BCV IV primarily in Japan, the US, and Europe, targeting disseminated AdV infections occurring after hematopoietic stem cell transplantation, a niche area with a high unmet medical need. In March 2021, the company filed an IND application with the US Food and Drug Administration (FDA) to conduct a Phase II clinical trial primarily in pediatric patients suffering from AdV infections (also including adults). This development program was granted fast-track designation by the FDA in April 2021, and the investigational drug was administered to the first patient in August 2021. In May 2023, BCV has demonstrated proof of concept in humans in the same study. Positive data demonstrating efficacy from the study were presented orally at the 65th Annual Meeting of the American Society of Hematology in December 2023. In January 2024, a use patent for BCV related to the treatment of AdV infections and infectious diseases was established and registered in Japan.

BK virus nephropathy after kidney transplantation is considered a disease with serious consequences for the recipient, the donor, the medical practitioner, and society, as it may result in serious conditions such as decreased renal function and graft loss. In order to find an early solution to this problem, SymBio submitted a clinical trial notification for a global Phase II study in patients infected with BK virus after receiving kidney transplant to the Pharmaceuticals and Medical Devices Agency (PMDA) of Japan in May 2022 and to the Therapeutic Goods Administration (TGA) of Australia in August 2022. The investigational drug was administered to the first patient in Australia in August 2022. While the trial was initially planned for completion in 2025, delays in the accumulation of cases have led to a review of the protocol.

SymBio has been preparing for clinical development of brincidofovir for multiple sclerosis, a rare disease related to EB virus. In August 2022, the company signed a collaboration agreement for the transfer of human materials with the National Institute of Neurological Disorders and Stroke (NINDS) of the US National Institute of Health (NIH). In March 2023, SymBio signed a cooperative research and development agreement (CRADA) with NINDS to obtain information necessary to conduct future clinical trials. In October 2023, the results of the research were presented at the 9th Joint ECTRIMS-ACTRIMS Meeting in Milan, Italy.

In April 2023, SymBio also signed a CRADA with the National Institute of Allergy and Infectious Diseases (NIAID), part of the NIH, to evaluate the efficacy of BCV in EB virus-related lymphoproliferative disorders.

In November 2022, the company concluded a material transfer agreement (MTA) with US-based Penn State College of Medicine, and initiated a non-clinical study evaluating the efficacy of BCV in a mouse model of polyomavirus infection.

In December 2022, the company concluded a sponsored research agreement with US-based Tufts University, and began a joint research study evaluating the efficacy of BCV in a herpes simplex virus infection model. This study aims to explore BCV's potential to treat neurological diseases, including Alzheimer's disease.

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

In December 2022, the results of collaborative research with the National Cancer Centre Singapore (NCCS) on the therapeutic efficacy of BCV in the treatment of rapidly progressing NK/T-cell lymphoma were presented at the 64th American Society of Hematology (ASH) Annual Meeting.

At the 17th International Conference on Malignant Lymphoma (ICML) in June 2023, research into biomarkers that predict the anti-tumor effect of BCV was presented.

Overseas (SymBio Pharma USA)

In August 2023, the company appointed Dr. Stephane Berthier as CEO and President of its wholly-owned subsidiary SymBio Pharma USA, Inc. In September 2023, SymBio added Nkechi Azie, MD, as Global Chief Medical Officer (CMO) to further reinforce its global development structure. SymBio Pharma USA plans to accelerate global development of the antiviral drug brincidofovir.

In-licensing of drug candidates

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

Full-year company forecast

FY12/23 company forecast (revised in November 2023)

	FY12/22			FY12/23			FY12/24	
(JPYmn)	1H results	2H results	FY results	1H results	2H results	FY results	FY forecast	YoY
Sales	4,874	5,135	10,008	3,179	2,411	5,590	3,641	-34.9%
R&D expenses	1,009	1,545	2,555	1,204	1,434	2,638	3,207	21.6%
SG&A expenses excl. R&D	1,629	1,453	3,081	1,319	1,266	2,584	-	-
Operating profit	1,372	591	1,964	-50	-762	-812	-2,837	-
Operating profit margin	28.2%	11.5%	19.6%	-	-	-	-	
Recurring profit	1,447	553	2,000	67	-803	-736	-2,867	-
Recurring profit margin	29.7%	10.8%	20.0%	2.1%	-	-	-	
Net income	1,108	71	1,179	-80	-1,883	-1,963	-2,870	-
Net margin	22.7%	1.4%	11.8%	-	-	-	-	

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

FY12/24 company forecast (announced in February 2024)

The company's full-year forecast for FY12/24 calls for sales of JPY3.6bn (-34.9% YoY), an operating loss of JPY2.9bn (compared to an operating loss of JPY812mn in the previous year), a recurring loss of JPY2.9bn (compared to a recurring loss of JPY736mn), and a net loss of JPY2.9bn (compared to a net loss of JPY2.0bn).

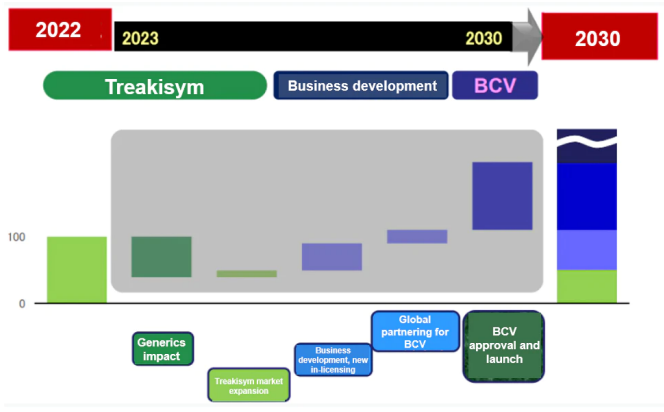
The company expects a significant reduction in the drug price for Treakisym® in FY12/24 due to its removal from the scope of price maintenance premiums given to certain new drugs. It also factored in the impact of generic drug sales. The company has filed patent infringement litigation regarding the generic versions of Treakisym® asking for an injunction against their manufacture and sale, but has not included any impact on sales due to the time required to reach a decision.

The company forecasts R&D spending of JPY3.2bn (+21.6% YoY), including the following items.

- Global development of antiviral drug BCV IV for adenovirus infection and other infectious diseases
- Development of new indications and evaluation of new drug development candidates through joint research with academia

Long-term outlook

Sales projections from 2023 to 2030 (as of February 2023)



Source: Shared Research based on company information.
*Company projections as of the FY12/22 earnings results briefing (February 2023)
**Unit value for figures in the vertical axis is JPY100mn

In the medium-term plan to FY12/23 (announced February 2020), SymBio forecasted Treakisym® sales would continue to grow YoY in FY12/23. This was based on the expectations that although the re-examination period for Treakisym® would end in 2020, SymBio could potentially extend the product life to 2031 through commercialization and switching to Treakisym® RTD and Treakisym® RI, formulations for which SymBio retains exclusive marketing rights. However, following the launch of generic Treakisym® by two companies in June 2022 and December 2022, the company revised its medium-term plan forecasts and now expects FY12/23 Treakisym® sales to decline 30.1% YoY.

At the FY12/22 earnings results briefing held in February 2023, the company explained the rationale for the revised medium-term plan forecasts and presented an overall image of sales from 2023 through 2030. As of February 2023, SymBio has not yet issued a new medium-term plan, including new earnings forecasts.

Treakisym® sales projection in 2030

The reason for management's revision of the medium-term guidance is that the MHLW approved generic Treakisym® and two companies commercialized their versions despite SymBio's patent infringement warnings. Management noted that market share erosion to generic competition in public and quasi-public medical institutions is inevitable given government policies promoting the use of generic drugs. Accordingly, SymBio has reduced its 2030 forecast for Treakisym® to half of the estimated peak sales level of JPY10bn (i.e., approximately JPY5bn). This halving of the Treakisym® sales forecast still accounts for market expansion due to the aging population and the increasing share of Treakisym®. The company still expects Treakisym® to have a 50% share of the prescription market in 2030.

Business development and new in-licensing opportunities

The company is considering multiple licensing opportunities and conducting exploratory assessments to acquire licensing rights to new development candidates. Management indicated that sales contributions from these new acquisitions could generate sales of JPY3bn by 2030.

Business development and BCV global partnering

The company has decided against independent large-scale development of BCV in areas such as multiple sclerosis and Alzheimer's disease, but is considering transfer of rights, including joint development with a large pharmaceutical company capable of global development (i.e., global partnering). Compensation for the transfer of rights for the last five years to 2030 is expected to reach JPY10bn, or an average of JPY2bn per year during this period.

Development of BCV

The company aims to obtain approval for two to three indications for BCV currently under development and generate JPY10.0bn in sales from BCV by 2030, equivalent to the peak annual sales of Treakisym®.

R&D development from 2023 to 2030 (as of February 2023)

Management provided a rough roadmap of its R&D plan through 2030 at the FY12/22 earnings results briefing held in February 2023. Development of Treakisym® has been completed and development from 2023 will focus on BCV. As BCV has potential in multiple therapeutic categories, prioritization of development will be important. The development of BCV will focus on three therapeutic categories: hematopoietic stem cell and organ transplantation, hematological malignancies/oncology, and neurodegenerative diseases (NDD). Management explained the development prioritization and the timeline of the development plan, noting that clinical development for hematopoietic stem cell and organ transplantation will be prioritized as approval is the most likely.

- Hematopoietic stem cell and organ transplantation
  - Adenovirus trials, BKVN trials, CMV trials
- Hematological malignancies and oncology
  - CMV (+) brain tumor, NK/T lymphoma
- Neurodegenerative diseases
  - EBV multiple sclerosis, HSV-1 Alzheimer's type dementia

Initial clinical development for hematopoietic stem cell and organ transplantation

Initial clinical development in hematopoietic stem cell and organ transplantation will focus on two indications: adenovirus infection and BK virus infection. In the development plan to 2030, management believes that approval for these indications is most likely.

- Adenovirus trial (post-hematopoietic stem cell transplantation adenovirus infection)
  Phase IIa escalating-dose confirmatory study on safety and tolerability underway. Slated for completion in Q4 2023

- BKVN trial (post-kidney transplantation BK viral infection)
  Phase II underway. Slated for completion in Q2 2025

Announces full-scale development of CMV therapeutics in the transplantation field

- CMV trial (post-hematopoietic stem cell cytomegalovirus infection)
  Preparation for Phase Ib (Slated to start in Q4 2023 and be completed in Q1 2025)

At the FY12/22 earnings results information briefing held in February 2023, management explained the company's policy for full-scale development of BCV for cytomegalovirus (CMV) infection in transplant recipients and its significance. Although CMV is a strong development candidate, SymBio had put development in this indication on hold pending clarification of the therapeutic effect of Takeda's competitor maribavir (approved in November 2021).

After evaluating the therapeutic efficacy of maribavir, management identified an unmet therapeutic need for CMV in the transplantation field and announced the full-scale development of BCV for this indication. SymBio's determination that there is an unmet therapeutic need, even after maribavir has been marketed, is based on the following three points.

- Resistance to maribavir is 44.3% and no effective therapy is available for these resistant patients
- Even after the virus is no longer detectable following maribavir treatment, relapse and resistance occurred in 23% of patients at six weeks and 30% at 12 weeks.
- Maribavir failed to demonstrate equivalence to the original drug (valganciclovir) in a non-inferiority trial

The number of transplant recipients treated for CMV is exceptionally high for a rare disease (25,000, of which 10,000 are resistant or refractory). One reason that megapharma Takeda decided to develop maribarivir independently was likely that the large potential patient base made it look more lucrative. The company noted that the large patient base made patient enrollment for clinical trials much easier. The Phase Ib clinical trial is being prepared to start with dose selection. The trial is expected to begin in Q4 2023 and be completed by Q1 2025.

Hematological malignancies and oncology

- CMV (+) brain tumors (collaboration with Brown University in the US; glioblastoma [GBM])
  Phase I clinical trial / Slated to start in Q2 FY12/24 and be completed in 1Q FY12/26

The only pipeline in the hematological malignancies and oncology field for which a development timeline has been proposed is glioblastoma, a type of CMV (+) brain tumor. In March 2022, the company launched a joint non-clinical study with Brown University of the US to investigate the antitumor effect on cytomegalovirus positive infection and glioblastoma (GBM). This non-clinical study is expected to be completed in Q3 2023 with the goal of establishing PoC in animals. The Phase I clinical trial is expected to begin in Q2 2024 and be completed in Q1 2026.

- NK/T lymphoma (joint research with National Cancer Centre Singapore)

BCV demonstrated anticancer activity against NK/T cell lymphoma in the non-clinical study regardless of EB viral infection. No clinical trial timeline was disclosed for NK/T lymphoma.

Neurodegenerative diseases (NDD)

SymBio announced that it will not independently develop BVC for neurodegenerative diseases (NDD) such as multiple sclerosis and Alzheimer's disease. Rather, SymBio seeks to partner with a large pharmaceutical company capable of global development (global partnering) and receive compensation through the transfer of rights. The company aims to establish early proof-of-concept in animals through collaborations with world-renowned academic institutions. For the multiple sclerosis indication, SymBio is advancing a Phase I study with the US NIH. For the Alzheimer's disease indication, management is planning a co-development with a partner starting with Phase I.

- EBV multiple sclerosis (joint research with US NIH)
  Basic study (NIH/SymBio) started from Q3 2022
  Animal model (NIH/SymBio) plans to start from Q3 2023
  Phase I clinical trial (NIH/SymBio) plans to start from Q2 2024 with completion projected for Q2 2025

- HSV-1 Alzheimer's type dementia (under joint research with Tufts University of the US)
  3-D brain modeling (Tufts University) started from Q4 2022
  Animal modeling (SymBio) plans to start from Q4 2023
  Phase I clinical trial (partner/SymBio) plans to start from Q1 2025 with completion projected after end-2026

Therapeutic categories under consideration for development

Not specified, but the following therapeutic categories are potentially under consideration for development (as of February 2023).

- Post-transplantation infection
  - Post-hematopoietic stem cell transplantation adenovirus/BK viral hemorrhagic cystitis (VHC) and HHV-6 encephalitis, EBV infectious mononucleosis
- Hematological malignancies/oncology
  - EBV (+) lymphoma
- Neurological
  - EBV sequelae
- Ophthalmological
  - Adenovirus epidemic keratoconjunctivitis

Unexplored development possibilities

Additional potential therapeutic categories that have not been explored for development are listed below (as of February 2023).

- Post-transplantation infections
  - Prevention of post-hematopoietic stem cell transplantation CMV infection, multiviral agent for post-hematopoietic stem cell transplantation use
- Hematological malignancies/oncology
  - HPV (+) head and neck cancer, HPV (+) endometrial cancer
- Dermatological
  - Varicella-zoster virus (VZV)/Herpes virus (HPV)

Business

Business description

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

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

Strategy Overview (details to follow)

- **Post proof-of-concept**: The company reduces product development risk by focusing on drug candidates undergoing clinical development with preclinical/clinical data establishing safety and efficacy in human subjects.

- **Screening**: The company uses an in-house search and evaluation team to screen and evaluate drug candidates having a high unmet medical in Japan and other Asia Pacific markets with the potential to secure marketing approval in a shorter clinical development period. A select number of drug candidates will then undergo rigorous review by the company's Scientific Advisory Board (SAB).

- **Fabless**: The company outsources preclinical/clinical studies and manufacturing to reduce fixed costs.

- **Niche market:** The company targets drugs with the potential to receive orphan drug designation and thus, secure a longer marketing exclusivity period due to high unmet medical needs—including oncology, hematology, and rare diseases—and smaller patient populations. Larger pharmaceutical companies may be reluctant to develop drugs in niche markets due to limited sales potential—SymBio sees an opportunity to avoid intense competition in the marketplace by focusing on the development of orphan or 'orphan-like' drugs.

- **Global expansion**: The company identifies and capitalizes on opportunities to grow sales by acquiring the right to develop drug candidates in Japan and other international markets.

The company have in-licensed new drug candidates after rigorously evaluating them.

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

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

Additional indications for Treakisym®

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

- Refractory or relapsed low-grade non-Hodgkin's lymphoma and mantle cell lymphoma: After designation as an orphan drug (drug for the treatment of rare diseases), Treakisym® won marketing approval for this indication in October 2010.

- Chronic lymphocytic leukemia: SymBio received approval for this to be added as indication for Treakisym® in August 2016.
- First-line treatment of untreated low-grade non-Hodgkin's lymphoma and mantle cell lymphoma: The company gained approval for this to be added as indication for Treakisym® in December 2016.
- Relapsed or refractory diffuse large B-cell lymphoma (DLBCL): Approved as additional indication in March 2021.

Treakisym® (RTD formulation and RI formulation)

In September 2017, Eagle Pharmaceuticals and SymBio concluded a license agreement that licenses to SymBio rights to develop, market, and sell Eagle's bendamustine hydrochloride ready-to-dilute (RTD) formulation and rapid infusion (RI) administration products in Japan. Securing products to replace freeze-dried (FD) product (whose exclusive sales rights in Japan expired in 2H 2020) had been a priority for the company. SymBio obtained approval for the RTD formulation in September 2020, and launched the product in January 2021. The company obtained approval for the RI formulation in February 2022.

With this, it aims to promote a switch in clinical settings from lyophilized powder formulation to RTD and RI formulations that lighten the workload for medical professionals, at the same time curtailing uptake of Treakisym® generics. Because it has exclusive rights to sell the RTD and RI formulations in Japan, SymBio will be able to extend Treakisym®'s product lifecycle until 2031.

Rigosertib

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

In February 2014, Onconova completed phase III clinical trials of rigosertib (injection) in patients with relapsed or refractory MDS in Europe, and its efficacy was proven in subgroup analysis. SymBio also completed patient registration for phase I domestic clinical trials in January 2015.

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

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

Brincidofovir

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

In September 2019, SymBio entered an exclusive global license agreement with Chimerix Inc. for brincidofovir. As a result, the company acquired exclusive worldwide rights to develop, market, and manufacture brincidofovir for all indications except smallpox. In August 2021, the company launched phase II clinical trials in the US targeting adenovirus infection in children.

Revenue source: Treakisym® sales

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

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

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

Business strategy

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

The company focuses on developing drugs that have strong safety and efficacy data in clinical trials, providing an opportunity to develop new drugs more likely to succeed and secure regulatory approval with the use of bridging data whenever possible to shorten development timelines. It can obtain approval and start selling a drug within five to six years of securing the development and commercialization right. The company increases the chance that drug candidates it in-licenses will be approved in the future through an effective in-house screening process and rigorous evaluation by the company's Scientific Advisory Board.

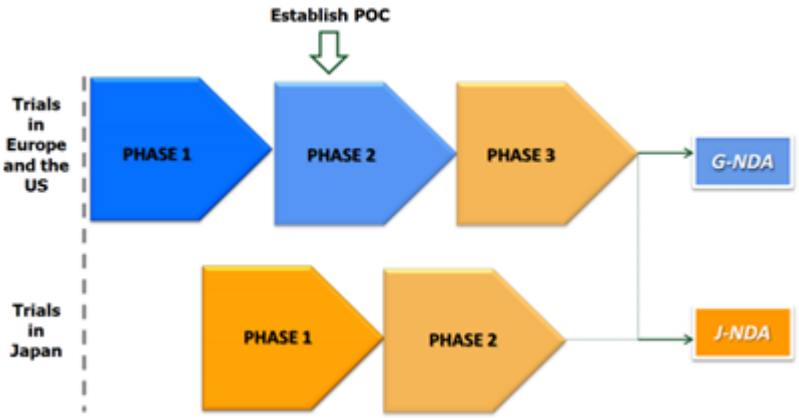
The overall aim is to reduce development risk, streamline expenses, and expand revenue opportunities. This hinges on the following five strategies, namely post proof-of-concept, screening, fabless, niche market, and global expansion.

Post-POC strategy: SymBio targets compounds with an established proof-of-concept

The pharmaceutical business requires substantial financial commitment in terms of upfront investment, not to mention the number of years of development required in order to realize a return on the investment and the high risk of failure in clinical studies from phase I through III. According to the company, the probability of a chemical compound having a signal with pharmacological activity in a particular disease being approved as a drug is 1/20,000 to 1/25,000, and only 15–20% of drugs that manage to enter the marketplace achieve profitability for the sponsor.

Given the high rate of attrition of drug candidates in clinical development, SymBio reduces development risk by only targeting quality drug candidates undergoing clinical development with proof-of-concept (confirming efficacy and safety of a new drug candidate through administration to animals or humans) established in human subjects and/or market sales. NDA filings that use clinical data generated overseas can expedite product development in Japan and other parts of Asia, slashing development costs and improving the overall success rate.

Post-proof-of-concept strategy



Source: Shared Research based on company data

Screening strategy: independent search network plus evaluation experience

Identify candidate drugs by utilizing independent search network and evaluation experience

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

Onsite due diligence

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

Evaluation by a panel of pharmaceutical experts

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

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

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

Scientific Advisory Board

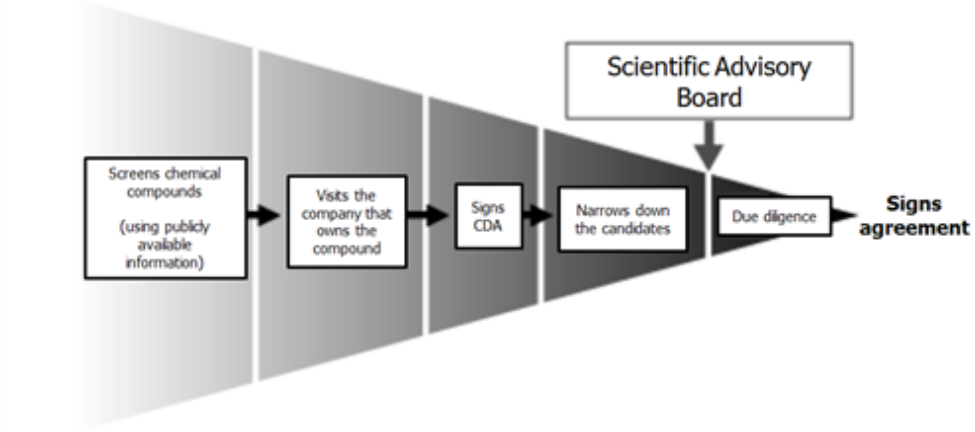
The Scientific Advisory Board is comprised of former directors of pharmaceutical companies, researchers, and doctors, and meets three times a year. Typically, the SAB panel evaluates two to three drug candidates that have been selected via the company's in-house screening process. This in-house screening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

Scientific Advisory Board members

Name	Profile
George Morstyn, M.D., Ph.D.	Presently Chairman GBS Venture Capital firm, Deputy Chairman Victorian Comprehensive Cancer Centre, Director of Co-operative Research Centre for Cancer Therapeutics and Proacta. Former Senior Vice-President of Development and CMO at Amgen Inc.
Robert Lewis, M.D., Ph.D.	Former Senior Vice-President of US R&D, Aventis Pharmaceuticals; Chief Scientific Officer, Cell Therapeutics; Head of Discovery Research, Syntex Pharmaceuticals; Associate Professor, Harvard Medical School Currently serves as consultant in Immunology/Inflammation, Roche Palo Alto; Adjunct Faculty Member, Rockefeller University, New York
Tomomitsu Hotta, M.D.	Honorary President, National Cancer Center Honorary Director, Nagoya Medical Center
Makoto Ogawa, M.D., Ph.D.	Honorary President, Aichi Cancer Center
Tatsutoshi Nakahata, M.D., Ph.D.	Advisor and Program-Specific Research Center Professor at Center for iPS Cell Research and Application (CiRA), and Head of Drug Discovery Technology Development Office, Kyoto University Honorary member, The Japanese Society of Hematology
Toshio Suda, M.D., Ph.D.	Distinguished Professor, International Research Center for Medical Sciences, Kumamoto University Professor, Cancer Science Institute of Singapore, National University of Singapore Vice President, The Japanese Society of Hematology in 2012
Tsutomu Takeuchi, M.D., Ph.D.	Professor of Medicine, Keio University, School of Medicine (Division of Rheumatology, Department of Internal Medicine)
Shinji Nakao, M.D., Ph.D.	Professor, Kanazawa University College of Medical, Pharmaceutical and Health Sciences, Division of Cancer Medicine Cellular Transplantation Biology (Hematology/Respirology) Executive Director, The Japanese Society of Hematology in 2012
Koichi Takahashi, M.D.	Assistant Professor, Department of Leukemia, Division of Cancer Medicine, MD Anderson Cancer Center, The University of Texas

Source: Shared Research based on company data

Drug candidate selection process



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

Fabless strategy with a lean management team

SymBio seeks to reduce costs and raise profits by finding the right partner(s) to develop and commercialize drugs nimbly and efficiently through flawless execution. Specifically, the company designs clinical trial protocols and whenever possible, will participate in global phase III studies being conducted by its partner(s) overseas with the aim of shortening development timelines in Japan.

It may be possible to file NDAs in Japan using foreign data to support or "bridge" data generated in Japanese clinical trials, thereby avoiding the need to complete domestic phase II and/or phase III studies for marketing approval.The company uses its well-established network for bendamustine to coordinate with medical professionals, outsourcing routine development duties. Production is also outsourced either to the company that originally granted the product license, or to other domestic or foreign manufacturer(s). The company began in-house sales in Japan of Treakisym® on December 10, 2020, taking over from Eisai, which marketed the product until December 9, 2020.

Niche markets: oncology, hematology, and rare diseases

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

According to the company, globally Japan has the third largest oncology market after the US and EU, and the market is expected to continue to expand due to Japan's aging population. However, regarding the type of tumors that anticancer drugs can effectively treat, there is a considerable range of indications with a limited number of patients who will benefit from approved cancer treatments, particularly in the elderly population where the occurrence of serious adverse events can be prohibitive. As a result, barriers to entry are high—developing cancer drugs for niche markets is especially difficult and requires a high level of expertise.

Concerns about having sufficient profit margins from marketed drugs to fund large operations means that major pharmaceutical companies may be reluctant to target indications with limited patient numbers for development, presenting an opportunity with fewer competitors in the marketplace for smaller and more specialized pharmaceutical companies such as SymBio. The company can also increase value added of niche disease areas by additional indications and putting new products on the market. For example, its first in-house proprietary drug Treakisym® has gained over 50% market share three years after going on sale. In July 2018, Treakisym® was newly included as a standard option for first-line treatment of low-grade NHL and mantle cell lymphoma in the Guidelines for Hematological Malignancies 2018 issued by the Japan Society of Hematology in July 2018.

Strategy for global expansion

The company is seeking to develop new drugs that are complementary to Treakisym® and rigosertib to sell in China/Hong Kong, Taiwan, South Korea, and Singapore, as well as in Japan. Also, it acquired exclusive worldwide rights to develop, manufacture, and market brincidofovir.

Pipeline

Pipeline

Name/Code	Licensed country	Indications	Development stage	Sales partner
Treakisym® SyB L-0501 (FD)	Japan	Relapsed or refractory low-grade NHL and MCL	Approved (Oct. 2010)	In-house sales
		Relapsed or refractory DLBCL (aggressive NHL)	Approved (Mar. 2021)	
		Untreated low-grade NHL and MCL	Approved (Dec. 2016)	
		CLL	Approved (Aug. 2016)	
	Singapore	Low-grade B-cell NHL	Approved (Jan. 2010)	Eisai Co., Ltd. (Exclusive development and sales rights granted to Eisai)
		CLL		
	South Korea	CLL MM	Approved (May 2011)	Eisai Co., Ltd. (Exclusive development and sales rights granted to Eisai)
		Relapsed or refractory low-grade NHL	Approved (Jun. 2014)	
	China	Low-grade NHL	Clinical trials underway	Cephalon, Inc. (US) (Exclusive development and sales rights granted to Eisai)
	Hong Kong	Low-grade NHL	Approved (Dec. 2009)	
		CLL		
	Taiwan	Low-grade NHL	Approved (Oct. 2011)	InnoPharmax, Inc. (Taiwan) (Exclusive development and sales rights granted to Eisai)
		CLL		
Treakisym® SyB L-1701 (RTD)	Japan	All indications	Approved (Sep 2020)	In-house sales
Treakisym® SyB L-1702 (RI)	Japan	All indications	Approved (Feb. 2022)	In-house sales
Rigosertib (IV) SyB L-1101	Japan	Relapsed or refractory higher-risk MDS	Global phase III clinical trials Additional analysis underway	—
Rigosertib (oral) SyB C-1101	Japan	Relapsed or refractory higher-risk MDS (monotherapy)	Phase I clinical trials underway	—
		Untreated higher-risk MDS (with azacitidine)	Global phase I/II clinical trials completed	—
Brincidofovir (IV) SyB V-1901	Worldwide	Adenovirus infection after hematopoietic stem cell and kidney transplantation	Phase II clinical trials underway	—

Source: Shared Research based on the company website

As of February 2023, the main drugs for which SymBio was preparing to file for approval or in the development pipeline were as follows:

- Rigosertib (intravenous formulation), for the indication of relapsed or refractory higher-risk MDS: Conducting additional analysis of global phase III clinical trial results

- Rigosertib (oral formulation), for the indication of higher-risk MDS: Completed patient enrollment for the phase I clinical trial in June 2019, and completed global phase I/II clinical trials of the combination therapy with azacitidine. Preparing for phase I clinical trial of the combination therapy with azacytidine.

- Antiviral drug brincidofovir: Under development for multiple indications. Refer to the "R&D development from 2023 to 2030" for details.

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

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

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

According to the company, no cross-resistance (resistance to drugs with a similar structure or action as the study drug) has been shown for this drug, which means it is safer and more efficacious than existing treatments for target indications. In October 2010, SymBio received regulatory approval in Japan to market the drug for relapsed or refractory low-grade NHL and MCL. Eisai has been selling the drug since its launch in December 2010. The company received permission to add CLL as an indication for Treakisym® in August 2016, and first-line treatment of low-grade NHL and MCL in December 2016. In March 2021, the company gained approval of Treakisym® for the additional indication of relapsed or refractory DLBCL (aggressive NHL).

Lymphatic cancer

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

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

Lymphatic cancer is divided into Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL). Among the Japanese population, only 4% of lymphatic malignancies are HL. About 70–80% of NHL cases affect B-cells; the remaining 20–30% affect T/NK cells. According to the Japanese Association of Clinical Cancer Centers (JACCC), the five-year relative survival rates for lymphatic malignancies (among patients diagnosed between 2001 and 2005) are as outlined in the table below. In Hodgkin's lymphoma (all cases) the five-year relative survival rate was 76.0%, as compared with 68.3% for non-Hodgkin's lymphoma (all cases).

Lymphatic malignancy: frequency by type

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

Source: Shared Research based on materials from Japanese Society for Lymphoreticular Tissue Research (JSLTR)

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

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

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

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

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

Treakisym® in-licensed from Astellas; developed jointly with Eisai in Japan; sold in-house from December 2020

In December 2005, SymBio signed a license agreement for the exclusive right to bendamustine in Japan with Astellas Deutschland GmbH, a subsidiary of Astellas Pharma Inc (TSE Prime: 4503). The company entered into a second license agreement with Astellas in March 2007 to extend its exclusive development and commercialization right for bendamustine to China/Hong Kong, Taiwan, South Korea, and Singapore.

In August 2008, SymBio granted Eisai Co., Ltd. the co-development and exclusive marketing right for Treakisym® in Japan. Under the agreement, SymBio receives one-time payments from Eisai as well as milestone payments based on the clinical trial stage for a particular indication, plus revenues after supplying Treakisym® to Eisai. Eisai shoulders half of the development costs for Treakisym®, including labor costs for researchers and outsourcing costs for clinical trials (see the Earnings structure section). The marketing agreement with Eisai expired in December 2020, after which SymBio began to independently market Treakisym® in Japan.

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

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

In October 2010, five years after acquiring the right to Treakisym®, SymBio received marketing approval in Japan for relapsed or refractory low-grade NHL and MCL. The domestic launch of the drug was in December 2010.

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

Treakisym®: additional indications, RTD and RI formulations

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

August 2016

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

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

Market for Treakisym® and number of patients

		Non-Hodgkin's lymphoma		Chronic Lymphatic Leukemia
		Low-grade B-cell	Moderate- to high-grade	
First-line	Number of patients	6,967	-	656
	Approval	Obtained	- Obtained	
	Development status	Obtained approval (Dec. 2016)	- Obtained approval (Aug. 2016)	
Relapsed and refractory	Number of patients	9,336	18,672	
	Approval	Obtained	Completed patient enrollment for phase III clinical trials in Japan	
	Development status	Obtained approval in Japan (Oct. 2010)	Applied approval (May 2020)	

Source: Shared Research based on company data

Treakisym® indicated for untreated low-grade NHL and MCL

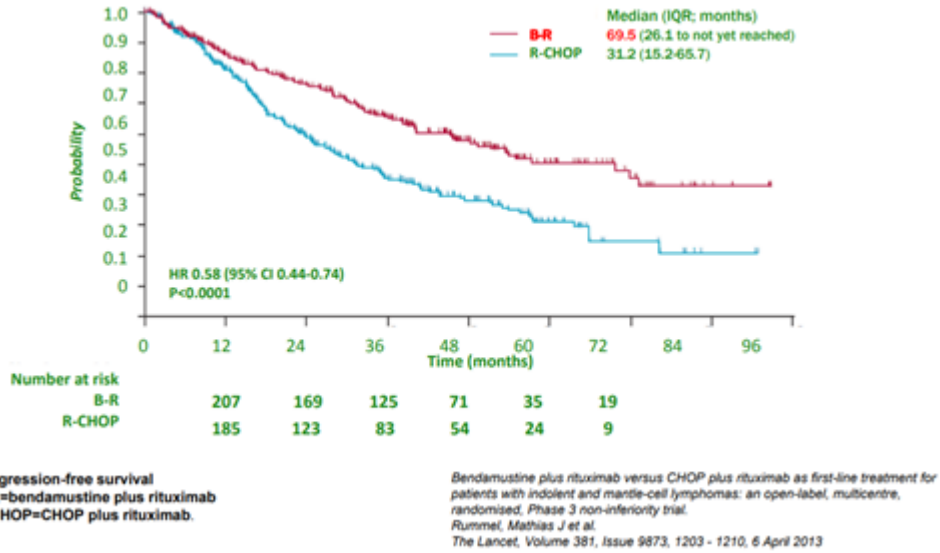
According to the company, R-CHOP therapy—a combination of rituximab with CHOP chemotherapy drugs (cyclophosphamide, doxorubicin (hydroxydaunomycin), vincristine (oncovin), and prednisolone)—was standard first-line treatment for low-grade NHL and MCL in Japan prior to December 2016. In December 2016,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

In Phase III clinical trials conducted overseas, rituximab in combination with Treakisym® (bendamustine hydrochloride; BR therapy) demonstrated safety and efficacy superior to those of the standard R-CHOP therapy for previously untreated low-grade B-cell NHL. These findings were presented at the American Society of Hematology Annual Meeting in December 2012. Based on these results, the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines recommend the use of BR therapy as first-line therapy for patients with untreated low-grade NHL.

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

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

Results of comparative study of BR and R-CHOP therapies in patients with untreated low-grade NHL/MCL



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

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

Source: Company data

Treakisym® approved in December 2016 for untreated low-grade NHL and MCL

In December 2016, SymBio received marketing approval of Treakisym® in Japan, for untreated low-grade NHL and MCL. Shared Research believes this shift will gain support from the aforementioned data demonstrating that BR therapy is more efficacious than R-CHOP therapy, and inclusion of BR therapy as a standard treatment option in the Guidelines for Tumors of Hematopoietic and Lymphoid Tissues 2018.

Untreated low-grade NHL and MCL: patient population and estimated sales

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

Treakisym® indicated for chronic lymphocytic leukemia (CLL)

Additional indication of CLL approved in August 2016

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

Potential patient population, estimated sales

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

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

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

But according to the company, 40% of untreated patients treated with R-CHOP relapse or become refractory, and only patients who are 65 or younger can undergo chemotherapy at higher doses together with autologous stem cell transplants. Because the majority of relapsed or refractory DLBCL patients are elderly, physicians must consider potential side effects

when selecting a suitable treatment. Weaker patients—due to age or other illnesses—have limited choices for treatment, and there was a need for a safer, more efficacious method of treatment such as Treakisym®.

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

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

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

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

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

Patient population, estimated sales

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

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

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

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

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

The FD powder injection product currently available must be reconstituted manually before administration by intravenous infusion. Since RTD and RI products are already liquidized, they do not require the time-consuming process of reconstitution and reduce the workload of healthcare professionals. RI formulation also does not require reconstitution and can be administered by intravenous infusion in 10 minutes instead of 60 minutes for FD powder injection and RTD products, which reduces stress on patients. The volume of diluted saline solution is one-fifth that of the RTD formulation, with the lower salt content making it suitable for elderly patients.

Comparison of RTD/RI formulations and freeze-dried formulation

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

Scenario of extending life cycle of Treakisym® until 2031

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

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

Bendamustine hydrochloride RTD and RI injection products are marketed in the US by Eagle Pharmaceuticals as BENDEKA®, which captured a 97% share of the US bendamustine market within two years after its launch. According to the company, some companies in the US have attempted to launch generic versions of Treakisym® liquid formulations, but they all infringed on Eagle Pharmaceuticals' patents, and Eagle prevailed in lawsuits. The company did not think generic versions of Treakisym® liquid formulations would be marketed in Japan.

However, the situation changed with the commercialization of generic Treakisym by Towa Pharmaceutical in June 2022, followed by Pfizer Japan in December 2022. SymBio filed patent infringement lawsuits against both companies in December 2022, and the litigation is ongoing.

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

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

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

In March 2019, Novartis Pharma K.K. received approval in Japan for the chimeric antigen receptor T-cell (CAR-T) therapy CTL019 (US product name: Kymriah®), for the treatment of relapsed or refractory B-cell acute lymphoblastic leukemia (ALL) in patients aged 25 years or younger and relapsed or refractory DLBCL. Shared Research understands that Novartis Pharma's CTL019 is limited to adult patients for whom two or more lines of therapy have proved ineffective, and is thus different from SymBio's Treakisym® used to treat DLBCL, so the two do not compete.

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

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

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

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

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

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

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

Myelodysplastic Syndromes (MDS)

MDS is a refractory disease with a poor prognosis and progression to acute myeloid leukemia (AML) in approximately 30% of cases. It leads to abnormalities in hematopoietic stem cells that produce blood cells, resulting in a lack of blood. Blood cells produced this way are abnormally shaped. This change in the cells is called dysplasia.

The disease typically leads to frequent anemia with some patients dying from infection or bleeding due to the reduction in blood cells. The average survival period is about three to five years, with some patients surviving 10 years or longer. It is still not clear what environmental or genetic factors are responsible for the occurrence of MDS, although those who have received radiation treatment or taken anticancer drugs may have a higher risk of developing the disease (source: Japan Adult Leukemia Study Group: JALSG).

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

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

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

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

Development status of rigosertib

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

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

Market for rigosertib (oral form) and number of patients

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

Source: Shared Research based on company data

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

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

However, some cases of higher-risk MDS show resistance to standard treatment with hypomethylating agents (HMAs) such as Vidaza and Dacogen, including relapse following treatment. The advanced research being conducted for rigosertib was for the treatment of patients with higher-risk MDS who had progressed on, failed or relapsed after prior therapy with HMAs.

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

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

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

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

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

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

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

In August 2020, Onconova announced that the primary endpoint (overall survival compared with physician's choice [PC] treatment) was not met in the phase III clinical trial. More specifically, the primary endpoint of the trial was overall survival, comparing IV rigosertib plus best supportive care to PC plus best supportive care. Onconova also analyzed a pre-specified subgroup of very high risk (VHR-MDS) patients. Results of the trial demonstrated that in the intent-to-treat analysis patients given IV rigosertib achieved overall survival of 6.4 months, versus 6.3 months for PC (p=0.33) in the overall HR-MDS population. There was also no significant difference in overall survival between the two study arms in the VHR-MDS subgroup.

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

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

Oral rigosertib in patients with higher-risk MDS

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

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

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

Phase I clinical trials in Japan

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

Exploring new indications

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

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

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

He is also studying molecular mechanisms in the development of hematopoietic tumors caused by epigenetic abnormalities, looking to develop novel therapies using hematopoietic tumor models. SymBio will leverage its experience in winning early

approval for proprietary anticancer drugs in collaborating with IMSUT to search for new indications for bendamustine and rigosertib.

Patient population, estimated sales

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

Nippon Shinyaku Co., Ltd. (TSE Prime: 4516) has been selling azacitidine in Japan as first-line therapy for MDS under the product name Vidaza since March 2011. According to Nippon Shinyaku, sales of Vidaza were JPY15.4bn in FY03/21 (-1.9% YoY) and forecast to reach JPY18.0bn in FY03/22.

SyB V-1901 (antiviral drug, brincidofovir)

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

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

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

Mechanism of action and target indications of brincidofovir

Brincidofovir is an antiviral drug formed by conjugating a lipid chain (hexadecyloxypropyl, or HDP) of specified length to cidofovir (antiviral drug already approved and marketed in the EU and the US, but not approved in Japan). As a lipid conjugate, it has a novel mechanism of action and can be taken up by cells at enhanced efficiency compared to cidofovir (i.e., brincidofovir has higher cell membrane permeability).

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

Cidofovir (CDV): Approved by FDA in 1996 for the treatment of cytomegalovirus retinitis in AIDS patients. It inhibits replication of multiple families of DNA viruses other than herpes viruses, including adenoviruses, papillomaviruses, and polyomaviruses.

CDV is taken up by renal tubular epithelial cells through organic anion transporter 1 (OAT1), and its accumulation in the cells cause nephrotoxicity. brincidofovir is expected to have a low risk of nephrotoxicity as its lipid chain prevents it from being taken up by OAT1 and accumulating in renal tubular epithelial cells.

Comparison of brincidofovir (BCV) antiviral activity versus other agents

Viral Family	Virus	BCV	Cidofovir	Maribavir	Letermovir	Ganciclovir*	Foscarnet	Acyclovir
Herpes	Cytomegalovirus	0.001	0.4	0.31	0.005	3.8	50-800	>200
	Epstein-Barr Virus	0.03	65.6	0.63	>10	0.9	<500	6.2
	Human Herpesvirus 6	0.003	2.7	Inactive	>10	5.8	16	10
	Human Herpesvirus 8	0.02	2.6	Inactive	—	8.9	177	>100
	Herpes Simplex Virus 1	0.01	3.0	Inactive	>10	0.7	92-95	3.8
	Herpes Simplex Virus 2	0.02	6.5	Inactive	>10	2.5	91-96	4.4
	Varicella Zoster Virus	0.0004	0.5	Inactive	>10	1.3	39.8	3.6
Adenovirus	Adenovirus (AdV-B7)	0.02	1.3	—	>10	4.5-33	Inactive	>100
Polyoma	BK Virus (BKV)	0.13	115	—	—	>200	Inactive	>200
	JC Virus (JCV)	0.045	>0.1	—	—	—	Inactive	—
Papilloma	Human Papillomavirus	17	716	—	—	Inactive	—	Inactive
Pox	Variola	0.1	27	—	—	—	—	—
	Vaccinia	0.8	46	—	—	>392	Inactive	>144

Source: Company data

Note: Table shows IC50 (μM) values (concentration at which 50% of viruses targeted by pharmaceutical agent can be inhibited). The lower the IC50 value, the greater the antiviral activity.

Note: Cidofovir, Maribavir, Letemovir, Ganciclovir, Foscarnet, and Acyclovir are antiviral agents.

Development status of IV formulation of brincidofovir

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

Phase II clinical trials targeting adenovirus diseases in children

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

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

Transplants

Proceeding with development targeting AdV infections following hematopoietic stem cell transplants

After a review at the global advisory board held in February 2020, the company concluded that it would prioritize global development of brincidofovir (mainly in Japan, the US, and Europe) to treat adenovirus (AdV) infections in patients receiving hematopoietic stem cell transplantation to address an unmet medical need. In Q1 2022, the company started the global phase II study targeting ADV infections following hematopoietic stem cell transplants and completion is projected for Q4 2023. Based on safety and efficacy data acquired from its study, the company plans to review the drug's efficacy against dsDNA viral infections in patients receiving hematopoietic stem cell transplantation and extend its target indications to include multiviral infections.

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

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

Expanding target disease areas to cover organ transplants

In a bid to grow the market for brincidofovir and maximize its business value, the company is exploring the potential for expanding target disease areas to viral infections related to kidney and other organ transplants, in addition to ADV infections following hematopoietic stem cell transplants. In Q3 2022, the Phase III clinical trial targeting BK virus infections following kidney transplants was started and the completion is projected for Q2 2025.

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

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

HHV-6 encephalitis: HHV-6 (Human Herpesvirus 6) is the sixth human herpesvirus to be discovered. It reactivates in 30–70% of patients after allogenic hematopoietic stem cell transplantation and can cause HHV-6 encephalitis. Most cases of HHV-6 encephalitis develop within 2–6 weeks of transplantation, most frequently in the third week. It is characterized by the three major symptoms of impaired memory, disordered consciousness, and convulsions, which in typical cases gradually appear in the same order (convulsions occur in 30–70% of patients). In rapidly progressing cases, which are common, neurological symptoms worsen by the hour, often requiring ventilator management for repeated convulsions and respiratory depression.

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

Cancer

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

As of February 2023, the company was conducting a nonclinical study targeting glioblastoma multiforme (GBM), brain tumors associated with cytomegalovirus infection. According to the company, roughly 50% of GBM patients have cytomegalovirus infections, and it is possible that cytomegalovirus promotes tumorigenesis. Further, while many GBM therapies are being developed, none of them target cytomegalovirus and GBM (other than brincidofovir). In March 2022, the company launched a joint nonclinical study with Brown University of the US to investigate the antitumor effect of BCV IV on brain tumors associated with cytomegalovirus infection.

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

Neuro-infectious diseases

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

MS. The magazine says that this suggests eradication of the EBV from the body after the onset of MS could hinder its progression.

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

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

Earnings structure

(JPYmn)	FY12/13	FY12/14	FY12/15	FY12/16	FY12/17	FY12/18	FY12/19	FY12/20	FY12/21	FY12/22
Sales	1,532	1,955	1,933	2,368	3,444	3,836	2,838	2,987	8,257	10,008
YoY	-21.6%	27.6%	-1.1%	22.5%	45.4%	11.4%	-26.0%	5.3%	176.4%	
Product sales	1,432	1,940	1,933	2,137	3,444	3,810	2,811	2,977	8,257	10,008
YoY	-26.8%	35.5%	-0.3%	10.6%	61.1%	10.6%	-26.2%	5.9%	177.4%	21.2%
Treakisym sales (NHI price basis; reference)( )	4,230	4,320	4,760	4,720	7,600	8,500	-	-	-	-
Product sales/Sales (NHI price basis)	33.9%	44.9%	40.6%	45.3%	45.3%	44.8%	-	-	-	-
Royalty revenue	100	15	-	231	-	26	26	10	-	-
Sales to Eisai	1,486	1,908	1,852	2,265	3,382	3,648	2,831	2,546	-	-
YoY	-23.0%	28.4%	-2.9%	22.3%	49.4%	7.9%	-22.4%	-10.1%	-	-
Sales to other partners	46	47	81	104	62	187	6	441	8,257	10,008
CoGS	1,214	1,428	1,350	1,464	2,413	2,663	1,973	2,120	2,452	2,408
COGS / Product sales	84.8%	73.6%	69.8%	68.5%	70.1%	69.9%	70.2%	71.2%	29.7%	24.1%
Cost ratio(CoGS/Sales (NHI price basis))	28.7%	33.1%	28.4%	31.0%	31.7%	31.3%	-	-	-	-
Product procurement	1,175	1,550	1,242	1,606	2,589	2,969	1,684	3,163	2,145	
Gross profit	318	527	583	904	1,031	1,173	865	867	5,800	7,600
Product gross profit	218	512	583	673	1,031	1,147	838	857	5,800	7,600
Gross profit margin	15.2%	26.4%	30.2%	31.5%	29.9%	30.1%	29.8%	28.8%	70.2%	75.9%
Royalty revenue	100	15	-	231	-	26	26	10	-	-
SG&A expenses	1,999	1,830	3,135	3,031	4,978	3,829	5,166	5,373	4,784	5,636
Personnel expenses	441	479	488	541	554	504	506	530	574	
R&D expenses	1,053	774	2,035	1,667	3,018	1,833	2,442	2,267	1,736	2,555
Other	505	577	612	823	1,406	1,492	2,219	2,576	2,474	
Operating profit	-1,681	-1,303	-2,552	-2,127	-3,947	-2,656	-4,302	-4,506	1,016	1,964

Source: Shared Research based on company data

*SymBio Pharma USA, Inc was consolidated from FY12/22 in line with the start of operation. Note that FY12/22 results are consolidated figures and the year-on-year changes are for reference.

Sales

The company's sales are made up of product sales and royalty revenue. Per the above table, most of the sales through FY12/19 have originated from Eisai. The company began own sales of Treakisym® from December 10, 2020 and recorded sales to non-Eisai partners (i.e., wholesalers) of JPY441mn in FY12/20. From FY12/21, all sales were to non-Eisai partners.

Product sales

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

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

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

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

Royalty revenue

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

CoGS

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

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

SG&A expenses

Personnel and R&D are the main SG&A expenses.

Personnel expenses

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

R&D expenses

R&D expenses include personnel expenses for R&D staff as well as clinical trial outsourcing expenses and upfront payments accompanying product in-licensing. R&D expenses fluctuate depending on the progress of clinical trials and new license agreements from in-licensing activities. According to the company, in-licensing expenses are between JPY500mn and JPY1bn per drug, and domestic clinical trials cost between JPY1bn and JPY2bn.

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

Strengths and weaknesses

Strengths

Unique candidate selection process: SymBio makes decisions on in-licensing new drug candidates based on an initial assessment and screening process by its in-house search and evaluation team. The final decision is made by the company after evaluation by a team of medical experts—the Scientific Advisory Board (SAB). President Yoshida's extensive range of contacts in the pharmaceutical industry built during his tenure at Amgen Japan and Amgen Inc. is a significant hurdle for competitors attempting to emulate the quality of the company's search and evaluation team, SAB panel and selection process.

Strong product development: Treakisym® (bendamustine hydrochloride)—the first drug the company developed—received marketing approval in Japan just five years after the license agreement was signed with Astellas. Treakisym®, launched by the company in December 2010, is being used by a number of Japanese physicians and is considered to be an essential drug for the treatment of relapsed or refractory low-grade NHL and MCL. The company's success with Treakisym® demonstrates its strong product development capabilities and nimbleness.

Strong share in niche markets: SymBio focuses on niche markets for rare oncologic, hematologic, and multiviral infectious diseases and rare diseases. The company takes advantage of a less competitive environment by developing drugs for indications that serve a limited number of patients and require a high degree of in-house expertise. Thus, the company has succeeded in securing more than 50% of the target market for Treakisym® in relapsed or refractory low-grade NHL and MCL in the third year after launch.

Weaknesses

Dependence on a single individual: Founding President and CEO, Fuminori Yoshida, has played a central role in all aspects of SymBio's management since its foundation. If for any reason Mr. Yoshida is unable to perform his duties, this could have an impact on company operations.

Dependence on a single product: As of February 2023, Treakisym® accounted for all product sales of the company. SymBio is a biotech startup whose strength lies in having brought a pharmaceutical product to market, but its dependence on a single product raises the risk of earnings volatility. Sales and gross profit declined in FY12/19 and FY12/20 due to contamination and irregular appearance of lyophilized Treakisym® imported from Astellas Deutschland GmbH, which led to a temporary slump in product sales.

Market overview

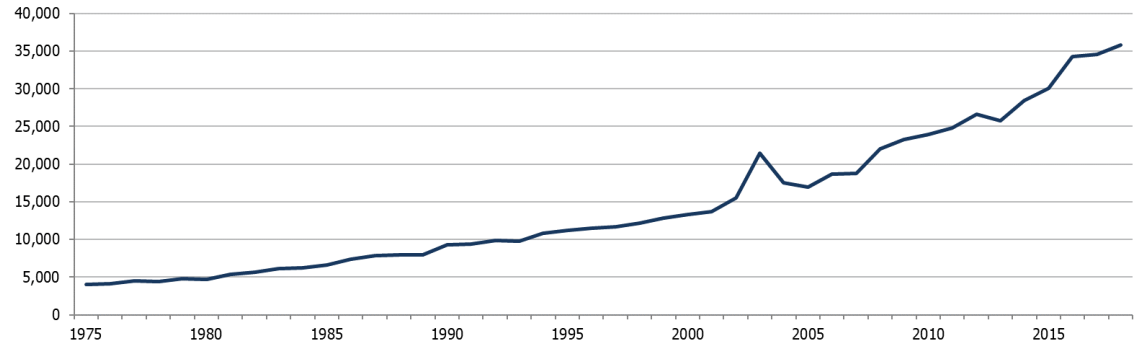
Lymphatic cancer: patient population, market size, treatment drugs

Morbidity of lymphatic cancer

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

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

Morbidity of lymphatic malignancy



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

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

Treakisym® market potential and patient population

The company estimates that the number of patients being treated for relapsed or refractory low-grade NHL and MCL in Japan is 9,336 and the number of patients with untreated low-grade NHL and MCL is 6,967. On an NHI drug reimbursement price basis, Treakisym® sales reached JPY8.5bn in FY12/18 (JPY7.6bn in FY12/17).

The company estimates that the number of Japanese patients with relapsed or refractory DLBCL is 18,672.

Treakisym® indications and number of patients

Indications	Patients	Progress	Notes
Relapsed or refractory low-grade NHL and relapsed or refractory MCL	9,336	Approved	Sales: JPY8.5bn (FY12/18)
Untreated low-grade NHL, and untreated MCL	6,967	Approved	
CLL	656	Approved	
Relapsed or refractory NHL	18,672	Clinical trials underway	

Drugs competing with Treakisym®

Drugs that compete with Treakisym® include rituximab and ibritumomab tiuxetan. SymBio has successfully pursued a development policy aimed at demonstrating that the co-administration of Treakisym® improves the efficacy of these drugs.

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.

Ibritumomab tiuxetan (product name: Zevalin)

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

Zevalin was approved in January 2008 as a treatment for refractory lymphatic cancer (low-grade B-cell NHL). It is sold by Fujifilm Toyama Chemical Co., Ltd., a subsidiary of Fujifilm Holdings Corporation (TSE Prime: 4901).

Patient population, treatment drugs for MDS

MDS patient population estimated at 11,000

A high proportion of people aged 60 or older suffer from MDS. The number of patients totaled 9,000 in 2008, with 2,781 deaths from the disease according to Japan's Ministry of Health, Labour and Welfare (MHLW).

SymBio estimates that there are currently about 11,000 MDS patients in Japan amid a larger elderly population. Even though the number of patients continues to rise, there is a high unmet medical need in Japan with no efficacious treatment available.

Rigosertib indications and number of patients

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

Source: Shared Research based on company data

Drugs competing with rigosertib

Nippon Shinyaku Co., Ltd.'s Vidaza is an IV drug approved in Japan for the main indication of MDS.

Azacitidine (product name: Vidaza)

Vidaza, developed by Pharmion Corporation (now Celgene Corporation) in the US, is a treatment for first-line intermediate and higher-risk MDS. Nippon Shinyaku Co., Ltd. (TSE Prime: 4516) signed a license agreement with Pharmion in 2006 to sell this drug in Japan, obtaining marketing approval in January 2011 following the completion of domestic clinical trials.

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

According to Nippon Shinyaku, Vidaza is the only approved drug in Japan for the first-line treatment of higher-risk MDS, with no efficacious treatment available once patients treated with Vidaza relapse. Nippon Shinyaku booked Vidaza sales of JPY15.4bn (-1.9% YoY) in FY03/21 and expects sales of JPY18.0bn in FY03/22.

Historical performance

Cumulative Q3 FY12/23 results

- Sales: JPY4.4bn (-39.9% YoY)
- Operating loss: JPY283mn (versus an operating profit of JPY1.6bn in cumulative Q3 FY12/22)
- Recurring loss: JPY156mn (versus a recurring profit of JPY1.8bn in cumulative Q3 FY12/22)
- Net loss attributable to owners of the parent: JPY789mn (versus a net income of JPY1.6bn in cumulative Q3 FY12/22)

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

The switch from the FD to RTD formulation is almost complete. With over 90% of medical institutions administering the RI formulation to patients as of end-June 2023, progress was made in the switch to the RI formulation. On the quality assurance front, SymBio also has taken steps to ensure the stable supply of the RTD formulation of Treakisym®.

Sales decreased by 39.9% YoY to JPY4.4bn. This decline can be attributed to several factors: firstly, the reduced amount of drugs used per patient due to the impact of COVID-19 and seasonal flu; secondly, the launch of generic drugs in June 2022, which affected SymBio's product sales. Additionally, there was a temporary sales spike in the same period last year resulting from the switch from the FD formulation to the RTD formulation, which impacted this year's sales.

- The 39.9% YoY drop in cumulative Q3 sales outpaced the decline projected in the company's previous forecast. As a result, the company further downgraded its sales forecast from JPY6.5bn (-35.3% YoY) to JPY5.6bn (-44.0% YoY). The company had expected the sales volume of the RTD formulation of Treakisym® to return to pre-pandemic levels, but the recovery of usage in the treatment of malignant lymphoma fell short of expectations.

- The decline in Treakisym® RTD sales was primarily due to generic competition, the impact of the pandemic, and the seasonal influenza outbreak. As a result, drug usage per malignant lymphoma case continued to decline and treatment delays persisted, leading to a contraction of the overall bendamustine market (which include both Treakisym® and generic products).

- The company expects a decision from the Tokyo District Court in early 2024 on its patent infringement lawsuit against the generic version of Treakisym® RTD. The company is seeking an injunction to stop sales of the generic products and damages for patent infringement.

Gross profit totaled JPY3.5bn (-36.4% YoY) and the gross profit margin was 78.6% (+4.3pp YoY). SG&A expenses came to JPY3.8bn (-3.1% YoY), including R&D expenses of JPY1.8bn (+16.6% YoY). As a result, the company recorded an operating loss of JPY283mn (versus an operating profit of JPY1.6bn in cumulative Q3 FY12/22).

- SG&A expenses, excluding R&D expenses, were JPY1.9bn (-16.4% YoY). In FY12/22, the company reduced its employee count by 19 compared to the end of the previous fiscal year. SymBio has continued downsizing in FY12/23, and the associated reduction in personnel costs also contributed to the lower SG&A expenses.

- GPM was 78.6% (+4.3pp YoY) in cumulative Q3. This improvement was due to the absence of a one-time milestone payment of JPY550mn recorded in Q3 of the previous year.

Progress versus full-year FY12/23 company forecast (revised on August 2023)

In November 2023, SymBio announced a second revision to its full-year forecast for FY12/23, lowering projections for both sales and operating profit (refer to the Full-year company forecast section for details). Cumulative Q3 sales of JPY4.4bn, compared to the revised full-year forecast of JPY5.6bn, represent a progress rate of 78.9%. The company's sales are normally weighted toward 2H, but the revised forecast takes into account the latest sales trend.

Against the full-year company forecast of an operating loss of JPY680mn, the operating loss for cumulative Q3 was JPY283mn. This implies that the projected operating loss for Q4 is JPY397mn. The larger projected loss in Q4 is partly due to

R&D expenses, which are typically higher in 2H for SymBio, particularly in Q4.

Business progress

As of November 2023, the year-to-date progress in the company's key businesses was as follows.

- In November 2023, SymBio announced the results of Phase II clinical trials for BCV targeting adenovirus infections. These results will be presented at the 65th American Society of Hematology Annual Meeting in December 2023.
- In October 2023, US licensor Onconova the released data related to rigosertib in treating squamous cell carcinoma.
- In October 2023, SymBio published the results of a collaborative study on the treatment of multiple sclerosis with BCV.
- In October 2023, the company announced the conclusion of STraight-Equity Issue Program (STEP) and the issuance of new shares through third-party allotment.
- In August 2023, SymBio announced a change in the global chief medical officer.
- In August 2023, SymBio announced changes to the clinical development plan for the injectable drug brincidofovir (BCV) for the treatment of BK virus infections.
- In July 2023, the company's US subsidiary, Symbio Pharma USA, appointed Dr. Stephane Berthier, PharmD, as CEO and president to expand its global development structure.
- In June 2023, research findings related to a biomarker (TLE1/transcription factor) predicting the anti-tumor effect of BCV were published.
- In May 2023, the proof of concept (POC) was established in the Phase II clinical trial of BCV for the treatment of adenovirus infection.
- In April 2023, the company entered into a CRADA with the National Institute of Allergy and Infectious Diseases (NIAID), part of the NIH, to evaluate the therapeutic effects of BCV in diseases caused by the EBV.
- In March 2023, the company entered into a cooperative research and development agreement (CRADA) with the National Institute of Neurological Disorders and Stroke (NINDS), part of the US National Institutes of Health (NIH), to develop brincidofovir (BCV) as a treatment for multiple sclerosis. Since August 2022, the company and NINDS have been collaborating on evaluating the antiviral effects of BCV against the Epstein-Barr virus (EBV).

Establishment of an in-house sales organization

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

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

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

In March 2021, SymBio obtained approval for the use of the FD formulation of TREAKISYM® in BR therapy to treat r/r DLBCL as an additional indication. In February 2022, the company secured approval for a partial amendment to the marketing authorization for the ready-to-dilute (RTD) formulation of TREAKISYM® (in-licensed from US-based Eagle Pharmaceuticals, Inc.), enabling the use of RI administration for all approved indications of the RTD formulation.

SymBio will continue to explore new potential applications of TREAKISYM® through joint research with Kyoto University.

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

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

For rigosertib and TREAKISYM®, the company is searching for new indications as well as new applications for the drugs used in combination with each other or with other existing drugs, through joint research and the offering of academia-industry collaborative courses with the University of Tokyo.

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

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

Broad potential of BCV and rights relative to Chimerix

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

In September 2022, Chimerix announced that it had completed procedures to transfer the rights to brincidofovir to Emergent BioSolutions Inc. (headquarters: Maryland, US). The agreement, however, has no impact on the company's exclusive rights to develop, manufacture, and sell brincidofovir globally for all indications except orthopoxvirus diseases including smallpox and monkeypox.

BCV clinical development: disseminated AdV infections following hematopoietic stem cell transplantation

Based on a global advisory board review held in February 2020, the company has decided to prioritize the global development of BCV IV primarily in Japan, the US, and Europe, targeting disseminated AdV infections occurring after hematopoietic stem cell transplantation, a niche area with a high unmet medical need.

In March 2021, the company filed an IND application with the US Food and Drug Administration (FDA) to conduct a Phase II clinical trial primarily in pediatric patients suffering from AdV infections (also including adults). This development program was granted fast-track designation by the FDA in April 2021, and the investigational drug was administered to the first patient in August 2021. In January 2022, a clinical trial application (CTA) was submitted to the UK's Medicines and Healthcare products Regulatory Agency (MHRA). In May 2023, the same study demonstrated proof of concept (POC) for BCV in human patients. Positive trial data demonstrating the BCV's effectiveness will be orally presented at the 65th American Society of Hematology Annual Meeting in December 2023.

- The Data Safety Monitoring Board (DSMB) and the FDA confirmed the POC in terms of both safety and efficacy. While the POC has been confirmed in trials up to cohort 3, the company is continuing to verify the POC with cohort 4 at the request of the FDA. The dosage regimens for cohorts 1 through 4 are as follows.

- For cohorts 1 to 3, BCV was administered twice weekly, at doses of 0.2mg/kg for cohort 1, 0.3mg/kg for cohort 2, and 0.4mg/kg for cohort 3. In cohort 3 (0.4mg/kg, twice weekly via IV), the disappearance of AdV in the blood was confirmed in 100% of patients (n=10). Of these, 90% of patients (n=9) achieved viral clearance within four weeks of treatment.

BCV clinical development: BK virus infection following kidney transplantation

BK virus nephropathy after kidney transplantation is considered a disease with serious consequences for the recipient, the donor, the medical practitioner, and society, as it may result in serious conditions such as decreased renal function and graft loss. In order to find an early solution to this problem, SymBio submitted a clinical trial notification for a global Phase II study in patients infected with BK virus after receiving kidney transplant to the Pharmaceuticals and Medical Devices Agency

(PMDA) of Japan in May 2022 and to the Therapeutic Goods Administration (TGA) of Australia in August 2022. The investigational drug was administered to the first patient in Australia in August 2022. The trial was originally planned to conclude in 2025, but progress has been slower than expected due to delays in patient enrollment. SymBio announced a change to its clinical development plan in August 2023, stating that it will consider a protocol amendment.

- The company has decided to prioritize two clinical trials: a Phase Ib clinical trial for cytomegalovirus infection following hematopoietic stem cell transplantation and another Phase Ib clinical trial for brain tumors. Typically, it is easier to accumulate cases in trials targeting larger markets.

BCV non-clinical studies: EB virus, multiple sclerosis, lymphoproliferative disorders

SymBio has been preparing for clinical development of brincidofovir for multiple sclerosis, a rare disease related to EB virus. In August 2022, the company signed a collaboration agreement for the transfer of human materials with the National Institute of Neurological Disorders and Stroke (NINDS) of the US National Institute of Health (NIH). In March 2023, SymBio signed a cooperative research and development agreement (CRADA) with NINDS to obtain information necessary to conduct future clinical trials. In October 2023, the research results were presented at the 9th Joint ECTRIMS-ACTRIMS Meeting in Milan, Italy.

CRADA: Refers to a contract on collaborative R&D between a US government organization and entities such as a private-sector company. The private-sector company may be able to obtain licensing of patent rights regarding inventions developed under the CRADA. Because a company may receive patent rights from a project using government funds, the barriers to being selected for a CRADA are significant (SymBio is the second Japanese company to be selected).

In April 2023, SymBio also signed a CRADA with the National Institute of Allergy and Infectious Diseases (NIAID), part of the NIH, to evaluate the efficacy of BCV in EB virus-related lymphoproliferative* disorders.

*Refers to a wide range of diseases related to the EB virus: Cancers such as T-cell lymphoma, Burkitt lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, NK T-cell lymphoma, and post-transplant lymphoproliferative disease, X-linked lymphoproliferative syndrome, and AIDS-related lymphoproliferative disease. (Source: Materials for company's 18th ordinary general meeting of shareholders.)

BCV non-clinical study: polyomavirus

In November 2022, the company concluded a material transfer agreement (MTA) with US-based Penn State College of Medicine, and initiated a non-clinical study evaluating the efficacy of BCV in a mouse model of polyomavirus infection.

BCV non-clinical joint research: herpes simplex virus, Alzheimer's type dementia

In December 2022, the company concluded a sponsored research agreement with US-based Tufts University, and began a joint research study evaluating the efficacy of BCV in a herpes simplex virus infection model. This study aims to explore BCV's potential to treat neurological diseases, including Alzheimer's disease.

BCV non-clinical joint research: applications for hematological malignancies/oncology

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

In December 2022, the results of collaborative research with the National Cancer Centre Singapore (NCCS) on the therapeutic efficacy of BCV in the treatment of rapidly progressing NK/T-cell lymphoma were presented at the 64th American Society of Hematology (ASH) Annual Meeting.

At the 17th International Conference on Malignant Lymphoma (ICML) in June 2023, research into a biomarker* (TLE1/transcription factor) that predicts the anti-tumor effect of BCV was presented.

*The use of biomarkers allows for the selection of patients who are likely to respond well to treatment, which increases the probability of successful clinical trials.

Development potential for BCV in other areas

Joint research with the National Institute of Infectious Diseases has found BCV to have potent antiviral activity against viral hemorrhagic cystitis (VHC) after hematopoietic stem cell transplantation, a disease associated with adenovirus type B11, and epidemic keratoconjunctivitis, a disease associated with adenovirus type D54. Of these, epidemic keratoconjunctivitis in the ophthalmic area is a non-core area. Herpes virus development in the dermatological space is also outside of the company's core competency. Shared Research believes development of non-core areas is a low priority.

BCV development policy

SymBio aims to maximize the business value of BCV by examining the efficacy of the drug in dsDNA virus infections, expanding target indications to include multiviral infections, and striving to meet the underserved medical needs for treatments of viral diseases and accompanying complications.

SymBio explained its BCV development policy to 2030 at the FY12/22 earnings results information briefing. In addition to the core areas of hematological cancer/oncology, the company is entering the neurodegenerative diseases (NDD) space, such as multiple sclerosis and Alzheimer's type dementia. SymBio will not develop BCV independently for neurodegenerative diseases but looks to partner with a major pharmaceutical company capable of global development (see details in the Long-term outlook section, R&D image to 2030). The company expects to receive about JPY10bn in compensation for transferring rights to the joint development over five years (2025–2030).

SymBio aims for approval and commercialization of two or three indications for BCV by 2030. The indication with the highest potential for approval is viral infection following hematopoietic stem cell and kidney transplantation, two areas of clinical development prioritization.

Overseas development bases (SPU/SymBio Pharma USA)

In August 2023, the company's US-based wholly-owned subsidiary SymBio Pharma USA, Inc. appointed Dr. Stephane Berthier as CEO and President to further reinforce its global development structure. SymBio Pharma USA plans to accelerate global development of the antiviral drug brincidofovir.

In-licensing of drug candidates

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

Topics: Drug Discovery AI

The company has been pursuing a lab-less and fab-less strategy, without owning any research institutes or manufacturing sites. During its earnings announcement in August 2023, the company announced the establishment of the Institute of AI Biosciences (IOAB). At this institute, the company has built its own AI drug discovery system and implemented the Global Medical & Science Information collection system, a system on par with those of the world's most advanced research institutes, into its proprietary platform.

Fundraising

In October 2023, SymBio announced it will enter into an agreement with EVO FUND to set up a STraight-Equity Issue Program (STEP) and issue new shares through third-party allotment under this program. The total number of shares that may be issued under the program is 6,000,000, and the dilution rate, based on the total number of issued shares of 39,841,000 at end-June 2023, is 15.06% (15.25% based on voting rights). The estimated net proceeds are JPY2.2bn. (See the Recent update section for details.)

1H FY12/23 results

- Sales: JPY3.2bn (-34.8% YoY)
- Operating loss: JPY50mn (operating profit of JPY1.4bn in 1H FY12/22)

- Recurring profit: JPY67mn (-95.4% YoY)
- Net loss attributable to owners of the parent: JPY80mn (net income of JPY1.1bn in FY12/22)

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

The switch from the FD to RTD formulation is almost complete. With over 90% of medical institutions administering the RI formulation to patients as of end-June 2023, progress was made in the switch to the RI formulation. On the quality assurance front, SymBio also has taken steps to ensure the stable supply of the RTD formulation of Treakisym®.

Sales decreased 34.8% YoY to JPY3.2bn. The decline was due to the following factors: 1) medical institutions were reluctant to purchase drugs due to price revisions; 2) the amount of drugs used per patient decreased during the COVID-19 pandemic; and 3) the launch of generic drugs in June 2022 affected SymBio's product sales. In addition, there was a temporary sales spike last year due to the switch from the FD formulation to the RTD formulation, which impacted this year's sales.

- The 34.8% YoY decline in 1H sales exceeded the company's initial forecast of a 30.1% YoY decrease for the full year. As a result, the company has downgraded its full-year sales forecast from JPY7.0bn to JPY6.5bn (-35.3% YoY). The company had expected the sales volume of the RTD formulation of Treakisym® to return to pre-pandemic levels, but the recovery of usage in the treatment of malignant lymphoma fell short of expectations.

- The price reduction for Treakisym® RTD in the April 2023 NHI price revision was relatively small at around 3.5%. The drop in sales is therefore mainly due to generic penetration and the impact of the pandemic. Although the rate of market share loss for Treakisym® is relatively slow compared to other anticancer drugs for which generics have been introduced, the company noted that incentives for hospitals to use generics (reimbursement premium) are impacting sales of its branded drug.

- The company expects a decision from the Tokyo District Court in early 2024 on its patent infringement lawsuit against the generic version of Treakisym® RTD. The company is seeking an injunction to stop sales of the generic products and damages for patent infringement.

Gross profit totaled JPY2.5bn (-38.3% YoY) and the gross profit margin was 77.8% (-4.5pp YoY). SG&A expenses came to JPY2.5bn (-4.4% YoY), including R&D expenses of JPY1.2bn (+19.3% YoY). As a result, the company recorded an operating loss of JPY50mn (vs. operating profit of JPY1.4bn in 1H FY12/22).

- SG&A expenses excluding R&D expenses were JPY1.3bn (-19.0% YoY). In FY12/22, the company reduced its employee count by 19 compared to the previous fiscal year (as of December 2022). The company said it further downsized its workforce in 1H, and the associated reduction in personnel costs also contributed to the lower SG&A expenses.

- The gross profit margin was 80.4% in Q4 FY12/22, 80.5% in Q1 FY12/23, and 75.3% in Q2 FY12/23. The decrease in GPM in Q2 was due to the drug price revision in April 2023, which reduced the price of Treakisym® by approximately 3.5%.

Progress versus full-year FY12/23 company forecast (revised on August 2023)

In August 2023, SymBio announced a revision to its full-year forecast for FY12/23. While the sales forecast was lowered, the operating profit forecast remained unchanged (see the Full-year company forecast section for details). The 1H sales of JPY3.2bn represent a progress rate of 49.1% against the revised full-year forecast of JPY6.5bn. The company's sales are normally skewed towards 2H due to seasonal factors.

The company reported an operating loss of JPY50mn in 1H, compared with a full-year operating loss forecast of JPY331mn. The relatively smaller loss was partly due to the fact that SG&A expenses in 1H were only 46.9% of the full-year budget of JPY5.4bn (of which, R&D expenses were 41.8% of the budget). Typically, the company's R&D expenses are more heavily burdened in 2H.

Business progress

As of August 2023, the year-to-date progress in the company's key businesses was as follows.

- In August 2023, SymBio announced changes to the clinical development plan for the injectable drug brincidofovir (BCV) for the treatment of BK virus infections.
- In July 2023, the company's US subsidiary, Symbio Pharma USA, appointed Dr. Stephane Berthier, PharmD, as CEO and president to expand its global development structure.
- In June 2023, research findings related to a biomarker (TLE1/transcription factor) predicting the anti-tumor effect of BCV were published.
- In May 2023, the proof of concept (POC) was established in the Phase II clinical trial of BCV for the treatment of adenovirus infection.
- In April 2023, the company entered into a CRADA with the National Institute of Allergy and Infectious Diseases (NIAID), part of the NIH, to evaluate the therapeutic effects of BCV in diseases caused by the EBV.
- In March 2023, the company entered into a cooperative research and development agreement (CRADA) with the National Institute of Neurological Disorders and Stroke (NINDS), part of the US National Institutes of Health (NIH), to develop brincidofovir (BCV) as a treatment for multiple sclerosis. Since August 2022, the company and NINDS have been collaborating on evaluating the antiviral effects of BCV against the Epstein-Barr virus (EBV).

Establishment of an in-house sales organization

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

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

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

In March 2021, SymBio obtained approval for the use of the FD formulation of TREAKISYM® in BR therapy to treat r/r DLBCL as an additional indication. In February 2022, the company secured approval for a partial amendment to the marketing authorization for the ready-to-dilute (RTD) formulation of TREAKISYM® (in-licensed from US-based Eagle Pharmaceuticals, Inc.), enabling the use of RI administration for all approved indications of the RTD formulation.

SymBio will continue to explore new potential applications of TREAKISYM® through joint research with Kyoto University.

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

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

For rigosertib and TREAKISYM®, the company is searching for new indications as well as new applications for the drugs used in combination with each other or with other existing drugs, through joint research and the offering of academia-industry collaborative courses with the University of Tokyo.

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

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

Broad potential of BCV and rights relative to Chimerix

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

In September 2022, Chimerix announced that it had completed procedures to transfer the rights to brincidofovir to Emergent BioSolutions Inc. (headquarters: Maryland, US). The agreement, however, has no impact on the company's exclusive rights to develop, manufacture, and sell brincidofovir globally for all indications except orthopoxvirus diseases including smallpox and monkeypox.

BCV clinical development: disseminated AdV infections following hematopoietic stem cell transplantation

Based on a global advisory board review held in February 2020, the company has decided to prioritize the global development of BCV IV primarily in Japan, the US, and Europe, targeting disseminated AdV infections occurring after hematopoietic stem cell transplantation, a niche area with a high unmet medical need.

In March 2021, the company filed an IND application with the US Food and Drug Administration (FDA) to conduct a Phase II clinical trial primarily in pediatric patients suffering from AdV infections (also including adults). This development program was granted fast-track designation by the FDA in April 2021, and the investigational drug was administered to the first patient in August 2021. In January 2022, a clinical trial application (CTA) was submitted to the UK's Medicines and Healthcare products Regulatory Agency (MHRA). In May 2023, the same study demonstrated proof of concept (POC) for BCV in human patients. As of end-June 2023, a total of 27 cases have been enrolled and patient enrollment is ongoing.

- The Data Safety Monitoring Board (DSMB) and the FDA confirmed the POC in terms of both safety and efficacy. While the POC has been confirmed in trials up to cohort 3, the company is continuing to verify the POC with cohort 4 at the request of the FDA. The dosage regimens for cohorts 1 through 4 are as follows.

- In cohorts 1 to 3, BCV was administered twice a week for four weeks, with dosages of 0.2mg/kg for cohort 1, 0.3mg/kg for cohort 2, and 0.4mg/kg for cohort 3. The dosage for cohort 4 (0.4mg/kg) is the same as that for cohort 3, but the number of doses is reduced to once weekly for four weeks.

BCV clinical development: BK virus infection following kidney transplantation

BK virus nephropathy after kidney transplantation is considered a disease with serious consequences for the recipient, the donor, the medical practitioner, and society, as it may result in serious conditions such as decreased renal function and graft loss. In order to find an early solution to this problem, SymBio submitted a clinical trial notification for a global Phase II study in patients infected with BK virus after receiving kidney transplant to the Pharmaceuticals and Medical Devices Agency (PMDA) of Japan in May 2022 and to the Therapeutic Goods Administration (TGA) of Australia in August 2022. The investigational drug was administered to the first patient in Australia in August 2022. The trial was originally planned to conclude in 2025, but progress has been slower than expected due to delays in patient enrollment. SymBio announced a change to its clinical development plan in August 2023, stating that it will consider a protocol amendment.

- The company has decided to prioritize two clinical trials: a Phase Ib clinical trial for cytomegalovirus infection following hematopoietic stem cell transplantation and another Phase Ib clinical trial for brain tumors. Typically, it is easier to accumulate cases in trials targeting larger markets.

BCV non-clinical studies: EB virus, multiple sclerosis, lymphoproliferative disorders

SymBio has been preparing for clinical development of brincidofovir for multiple sclerosis, a rare disease related to EB virus. In August 2022, the company signed a collaboration agreement for the transfer of human materials with the National Institute of Neurological Disorders and Stroke (NINDS) of the US National Institute of Health (NIH). In March 2023, SymBio

signed a cooperative research and development agreement (CRADA) with NINDS to obtain information necessary to conduct future clinical trials.

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In April 2023, SymBio also signed a CRADA with the National Institute of Allergy and Infectious Diseases (NIAID), part of the NIH, to evaluate the efficacy of BCV in EB virus-related lymphoproliferative* disorders.

*Refers to a wide range of diseases related to the EB virus: Cancers such as T-cell lymphoma, Burkitt lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, NK T-cell lymphoma, and post-transplant lymphoproliferative disease, X-linked lymphoproliferative syndrome, and AIDS-related lymphoproliferative disease. (Source: Materials for company's 18th ordinary general meeting of shareholders.)

BCV non-clinical study: polyomavirus

In November 2022, the company concluded a material transfer agreement (MTA) with US-based Penn State College of Medicine, and initiated a non-clinical study evaluating the efficacy of BCV in a mouse model of polyomavirus infection.

BCV non-clinical joint research: herpes simplex virus, Alzheimer's type dementia

In December 2022, the company concluded a sponsored research agreement with US-based Tufts University, and began a joint research study evaluating the efficacy of BCV in a herpes simplex virus infection model. In the future, the company is looking for applications to use BCV to treat Alzheimer's type dementia as a target treatment for HSV.

BCV non-clinical joint research: applications for hematological malignancies/oncology

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

In December 2022, the results of collaborative research with the National Cancer Centre Singapore (NCCS) on the therapeutic efficacy of BCV in the treatment of rapidly progressing NK/T-cell lymphoma were presented at the 64th American Society of Hematology (ASH) Annual Meeting.

At the 17th International Conference on Malignant Lymphoma (ICML) in June 2023, research into a biomarker* (TLE1/transcription factor) that predicts the anti-tumor effect of BCV was presented.

*The use of biomarkers allows for the selection of patients who are likely to respond well to treatment, which increases the probability of successful clinical trials.

Development potential for BCV in other areas

Joint research with the National Institute of Infectious Diseases has found BCV to have potent antiviral activity against viral hemorrhagic cystitis (VHC) after hematopoietic stem cell transplantation, a disease associated with adenovirus type B11, and epidemic keratoconjunctivitis, a disease associated with adenovirus type D54. Of these, epidemic keratoconjunctivitis in the ophthalmic area is a non-core area. Herpes virus development in the dermatological space is also outside of the company's core competency. Shared Research believes development of non-core areas is a low priority.

BCV development policy

SymBio aims to maximize the business value of BCV by examining the efficacy of the drug in dsDNA virus infections, expanding target indications to include multiviral infections, and striving to meet the underserved medical needs for

treatments of viral diseases and accompanying complications.

SymBio explained its BCV development policy to 2030 at the FY12/22 earnings results information briefing. In addition to the core areas of hematological cancer/oncology, the company is entering the neurodegenerative diseases (NDD) space, such as multiple sclerosis and Alzheimer's type dementia. SymBio will not develop BCV independently for neurodegenerative diseases but looks to partner with a major pharmaceutical company capable of global development (see details in the Long-term outlook section, R&D image to 2030). The company expects to receive about JPY10bn in compensation for transferring rights to the joint development over five years (2025–2030).

SymBio aims for approval and commercialization of two or three indications for BCV by 2030. The indication with the highest potential for approval is viral infection following hematopoietic stem cell and kidney transplantation, two areas of clinical development prioritization.

Overseas development bases (SPU/SymBio Pharma USA)

In August 2023, the company's US-based wholly-owned subsidiary SymBio Pharma USA, Inc. appointed Dr. Stephane Berthier as CEO and President to further reinforce its global development structure. SymBio Pharma USA plans to accelerate global development of the antiviral drug brincidofovir.

In-licensing of drug candidates

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

Topics: Drug Discovery AI

The company has been pursuing a lab-less and fab-less strategy, without owning any research institutes or manufacturing sites. During its earnings announcement in August 2023, the company announced the establishment of the Institute of AI Biosciences (IOAB). At this institute, the company has built its own AI drug discovery system and implemented the Global Medical & Science Information collection system, a system on par with those of the world's most advanced research institutes, into its proprietary platform.

Q1 FY12/23 results

- Sales: JPY1.5bn (-33.3% YoY)
- Operating profit: JPY51mn (-89.9% YoY)
- Recurring profit: JPY48mn (-89.9% YoY)
- Net income attributable to owners of the parent for the quarter: JPY4mn (-97.3% YoY)

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

The switch from the FD to RTD formulation is almost complete. With over 80% of medical institutions administering the RI formulation to patients as of end-March 2023, progress was made in the switch to the RI formulation. On the quality assurance front, SymBio also has taken steps to ensure the stable supply of the RTD formulation of TREAKISYM®.

Sales decreased 33.3% YoY to JPY1.5bn. The decline was due to the following factors: 1) medical institutions were reluctant to purchase drugs due to price revisions; 2) the amount of drugs used per patient decreased during the COVID-19 pandemic; and 3) the launch of generic drugs in June 2022 affected SymBio's product sales. In addition, there was a temporary sales spike last year due to the switch from the FD formulation to the RTD formulation, which impacted this year's sales.

- According to the company, the biggest factor in the steeper 33.1% YoY fall in Q1 versus its forecast of a 30.1% YoY decline in sales in FY12/23 was a fallback from the temporary spike in sales the previous year. It explains that sales of JPY2.3bn (+63.1% YoY) in Q1 FY12/22 were significantly boosted by a temporary sales spike accompanying the switch to the RTD formulation. It thinks the penetration of generic drugs will have an increasingly large impact from Q2 onward.

Gross profit totaled JPY1.2bn (-34.5% YoY) and the gross profit margin was 80.5% (-1.5pp YoY). SG&A expenses came to JPY1.2bn (-14.2% YoY), including R&D expenses of JPY550mn (+10.8% YoY). As a result, operating profit was JPY51mn (-89.9% from operating profit of JPY509mn in FY12/22).

- GPM was 80.5% (-1.5pp YoY) and up 0.1pp from 80.4% in Q4 FY12/22.
- SG&A expenses excluding R&D expenses were JPY642mn (-28.1% YoY). The company explained that at end-December 2022, the number of employees decreased by 19 YoY, resulting in a decline in personnel expenses.

April 2023 NHI drug price revisions

In the April 2023 drug price revisions, the new price for the intravenous formulation of TREAKISYM® 100mg/4ml was JPY92,175, a cut of just 3.5% from the previous JPY95,515. TREAKISYM® had benefited from the price maintenance incentive system for newly discovered drugs, but the impact of losing this incentive was minor (Shared Research previously assumed a price cut of at least 10%).

Progress in Q1 versus full-year FY12/23 company forecast

Sales progress versus the full-year FY12/23 company forecast was 22.1%, versus 23.1% of full-year sales in Q1 FY12/22. However, Shared Research understands that progress was in line with company expectations given that sales in FY12/22 got a temporary boost with the switchover to the RTD formulation, and that in Q1 FY12/23, some customers were putting off purchases ahead of the NHI drug price revisions.

The company booked operating profit of JPY51mn in Q1 FY12/23, versus a full-year forecast operating loss of JPY331mn. One reason was that SG&A expenses were just 20.4% of the full-year budget of JPY5.9bn. Shared Research understands that progress at the profit line was also in line with company expectations, as the company made progress in using up R&D expenses in Q4 FY12/22.

Business progress

In Q1 FY12/23, progress in the company's main businesses was as follows:

- In March 2023, the company entered into a cooperative research and development agreement (CRADA) with the National Institute of Neurological Disorders and Stroke (NINDS), part of the US National Institutes of Health (NIH), to develop brincidofovir (BCV) as a treatment for multiple sclerosis. Since August 2022, the company and NINDS have been collaborating on evaluating the antiviral effects of BCV against the Epstein-Barr virus (EBV).
- In April 2023, the company entered into a CRADA with the National Institute of Allergy and Infectious Diseases (NIAID), part of the NIH, to evaluate the therapeutic effects of BCV in diseases caused by the EBV.

Establishment of an in-house sales organization

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

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

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

In March 2021, SymBio obtained approval for the use of the FD formulation of TREAKISYM® in BR therapy to treat r/r DLBCL as an additional indication. In February 2022, the company secured approval for a partial amendment to the marketing authorization for the ready-to-dilute (RTD) formulation of TREAKISYM® (in-licensed from US-based Eagle Pharmaceuticals, Inc.), enabling the use of RI administration for all approved indications of the RTD formulation.

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

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

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

For rigosertib and TREAKISYM®, the company is searching for new indications as well as new applications for the drugs used in combination with each other or with other existing drugs, through joint research and the offering of academia-industry collaborative courses with the University of Tokyo.

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

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

Broad potential of BCV and rights relative to Chimerix

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

In September 2022, Chimerix announced that it had completed procedures to transfer the rights to brincidofovir to Emergent BioSolutions Inc. (headquarters: Maryland, US). The agreement, however, has no impact on the company's exclusive rights to develop, manufacture, and sell brincidofovir globally for all indications except orthopoxvirus diseases including smallpox and monkeypox.

BCV clinical development: disseminated AdV infections following hematopoietic stem cell transplantation

Based on a global advisory board review held in February 2020, the company has decided to prioritize the global development of BCV IV primarily in Japan, the US, and Europe, targeting disseminated AdV infections occurring after hematopoietic stem cell transplantation, a niche area with a high unmet medical need.

In March 2021, the company filed an IND application with the US Food and Drug Administration (FDA) to conduct a Phase II clinical trial primarily in pediatric patients suffering from AdV infections (also including adults). This development program was granted fast-track designation by the FDA in April 2021, and the investigational drug was administered to the first patient in August 2021. In January 2022, a clinical trial application (CTA) was submitted to the UK's Medicines and Healthcare products Regulatory Agency (MHRA). Completion of the study is projected for Q2 FY12/23. As of end-March 2023, cumulative patient enrollment came to 22.

BCV clinical development: BK virus infection following kidney transplantation

BK virus nephropathy after kidney transplantation is considered a disease with serious consequences for the recipient, the donor, the medical practitioner, and society, as it may result in serious conditions such as decreased renal function and graft loss. In order to find an early solution to this problem, SymBio submitted a clinical trial notification for a global Phase II study in patients infected with BK virus after receiving kidney transplant to the Pharmaceuticals and Medical Devices Agency (PMDA) of Japan in May 2022 and to the Therapeutic Goods Administration (TGA) of Australia in August 2022. The investigational drug was administered to the first patient in Australia in August 2022.

BCV non-clinical studies: EB virus, multiple sclerosis, lymphoproliferative disorders

SymBio has been preparing for clinical development of brincidofovir for multiple sclerosis, a rare disease related to EB virus. In August 2022, the company signed a collaboration agreement for the transfer of human materials with the National Institute of Neurological Disorders and Stroke (NINDS) of the US National Institute of Health (NIH). In March 2023, SymBio

signed a cooperative research and development agreement (CRADA) with NINDS to obtain information necessary to conduct future clinical trials.

CRADA: Refers to a contract on collaborative R&D between a US government organization and entities such as a private-sector company. The private-sector company may be able to obtain licensing of patent rights regarding inventions developed under the CRADA. Because a company may receive patent rights from a project using government funds, the barriers to being selected for a CRADA are significant.

In April 2023, SymBio also signed a CRADA with the National Institute of Allergy and Infectious Diseases (NIAID), part of the NIH, to evaluate the efficacy of BCV in EB virus-related lymphoproliferative* disorders.

*Refers to a wide range of diseases related to the EB virus: Cancers such as T-cell lymphoma, Burkitt lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, NK T-cell lymphoma, and post-transplant lymphoproliferative disease, X-linked lymphoproliferative syndrome, and AIDS-related lymphoproliferative disease. (Source: Materials for company's 18th ordinary general meeting of shareholders.)

BCV non-clinical study: polyomavirus

In November 2022, the company concluded a material transfer agreement (MTA) with US-based Penn State College of Medicine, and initiated a non-clinical study evaluating the efficacy of BCV in a mouse model of polyomavirus infection.

BCV non-clinical joint research: herpes simplex virus, Alzheimer's type dementia

In December 2022, the company concluded a sponsored research agreement with US-based Tufts University, and began a joint research study evaluating the efficacy of BCV in a herpes simplex virus infection model. In the future, the company is looking for applications to use BCV to treat Alzheimer's type dementia as a target treatment for HSV.

BCV non-clinical joint research: applications for hematological malignancies/oncology

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

In December 2022, the results of collaborative research with the National Cancer Centre Singapore (NCCS) on the therapeutic efficacy of BCV in the treatment of rapidly progressing NK/T-cell lymphoma were presented at the 64th American Society of Hematology (ASH) Annual Meeting.

Development potential for BCV in other areas

Joint research with the National Institute of Infectious Diseases has found BCV to have potent antiviral activity against viral hemorrhagic cystitis (VHC) after hematopoietic stem cell transplantation, a disease associated with adenovirus type B11, and epidemic keratoconjunctivitis, a disease associated with adenovirus type D54. Of these, epidemic keratoconjunctivitis in the ophthalmic area is a non-core area. Herpes virus development in the dermatological space is also outside of the company's core competency. Shared Research believes development of non-core areas is a low priority.

BCV development policy

SymBio aims to maximize the business value of BCV by examining the efficacy of the drug in dsDNA virus infections, expanding target indications to include multiviral infections, and striving to meet the underserved medical needs for treatments of viral diseases and accompanying complications.

SymBio explained its BCV development policy to 2030 at the FY12/22 earnings results information briefing. In addition to the core areas of hematological cancer/oncology, the company is entering the neurodegenerative diseases (NDD) space, such as multiple sclerosis and Alzheimer's type dementia. SymBio will not develop BCV independently for neurodegenerative diseases but looks to partner with a major pharmaceutical company capable of global development (see details in the Long-term outlook section, R&D image to 2030). The company expects to receive about JPY10bn in compensation for transferring rights to the joint development over five years (2025–2030).

SymBio aims for approval and commercialization of two or three indications for BCV by 2030. The indication with the highest potential for approval is viral infection following hematopoietic stem cell and kidney transplantation, two areas of clinical development prioritization.

Overseas development bases (SPU/SymBio Pharma USA)

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

In-licensing of drug candidates

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

Full-year FY12/22 results

- Sales: JPY10.0bn (+21.2% YoY)
- Operating profit: JPY2.0bn (+93.3%YoY)
- Recurring profit: JPY2.0bn (+99.8% YoY)
- Net income attributable to owners of the parent: JPY1.2bn (-42.0% YoY)

SymBio has applied the Accounting Standard for Revenue Recognition (ASBJ Statement No. 29) from Q1 FY12/22. Under the previous accounting standard, the company recorded allowance for sales returns in the amount equivalent to gross profit. However, in accordance with the new accounting standard regarding variable consideration, the company no longer recognizes revenue at the time of sale and records refund liabilities as "other" under the current liabilities section of the balance sheet.

As a result of adopting the Accounting Standard for Revenue Recognition, full-year sales, operating profit, and recurring profit each increased by JPY63mn.

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

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

The switch from the FD to RTD formulation is almost complete. With over 80% of medical institutions administering the RI formulation to patients as of end-December 2022, progress was made in the switch to the RI formulation. On the quality assurance front, SymBio also has taken steps to ensure the stable supply of the RTD formulation of TREAKISYM®.

Despite sales activities being constrained by factors including delays in treatment and restrictions on medical facility visits due to the COVID-19 pandemic, sales rose 21.2% YoY to JPY10.0bn. The increase was largely due to the approval in March 2021 of TREAKISYM® for the additional indication of combination use in bendamustine-rituximab (BR) therapy and in polatuzumab vedotin plus bendamustine-rituximab (Pola-BR) therapy to treat recurrent/refractory diffuse large B-cell lymphoma (r/r DLBCL). The May 2021 NHI price listing of Chugai Pharmaceutical's antibody drug conjugate polatuzumab vedotin contributed to an increase in sales for the indication of r/r DLBCL.

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

Gross profit was JPY7.6bn (+31.0% YoY), and GPM was 75.9% (+5.7pp YoY). The rise in GPM was mainly attributable to the abovementioned switch to the liquid (RTD and RI) formulations of Treakisym®.

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

SG&A expenses were JPY5.6bn (+17.8% YoY).

- R&D expenses rose 47.2% YoY to JPY2.6bn. This included expenses for conducting clinical trials for the intravenous formulation of brincidofovir.
- Excluding R&D expenses, SG&A expenses increased 1.1% YoY to JPY3.1bn.

As a result of the above, operating profit expanded 93.3% YoY, from JPY1.0bn to JPY2.0bn.

Q4 FY12/22 (October-December 2022) results

In Q4 FY12/22, sales were JPY2.7bn (-1.9% YoY), gross profit was JPY2.1bn (+21.6% YoY), GPM was 80.4% (+15.5pp YoY), and operating profit was JPY375mn (-36.7% YoY).

Factors that contributed to sales growth were the March 2021 approval of bendamustine-rituximab (BR) therapy and bendamustine-rituximab plus genetically engineered polatuzumab vedotin (Pola-BR) therapy for treatment of r/r DLBCL and the May 2021 NHI price listing of Chugai's polatuzumab vedotin (genetically engineered), which boosted sales for the r/r DLBCL indication. However, Q4 sales declined 1.9% YoY due to market share losses to generic competition.

The increase in GPM was driven by progress in the switch to the RTD and RI formulations of Treakisym®. Although the milestone payment* booked in Q3 was not repeated, GPM did not recover to the 82.3% level of the first half. The company cited a change in the royalty rate as a factor.

*In Q3 FY12/22, the company booked as cost of sales JPY550mn in a sales milestone payment paid to Eagle Pharmaceuticals, triggered by cumulative sales of the Treakisym® RTD formulation reaching JPY11.0bn. This was a one-time payment, and was the last such milestone payment the company expects to pay.

Sales increased JPY171mn QoQ while gross profit was up JPY677mn, GPM increased 21.7pp, and operating profit rose JPY158mn. This was largely attributable to the JPY550mn milestone payment in Q3 and higher SG&A expenses in Q4.

Full-year FY12/22 results versus company forecasts

The progress rate versus full-year FY12/22 company forecasts was 100.1% for sales (JPY5mn above forecast) and 98.2% for operating profit (JPY36mn below forecast).

When SymBio reported Q3 results (November 2022), it raised its guidance for all profit categories below the operating line, citing lower SG&A expenses. Overall, FY12/22 results were in line with the company's guidance.

Overview of business progress

FY12/22 progress in main businesses was as follows:

- In December 2022, the company concluded a sponsored research agreement with US-based Tufts University, and began a joint research study evaluating the efficacy of BCV in treating herpes simplex virus (HSV) infection. In this joint research, the company will conduct a nonclinical study evaluating the efficacy of BCV in a herpes simplex virus infection model with a three-dimensional brain model established by Tufts University.
- In December 2022, SymBio and Eagle initiated a lawsuit against Pfizer Japan and Towa Pharmaceutical Co., Ltd (TSE Prime: 4553) seeking injunction against the manufacture and sale of generic drugs arising from patent infringement as

- well as compensation for damages.

- In December 2022, SymBio commenced a global Phase II study of BCV for kidney transplant recipients with BK virus infection in Australia. This is the second indication being developed for BCV, following a global Phase II study for patients infected with adenovirus after hematopoietic stem cell transplantation.

- In December 2022, the results of collaborative research with the National Cancer Centre Singapore (NCCS) on the therapeutic efficacy of BCV in the treatment of rapidly progressing NK/T-cell lymphoma were presented at the 64th American Society of Hematology (ASH) Annual Meeting.

- In November 2022, the company concluded a material transfer agreement (MTA) with US-based Penn State College of Medicine, and initiated a non-clinical study evaluating the efficacy of BCV in a mouse model of polyomavirus infection.

- In August 2022, SymBio concluded a contract to supply the US National Institute of Neurological Disorders and Stroke (NINDS; a part of the National Institutes of Health) with brincidofovir intravenous injections for use in joint research to evaluate antiviral activity against the Epstein-Barr (EB) virus. Under the agreement, the company will supply BCV so that NINDS can conduct non-clinical studies to evaluate the potential effects of BCV on diseases caused by EB virus.

- In June 2022, Symbio announced the submission of a clinical trial notification to the PMDA for a global Phase II trial of B BCV IV as a treatment for BK virus infection in kidney transplant recipients. The company aims to evaluate the safety, tolerability, and efficacy of BCV in kidney transplant recipients with BK virus infections. In August 2022, the company submitted another clinical trial notification to the Therapeutic Goods Administration (TGA) of the Australian Department of Health.

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

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

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

- In February 2022, the Ministry of Health, Labour and Welfare approved manufacture and marketing of generic drugs of the company's Treakisym® intravenous infusion (RTD formulation). As this could possibly infringe the company's exclusive rights to develop and commercialize the patent-protected product in Japan, the company consulted with the licensor Eagle Pharmaceuticals, and notified the four companies that had obtained the approval for generic drugs of the possibility of patent infringement, demanding they take appropriate actions. Among the four companies, only Towa Pharmaceutical had its drug listed in the NHI drug price list, and then Pfizer Japan also had a version price-listed in December 2022. SymBio initiated a patent infringement lawsuit against Towa Pharmaceutical and Pfizer in December 2022 seeking an injunction to halt the manufacture and sale of generic Treakisym.

- Advantages of Symbio's Treakisym® Intravenous Infusion over generic competition have included: 1) availability of RI formulation, 2) approved for more indications, and 3) established safety profile. However, additional approvals for the generic versions is gradually eroding these advantages.

    - RI formulation available: The company obtained approval for the rapid infusion (RI) administration of Treakisym®, which reduces the administration time to only 10 minutes. SymBio has licensed exclusive rights in Japan to the RI formulation from patent holder Eagle Pharmaceuticals, so Shared Research's understanding was that generic companies could not use this administration method. However, in November 2022, generic drugs also received approval for the RI administration, which can reduce the administration time to 10 minutes, diminishing the advantage of Treakisym®.

- Approved for more indications than generic competition: Approved indications for SymBio's Treakisym® include use with Pola-BR therapy for relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL) and chronic lymphocytic leukemia. Generic drugs were approved for r/r DLBCL in June 2022, thereby further eroding advantages of the original drug.

- Established safety profile: A clinical trial with 38 Japanese patients was conducted evaluating SymBio's Treakisym®. The data from this trial, coupled with safety data from US clinical trials conducted by Eagle Pharmaceuticals, were used in the approval filing. In contrast, the generic versions have only been proven safe through physico-chemical equivalence.

In September 2017, the company entered into a license agreement with Eagle Pharmaceuticals, Inc., based on which Eagle granted the company exclusive rights to develop and commercialize bendamustine liquid formulation BENDEKA® (RTD and RI formulations of Treakisym®) in Japan. According to the company, some companies in the US have attempted to launch generic versions of Treakisym® liquid formulations, but they all infringed on Eagle's patents, and Eagle prevailed in lawsuits. In February 2022, four companies obtained marketing approval for generic versions of Treakisym®, and in June 2022, only one (Towa Pharmaceutical) had its drug listed in the NHI drug price list and commercialized it. Then in December 2022, Pfizer Japan also marketed a generic version. In December 2022, Symbio and Eagle jointly filed a patent infringement lawsuit against Pfizer and Towa Pharmaceutical seeking an injunction to halt the manufacture and sales of their generic versions and compensation for damages, but a final ruling will likely take time.

Establishment of an in-house sales organization

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

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

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

In March 2021, SymBio obtained approval for the use of the FD formulation of TREAKISYM® in BR therapy to treat r/r DLBCL as an additional indication. In January 2021, the company commenced sales of the ready-to-dilute (or RTD) formulation of Treakysym® in-licensed from US-based Eagle Pharmaceuticals, Inc., having obtained marketing approval in September 2020. In April 2021, the company obtained approval for a partial change to the marketing approval of the RTD formulation for its use in BR and Pola-BR therapy for the treatment of r/r DLBCL. For the RI administration, the company completed clinical studies on safety and filed a partial change application in May 2021. This application was approved in February 2022, enabling the use of RI administration for all approved indications of the RTD formulation.

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

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

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

For rigosertib and TREAKISYM®, the company is searching for new indications as well as new applications for the drugs used in combination with each other or with other existing drugs, through joint research and the offering of academia-industry collaborative courses with the University of Tokyo.

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

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

Broad potential of BCV and rights relative to Chimerix

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

In September 2022, Chimerix announced that it had completed procedures to transfer the rights to brincidofovir to Emergent BioSolutions Inc. (headquarters: Maryland, US). The agreement, however, has no impact on the company's exclusive rights to develop, manufacture, and sell brincidofovir globally for all indications except orthopoxvirus diseases including smallpox and monkeypox.

BCV clinical development: disseminated AdV infections following hematopoietic stem cell transplantation

Based on a global advisory board review held in February 2020, the company has decided to prioritize the global development of BCV IV primarily in Japan, the US, and Europe, targeting disseminated AdV infections occurring after hematopoietic stem cell transplantation, a niche area with a high unmet medical need.

In March 2021, the company filed an IND application with the US Food and Drug Administration (FDA) to conduct a Phase II clinical trial primarily in pediatric patients suffering from AdV infections (also including adults). This development program was granted fast-track designation by the FDA in April 2021, and the investigational drug was administered to the first patient in August 2021. In January 2022, a clinical trial application (CTA) was submitted to the UK's Medicines and Healthcare products Regulatory Agency (MHRA). Completion of the study is projected for Q2 FY12/23. As of end-December 2022, cumulative patient enrollment came to 20.

BCV clinical development: BK virus infection following kidney transplantation

BK virus nephropathy after kidney transplantation is considered a disease with serious consequences for the recipient, the donor, the medical practitioner, and society, as it may result in serious conditions such as decreased renal function and graft loss. In order to find an early solution to this problem, SymBio submitted a clinical trial notification for a global Phase II study in patients infected with BK virus after receiving kidney transplant to the Pharmaceuticals and Medical Devices Agency (PMDA) of Japan in May 2022 and to the Therapeutic Goods Administration (TGA) of Australia in August 2022. The investigational drug was administered to the first patient in Australia in August 2022. The company is also preparing to conduct clinical trials in South Korea.

BCV non-clinical studies: EB virus, multiple sclerosis

SymBio has been preparing for clinical development of brincidofovir for multiple sclerosis, a rare disease related to EB virus. In August 2022, the company signed a collaboration agreement for the transfer of human materials with the National Institute of Neurological Disorders and Stroke (NINDS) of the US National Institute of Health (NIH).

BCV non-clinical study: polyomavirus

In November 2022, the company concluded a material transfer agreement (MTA) with US-based Penn State College of Medicine, and initiated a non-clinical study evaluating the efficacy of BCV in a mouse model of polyomavirus infection.

BCV non-clinical joint research: herpes simplex virus, Alzheimer's type dementia

In December 2022, the company concluded a sponsored research agreement with US-based Tufts University, and began a joint research study evaluating the efficacy of BCV in a herpes simplex virus infection model. In the future, the company is looking for applications to use BCV to treat Alzheimer's type dementia as a target treatment for HSV.

BCV non-clinical joint research: applications for hematological malignancies/oncology

In addition to antiviral activity, the company expects brincidofovir to have antitumor effects. Through joint research with the National Cancer Centre Singapore and University of California San Francisco Brain Tumor Center, SymBio is investigating

new indications for the drug in oncology, including rare brain tumors and EB virus-positive lymphoma. In March 2022, the company commenced joint research with Brown University of the US to investigate the antitumor effects of brincidofovir on glioblastoma (GBM) caused by cytomegalovirus (CMV) infection.

In December 2022, the results of collaborative research with the National Cancer Centre Singapore (NCCS) on the therapeutic efficacy of BCV in the treatment of rapidly progressing NK/T-cell lymphoma were presented at the 64th American Society of Hematology (ASH) Annual Meeting.

Development potential for BCV in other areas

Joint research with the National Institute of Infectious Diseases has found BCV to have potent antiviral activity against viral hemorrhagic cystitis (VHC) after hematopoietic stem cell transplantation, a disease associated with adenovirus type B11, and epidemic keratoconjunctivitis, a disease associated with adenovirus type D54. Of these, epidemic keratoconjunctivitis in the ophthalmic area is a non-core area. Herpes virus development in the dermatological space is also outside of the company's core competency. Shared Research believes development of non-core areas is a low priority.

BCV development policy

SymBio aims to maximize the business value of BCV by examining the efficacy of the drug in dsDNA virus infections, expanding target indications to include multiviral infections, and striving to meet the underserved medical needs for treatments of viral diseases and accompanying complications.

SymBio explained its BCV development policy to 2030 at the FY12/22 earnings results information briefing. In addition to the core areas of hematological cancer/oncology, the company is entering the neurodegenerative diseases (NDD) space, such as multiple sclerosis and Alzheimer's type dementia. SymBio will not develop BCV independently for neurodegenerative diseases but looks to partner with a major pharmaceutical company capable of global development (see details in the Long-term outlook section, R&D image to 2030). The company expects to receive about JPY10bn in compensation for transferring rights to the joint development over five years (2025–2030).

SymBio aims for approval and commercialization of two or three indications for BCV by 2030. The indication with the highest potential for approval is viral infection following hematopoietic stem cell and kidney transplantation, two areas of clinical development prioritization.

Overseas development bases (SPU/SymBio Pharma USA)

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

In-licensing of drug candidates

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

Income statement

Income statement	FY12/14	FY12/15	FY12/16	FY12/17	FY12/18	FY12/19	FY12/20	FY12/21	FY12/22	FY12/23
(JPYmn)	Parent	Parent	Parent	Parent	Parent	Parent	Parent	Parent	Cons.	Cons.
Sales	**1,955**	**1,933**	**2,368**	**3,444**	**3,836**	**2,838**	**2,987**	**8,257**	**10,008**	**5,590**
YoY	27.6%	-1.1%	22.5%	45.4%	11.4%	-26.0%	5.3%	176.4%	21.2%	-44.1%
CoGS	1,428	1,350	1,464	2,413	2,663	1,973	2,120	2,452	2,408	1,179
Gross profit	**527**	**583**	**904**	**1,031**	**1,173**	**865**	**867**	**5,800**	**7,600**	**4,411**
Gross profit margin	26.9%	30.2%	38.2%	29.9%	30.6%	30.5%	29.0%	70.2%	75.9%	78.9%
SG&A expenses	1,830	3,135	3,031	4,978	3,829	5,166	5,373	4,784	5,636	5,223
SG&A ratio	93.6%	162.1%	128.0%	144.5%	99.8%	182.1%	179.9%	57.9%	56.3%	93.4%
Operating profit	**-1,303**	**-2,552**	**-2,127**	**-3,947**	**-2,656**	**-4,302**	**-4,506**	**1,016**	**1,964**	**-812**
YoY	-	-	-	-	-	-	-	-	93.3%	-
Operating profit margin	-	-	-	-	-	-	-	12.3%	19.6%	-
Non-operating income	215	17	7	5	2	4	3	17	139	133
Non-operating expenses	22	96	196	34	95	79	112	32	103	57
Recurring profit	**-1,110**	**-2,630**	**-2,317**	**-3,977**	**-2,749**	**-4,377**	**-4,616**	**1,001**	**2,000**	**-736**
YoY	-	-	-	-	-	-	-	-	99.8%	-
Recurring profit margin	-	-	-	-	-	-	-	12.1%	20.0%	-
Extraordinary gains	2	3	9	17	10	4	529	0	106	101
Extraordinary losses	3	1	1	15	10	-	-	-	-	561
Income taxes	4	4	4	4	4	4	4	-1,031	927	767
Implied tax rate	-	-	-	-	-	-	-	-	-	-
Net income	**-1,116**	**-2,632**	**-2,313**	**-3,978**	**-2,753**	**-4,376**	**-4,090**	**2,032**	**1,179**	**-1,963**
YoY	-	-	-	-	-	-	-	-	-42.0%	-
Net margin	-	-	-	-	-	-	-	24.6%	11.8%	-

Source: Shared Research based on company data

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

See the Earnings Structure section for more information about specific items (from total sales to recurring profit) on the company's income statement. Regarding non-operating profit/loss, extraordinary gain/loss, corporate income tax, etc., extraordinary gain of JPY529mn in FY12/20 mainly comes from the booking of JPY525mn in settlement payment. Income taxes of -JPY1.0bn in FY12/21 were due to the booking of JPY1.3bn in deferred tax assets.

Historical forecast accuracy

Results vs. initial forecast	FY12/13	FY12/14	FY12/15	FY12/16	FY12/17	FY12/18	FY12/19	FY12/20	FY12/21	FY12/22
(JPYmn)	Parent	Parent	Parent	Parent	Parent	Parent	Parent	Parent	Parent	Cons.
Sales (initial forecast)	1,927	1,785	1,785	2,339	2,903	4,201	4,465	3,404	9,151	10,992
Sales (Results)	1,532	1,955	1,933	2,368	3,444	3,836	2,838	2,987	8,257	10,008
Results vs. initial forecast	**-20.5%**	**9.5%**	**8.3%**	**1.2%**	**18.6%**	**-8.7%**	**-36.4%**	**-12.2%**	**-9.8%**	**-8.9%**
Operating profit (initial forecast)	-1,889	-1,654	-1,654	-2,778	-3,238	-2,981	-3,587	-5,090	1,361	1,770
Operating profit (Results)	-1,681	-1,303	-2,552	-2,127	-3,947	-2,656	-4,302	-4,506	1,016	1,964
Results vs. initial forecast	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-25.3%**	**10.9%**
Recurring profit (initial forecast)	-1,922	-1,650	-1,650	-2,811	-3,303	-3,044	-3,612	-5,134	1,350	1,750
Recurring profit (Results)	-1,601	-1,110	-2,630	-2,317	-3,977	-2,749	-4,377	-4,616	1,001	2,000
Results vs. initial forecast	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-25.8%**	**14.3%**
Net income (initial forecast)	-1,926	-1,654	-1,654	-2,815	-3,306	-3,056	-3,612	-4,803	1,149	1,480
Net income (Results)	-1,605	-1,116	-2,632	-2,313	-3,978	-2,753	-4,376	-4,090	2,032	1,179
Results vs. initial forecast	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**76.9%**	**-20.3%**

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)	FY12/14	FY12/15	FY12/16	FY12/17	FY12/18	FY12/19	FY12/20	FY12/21	FY12/22	FY12/23
	Parent	Parent	Parent	Parent	Parent	Parent	Parent	Parent	Cons.	Cons.
Assets										
Cash and deposits	5,692	4,261	5,719	2,947	4,821	3,911	3,849	3,860	6,283	6,517
Marketable securities	899	-	-	-	-	-	-	-	-	-
Accounts receivable	273	301	487	490	412	549	407	2,148	2,085	913
Inventories	245	133	273	363	534	1	945	386	469	232
Other current assets	181	131	205	237	271	427	615	355	476	420
Total current assets	**7,290**	**4,827**	**6,685**	**4,037**	**6,038**	**4,887**	**5,815**	**6,748**	**9,313**	**8,083**
Buildings (net)	22	22	31	28	37	47	43	45	41	-
Tools, furniture, and fixtures (net)	27	31	43	18	20	19	34	39	28	-
Total tangible assets	**49**	**53**	**75**	**47**	**57**	**75**	**77**	**84**	**69**	**-**
Investments and other assets	**49**	**53**	**77**	**100**	**73**	**70**	**81**	**1,362**	**829**	**88**
Software	62	51	42	66	51	95	296	255	222	-
Other	4	1	-	3	20	146	6	4	-	-
Total intangible assets	**66**	**52**	**42**	**69**	**71**	**241**	**302**	**259**	**222**	**-**
Total fixed assets	**164**	**158**	**193**	**216**	**201**	**386**	**459**	**1,705**	**1,121**	**88**
Total assets	**7,454**	**4,984**	**6,878**	**4,252**	**6,239**	**5,274**	**6,275**	**8,453**	**10,433**	**8,170**
Liabilities										
Accounts payable	306	320	322	604	726	121	665	70	47	-
Unearned revenue	-	-	-	-	-	-	193	-	-	-
Accounts payable–other	143	184	553	331	504	639	646	515	1,164	854
Short-term debt	-	-	-	-	-	-	-	-	-	-
Other	39	47	68	76	107	112	111	933	697	103
Total current liabilities	**488**	**551**	**942**	**1,011**	**1,336**	**872**	**1,615**	**1,518**	**1,924**	**957**
Long-term debt	-	-	-	-	-	-	-	-	-	
Corporate bonds		-	450	-	-	-	-	-	-	
Other fixed liabilities	2	2	1	1	1	2	2	189	20	4
Total fixed liabilities	**2**	**2**	**451**	**1**	**1**	**2**	**2**	**189**	**3**	**4**
Total interest-bearing debt	-	-	-	-	-	-	-	-	-	-
Total liabilities	**490**	**552**	**1,394**	**1,013**	**1,338**	**874**	**1,617**	**1,707**	**1,927**	**960**
Net assets										
Capital stock	8,331	8,331	9,948	10,762	12,973	14,871	17,045	17,158	17,548	17,953
Capital surplus	8,301	8,301	9,918	10,732	12,943	14,841	17,019	17,133	17,523	17,928
Retained earnings	-9,868	-12,500	-14,813	-18,791	-21,543	-25,919	-30,010	-27,978	-26,889	-28,852
Treasury stock	-0	-0	-0	-0	-0	-15	-18	-86	-88	-89
Share subscription rights	200	300	431	537	530	621	620	519	412	277
Net assets	**6,964**	**4,432**	**5,485**	**3,239**	**4,902**	**4,400**	**4,657**	**6,746**	**8,506**	**7,210**
Working capital	212	114	439	249	220	429	686	2,464	2,508	1,145
Total interest-bearing debt	-	-	-	-	-	-	-	-	-	-
Net debt	-5,692	-4,261	-5,719	-2,947	-4,821	-3,911	-3,849	-3,860	-6,283	-6,517

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

Assets

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

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

Liabilities

As of FY12/21, the company did not have interest-bearing liabilities. Booked liabilities are accounts payable and arrears.

Net assets

Capital stock and capital surplus are increasing as a result of fundraising efforts. However, there is a deficit in retained earnings as the company continued to post losses.

Cash flow statement

Cash flow statement (JPYmn)	FY12/14	FY12/15	FY12/16	FY12/17	FY12/18	FY12/19	FY12/20	FY12/21	FY12/22	FY12/23
	Parent	Parent	Parent	Parent	Parent	Parent	Parent	Parent	Cons.	Cons.
Cash flows from operating activities (1)	-1,266	-2,272	-1,960	-3,817	-2,325	-4,351	-4,122	140	1,614	-195
Cash flows from investing activities (2)	314	1,489	-44	-78	-26	-216	-160	-71	-47	-377
Free cash flow (1+2)	-952	-783	-2,004	-3,894	-2,351	-4,567	-4,283	69	1,567	-571
Cash flows from financing activities	544	-3	3,658	1,164	4,272	3,740	4,222	-72	628	680
Depreciation and good will amortization (A)	13	24	26	30	35	38	64	94	98	96
Capital expenditures (B)	-109	-24	-28	-57	-40	-217	-149	-64	-52	-233
Change in working capital (C)	86	-98	325	-190	-29	209	257	1,777	44	-1,363
Simple FCF (NI + A + B - C)	-1,298	-2,534	-2,640	-3,815	-2,729	-4,764	-4,433	285	1,182	-737
Cash and cash equivalents (year-end)	5,092	4,261	5,719	2,947	4,821	3,911	3,849	3,860	6,283	6,517

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

Cash flows from operating activities

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

Cash flows from investing activities

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

Cash flows from financing activities

The company has historically often reported inflows from financing activities.

Main sources of funding

Date	Change in shares issued	Total shares issued	Change in capital stock and capital surplus (JPYmn)	Capital stock and capital surplus (JPYmn)	
Feb. 2011	11,032	122,769	772	8,164	Paid-in private placement
Feb. 2011	17,368	140,137	1,216	9,380	Paid-in private placement
Oct. 2011	5,100,000	19,130,900	2,628	12,019	Paid-in public offering (price determined by the book building process)
Jan. to Dec. 2013	3,921,257	23,052,157	1,244	13,263	Exercise of stock options attached to convertible corporate bonds and other stock options
Dec. 2013	6,720,200	29,772,357	2,504	15,767	Paid-in public offering (price determined by the book building process)
Dec. 2014	1,756,666	32,390,923	544	16,632	Exercise of stock options attached to convertible corporate bonds and other stock options
Jan. to Dec. 2016	14,139,901	46,530,824	3,235	19,867	Exercise of stock options attached to convertible corporate bonds and other stock options
Jan. to Dec. 2017	7,518,400	54,049,224	1,627	21,493	Exercise of stock options attached to convertible corporate bonds and other stock options
Apr. to Dec. 2018	28,349,700	82,398,924	4,422	25,915	Exercise of stock options
Jan. to Dec. 2019	1,726,800	26,437,681	3,796	29,711	Exercise of stock options
Jan. to Dec. 2020	11,765,275	38,202,956	4,349	34,064	Exercise of stock options

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

Other information

History

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

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

After its establishment, SymBio obtained financing totaling JPY1bn from Daiichi Pharmaceutical Co., Ltd. (now Daiichi Sankyo, Inc.; TSE Prime: 4568), Medical & Biological Laboratories Co., Ltd., EPS Corporation, and SBI Holdings, Inc. (TSE Prime: 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.

Treakisym® for relapsed or refractory low-grade NHL and MCL is the company's mainstay product. Clinical trials are also in preparation or under way toward attaining domestic approval for additional Treakisym® indications, RI formulation of Treakisym®, and anticancer drug rigosertib for myelodysplastic syndromes.

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

March 2005	**SymBio Pharmaceuticals Limited established with JPY30mn in capital.**
December 2005	License Agreement finalized with Astellas Pharma GmbH for SyB L-0501 (bendamustine) development and commercialization rights in Japan.
March 2006	Manufacturer's License (packaging, labeling and storage) obtained from Tokyo Metropolitan Government (License #13AZ200010).
March 2007	License Agreement finalized with Astellas Deutschland GmbH for SyB L-0501 (bendamustine) development & commercialization rights in China (HK), Taiwan, South Korea and Singapore.
August 2008	License Agreement finalized with Eisai Co., Ltd. for co-development and commercialization rights of SyB L-0501 (bendamustine) in Japan.
March 2009	SymBio Pharmaceuticals concluded Sublicense Agreement with Cephalon, Inc. for development and commercialization rights of bendamustine hydrochloride in China (HK).
May 2009	License Agreement finalized with Eisai Co., Ltd. for co-development and commercialization rights of SyB L-0501 (bendamustine) in South Korea and Singapore.
September 2010	SymBio Pharmaceuticals and Eisai launch SYMBENDA® (bendamustine) in Singapore for the treatment of Low-grade Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukemia.
October 2010	Announced NDA Approval of Treakisym® (bendamustine) in Japan.
December 2010	Launched Treakisym® in Japan.
July 2011	Onconova and SymBio Pharmaceuticals concluded License Agreement for SyB L-1101/SyB C-1101 (rigosertib, a phase III stage multi-kinase inhibitor for Myelodysplastic Syndromes).
October 2011	Launched Symbenda® (bendamustine hydrochloride) in South Korea for the treatment of Chronic Lymphocytic Leukemia and multiple myeloma.
October 2011	Listed on Osaka Securities Exchange JASDAQ Growth Market.
February 2012	Launched Innomustine® (bendamustine hydrochloride) in Taiwan for the treatment of Low-grade Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukemia.
August 2016	Received approval for the additional indication of chronic lymphocytic leukemia for Treakisym®.
December 2016	Obtained approval for the additional indication of untreated low-grade non-Hodgkin's lymphoma and mantle cell lymphoma for the anticancer drug Treakisym®
September 2017	Concluded an exclusive license agreement with Eagle Pharmaceuticals, Inc. (US) on rights to develop, market, and sell Eagle's bendamustine hydrochloride RTD and RI formulations in Japan.
September 2019	Concluded an exclusive global license agreement with Chimerix Inc. (US) on rights to develop, manufacture, and market antiviral brincidofovir for all indications except smallpox.
December 2020	Began in-house sales of anticancer drug Treakisym®
January 2021	Launched Treakisym® liquid formulation (RTD)
March 2021	Obtained approval for use of Treakisym® in bendamustine-rituximab combination therapy to treat r/r DLBCL
February 2022	Received approval for Treakisym® rapid infusion (RI) administration

Major shareholders

Top shareholders	Shares held (shares)	Shareholding ratio
Fuminori Yoshida	1,109,700	2.8%
ML PRO SEGREGATION ACCOUNT	1,001,000	2.5%
Sukenori Ito	430,000	1.1%
Daisuke Gomi	300,000	0.8%
Matsui Securities Co., Ltd.	250,200	0.6%
SMBC Nikko Securities Inc.	221,700	0.6%
Toshitaka Kashiwabara	220,025	0.6%
Nomura Securities Co., Ltd.	178,600	0.5%
Daiwa Securities Co. Ltd.	155,250	0.4%
JPMorgan Securities Japan Co., Ltd.	136,193	0.3%
Total	4,002,668	10.1%

Source: Shared Research based on company data
As of December 31, 2022
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 122 employees as of December 31, 2022.

Number of employees	FY12/13 Parent	FY12/14 Parent	FY12/15 Parent	FY12/16 Parent	FY12/17 Parent	FY12/18 Parent	FY12/19 Parent	FY12/20 Parent	FY12/21 Parent	FY12/22 Cons.
Number of employees	72	69	74	77	78	90	107	127	141	122
Change	-4	-3	5	3	1	12	17	20	14	-19

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%, and Regulatory approval: 90%.

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

Ethnic factors in the acceptability of foreign clinical data

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

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

Glossary

Immunoglobulin G (IgG)

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

Special Protocol Assessment (SPA)

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

Medical Representative (MR)

A medical information specialist is responsible for providing, collecting, and transmitting information on the quality, efficacy, safety, and other aspects of pharmaceuticals by visiting medical institutions and holding discussions with healthcare professionals. The specialist is an expert on the company's pharmaceutical products.

Overall Survival (OS)

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

Rare Disorders

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

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

Antigen

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

Myelodysplastic Syndromes

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

Contract Research Organization (CRO)

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

First-line Drug

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

Non-Hodgkin's Lymphoma (NHL)

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

Standard Therapy

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

Bridging Data

Data generated from overseas clinical trials that can be applied to Japanese patients and used in Japan regulatory filings for marketing approval. The goal is to shorten the number of preclinical/clinical studies required for marketing approval in

Japan by avoiding the need to repeat the same studies that have already been carried out overseas (e.g., dispense with the need to do a phase II and/or III clinical trial in Japan).

Progression-Free Survival (PFS)

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

Proof-of-Concept (POC)

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

Multikinase Inhibitor

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

Chronic Lymphocytic Leukemia (CLL)

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

Mantle-Cell Lymphoma (MCL)

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

Monoclonal Antibody

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

Dose-Responsiveness

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

Company name

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

News and topics

Announcement of results from Phase II clinical trial of BCV for AdV infection

2023-11-06

SymBio Pharmaceuticals Limited announced results from a Phase II clinical trial of brincidofovir (BCV) for adenovirus (AdV) infection.

The results of a Phase IIa clinical trial of BCV in patients with AdV infection will be presented at the 65th American Society of Hematology Annual Meeting and Exposition scheduled to be held in San Diego, US, in December 2023.

In this study, 27 immunocompromised patients with AdV infection received intravenous (IV) BCV twice-weekly. In the group receiving 0.4mg/kg IV BCV twice-weekly (Cohort 3), AdV clearance was confirmed in 100% of patients, and 90% of these patients achieved viral clearance within four weeks of treatment. No serious adverse events were observed.

Based on the data from this trial, the company plans to consider a Phase III trial for BCV.

US licensor Onconova releases rigosertib data for squamous cell carcinoma

2023-10-16

SymBio Pharmaceuticals Ltd. has announced that Onconova Therapeutics, Inc., the US licensor of the anticancer drug rigosertib, has revealed research findings on this drug.

Onconova presented the research data on rigosertib for the treatment of recessive dystrophic epidermolysis bullosa at the European Academy of Dermatology and Venereology Congress held in Berlin, Germany, on October 12, 2023.

Announcement of research results on multiple sclerosis treatment with BCV

2023-10-12

SymBio Pharmaceuticals Limited announced the results of the collaborative research on the use of brincidofovir (BCV) for the treatment of multiple sclerosis.

The company has been collaborating with the National Institute of Neurological Disorders and Stroke (NINDS), a part of the National Institutes of Health (NIH) in the US, on research into the treatment of multiple sclerosis. The following results were presented at the 9th Joint ECTRIMS-ACTRIMS Meeting in Milan, Italy.

- In Epstein-Barr virus (EBV)-immortalized lymphoblastoid cell lines (EBV-positive B-cell lines) derived from both multiple sclerosis patients and healthy individuals, BCV inhibited viral replication.
- In EBV-negative B-cell lines used as controls, no effects of BCV, including growth suppression, were observed.
- These data suggest the potential utility of BCV in anti-EBV therapy for patients with multiple sclerosis.

The company stated that these results indicate the potential for using BCV in the treatment of multiple sclerosis by directly targeting EBV.

Conclusion of an equity issue program and issuance of new shares through third-party allotment

2023-10-06

SymBio Pharmaceuticals Limited announced it will enter into an agreement with EVO FUND to set up a STraight-Equity Issue Program (STEP). Under this program, the company will issue new shares through third-party allotment.

Under STEP, the allotment can be made up to five times, in the 1st through 5th allotment. The total number of shares that may be issued under the program is 6,000,000, and the dilution rate, based on the total number of issued shares of 39,841 thousand at end-June 2023, is 15.06% (15.25% based on voting rights).

Funds to be raised

- Expected total payment for new shares under STEP: JPY2.2bn
- Estimated amount of issuance costs: JPY24mn
- Estimated net proceeds: JPY2.2bn

Specific use of funds to be raised

The specific use and planned expenditure period of the funds to be raised (JPY2.2bn) through the issuance of the shares are as follows.

- Development funds for antiviral drug brincidofovir (direct expenses): JPY658mn (to be expended from October 2023 to June 2024)
- Indirect expenses related to brincidofovir development: JPY742mn (to be expended from October 2023 to June 2024)
- Investment funds for new in-licensing, M&A, etc.: JPY783mn (to be expended from October 2023 to June 2024)

Summary of offer

Overview of the 1st to 5th allotment

Due date of payment	November 10, 2023, December 20, 2023, February 7, 2024, March 18, 2024, April 19, 2024 (5 times in total)
Number of shares to be issued	1.2mn common shares each time, a total of five times
Issue price	To be determined
Amount of funding	To be determined
Method for subscription or allotment	Third-party allotment
Allottee	EVO FUND

Source: Shared Research based on company data

Announcement of change in Global CMO

2023-08-29

SymBio Pharmaceuticals Ltd. has announced a change in its Global Chief Medical Officer (CMO).

The company announced that Dr. Nkechi E. Mbanefo-Azie will assume the position of Global CMO in September 2023. Dr. Mbanefo-Azie is a fellow of the Infectious Diseases Society of America and will also serve as Senior Vice President and Head of R&D of SymBio Pharma USA, a US subsidiary.

The company is working to expand SymBio Pharma USA, the development site for the injectable drug brincidofovir.

Changes to BCV IV clinical development plan for BK virus infections

2023-08-14

SymBio Pharmaceuticals Ltd. has announced changes to the clinical development plan for its intravenous formulation of brincidofovir (BCV IV) for the treatment of BK virus infections.

The company has decided to revise the clinical development plan for the Phase II clinical trial of BCV IV in patients with post-kidney transplant BK virus infections. The Phase II trial, which was originally planned to be completed in 2025, is experiencing delays in patient enrollment, and as a result the company is considering protocol amendments.

In addition, the company will prioritize two clinical trials for BCV IV that were planned to start in FY12/24. These trials are a Phase Ib trial in patients with cytomegalovirus (CMV) infection following hematopoietic stem cell transplantation and a Phase Ib trial in patients with brain tumors.

According to the company, these changes will have no impact on the financial results for FY12/23.

Revision to full-year earnings forecast for FY12/23

2023-08-03

SymBio Pharmaceuticals Limited announced a revision to its full-year earnings forecast for FY12/23.

Revision to full-year earnings forecast for FY12/23

- Sales: JPY6.5bn (vs. the previous forecast of JPY7.0bn)
- Operating loss: JPY331mn (unchanged from the previous forecast)
- Recurring loss: JPY219mn (vs. previous forecast loss of JPY351mn)
- Net loss attributable to owners of the parent: JPY370mn (unchanged from the previous forecast)

Reasons for revision

- The company downgraded its sales forecast to JPY6.5bn, a decrease of JPY523mn from the previous forecast. While the impact of bendamustine generic drugs was largely within the company's expectations, delays in the treatment of malignant lymphoma due to the impact of COVID-19 continued, despite the disease being reclassified as a Class 5 infection.

- The company maintained its operating loss outlook. While prioritizing R&D investments for the global development of brincidofovir (BCV), the company reviewed expenses to reduce SG&A spending and limit the impact of lower sales. The recurring loss forecast was revised upwards to JPY219mn due to foreign exchange gains on foreign currency-denominated assets. The net loss forecast remained unchanged, with the impact of the foreign exchange gain offset by an increase in deferred income taxes.

Change of CEO at US subsidiary

2023-07-20

SymBio Pharmaceuticals Ltd. has announced a change of CEO at its US subsidiary.

SymBio Pharma USA, Inc., a wholly owned subsidiary of SymBio Pharmaceuticals, has announced that its current CEO, Fuminori Yoshida, will be succeeded by Stephane Berthier. Mr. Yoshida will continue to serve as chairman of the Board of Directors of Symbio Pharma USA. The US subsidiary is becoming increasingly important as a development base for brincidofovir injection.

Joint research finds biomarker to predict efficacy of BCV

2023-06-12

SymBio Pharmaceuticals Limited announced that it has identified a biomarker that predicts the anti-tumor effect of the antiviral drug brincidofovir (BCV) in a joint study with the National Cancer Centre Singapore (NCCS).

The joint research by the two organizations found that BCV is highly sensitive to NK/T cell lymphoma when the cell lines have low expression of a transcriptional repressor called TLE1. NCCS will present these findings at the 17th International Conference on Malignant Lymphoma.

SymBio noted the possibility that TLE1 could be used as a biomarker to predict the efficacy of BCV in advance.

POC established for BCV IV in patients with adenovirus infections in Phase II study

2023-05-29

SymBio Pharmaceuticals Limited announced that it has established proof of concept (POC) for the antiviral effects of brincidofovir injection (BCV IV) in patients with adenovirus infections in a Phase II clinical trial.

The company is conducting a Phase II clinical trial for BCV IV in the US in patients with adenovirus infection following hematopoietic stem cell transplantation. In this trial, the company established POC for the antiviral effects of BCV IV.

Following the independent Data and Safety Monitoring Board's review of the 24-case clinical data from the Phase II trial, the company submitted the data to the FDA, which confirmed POC in humans.

The company plans to review the dose regimen for Cohort 4 (with increased dosage) while continuing discussions with the FDA to initiate a Phase III trial.

Onconova provides update on clinical study evaluating rigosertib monotherapy in squamous cell carcinoma

2023-05-10

SymBio Pharmaceuticals Limited announced that Onconova Therapeutics, Inc. (Pennsylvania, US), the licensor of rigosertib, presented at the International Society of Investigative Dermatology (ISID)'s International Epidermolysis Bullosa Symposium held in Osaka. Onconova provided an overview of its investigator-sponsored clinical trial evaluating rigosertib monotherapy in squamous cell carcinoma associated with recessive dystrophic epidermolysis bullosa (RDEB-associated SCC).

In July 2011, SymBio entered into a license agreement with Onconova for exclusive rights to develop and commercialize rigosertib in Japan and South Korea. Onconova plans to submit study results to regulatory authorities to seek approval for rigosertib in RDEB-associated SCC.

(Click here for details on the Onconova's announcement)

Announcement of cooperative research and development agreement with the US National Institute of Allergy and Infectious Diseases to evaluate brincidofovir

2023-04-24

SymBio Pharmaceuticals announced that it has entered into a cooperative research and development agreement (CRADA) with the National Institute of Allergy and Infectious Diseases (NIAID), part of the US National Institutes of Health (NIH), to evaluate the therapeutic effects of brincidofovir (BCV) in diseases caused by Epstein-Barr virus (EBV).

The company has already signed a material transfer agreement with the National Institute of Neurological Disorders and Stroke (NINDS), also part of the NIH, to evaluate the antiviral effect of BCV against EBV. The new CRADA with NIAID will evaluate the potential of BCV as a targeted therapy for EBV-related diseases using a translational platform (which serves as a bridge to clinical research) that can reproduce EBV infections and related diseases in cell and animal models.

Announcement regarding joint development of brincidofovir for multiple sclerosis

2023-03-22

SymBio Pharmaceuticals Limited announced the joint development of brincidofovir (BCV) for the treatment of multiple sclerosis.

The company has entered into a cooperative research and development agreement with the National Institute of Neurological Disorders and Stroke (NINDS), part of the US National Institutes of Health (NIH), to develop BCV for the treatment of multiple sclerosis. SymBio and NINDS have previously collaborated to evaluate the antiviral effects of BCV against the EB virus.

This joint development will accumulate information for clinical trials through in vitro testing and animal model testing of cells derived from multiple sclerosis patients infected with EB virus infections.

Profile

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2005-03-25

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Tokyo Stock Exchange, Growth Market

Exchange Listing

2011-10-20

Fiscal Year-End

Dec

About Shared Research Inc.

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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