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SymBio Pharmaceuticals | 4582 |

Research Report by Shared Research Inc.

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Executive summary

SymBio in-licenses drugs for development and sale

SymBio is a specialty pharmaceutical company that buys the right to develop and commercialize drug candidates in order to address the underserved medical needs of patients in Japan and the rest of Asia. With its main focus on the areas of oncology, hematology, and pain management, the company typically seeks in-licensing opportunities for niche markets from pharmaceutical and biotech companies based in the US or EU.

Notably, the company does not conduct basic research and outsources preclinical/clinical development, employing a fabless in-licensing approach. Using its proprietary in-house "search engine," the company identifies, assesses and in-licenses only quality drug candidates having proof-of-concept established in human subjects. The company first screens third-party drug candidates being tested in clinical trials, then presents the in-licensing opportunities to its Scientific Advisory Board for further assessment of the science behind each molecule, preclinical/clinical data, target market, and the feasibility of receiving marketing approval from Japanese regulatory authorities.

According to the company, the typical development timeline of an oncology drug in Japan from preclinical studies to marketing approval is about 10 to 17 years. However, the company secured marketing approval for its first oncology drug under development in Japan, Treakisym, in only four years after the first clinical trial was initiated, with product launch only two years after US marketing approval and around the same time that approval was granted in Europe. Within three years of its launch, Treakisym captured more than 50% of the non-Hodgkin's lymphoma (NHL) and mantle cell lymphoma (MCL) market in Japan.

As of February 2016, the company's pipeline consisted of four drugs in the development pipeline: Treakisym (anticancer agent for hematologic malignancies), rigosertib (anticancer agent for myelodysplastic syndromes) IV and oral formulations, and SyB P-1501 (patient-controlled analgesia for pain management).

Earnings

In its mid-term plan, SymBio projects sales of JPY2.3bn–JPY3.0bn and a net loss of JPY3.6bn–JPY3.8bn in FY12/18. The company will seek regulatory approval for first-line treatment for low-grade NHL and MCL in FY12/16, and aims for approval of Treakisym for chronic lymphocytic leukemia (CLL). This will result in milestone payments and recording of sales. The company expects R&D expenses to fall for Treakisym, but to rise for rigosertib and clinical trials for SyB P-1501, resulting in higher overall SG&A expenses.

Strengths and weaknesses

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

Key financial data

Income Statement (JPYmn)	FY12/09 Par.	FY12/10 Par.	FY12/11 Par.	FY12/12 Par.	FY12/13 Par.	FY12/14 Par.	FY12/15 Par.	FY12/16 Est.
Sales	**1,191**	**1,450**	**1,883**	**1,955**	**1,532**	**1,955**	**1,933**	**2,339**
YoY	-26.9%	21.7%	29.8%	3.9%	-21.6%	27.6%	-1.1%	21.0%
Gross Profit	**1,191**	**1,212**	**658**	**593**	**318**	**527**	**583**	
YoY	-26.9%	1.7%	-45.7%	-9.9%	-46.4%	65.6%	10.7%	
GPM	100.0%	83.6%	35.0%	30.3%	20.8%	26.9%	30.2%	
Operating Profit	**-208**	**-613**	**-2,067**	**-1,700**	**-1,681**	**-1,303**	**-2,552**	**-2,778**
YoY	-	-	-	-	-	-	-	-
OPM	-	-	-	-	-	-	-	-
Recurring Profit	**-214**	**-638**	**-2,095**	**-1,729**	**-1,601**	**-1,110**	**-2,630**	**-2,811**
YoY	-	-	-	-	-	-	-	-
RPM	-	-	-	-	-	-	-	-
Net Income	**-218**	**-642**	**-2,105**	**-1,733**	**-1,605**	**-1,116**	**-2,632**	**-2,815**
YoY	-	-	-	-	-	-	-	-
Net Margin	-	-	-	-	-	-	-	-
Per Share Data								
Number of Shares ('000)	101	112	19,131	19,131	30,634	30,634	32,391	
EPS	-32.5	-59.3	-143.6	-90.6	-69.3	-36.3	-81.3	-86.9
EPS (Fully Diluted)	-	-	-	-	-	-	-	
Dividend Per Share	-	-	-	-	-	-	-	
Book Value Per Share	402.8	365.4	345.3	254.7	239.5	208.8	127.6	
Balance Sheet (JPYmn)								
Cash and Equivalents	4,121	4,016	6,511	4,840	7,264	6,591	4,261	
Total Current Assets	**4,218**	**4,213**	**7,178**	**5,421**	**7,634**	**7,290**	**4,827**	
Tangible Fixed Assets, net	13	22	17	14	9	49	53	
Other Fixed Assets	27	27	48	57	37	49	53	
Intangible Assets	2	1	13	11	8	66	52	
Total Assets	**4,261**	**4,263**	**7,256**	**5,502**	**7,687**	**7,454**	**4,984**	
Accounts Payable	-	1	309	330	-	306	320	
Short-Term Debt	-	-	-	-	-	-	-	
Total Current Liabilities	**205**	**178**	**646**	**599**	**251**	**488**	**551**	
Long-Term Debt	-	-	-	-	-	-	-	
Total Fixed Liabilities	**2**	**2**	**5**	**4**	**3**	**2**	**2**	
Total Liabilities	**207**	**180**	**651**	**602**	**254**	**490**	**552**	
Net Assets	**4,054**	**4,083**	**6,606**	**4,900**	**7,433**	**6,964**	**4,432**	
Interest-Bearing Debt	-	-	-	-	-	-	-	
Cash Flow Statement (JPYmn)								
Operating Cash Flow	-211	-754	-2,074	-1,659	-1,677	-1,266	-2,272	
Investment Cash Flow	-4	-116	-117	-411	-1,332	314	1,489	
Financing Cash Flow	2,963	663	4,611	-1	4,057	544	-3	
Financial Ratios								
ROA	-7.6%	-15.1%	-36.5%	-27.2%	-24.3%	-14.7%	-42.3%	
ROE	-8.1%	-15.8%	-39.4%	-30.2%	-26.3%	-15.8%	-48.3%	
Equity Ratio	95.1%	95.8%	91.0%	89.1%	96.7%	93.4%	88.9%	

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

Recent updates

Highlights

On **March 17, 2016**, Shared Research updated the report following interviews with the company.

On **February 10, 2016**, SymBio Pharmaceuticals announced earnings results for full-year FY12/15; see the results section for details.

On **February 8, 2016,** the company announced that it had signed an agreement with Teikyo Heisei University to jointly research and develop an innovative anti-cancer drug which uses the TTR1 nano-agonist molecule[1].

Based on the agreement, the company will provide resources to implement preclinical and IND-enabling studies in collaboration with Teikyo Heisei University. SymBio also acquired the right to enter into an exclusive license agreement with Teikyo Heisei University to globally develop and commercialize this innovative drug globally.

The team led by Dr. Isao Ishida, Professor of the Faculty of Pharmaceutical Sciences, Teikyo Heisei University, discovered an antibody that acts against TRAIL-R1, which is an expression on the surface of cancer cells or cancer stem cells, and modified it to impart more efficient anti-cancer activity (TTR1 nano-agonist). A drug delivery technique using an expression system in Bifidobacterium[2] was developed that enables the TTR1 nano-agonist to act selectively on hypoxic cancer tissue. The anti-cancer activity and safety of this new anti-cancer drug has been confirmed in animal models.

The impact of this agreement has been factored into the company's FY03/16 forecast that will be released when it announces FY12/15 results (February 10, 2016) and so will not have a significant impact on its FY12/16 earnings.

TTR1 nano-agonist[1]: Member of the tumor necrosis factor (TNF) family that exerts its apoptotic activity in human cells when it trimerizes by binding to its transmembrane receptors, TRAIL-R1 and TRAIL-R2. It is difficult to form a trimeric structure using conventional anti-TRAIL-R1antibodies, and thus apoptosis-inducing ability is typically weak. Camelids (e.g. camels, alpacas, llamas) produce functional antibodies devoid of light chains of which the single N-terminal domain is fully capable of antigen binding. These single-domain antibody fragments (VHHs or sdAb) have several advantages for biotechnological applications: they are well expressed in microorganisms, have a high stability and solubility, and can penetrate tissues relatively easily. Trivalent anti-TRAIL-R1 single-domain antibodies (TTR1: an abbreviation for Trivalent anti-TRAIL-R1) used in our collaboration have agonistic activities and induce apoptosis, thus we call them TTR1 nano-agonist(s).

Bifidobacterium[2]: Genus of Gram-positive bacteria, and are one of the major genera of bacteria that make up the colon flora in mammals, with probiotic activity limited to anaerobic environments. Bifidobacterium strains are important probiotics and widely used in the food industry (e.g. yogurt). As many types of cancer (specifically solid tumors such as pancreatic cancer) grow in a hypoxic environment, intravenously administered Bifidobacterium expressing the TTR1 nano-agonist molecule will selectively live in cancer tissue and effectively kill cancer cells via TTR1 nano-agonist molecule expression.

On **February 4, 2016**, the company made an announcement concerning its application for approval of bendamustine hydrochloride in Europe.

Symbio Pharmaceuticals had applied for approval of manufacturing and marketing of its anticancer agent Treakisym (generic name: bendamustine hydrochloride) in Europe for the treatment of first-line low-grade non-Hodgkin's lymphoma (NHL) and mantle cell lymphoma (MCL). It received notice from Astellas Pharma GmbH (a European subsidiary of Astellas Pharma Inc.) on February 2, 2016 that its application had been withdrawn on January 27, 2016.

The company is continuing with the regulatory approval process to receive approval for Treakisym domestically for the treatment of first-line low-grade NHL and MCL. The company does not expect this event to affect its earnings forecasts.

On **December 28, 2015**, the company announced the start of global phase III clinical trials for IV rigosertib to treat relapsed or refractory higher-risk myelodysplastic syndromes.

SymBio Pharmaceuticals started global phase III clinical trials in Japan for the IV formulation of rigosertib to treat relapsed or refractory higher-risk myelodysplastic syndromes. While SymBio will conduct the trials in Japan, its US partner Onconova Therapeutics will conduct the trial in the US and Europe. The company does not expect the start of clinical trials to affect its FY12/15 earnings forecasts.

On **December 24, 2015,** the company announced that it had applied for additional indications of anti-cancer drug Treakisym in CLL, as well as in first-line low-grade NHL and MCL. It also applied for approval for domestic manufacturing and marketing of small dose formulations of Treakisym.

Application for additional indication of Treakisym in CLL

On October 27, 2010, the company obtained approval for domestic manufacturing and marketing anti-cancer drug Treakisym (generic: bendamustine) for treating relapsed or refractory low-grade non-Hodgkin's lymphoma (NHL) and mantle cell lymphoma (MCL). It has applied for an additional indication, the treatment chronic lymphocytic leukemia (CLL). This drug has already been approved for the treatment of CLL in Europe and the US. It was designated as an orphan drug (drug for the treatment of rare diseases) to treat CLL in June 2012. In response to a request from the Evaluation Committee on Unapproved or Off-Labeled Drugs with High Medical Need for its development, SymBio has applied for approval for the additional indication.

Application for additional indication of Treakisym as first-line treatment of low-grade NHL and MCL

The company applied for approval to add an indication of Treakisym as the first-line treatment of low-grade non-Hodgkin's lymphoma (NHL) and mantle cell lymphoma (MCL).

Application for approval to manufacture and market Treakisym in small dose formulations in Japan

Considering the appropriate dosage for clinical use, the company has applied for approval to manufacture and market anti-cancer drug Treakisym in a 25mg vial.

The company does not expect these applications to impact its FY12/15 earnings.

For corporate releases and developments more than three months old, see the News and topics section.

Trends and outlook

Quarterly trends and results

Quarterly Performance (cumulative)	FY12/14				FY12/15				FY12/15	
(JPYmn)	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	% of FY	FY Est.
Sales	174	975	1,348	1,955	408	976	1,332	1,933	103.4%	1,870
YoY	-64.5%	20.3%	1.9%	27.6%	135.0%	0.1%	-1.2%	-1.1%		122.1%
Gross profit	32	247	353	527	120	283	395	583		
YoY	-78.6%	34.1%	29.4%	65.6%	272.1%	14.3%	11.8%	10.7%		
GPM	18.6%	25.3%	26.2%	26.9%	29.5%	28.9%	29.7%	30.2%		
SG&A expenses	448	893	1,320	1,830	453	931	1,383	3,135		
YoY	-9.0%	-9.9%	-10.0%	-8.4%	1.1%	4.2%	4.7%	71.3%		
SG&A / sales	257.9%	91.6%	97.9%	93.6%	110.9%	95.3%	103.8%	162.1%		
Operating profit	-416	-646	-967	-1,303	-332	-648	-988	-2,552		-2,452
YoY	-	-	-	-	-	-	-	-		-
OPM	-	-	-	-	-	-	-	-		-
Recurring profit	-454	-713	-941	-1,110	-419	-674	-1,056	-2,630		-2,481
YoY	-	-	-	-	-	-	-	-		-
RPM	-	-	-	-	-	-	-	-		-
Net income	-455	-715	-944	-1,116	-420	-676	-1,059	-2,632		-2,485
YoY	-	-	-	-	-	-	-	-		-
NPM	-	-	-	-	-	-	-	-		-

Quarterly Performance	FY12/14				FY12/15			
(JPYmn)	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Sales	174	802	373	607	408	568	356	601
YoY	-64.5%	149.1%	-27.3%	191.0%	135.0%	-29.2%	-4.5%	-1.0%
Gross profit	32	215	106	173	120	162	113	188
YoY	-78.6%	543.6%	19.8%	286.1%	272.1%	-24.5%	5.8%	8.5%
GPM	18.6%	26.8%	28.5%	28.5%	29.5%	28.6%	31.6%	31.3%
SG&A expenses	448	445	427	510	453	478	452	1,752
YoY	-9.0%	-10.8%	-10.1%	-4.3%	1.1%	7.3%	6.0%	243.7%
SG&A / sales	257.9%	55.6%	114.5%	84.0%	110.9%	84.1%	127.0%	291.6%
Operating profit	-416	-231	-320	-337	-332	-316	-340	-1,564
YoY	-	-	-	-	-	-	-	-
OPM	-	-	-	-	-	-	-	-
Recurring profit	-454	-259	-228	-170	-419	-255	-382	-1,574
YoY	-	-	-	-	-	-	-	-
RPM	-	-	-	-	-	-	-	-
Net income	-455	-261	-228	-172	-420	-256	-383	-1,573
YoY	-	-	-	-	-	-	-	-
NPM	-	-	-	-	-	-	-	-

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

FY12/15 results

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

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

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

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

Progress towards FY12/16 targets is as follows.

Domestic

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

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

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

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

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

Rigosertib (SyB L-1101 [IV]/SyB C-1101 [oral]; anticancer agent)
The company is conducting a domestic phase I clinical trial for the intravenous (IV) form of rigosertib in relapsed or refractory higher-risk myelodysplastic syndromes (MDS), a hematological malignancy. Patient enrollment was completed in January 2015, and the trial was completed in October 2015.

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

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

Overseas

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

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

Full-year company forecasts

FY12/16 Forecasts (JPYmn)	FY12/15 FY Act.	FY12/16 FY Est.
Sales	**1,933**	**2,339**
CoGS	1,350	
Gross Profit	**583**	
GPM	30.2%	
SG&A	3,135	3,605
SG&A / Sales	162.1%	154.1%
R&D expenses	2,035	2,180
Operating Profit	**-2,552**	**-2,778**
OPM	-	-
Recurring Profit	**-2,630**	**-2,811**
RPM	-	-
Net Income	**-2,632**	**-2,815**
Net Margin	-	-

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

Earnings outlook

Sales are expected to reach JPY2.3bn (+21.0% YoY), attributable to higher sales from Treakisym. The company also forecasts revenue from milestone payments as it attains expected regulatory approval for Treakisym as a treatment for non-Hodgkin's lymphoma (NHL) and mantle cell lymphoma (MCL).

R&D expense is expected to total JPY2.2bn (up from JPY2.0bn in FY12/15), while total SG&A expense–including R&D–is projected to reach JPY3.6bn (up from JPY3.1bn).

R&D spending is slated to increase with the targeting of additional indications for Treakisym and development toward NDA applications for 1) intravenous and oral rigosertib and 2) SyB P-1501, which was in-licensed in FY12/15. The company will also work jointly with Teikyo Heisei University on the development of an anti-cancer drug using the TTR1 nano-agonist molecule.

As a result, SymBio forecasts an operating loss of JPY2.8bn (operating loss of JPY2.6bn in FY12/15), a recurring loss of JPY2.8bn (recurring loss of JPY2.6bn in FY12/15), and a net loss of JPY2.8bn (net loss of JPY2.6bn in FY12/15).

Pipeline

Treakisym

Supplemental NDAs were filed in FY12/15 for indications as a first-line treatment for refractory/relapsed low-grade NHL, MCL and CLL. Work is under way to respond to matters raised by the PMDA and speed up the approvals. SymBio aims to acquire regulatory approval for these indications during FY12/16.

Intravenous and oral rigosertib

The company is moving ahead with the Japan edition of the global Phase III trial for the intravenous version of rigosertib, and hopes to quickly begin initial patient enrollment. Similarly, SymBio aims to quickly start initial patient enrollment for the domestic Phase I trial of the oral version of rigosertib for use in combination with azacitidine. Regarding development with low-risk MDS as the target efficacy, SymBio will consider it while watching development progress at Onconova Therapeutics.

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

SymBio reached an in-licensing agreement for SyB P-1501 in FY12/15. Preparations are under way to start a domestic phase III clinical trial in Q3 FY12/16.

Long-term outlook

When it released its FY12/15 results, SymBio also announced a mid-term plan for FY12/16 through FY12/18.

Midterm Plan

(JPYmn)	FY12/15 Act.	FY12/16 Est.	FY12/17 Target	FY12/18 Target
Sales	1,933	2,339	2,604～2,188	2,974～2,298
Operating Profit	-2,551	-2,778	-3,379～-3,521	-3,526～-3,778
Recurring Profit	-2,630	-2,811	-3,412～-3,554	-3,559～-3,811
Net Income	-2,632	-2,815	-3,416～-3,558	-3,563～-3,815

Source: Shared Research based on company data.

Main pipeline schedule

Main Pipeline Schedule	FY12/15	FY12/16	FY12/17	FY12/18
Treakisym (first-line treatment of low-grade NHL and MCL)	Apply for approval	Obtain approval		
Treakisym (CLL)	Apply for approval	Obtain approval		
Rigosertib (IV) (relapsed and refractory high-risk MDS)	Participate in global trials			Apply for approval
Rigosertib (oral) (high-risk MDS [in combination with azacitidine])	Phase I clinical trials		Complete phase I clinical trials	
SyB P-1501 Patient-controlled analgesia for pain management		Phase III clinical trials		Apply for approval

Source: Shared Research based on company data

Earnings targets

Sales

Based on the assumptions below, the company's mid-term plan calls for an increase in Treakisym sales growth by securing a larger market share alongside an expansion of its applications.

SymBio plans to hold seminars for doctors in Japan to promote Treakisym as an efficacious and safe alternative treatment to existing drug therapies within the relapsed or refractory low-grade NHL and MCL market. Such efforts may also lead to an increase in per-patient sales as patients complete additional treatment cycles.

The company filed a domestic sNDA for approval to use Treakisym in the treatment of first-line low-grade NHL, MCL, and CLL in December 2015. It expects to receive approval in FY12/16.

Sales of Treakisym for the indication of first-line low-grade NHL will likely affect overall sales in FY12/17 and FY12/18. According to the company, the upper estimate for sales is the case in which it receives approval, and the lower estimate is if approval is not granted.

SG&A

SG&A expenses, including R&D costs, are expected to increase under the medium-term management plan as the company pursues clinical trials of SyB P-1501 and the IV and oral forms of rigosertib. SymBio intends to continue with evaluations and deliberations regarding new product development candidates, but any expenses related to the launch and development of these candidates are not included in medium-term plan estimates.

Concerning other SG&A expenses, the company is considering the establishment of its own sales network, and has made expense estimates under the assumption that preparations will begin during FY12/17.

Mid-term plan assumptions

Pipeline progress

Treakisym

- To increase sales for indications of relapsed or refractory low-grade NHL and MCL, SymBio plans to promote a strategic marketing partnership with Eisai to continue with efforts to make Treakisym's benefits well-known.
- An approval application for the manufacturing and sale of Treakisym as a first-line treatment for refractory/relapsed low-grade NHL, MCL and CLL was completed in December 2015. The company plans for approval to be granted during FY12/16.
- Concerning the use of Treakisym for relapsed or refractory aggressive NHL, phase II clinical trials have been completed, and deliberations aimed at winning approval will continue. Sales and expenses related to these indications have not been incorporated into the medium-term plan.

Rigosertib

- Rigosertib (IV) for relapsed and refractory high-risk MDS is slated to undergo Japanese clinical trials as part of global phase III trials being undertaken in cooperation with Onconova. The company aims for approval during FY12/19.
- Phase I clinical trials are underway in Japan for rigosertib for high-risk MDS (in combination with azacitidine), and the trials are scheduled to be completed during FY12/17. Development that set out efficacy targets for blood transfusion-dependent low-risk MDS is being evaluated based on development progress at Onconova.

SyB P-1501: Patient-controlled analgesia for pain management

Phase III clinical trials for short-term management of acute postoperative pain are scheduled to begin during FY12/16, with plans for approval during FY12/18.

Anti-cancer drug using the TTR1 nano-agonist molecule

Joint development with Teikyo Heisei University will proceed in FY12/16, with evaluations being made toward implementing a global licensing scheme.

Reorganization of sales force ahead of rigosertib sales

The company will consider reorganizing its sales force in preparation for the launch of rigosertib. In August 2008, the company established an exclusive partnership with Eisai for Treakisym. Eisai agreed to cover one-time payments, milestone payments in accordance with clinical trial stage, and half of R&D expenses, as well as 100% of sales and marketing costs. Shared Research estimates that Eisai takes a margin of about 50% on domestic Treakisym sales at the National Health Insurance (NHI) drug price - SymBio's margin is just over 10%. The company also expects its margin to

improve as procurement costs fall in line with higher sales.

As of February 2016, SymBio had not entered into an exclusive domestic sales agreement for rigosertib with any company. According to its medium-term plan, the company will consider the creation of its own sales framework to coincide with approval to manufacture and sell rigosertib in IV form. Following conversations with the company, Shared Research estimates that Eisai has 120-130 specialist medical representatives focusing on oncologic conditions. Labor costs would increase if SymBio were to create its own sales force of 30-40 medical representatives to sell rigosertib, but the company could realize a significantly higher profit margin on rigosertib sales than with Treakisym.

Introduction of new drug candidates

According to the medium-term plan, the company will continue to evaluate numerous candidate drugs, and will move to acquire promising candidates that enhance its corporate value. Shared Research expects the company to spend between JPY500mn and JPY1bn in one-time payments per new drug candidate and incur additional R&D expenses.

Business

Business description

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

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

Strategy Overview (details to follow)

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

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

As of March 2016, the company had evaluated some 500 drug candidates since its establishment in March 2005, signing on four deals.

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

An example of the company's ability to identify and pursue quality in-licensing opportunities with proof-of-concept established is the license agreement signed for the development and commercialization right to rigosertib—currently in

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

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

Treakisym

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

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

As of February 2016, SymBio has been undergoing the approval process for Treakisym for the indications of first-line low-grade NHL, MCL, and CLL. The company expects to receive approval for these indications in FY12/16.

Rigosertib

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

In February 2014, Onconova completed phase III clinical trials for the IV form of rigosertib in patients with relapsed or refractory MDS in Europe, and its efficacy was proven in subgroup analysis. SymBio also completed patient registration for phase I domestic clinical trials in January 2015. From August 2015, Onconova has been conducting global phase III clinical trials for patients with higher-risk MDS who had failed or relapsed after prior therapy with hypomethylating agents (HMAs). Within Japan, the company has been conducting joint global phase III clinical trials in cooperation with Onconova.

For the oral form of the drug, Onconova is conducting phase II clinical trials in the US for high-risk MDS (in combination with azacitidine) and transfusion-dependent low-risk MDS. In Japan, SymBio is conducting a phase I clinical trial for high-risk MDS (with azacitidine). It may participate in global trials that Onconova plans to launch in FY12/16 or FY12/17.

SyB P-1501

SyB P-1501 (known as IONSYS in the US) is a drug delivery system allowing post-operative patients to manage their pain. As a needle-free alternative, SyB P-1501 is anticipated to improve treatment satisfaction as it lessens the physical and psychological burden on patients. It is also expected to offer increased safety and convenience for medical institutions, decreasing the labor and costs required to manage electric pumps. SymBio obtained exclusive development and marketing rights for the drug in Japan from The Medicines Company in October 2015.

The Medicines Company received approval for Ionsys from the US Food and Drug Administration (FDA) in April 2015. It has already begun marketing the drug in the US. The European regulatory agency also granted approval to the drug in November 2015. In Japan, safety of the drug has already been established in a phase I clinical trial on healthy adults, and

SymBio plans to launch phase III clinical trials in FY12/16, with application for approval to follow in FY12/18. The company aims to obtain approval in Japan in FY12/19.

Revenue: milestone payments and Treakisym

Revenue comes from milestone payments and product sales. Operating losses have persisted since the company's foundation with the exception of FY12/08 when the company booked an operating profit due to a one-time contract payment from Eisai for an exclusive domestic right to sell Treakisym (see Historical performance). For FY12/16, the company expects an operating loss, recurring loss, and net loss of JPY2.8bn each. Over the course of the mid-term plan (FY12/16–FY12/18), the company expects to post annual operating losses of JPY2.8–3.8bn.

SymBio expects annual operating losses of JPY9.8–10.2bn in total between FY12/16 and FY12/18. To achieve medium-term growth, the company needs to continue considering the in-licensing of new drug candidates for development and commercialization. As of the end of FY12/15, the company had cash and deposits plus securities of about JPY4.3bn. More cash may be necessary to continue bankrolling growth.

Business strategy

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

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

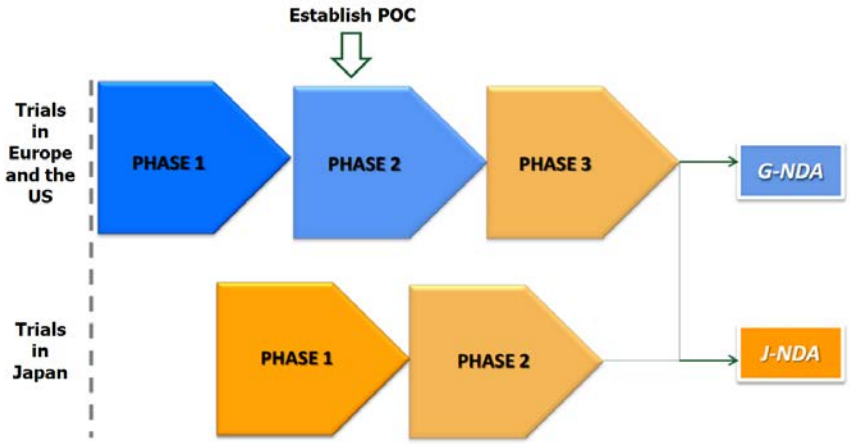
The company focuses on developing drugs that have strong safety and efficacy data in clinical trials, providing an opportunity to develop new drugs more likely to succeed and secure regulatory approval with the use of bridging data whenever possible to shorten development timelines. Because the company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

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

SymBio targets compounds with an established proof-of-concept

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

Post-proof-of-concept strategy



Source: Shared Research based on company data.

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

phase III studies for marketing approval.

Screening: independent search network plus evaluation experience

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

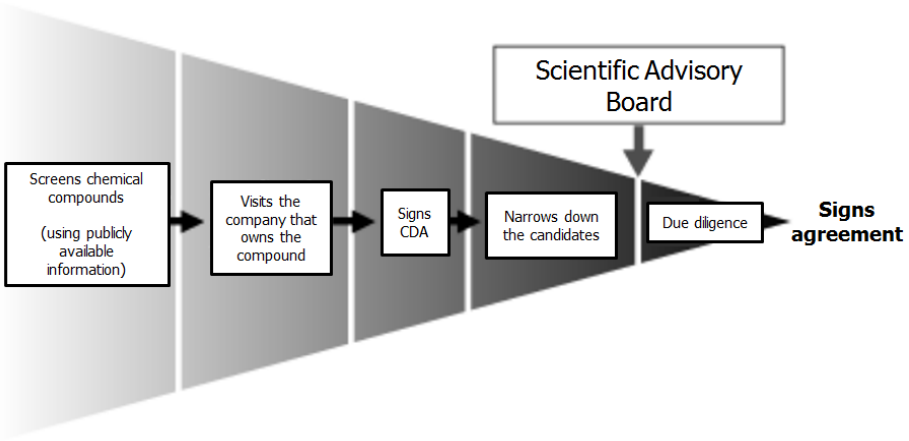
Onsite due diligence

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

Only four drugs out of 500+ have met the company's stringent criteria since its foundation

As of March 2016, the company had screened over 500 candidates. It acquired four. The first was Treakisym, which Eisai Co., Ltd. (TSE1: 4523) sells in Japan. Clinical trials for additional Treakisym indications are underway. In addition to Treakisym, the company is also developing intravenous and oral versions of rigosertib, an anti-cancer drug for myelodysplastic syndromes, and SyB P-1501, a patient-controlled analgesia for pain management.

Drug candidate selection process



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

Scientific Advisory Board

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

Scientific Advisory Board members

Name	Profile
George Morstyn, M.D., Ph.D.	Presently Chairman GBS Venture Capital firm, Deputy Chairman Victorian Comprehensive Cancer Centre, Director of Co-operative Research Centre for Cancer Therapeutics and Proacta. Former Senior Vice-President of Development and CMO at Amgen Inc..
Robert Lewis, M.D., Ph.D.	Former Senior Vice-President of US R&D, Aventis Pharmaceuticals; Chief Scientific Officer, Cell Therapeutics; Head of Discovery Research, Syntex Pharmaceuticals; Associate Professor, Harvard Medical School Currently serves as consultant in Immunology/Inflammation, Roche Palo Alto; Adjunct Faculty Member, Rockefeller University, New York
Makoto Ogawa, M.D., Ph.D.	Honorary President, Aichi Cancer Center
Tatsutoshi Nakahata, M.D., Ph.D.	Deputy Director and Professor of Center for iPS Cell Research and Application (CiRA), Institute for Integrated Cell-Material Sciences, Kyoto University Honorary member, The Japanese Society of Hematology
Toshio Suda, M.D., Ph.D.	Professor, Keio University School of Medicine (Chair in Developmental and Differential Biology) Guest Professor, Institute of Molecular Embryology and Genetics, Kumamoto University Vice President, The Japanese Society of Hematology in 2012
Tsutomu Takeuchi, M.D., Ph.D.	Professor of Medicine, Keio University, School of Medicine (Division of Rheumatology, Clinical Immunology, Department of Internal Medicine)
Shinji Nakao, M.D., Ph.D.	Professor, Kanazawa University College of Medical, Pharmaceutical and Health Sciences, Division of Cancer Medicine Cellular Transplantation Biology (Hematology/Respirology) Executive Director, The Japanese Society of Hematology in 2012
Toshio Heike, M.D., Ph.D.	Professor, Kyoto University Graduate School of Pharmaceutical Sciences (Developmental Medicine, Pediatrics) Director, Clinical Genetics Unit, Kyoto University Hospital Director, Division for iPS Cell Application Development, Kyoto University Hospital

Source: Shared Research based on company data.

A fabless strategy with a lean management team

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

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

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

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

According to the company, globally Japan has the third largest oncology market after the US and EU, and the market is

expected to continue to expand due to Japan's aging population. However, regarding the type of tumors that anticancer drugs can effectively treat, there is a considerable range of indications with a limited number of patients who will benefit from approved cancer treatments, particularly in the elderly population where the occurrence of serious adverse events can be prohibitive. As a result, barriers to entry are high—developing cancer drugs for niche markets is especially difficult and requires a high level of expertise. Concerns about having sufficient profit margins from marketed drugs to fund large operations means that major pharmaceutical companies may be reluctant to target indications with limited patient numbers for development, presenting an opportunity with fewer competitors in the marketplace for smaller and more specialized pharmaceutical companies such as SymBio.

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. In the medium-term plan announced in February 2016, the company maintains that it will not limit itself to the Japan and Asia regions, but will always look to acquiring global rights when discovering, evaluating, and negotiating terms for new drug development candidates. In line with this thinking, the SymBio acquired an exclusive license for the global development, manufacture, and commercialization for anti-cancer drugs utilizing the TTR1 nano-agonist molecule, a drug jointly developed with Teikyo Heisei University.

Pipeline

Name / Code	Category	Licensed country	Indications	Development stage	Sales partner
Treakisym SyB L-0501	Anti-cancer agent	Japan	Refractory/relapsed low-grade NHL	Market approval (2010/10/27)	Eisai Co., Ltd. (co-developed; exclusive sales rights granted to Eisai)
			Refractory/relapsed MCL		
			Refractory/relapsed MCL	PII (completed)	
			First-line low-grade NHL,MCL	Apply for approval	
			CLL	Apply for approval	
		Singapore	Low-grade B-cell NHL	Market approval (2010/1/20)	Eisai Co., Ltd. (exclusive development and sales rights granted to Eisai)
			CLL		
		Korea	CLL	Market approval (2011/5/31)	Eisai Co., Ltd. (exclusive development and sales rights granted to Eisai)
			MM		
			Refractory/relapsed low-grade NHL	Market approval (2014/6/16)	
		China	Low-grade NHL	Clinical trials underway	Teva Pharmaceutical Industries Ltd. (China) (exclusive development and sales rights granted to Teva)
		Hong Kong	Low-grade NHL	Market approval (2009/12/30)	
			CLL		
		Taiwan	Low-grade NHL	Market approval (2011/10/18)	Innopharmax, Inc. (Taiwan) (exclusive development and sales rights granted to Innopharmax)
			CLL		
Rigosertib (IV) SyB L-1101	Anti-cancer agent (IV)	Japan	Refractory/relapsed high-risk MDS	Global trials PIII	—
Rigosertib (oral) SyB C-1101	Anti-cancer agent (oral)	Japan	High-risk MDS	PI (completed: 2015/6)	—
			High-risk MDS (with azacitidine)	PI	—
SyB P-1501	Patient-controlled pain management	Japan	Management of acute postoperative pain	PI completed Preparations for PIII underway	—

Source: Shared Research based on the company website

As of February 2nd, the following drugs were in the development pipeline:

- Treakisym, targeting indication for first-line low grade NHL and MCL indications
- Treakisym, targeting indication for chronic lymphocytic leukemia
- Treakisym, targeting indication for first-line treatment for low-grade NHL and MCL
- Rigosertib (intravenous form), targeting indication for relapsed or refractory higher-risk myelodysplastic syndrome
- Rigosertib (oral form), targeting indication for high-risk MDS
- Rigosertib (oral form, in combination with azacitidine), targeting indication for high-risk MDS
- SyBP-1501, patient controlled analgesia for pain management

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

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

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

According to the company, no cross-resistance has been shown for this drug, which means it is safer and more effective than existing treatments for target indications. In October 2010, SymBio received regulatory approval in Japan to market the drug for relapsed or refractory low-grade NHL and MCL. Eisai covers 100% of the marketing and sales costs, and has been selling the drug since its launch in December 2010 (see Earnings structure).

As of February 2016, the company was preparing to file domestic applications for first-line treatment of low-grade NHL, MCL, and CLL. The domestic approval process is underway, and SymBio is aiming for approval during FY12/16.

Lymphatic cancer

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

Lymphatic malignancy: frequency by type

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

Source: Japanese Society for Lymphoreticular Tissue Research (JSLTR)

Treakisym in-licensed from Astellas; Eisai handles sales

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

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

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

sale of the drug to these companies.

Approval for relapsed or refractory low-grade NHL, MCL

In October 2010, five years after acquiring the right to Treakisym, SymBio received marketing approval in Japan for relapsed or refractory low-grade NHL and MCL. In FY12/15—following the domestic launch of the drug in December 2010—Treakisym sales to end users reached JPY4.8bn.

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

Treakisym: additional indications

As of February 2016, Treakisym was undergoing the domestic approval process for first-line treatment of low-grade NHL/MCL, CLL. It was also under development by the company for relapsed or refractory moderate to high-grade NHL as part of its plans for label expansion.

Market for Treakisym and number of patients

	Non-Hodgkin's Lymphoma		Chronic Lymphatic Leukemia
	Low-grade B-cell	High and intermediate grade	
Initial treatment	Number of patients: 7,100 Obtain approval in FY12/16 (planned) Phase III trials complete in Europe Filed for marketing approval in Japan		Number of patients: 700 Obtain approval in FY12/16 (planned) Approval already obtainedi n the US/Europe Filed for marketing approval in Japan
Relapsed and refractory conditions	Number of patients: 4,700 Approval obtained Approval obtained in Japan in Oct. 2010 Sales launched in Japan in Dec. 2010	Number of patients: 6,700 Consultation on application underway Phase II trials complete in Japan	

Source: Shared Research based on company data.

First-line treatment of low-grade NHL and MCL

In Japan, R-CHOP therapy—a combination of rituximab with CHOP chemotherapy drugs (cyclophosphamide, doxorubicin, vincristine, and prednisolone)—is standard first-line treatment for low-grade NHL and MCL despite the frequent occurrence of adverse events due to toxicity. Researchers have yet to establish the most appropriate method of treatment using rituximab in combination with chemotherapy.

Phase III clinical trials conducted overseas have demonstrated that rituximab in combination with bendamustine (R-B therapy) was safer and more efficacious than standard R-CHOP therapy for previously untreated low-grade B-cell NHL. Based on these results, the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines recommend the use of R-B therapy as first-line therapy for patients with untreated low-grade NHL. The efficacy and safety of R-B therapy demonstrated during clinical trials for previously untreated low-grade NHL led to recommendations as first-line treatment for this indication.

Development status: Astellas withdraws European approval request; final analysis for US BRIGHT trials planned

A randomized phase III trial was completed in March 2011 by Dr. M. J. Rummel and researchers affiliated with Study Group Indolent Lymphomas (StiL) in Germany investigating efficacy and safety of bendamustine + rituximab (B-R) vs R-CHOP in first-line low-grade NHL and MCL. An application based on the results of this study was submitted in March 2012 to the German Federal Institute for Drugs and Medical Devices (BfArM), but the submission was withdrawn in January 2016. According to the company, the Astellas subsidiary stated that its reasoning for withdrawal was not related to the efficacy nor the safety of Treakisym. BRIGHT trials (additional phase III trials) underway in the US are scheduled for final analysis in 2017, and the company plans to decide upon its course of action upon completion of the analysis.

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

> 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.

sNDA filing in Japan for first-line low-grade NHL and MCL in FY12/15

Since November 2011, the company has been conducting domestic phase II clinical trials in cooperation with Eisai for first-line low-grade NHL and MCL indications. Based on these results, and with data from European phase III clinical trials, SymBio filed an application for approval for first-line low-grade NHL and MCL indications for Treakisym. After submission in February 2016, the withdrawal for approval from the European subsidiary of Astellas was reported to the PMDA, and the Japanese approval process will not be affected by the developments in Europe.

The company plans to receive approval for Treakisym for first-line low-grade NHL and MCL indications during FY12/16.

Patient population

SymBio estimates that there are 7,100 first-line low-grade NHL and MCL patients in Japan—1.5 times the number of patients with relapsed or refractory low-grade NHL and MCL. Treakisym sales could reach JPY5.5bn–JPY6bn as the Japanese population continues to age.

Treakisym targeting chronic lymphocytic leukemia (CLL)

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

R&D status: application in FY12/15

The use of Treakisym to treat CLL has already been approved in the US and Europe. In October 2015, SymBio completed a pivotal phase II trial for Treakisym in CLL as a joint project with Eisai. In light of the phase II results, an application for approval was made in December 2015. Approval is planned to be obtained in FY12/16.

Potential patient population, expected sales

SymBio estimates that there are about 700 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.

Relapsed or refractory DLBCL (aggressive NHL)

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

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

R&D status

In March 2012, the company completed final analysis and evaluation of data from its phase II clinical trial using Treakisym in combination with rituximab for relapsed or refractory DLBCL (aggressive NHL). The trial, with clinical trial sites in both Japan and South Korea, demonstrated an improved prognosis with a median progression free survival (PFS) of 6.7 months as well as clinically manageable side effects in elderly patients.

SymBio had planned to file for marketing approval in Japan following completion of the phase II clinical trial and presentation of the data at the 54th American Society of Hematology (ASH) Annual Meeting in December 2012, however, the company decided to delay submission of the marketing application after subsequent consultations with the Pharmaceuticals and Medical Devices Agency (PMDA).

Potential patient population

According to SymBio, the number of relapsed or refractory DLBCL (aggressive NHL) patients in Japan is approximately 6,700.

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

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

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

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

Myelodysplastic Syndromes (MDS)

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

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

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

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

Development status of rigosertib

As of February 2016, SymBio is developing the IV form of rigosertib for the indication of relapsed or refractory high-risk MDS, and the oral form for high-risk MDS (in combination with azacitidine).

Onconova has been conducting joint global phase III clinical trials in over 10 countries since August 2015 for the intravenous form of rigosertib in high-risk MDS patients who had failed or relapsed after prior therapy with hypomethylating agents (HMAs). In the Japanese market, the company has been conducting the joint global phase III clinical trials in cooperation with Onconova since December 2015.

As of February 2016, Onconova is conducting phase II clinical trials for the oral form of rigosertib in the US for the indications of high-risk MDS (in combination with azacitidine) and transfusion-dependent lower-risk MDS. In Japan, SymBio conducted phase I clinical trials for the indication of high-risk MDS (without any supplements), completing the trials in June 2015. The company also initiated phase I trials for the indication of high-risk MDS (with azacitidine) in FY12/16.

Market for Rigosertib (oral form) and number of patients

	Low-risk MDS First-line	High risk MDS First-line	Relapsed/refractory
Intravenous			Number of patients: 3,200 Obtain approval in FY12/19 (planned) Joint international trial Phase III trials
Oral	Number of patients: 7,800 Obtain approval in 2019-2020 (planned) Phase II trials underway in the US	Number of patients: 3,200 Schedule TBC Phase II trials underway in the US Phase I trials complete in Japan Phase I trials underway in Japan (with azacitidine)	

Source: Shared Research based on company data.

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

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

However, some cases of higher-risk MDS show resistance to standard treatment with hypomethylating agents (HMAs) such as Vidaza and Dacogen, including relapse following treatment. The most advanced research being conducted for rigosertib as of February 2015 was for the treatment of patients with higher-risk MDS who had progressed on, failed or relapsed after prior therapy with HMAs. According to the company, no drugs have been approved for the treatment of post-HMA higher-risk MDS patients as of February 2016.

R&D status: ongoing joint international phase III clinical trial in patients with recurrent high-risk MDS following HMA therapy

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

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

Among patients whose condition had deteriorated or not responded to previous treatment using hypomethylating agents (184 of 299 people, or 62%), the overall survival period for higher-risk MDS patients who received rigosertib was 8.5 months, while for those in the control group (BSC) it was 4.7 months. The p-value was 0.022, showing a statistically

significant difference. The hematological toxicity of the conventional anti-cancer agent was approximately 60%. With rigosertib, toxicity of Grade 3 or above did not exceed 7%, and non-hematological toxicity did not exceed 3%, confirming safety of the drug.

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

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

SymBio initiated its phase I clinical trial for intravenous rigosertib to treat relapsed or refractory higher-risk MDS in June 2012. Patient registration was completed in January 2015, and phase I clinical trials were completed in October 2010. Based on the outcome of discussions with the FDA and European regulatory agencies and Onconova's future development, the company has been operating the global phase III clinical trials within Japan since December 2015, and aims for approval during FY12/19.

Oral form of rigosertib for first-line high-risk MDS (in combination with azacitidine)

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

As of February 2016, Onconova is conducting phase I and II clinical trials of the oral form of rigosertib for the indication of high-risk MDS (in combination with azacitidine).

During phase I of the trials, the 18 patients took only rigosertib (oral) in week one, rigosertib and azacitidine in week two, only rigosertib in week three, and nothing in week four. The safety profile of this treatment was comparable to monotherapy with azacitidine. Of the 18 patients, marrow complete remission or marrow complete remission with incomplete recovery of blood counts was reported in 9.

As of February 2016, phase II of the trial is underway by Onconova at three locations in the US and Europe, including the MD Anderson Cancer Center in Texas.

Domestic phase I clinical trials

SymBio completed domestic phase I clinical trial of rigosertib (oral, without supplements) for the indication of high-risk MDS in June 2015. In FY12/16, the company launched phase I clinical trials to confirm the safety of the drug in combination with azacitidine for treatment of high-risk MDS. The company may also participate in global trials conducted by Onconova between FY12/16 and FY12/17.

Oral form of rigosertib for transfusion-dependent lower-risk MDS

Lower-risk MDS corresponds to all the low-risk categories and intermediate-1 of the IPSS with a blast-cell ratio (the ratio of blast cells in the marrow and peripheral blood) of less than 5%. It is primarily caused by a decline in blood cells. It poses a low risk of progression to acute leukemia.

Patients who do not suffer a large decline in blood cells and who do not have any subjective symptoms are placed under observation instead of being treated. Those who develop anemia receive an infusion of red blood cells in accordance with their age. Sometimes an immunosuppressant is used to prevent lymphocyte cells from attacking hematopoietic stem cells. Depending on a patient's age and condition, and HLA compatibility with a donor, an allogeneic hematopoietic stem

cell transplant is sometimes carried out. Patients who are not suitable candidates for an allogeneic hematopoietic stem cell transplant, but who are in critical condition due to hematopoietic failure, may be given Vidaza.

R&D status

Onconova is conducting a phase II clinical trial in the US for the oral form of rigosertib in first-line transfusion-dependent, lower-risk MDS. As of February 2016, the company was in discussions with the FDA regard to design a phase III clinical trial.

The company plans to concentrate on domestic phase I clinical trials (with azacitidine) for the oral form of rigosertib for high-risk MDS patients. Concerning clinical trials for transfusion-dependent, lower-risk MDS patients, SymBio plans to make deliberations based on development progress at Onconova.

Patient population, estimated sales

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

Nippon Shinyaku Co., Ltd. (TSE1: 4516) has been selling azacitidine in Japan as first-line therapy for MDS under the product name Vidaza since March 2011. According to Nippon Shinyaku, sales of Vidaza were JPY9.7bn for FY03/14 (+38.1% YoY). The company expects to book sales of JPY10.8bn for FY03/15. Shared Research thinks that sales of the intravenous and oral forms of rigosertib could match or exceed sales of Vidaza, used when patients who receive treatment with Vidaza relapse.

SyB P-1501 (Ionsys [US product name] for patient-controlled analgesia)

SymBio obtained exclusive development and marketing rights to Ionsys in Japan from The Medicines Company (US) in October 2015. Ionsys is a patient-controlled analgesia (PCA) system for post-operative pain management. It uses a credit card-size device on the patient's arm or chest to deliver a set dose of fentanyl (a synthetic opiate painkiller) at the press of a button. This dose is absorbed transdermally without the need for needles or other invasive measures.

Post-operative pain management

Post-operative patients experience various forms of pain, so safe and effective forms of analgesia are key to improving treatment satisfaction and quality of life. BB Research has estimated the worldwide market for pain management drugs and devices at USD36.6bn in 2014, a figure expected to increase to USD44.3bn by 2020 based on 3.2% annual growth.

As of February 2016, many hospitals had begun using PCA, which allows patients to control administration of their pain medications based on their own symptoms. The drug is delivered through an electronic pump at the touch of a button. A cassette with diluted fentanyl is connected to an epidural or intravenous line. When necessary, the patient activates the device and a safe, effective dose of the analgesic is delivered automatically to control pain.

Conventional PCA methods used needles and constituted a mental and physical burden on patients. The electronic pumps used also required maintenance, incurring high costs. Both doctors and patients were looking for a safer, more convenient PCA method.

SyB P-1501: expected to alleviate mental and physical patient burden, improve treatment satisfaction, save on labor and costs.

According to SymBio, this needle-less PCA system operates through using a tiny electrical current to deliver ionized

fentanyl transdermally using the principle of iontophoresis. Older generations of PCA devices required electronic pump maintenance , but SyB P-1501 eliminates the need for programming, line installation, power cords, accessories, drug dilution, inspection, and refilling. This results in a safer, more convenient system which also allows hospitals to save labor and costs.

SyB P-1501 (left) and conventional PCA system (right)

Source: Company data

R&D status: Marketed in the US, approved in the EU, and phase III clinical trial ongoing in Japan

The Medicines Company received approval from the US Food and Drug Administration (FDA) in April 2015, and SyB P-1501 is already marketed in the US. European regulators approved the drug in November 2015.

In Japan, domestic phase I trials have already established safety of the drug in healthy adults, and SymBio plans to launch phase III trials in 2016. The company expects approval in Japan in FY12/19.

Patient population, estimated sales

According to SymBio, about 1 million patients receive PCA treatment in Japan each year, accounting for 20% of all surgeries. Of these, the company estimates 330,000 (about 34%) patients use IV-based PCA systems. The company envisions switching of IV-based PCA to SyB P-1501. Price for the drug is about USD200 in the US, so the company estimates annual sales of about JPY6.6bn assuming equivalent pricing in Japan and full switching of the IV-based PCA patient population to SyB P-1501.

Research and Development

Anti-cancer drug utilizing the TTR1 nano-agonist molecule

A team led by Dr. Isao Ishida, Professor of the Faculty of Pharmaceutical Sciences, Teikyo Heisei University, discovered an antibody that acts against TRAIL-R1, which is an expression on the surface of cancer cells or cancer stem cells, and modified it to impart more efficient anti-cancer activity (TTR1 nano-agonist). A drug delivery technique using an expression system in Bifidobacterium[1] was developed that enables the TTR1 nano-agonist to act selectively on hypoxic cancer tissue. The anti-cancer activity and safety of this new anti-cancer drug has been confirmed in animal models.

In February 2016, the company announced that it had signed an agreement with Teikyo Heisei University to jointly research and develop an innovative anti-cancer drug which uses the TTR1 nano-agonist molecule[2]. Based on the agreement, the company will provide resources to implement preclinical and IND-enabling studies in collaboration with

Teikyo Heisei University. SymBio also acquired the right to enter into an exclusive license agreement with Teikyo Heisei University to globally develop and commercialize this innovative drug globally.

Joint development with Teikyo Heisei University will occur throughout FY12/16, and evaluations will be made toward introducing a global licensing scheme.

Bifidobacterium[1]: Genus of Gram-positive bacteria, and are one of the major genera of bacteria that make up the colon flora in mammals, with probiotic activity limited to anaerobic environments. Bifidobacterium strains are important probiotics and widely used in the food industry (e.g. yogurt). As many types of cancer (specifically solid tumors such as pancreatic cancer) grow in a hypoxic environment, intravenously administered Bifidobacterium expressing the TTR1 nano-agonist molecule will selectively live in cancer tissue and effectively kill cancer cells via TTR1 nano-agonist molecule expression.

TTR1 nano-agonist[2]: Member of the tumor necrosis factor (TNF) family that exerts its apoptotic activity in human cells when it trimerizes by binding to its transmembrane receptors, TRAIL-R1 and TRAIL-R2. It is difficult to form a trimeric structure using conventional anti-TRAIL-R1antibodies, and thus apoptosis-inducing ability is typically weak. Camelids (e.g. camels, alpacas, llamas) produce functional antibodies devoid of light chains of which the single N-terminal domain is fully capable of antigen binding. These single-domain antibody fragments (VHHs or sdAb) have several advantages for biotechnological applications: they are well expressed in microorganisms, have a high stability and solubility, and can penetrate tissues relatively easily. Trivalent anti-TRAIL-R1 single-domain antibodies (TTR1: an abbreviation for Trivalent anti-TRAIL-R1) used in our collaboration have agonistic activities and induce apoptosis, thus we call them TTR1 nano-agonist(s).

Earnings structure

Earnings structure

(JPYmn)	FY12/09	FY12/10	FY12/11	FY12/12	FY12/13	FY12/14	FY12/15
Sales	1,191	1,450	1,883	1,955	1,532	1,955	1,933
Product Sales	-	326	1,632	1,955	1,432	1,940	1,933
Treakisym Sales to End Users (Reference)	-	644	3,390	3,940	4,230	4,320	4,760
Product Sales / Sales to End Users	-	50.6%	48.2%	49.6%	33.9%	44.9%	40.6%
Royalty Revenue	1,191	1,124	250	-	100	15	-
Sales to Eisai	1,085	1,446	1,872	1,930	1,486	1,908	-
Non-Eisai Sales	106	4	10	26	46	47	-
CoGS	-	238	1,224	1,362	1,214	1,428	1,350
CoGS / Product Sales	-	73.1%	75.0%	69.7%	84.8%	73.6%	69.8%
CoGS / Sales to End Users	-	37.0%	36.1%	34.6%	28.7%	33.1%	28.4%
Product Procurement	-	238	1,434	1,322	1,175	1,550	1,242
Gross Profit	1,191	1,212	658	593	318	527	583
SG&A	1,399	1,825	2,725	2,293	1,999	1,830	3,135
Personnel	323	343	365	413	441	479	488
Research	817	1,118	1,945	1,438	1,053	774	2,035
Other	259	364	415	442	505	577	612
Operating profit	-208	-613	-2,067	-1,700	-1,681	-1,303	-2,552

Source: Shared Research based on company data.

Sales

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

Product sales

Product sales are revenue from selling Treakisym. The company began booking product sales in FY12/10, when it obtained approval for Treakisym and started selling the anti-cancer agent in December 2010. In FY12/14, product sales comprised sales of bendamustine to Eisai and InnoPharmax. Bendamustine is supplied wholesale at the NHI price minus a percentage based on past transactions. Shared Research estimates this percentage to be about 40%.

Royalty revenue

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

CoGS

Cost of goods sold refers to procurement costs for drugs. As mentioned earlier, the company's only product on the market as of July 2014 was Treakisym (bendamustine). Astellas supplies bendamustine to the company for about 75% of SymBio's wholesale price. Margins may improve as sales increase.

SymBio receives bendamustine in nude vials from Astellas, carries out the packaging and labelling, and supplies the drug wholesale to Eisai. SymBio pays Astellas in euros, with these transactions usually taking place several months apart. Thus, the company faces the risk that euro-yen forex rates will change during this period. The company hedges this risk with

forward foreign-exchange contracts, and by reporting gains and losses on forex as a non-operating profit (or loss).

SG&A

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

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. Three additional indications are now under development by the company for the drug (relapsed or refractory aggressive NHL; first-line low-grade NHL and MCL; and chronic lymphocytic leukemia), which may receive marketing approval in the future.
- **Strong share in niche markets**: SymBio focuses on niche markets for rare oncologic and hematologic diseases, in addition to pain management. The company takes advantage of a less competitive environment by developing drugs for indications that serve a limited number of patients and require a high degree of in-house expertise. Thus, the company has succeeded in securing more than 50% of the target market for Treakisym in relapsed or refractory low-grade NHL and MCL in the third year after launch.

Weaknesses

- **Lack of sales force:** The company does not currently have its own sales force, thus Treakisym is being sold through Eisai, an alliance partner. The company is considering the creation of its own sales and marketing organization for rigosertib and other drugs approved beyond rigosertib. Such efforts could drive up costs and impact the company's future profitability.
- **Funding needs**: It takes time and significant investment for pharmaceutical and biotech companies to develop and commercialize drugs, and they must secure funding on a regular basis to cope with the uncertainty of their earnings. For SymBio, cash and equivalents plus short-term investments totaled about JPY4.3bn at the end of FY12/15. But the company expects a total net loss of JPY9.8–10.2bn over the period of its mid-term plan (FY12/16–FY12/18). The company's operations would be affected if it fails to secure additional funding.
- **Dependence on a single individual**: Founding President and CEO, Fuminori Yoshida, has played a central role in all aspects of SymBio's management since its foundation. If for any reason Mr. Yoshida is unable to perform his duties, this could have an impact on company operations.

Market and value chain

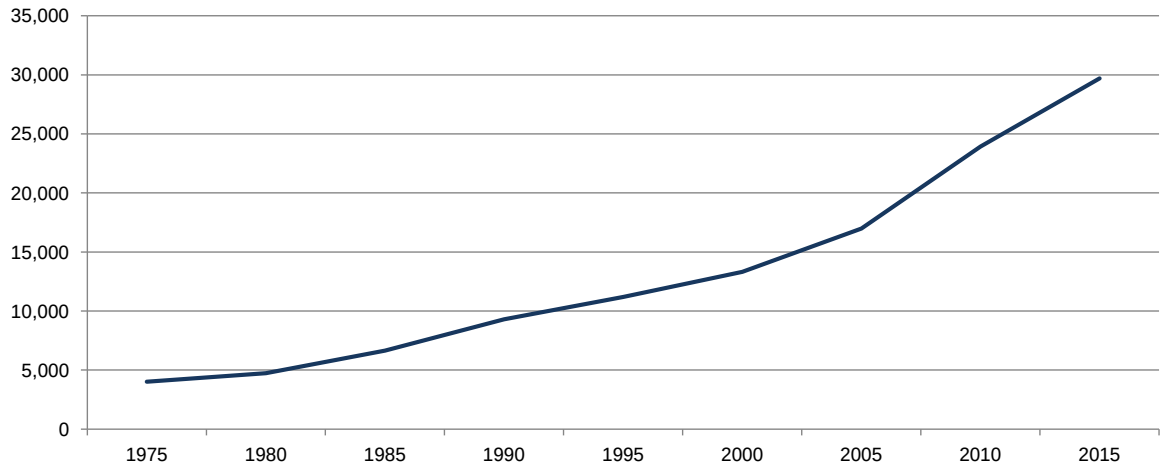
Market strategy

Lymphatic cancer: patient population, market size, drugs

Newly diagnosed patients with lymphatic cancer

In 2011, the number of people diagnosed with lymphatic cancer in Japan was 24,778, according to the Center for Cancer Control and Information Services. Of these, 19,080, or 77.0%, were 60 years or older. The number of people newly diagnosed with lymphatic cancer has been rising along with Japan's aging population. This number rose by 80% from 2001 to 2011. This number is expected to rise to 29,700. According to the Center for Cancer Control and Information Services, there were an estimated 29,700 lymphatic cancer patients in Japan in 2015.

Patients newly diagnosed with lymphatic malignancy



Patients newly diagnosed with lymphatic malignancy

	1975	1980	1985	1990	1995	2000	2005	2010	2015
Number of patients	4,013	4,741	6,635	9,297	11,195	13,307	16,991	23,919	29,700
Incidence rate (per 100,000)	3.6	4.1	5.5	7.5	8.9	10.5	13.3	18.7	-

Source: Center for Cancer Control and Information Services, National Cancer Center.
2015 data based on estimates

Market for lymphatic cancer drugs may expand

According to the Fuji Keizai Group, the domestic market potential for anticancer agents was JPY769.1bn in 2012. The market is growing, and is expected to hit JPY1.1tn by 2021—the result of a larger elderly population in Japan and more treatable patients as cancer is discovered at an earlier stage. Within this market, the market for lymphatic cancer drugs is expected to expand to JPY60.2bn in 2021 from JPY38.9bn in 2012.

Market for drugs for lymphatic malignancy

(JPYbn)	2012	YoY	2021 (Est.)	Growth (2021/2012)
Anticancer agents	769.1	105.0%	1,061.4	138.0%
Breast cancer	119.5	112.4%	199.4	166.9%
Lymphatic malignancy	38.9	111.5%	60.2	154.8%

Source: Fuji Keizai Group

Treakisym market potential and patient population

The company estimates that the number of patients being treated for relapsed or refractory low-grade NHL in Japan is 4,700. Treakisym sales reached JPY4.8bn (+10.3%) in FY12/15.

The company estimates that the number of Japanese patients receiving first-line treatment for low-grade NHL and MCL is about 7,100 (phase II completed); the number of patients with relapsed or refractory aggressive NHL is about 6,700 (phase II completed). Japanese patients with CLL is estimated to be about 700 (phase II ongoing). The estimate for total number of users and potential users of Treakisym: 19,200.

Treakisym indications and number of patients

Condition	Patients	Progress	Notes
Relapsed or refractory low-grade NHL, relapsed or refractory MCL	4,700	Approval granted	Sales: JPY4.8bn (FY12/15)
First-line low-grade NHL, first-line MCL	7,100	Clinical trials underway	Apply for marketing approval
Relapsed or refractory intermediate- or high-grade NHL	6,700	Clinical trials underway	Consultation on application underway
CLL	700	Clinical trials underway	Apply for marketing approval

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

Drugs competing with Treakisym

As of February 2015, these include rituximab and ibritumomab tiuxetan. Immunochemotherapy (the combination of immunotherapy and chemotherapy drugs) is often used to treat B-cell lymphatic malignancies.

Rituximab (product name: Rituxan)

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

Rituxan consists of a portion of both mouse antibody and IgG, a human antibody. It attaches itself to the CD20 antigen that appears on B cells in the body and fights tumors through complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity effects (source: Chugai, Zenyaku Kogyo).
In Japan, Zenyaku Kogyo and Chugai have been jointly selling the drug since September 2001. Chugai's Rituxan sales were JPY29.0bn in 2015.

Ibritumomab tiuxetan (product name: Zevalin)

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

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

MDS patients, drugs

Market potential and number of patients

MDS patient population estimated at 11,000

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

Rigosertib indications and number of patients

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

Source: Shared Research based on company data.

Drugs competing with rigosertib

According to the company, as of February 2016, Nippon Shinyaku Co., Ltd.'s Vidaza is the only IV drug approved in Japan for the main indication of MDS.

Azacitidine (product name: Vidaza)

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

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

According to Nippon Shinyaku, Vidaza is the only approved drug in Japan for the first-line treatment of higher-risk MDS, with no effective treatment available once patients treated with Vidaza relapse. Nippon Shinyaku booked Vidaza sales of JPY10.8bn in FY03/15 (+11.6% YoY) and expects sales of JPY12.0bn in FY03/16.

Historical performance

Q3 FY12/15 results

Sales for Q3 FY12/15 totaled JPY1.3bn (-1.2% YoY) due to domestic and overseas sales of SyB L-0501 (Treakisym).

Overall Treakisym sales fell 1.2% YoY. Though domestic sales of Treakisym increased 6.1% YoY, overseas sales declined due to shipments having been frontloaded in FY12/14.

SG&A expenses came to JPY1.4bn (+4.7% YoY), including research and development expenses worth JPY598mn (+9.7%). These expenses mainly covered clinical trials for additional SyB L-0501 indications and costs pertaining to preparing the New Drug Application (NDA) for submission, as well as clinical trials for SyB L-1101 (intravenous formulation) and SyB C-1101 (oral formulation), and preparation for the next phase of clinical trials. Other SG&A expenses came to JPY785mn (+1.3%).

As a result, operating loss totaled JPY988mn (Q3 FY12/14: loss of JPY967mn). The company also reported a recurring loss of JPY1.1bn (Q3 FY12/14: loss of JPY941mn), owing to non-operating expenses of JPY82mn, mainly from forex losses of JPY74mn. Net loss totaled JPY1.1bn (Q3 FY12/14: loss of JPY944mn)

Domestic

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

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

SymBio completed the phase II clinical trial of Treakisym for the first-line treatment of low-grade NHL and MCL in February 2014. Along with the regulatory approval process for the application submitted by Astellas Pharma Europe Ltd. (a European subsidiary of Astellas Pharma Inc.; TSE1: 4503) in the European Union, the company is also continuing to prepare the New Drug Application (NDA) for submission in Japan, having entered preliminary consultations with the Pharmaceuticals and Medical Devices Agency (PMDA).

The company completed patient enrollment for a phase II clinical trial for chronic lymphocytic leukemia (CLL) in October 2014, and completed the trial in October 2015. It plans to file a Supplemental New Drug Application (sNDA) for marketing approval in Q1 FY12/16.. Treakisym was designated as an orphan drug (drug for the treatment of rare diseases) for CLL in June 2012, and the Evaluation Committee on Unapproved or Off-Labeled Drugs with High Medical Need has also submitted a development request to the company.

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

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

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

Onconova Therapeutics, Inc., the U.S. licensor, is currently conducting a global Phase III trial for higher risk MDS patients who do not respond to treatment with hypomethylating agents (HMAs), the current standard of care ("Primary HMA Failure"), at clinical trial sites in more than ten countries worldwide. Following its completion of the domestic Phase I clinical trial, SymBio also decided to participate in the global clinical trial in October 2015.

As for SyB C-1101 (oral formulation, or Oral rigosertib), the company's domestic Phase I clinical trial for the target indication of higher risk MDS was completed in June, 2015. The company plans to continue clinical trials for the development of Oral rigosertib in combination with azacitidine for higher risk MDS, as well as for lower risk transfusion-dependent MDS, and is considering participating in the global clinical trial to be conducted by Onconova.

Ionsys (fentanyl iontophoretic transdermal system)

In October 2015, the company concluded a licensing agreement with The Medicines Company for development and commercialization of Ionsys, a drug system for post-operative patient-controlled pain management. The company obtained exclusive development and marketing rights in Japan, and plans to initiate a domestic phase III study in 2016.

Overseas

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

Q2 FY12/15 results

Sales for Q2 FY12/15 totaled JPY976mn (+0.1% YoY) due to domestic and overseas sales of SyB L-0501 (Treakisym).

Overall Treakisym sales rose 1.7% YoY. Though domestic sales of Treakisym increased 11.6% YoY, overseas sales declined 51.2% YoY. Shipments to South Korea totaled JPY273mn, but this was mainly because shipments had been frontloaded in FY12/14. Excluding this impact, overall product shipments rose 30% YoY.

SG&A expenses came to JPY931mn (+4.2% YoY), including research and development expenses worth JPY404mn (+9.0%), mainly for clinical trials for SyB L-1101 (intravenous formulation) and SyB C-1101 (oral formulation), and other SG&A expenses worth JPY527mn (+0.7%).

As a result, operating loss totaled JPY648mn (Q2 FY12/14: loss of JPY646mn). The company also reported a recurring loss of JPY674mn (Q2 FY12/14: loss of JPY713mn), owing to non-operating expenses of JPY35mn, mainly from forex losses of JPY29mn. Net loss totaled JPY676mn (Q2 FY12/14: loss of JPY715mn)

Domestic

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

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

SymBio completed the phase II clinical trial of Treakisym for the first-line treatment of low-grade NHL and MCL in February 2014. The company is preparing the New Drug Application (NDA) for submission in Japan. The company will apply for approval as soon as the regulatory approval process for the application submitted by Astellas Pharma Europe Ltd. (a European subsidiary of Astellas Pharma Inc.; TSE1: 4503) is completed in the European Union.

The company completed patient enrollment for a phase II clinical trial for chronic lymphocytic leukemia (CLL) in October 2014. It plans to complete the trial and file an sNDA for marketing approval as soon as possible. Treakisym was designated as an orphan drug (drug for the treatment of rare diseases) for CLL in June 2012.

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

Rigosertib (SyB L-1101 [IV]/SyB C-1101 [oral]; anticancer agent)
The company is conducting a domestic phase I clinical trial for the intravenous (IV) form of rigosertib in relapsed or refractory higher-risk myelodysplastic syndromes (MDS), a hematological malignancy. Patient enrollment was completed in January 2015.

Onconova Therapeutics, Inc., the U.S. licensor, plans to conduct a global Phase III trial for higher risk MDS patients who do not respond to treatment with hypomethylating agents (HMAs), the current standard of care ("Primary HMA Failure"), with clinical trial sites in more than ten countries worldwide. SymBio is considering its participation in the global clinical trial which is planned to begin in 2H of 2015 after completion of the domestic Phase I clinical trial.

As for SyB C-1101 (oral formulation, or Oral rigosertib), the company's domestic Phase I clinical trial for the target indication of higher risk MDS was completed in June, 2015. The company plans to continue clinical trials for the development of Oral rigosertib in combination with azacitidine for higher risk MDS, as well as for lower risk transfusiondependent MDS, and is considering participating in the global clinical trial to be conducted by Onconova.

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

Q1 FY12/15 results

Sales for Q1 FY12/15 totaled JPY408mn (+135.0% YoY) due to domestic and overseas shipments of Treakisym.

Domestic sales of Treakisym were up 2.1x YoY, owing to a favorable year-on-year comparison, as last year the company faced adjustments to distribution inventory.

SG&A expenses were JPY453mn (+1.1% YoY), including R&D expenses of JPY206mn (+15.2% YoY) owing to clinical trial expenses for Treakisym and the oral and IV forms of rigosertib. Other SG&A expenses totaled JPY247mn (-8.3% YoY).

As a result, operating loss totaled JPY332mn (Q1 FY12/14: loss of JPY416mn). The company also reported a recurring loss of JPY419mn (Q1 FY12/14: loss of JPY454mn), owing to non-operating expenses of JPY91mn, mainly from forex losses of JPY89mn. Net loss totaled JPY420mn (Q1 FY12/14: loss of JPY455mn).

Domestic
Treakisym (SyB L-0501; anticancer agent; generic name: bendamustine hydrochloride)
SymBio completed the phrase II clinical trial of Treakisym for the first-line treatment of low-grade NHL and MCL in February 2014. The company is analyzing and evaluating data from the trial as it prepares to file a supplemental new drug application (sNDA) for marketing approval. The company plans to build on Astellas Pharma GmbH ("Astellas"; European

subsidiary of Astellas Pharma Inc.; TSE1: 4503)'s ongoing application for approval in Europe as it files a domestic sNDA.

The company completed patient enrollment for a phase II clinical trial for CLL in October 2014. It plans to complete the trial and file an sNDA for marketing approval as soon as possible. Treakisym was designated as an orphan drug (drug for the treatment of rare diseases) for CLL in June 2012.

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

Rigosertib (SyB L-1101 [IV]/SyB C-1101 [oral]; anticancer agent)
The company is conducting a domestic phase I clinical trial for the intravenous (IV) form of rigosertib in relapsed or refractory higher-risk myelodysplastic syndromes (MDS). Patient enrollment was completed in January 2015.

In February 2014, licensor Onconova Therapeutics, Inc. (Nasdaq: ONTX) announced the results of its phase III ONTIME clinical trial in patients with higher-risk MDS. Compared with best supportive care (BSC), the clinical trial did not show a statistically significant improvement in the overall survival period (primary outcome measures). However, group analysis showed a statistically significant difference in the survival period for patients whose condition had deteriorated or those who had not responded to previous treatment using hypomethylating agents (HMAs).

Onconova held discussions with regulatory agencies in the US and Europe regarding the possibility of seeking approval based on the results of the phase III trial. The regulators have confirmed that patients who had not responded to HMAs would require a new treatment. In response, the company announced that it would develop the new treatment. In April 2015, Onconova submitted an international clinical trial protocol to the Food and Drug Administration (FDA) in the US, and the European Medicines Agency (EMA) in Europe. SymBio will continue with procedures to complete the current phase I clinical trials in Japan. Post-phase I development in Japan will depend on the development in the US and Europe.

A domestic phase I clinical trial using the oral form of rigosertib is also underway in Japan for the treatment of high-risk MDS patients. The patient enrollment for the trial was completed in August 2014, and the company worked toward the end of the clinical trials. It plans to complete the trials as soon as possible and continuing developing the drug for the indications of high-risk MDS (in combination with azacitidine) and blood transfusion-dependent low-risk MDS.

Overseas

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

New candidates

Negotiations regarding the in-licensing of new candidate drugs for development are ongoing.

FY12/14 results

Sales for FY12/14 totaled JPY2.0bn (+27.6% YoY) due to domestic and overseas shipments of Treakisym.

Sales of Treakisym were JPY1.9bn (+35.5% YoY). Domestic sales totaled JPY1.5bn (+12.9% YoY), while overseas sales were JPY472mn (up 3.6x). The significant increase in overseas sales was because the company added one year of inventory (JPY273mn) in South Korea following a change of manufacturing location.

Milestone revenues were JPY15mn (-85% YoY), which the company booked on the approval of Treakisym for the

indication of relapsed or refractory low-grade NHL in Korea.

SG&A expenses were JPY1.8bn (-8.4% YoY), including R&D expenses of JPY774mn (-26.5% YoY). Despite clinical trial expenses for Treakisym and the oral and IV forms of rigosertib, overall R&D expenses were down year-on-year because clinical trials for additional indications for Treakisym wound down. Other SG&A expenses totaled JPY1.1bn (+1.6% YoY).

As a result, operating loss totaled JPY1.3bn (FY12/13: loss of JPY1.7bn). The company also reported a recurring loss of JPY1.1bn (FY12/13: loss of JPY1.6bn). The recurring loss narrowed owing to non-operating gains of JPY215mn, including forex gains of JPY189mn, JPY16mn in interest received, and JPY8mn from interest on investment securities. Net loss totaled JPY1.1bn (FY12/13: loss of 1.6bn).

Domestic

Treakisym

SymBio completed the phrase II clinical trial of Treakisym for the first-line treatment of low-grade NHL and MCL in February 2014. The company is analyzing and evaluating data from the trial as it prepares to file a supplemental new drug application (sNDA) for marketing approval. Astellas Pharma GmbH ("Astellas"; European subsidiary of Astellas Pharma Inc.; TSE1: 4503) has already applied for approval in Europe.

The company completed the patient enrollment for a phase II clinical trial for CLL in October 2014. Treakisym was designated as an orphan drug (drug for the treatment of rare diseases) for CLL in June 2012.

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

Rigosertib

The company is conducting a domestic phase I clinical trial for the intravenous (IV) form of rigosertib in relapsed or refractory higher-risk myelodysplastic syndromes (MDS).

In February 2014, licensor Onconova Therapeutics, Inc. ("Onconova"; Nasdaq: ONTX) announced the results of its phase III ONTIME clinical trial in patients with higher-risk MDS. Compared with best supportive care (BSC), the clinical trial did not show a statistically significant improvement in the overall survival period (primary outcome measures). However, group analysis showed a statistically significant difference in the survival period for patients whose condition had deteriorated or those who had not responded to previous treatment using hypomethylating agents (HMAs).

Onconova held discussions with regulatory agencies in the US and Europe regarding the possibility of seeking approval based on the results of the phase III trial. The regulators have confirmed that patients who had not responded to HMAs would require a new treatment. In response, the company announced that it would develop the new treatment. SymBio will continue with its current phase I clinical trials in Japan. Post-phase I development in Japan will depend on the development in the US and Europe.

A domestic phase I clinical trial using the oral form of rigosertib is also underway in Japan for the treatment of high-risk MDS patients. The patient enrollment for the trial was completed in August 2014.

Overseas

Bendamustine (domestic product name: Treakisym) was approved in South Korea for the additional indication of relapsed

or refractory low-grade NHL in June 2014. The product is now sold by Eisai's Eisai Korea Inc. unit. The subsidiary also sells the drug for two other indications—CLL and multiple myeloma (MM).

In Taiwan, the drug is being marketed by InnoPharmax Inc. In Singapore, Eisai (Singapore) Pte. Ltd. markets the drug. Overseas sales increased by 2.2 times the estimate after the company added one year of inventory in South Korea in connection with a factory alignment.

FY12/13 results

Treakisym sales in Japan and other parts of Asia were JPY1.5bn (-21.6% YoY) due to adjustments in distribution inventory. Sales to end users were JPY4.2bn (+7.4% YoY). However, Treakisym sales totaled JPY1.4bn (-26.8% YoY) due to adjustments in Treakisym distribution inventory at Eisai.

The company earned JPY100mn in royalty revenue (no such revenue was posted a year earlier). The company received milestone payments associated with the start of the phase II clinical trial for CLL.

The company posted R&D costs of JPY1.1bn (-26.8% YoY) due to clinical trials for additional Treakisym indications, and rigosertib indications. R&D costs declined from a year earlier as development for Treakisym nears completion. With other expenses totaling JPY946mn (+10.6% YoY), total SG&A expenses were JPY2.0bn (-12.9% YoY).

Operating loss was JPY1.7bn (almost unchanged from a year earlier). There were non-operating expenses of JPY35mn associated with payment of fees and stock issuance costs. The company posted a non-operating profit of JPY114mn due to currency gains. Consequently, recurring loss was JPY1.6bn (a loss of JPY1.7bn a year earlier), and net loss was 1.6bn (a loss of JPY1.7bn a year earlier).

Income statement

Income Statement (JPYmn)	FY12/09 Par.	FY12/10 Par.	FY12/11 Par.	FY12/12 Par.	FY12/13 Par.	FY12/14 Par.	FY12/15 Par.
Total Sales	**1,191**	**1,450**	**1,883**	**1,955**	**1,532**	**1,955**	**1,933**
YoY	-26.9%	21.7%	29.8%	3.9%	-21.6%	27.6%	-1.1%
CoGS	-	238	1,224	1,362	1,214	1,428	1,350
Gross Profit	**1,191**	**1,212**	**658**	**593**	**318**	**527**	**583**
GPM	100.0%	83.6%	35.0%	30.3%	20.8%	26.9%	30.2%
SG&A	1,399	1,825	2,725	2,293	1,999	1,830	3,135
SG&A / Sales	117.5%	125.8%	144.8%	117.3%	130.4%	93.6%	162.1%
Operating Profit	**-208**	**-613**	**-2,067**	**-1,700**	**-1,681**	**-1,303**	**-2,552**
YoY	-	-	-	-	-		
OPM	-	-	-	-	-		
Non-Operating Income	20	13	56	7	114	215	17
Non-Operating Expenses	26	38	85	37	35	22	96
Recurring Profit	**-214**	**-638**	**-2,095**	**-1,729**	**-1,601**	**-1,110**	**-2,630**
YoY	-	-	-	-	-	-	-
RPM	-	-	-	-	-	-	-
Extraordinary Gains	-	-	-	-	-	2	3
Extraordinary Losses	-	0	5	0	-	3	1
Tax Charges	4	4	4	4	4	4	4
Implied Tax Rate	-	-	-	-	-	-	-
Net Income	**-218**	**-642**	**-2,105**	**-1,733**	**-1,605**	**-1,116**	**-2,632**
YoY	-	-	-	-	-	-	-
Net Margin	-	-	-	-	-	-	-

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

FY12/12

Sales were JPY2.0bn (+3.9% YoY). Product sales were JPY2.0bn (+19.8% YoY) due to an increase in Treakisym sales to end users, which totaled JPY3.9bn (+16.2% YoY). The company did not receive any royalty revenue.

SG&A expenses were JPY2.3bn (-15.8% YoY). R&D costs totaled JPY1.4bn (-26.1% YoY), which included the cost of clinical trials for additional Treakisym indications and rigosertib. The company, which made one-time payments for the acquisition of rigosertib a year earlier, did not make such payments, slashing R&D expenses.

FY12/11

Sales were JPY1.9bn (+29.8% YoY). Product sales were JPY1.6bn (+401.3% YoY). Sales of Treakisym to end users were JPY3.4bn (JPY64mn in FY12/10). Royalty revenues were JPY250mn. The company received milestone payments associated with the start of domestic development of first-line low-grade non-Hodgkin's lymphoma and mantle-cell lymphoma, plus the marketing approval of Treakisym in South Korea and Taiwan.

SG&A expenses were JPY2.7bn (+49.4% YoY). R&D costs were JPY1.9bn (+73.9% YoY). The company conducted clinical trials for additional Treakisym indications and SyB D-0701 (antiemetic transdermal patch for RINV). The company also made one-time payments for the acquisition of rigosertib rights (both IV and oral).

FY12/10

Sales were JPY1.5bn (+21.7% YoY). Product sales were JPY326mn (no product sales a year earlier). The company began to post product sales as it started to sell Treakisym in Japan. Royalty revenue totaled JPY1.1bn. The company received

milestone payments from Eisai associated with the marketing approval of Treakisym in Japan, marketing approval of Symbenda in Singapore, and the start of the phase II clinical trial for multiple myeloma in Japan.

SG&A expenses were JPY1.8bn (+30.4% YoY). R&D costs were JPY1.1bn (+36.9% YoY), which included spending for clinical trials, preparation for additional Treakisym indications and the clinical trial for SyB D-0701 (antiemetic transdermal patch for RINV). The company made one-time payments for SyB 0702 (HSP32 inhibitor).

FY12/09

Sales were JPY1.2bn (-26.9% YoY), all from royalty revenues. The pivotal phase II clinical trial for Treakisym targeting low-grade NHL and MCL patients who had received prior treatment was completed in March 2009. The company submitted an application for accelerated marketing approval of Treakisym in October 2009 (receiving orphan drug designation with 10-year marketing exclusivity once approved).

SG&A expenses were JPY1.4bn (-6.5% YoY). R&D costs were JPY817mn (-5.9% YoY). The company sought to develop its product pipeline with emphasis on phase II clinical trials for additional indications of Treakisym, and phase I clinical trial for the combination therapy of Treakisym plus rituximab in first-line low-grade NHL and MCL.

FY12/08

Sales were JPY1.6bn (no sales for FY12/07). All sales were comprised of royalty revenue. In August 2008, the company entered into a license agreement with Eisai for the co-development and exclusive marketing right to Treakisym in Japan. SymBio received one-time payments for the agreement. SG&A expenses: JPY1.5bn. R&D expenses: JPY868mn.

Historical forecast accuracy

Initial CE vs. results (JPYmn)	FY12/09 Par.	FY12/10 Par.	FY12/11 Par.	FY12/12 Par.	FY12/13 Par.	FY12/14 Par.	FY12/15 Par.
Sales (Initial CE)	-	-	1,933	2,338	1,927	1,785	1,785
Sales (Results)	-	-	1,883	1,955	1,532	1,955	1,933
Initial CE versus Results	**-**	**-**	**-2.6%**	**-16.4%**	**-20.5%**	**9.5%**	**8.3%**
Operating Profit (Initial CE)	-	-	-2,351	-1,625	-1,889	-1,654	-1,654
Operating Profit (Results)	-	-	-2,067	-1,700	-1,681	-1,303	-2,552
Initial CE versus Results	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Recurring Profit (Initial CE)	-	-	-2,398	-1,652	-1,922	-1,650	-1,650
Recurring Profit (Results)	-	-	-2,095	-1,729	-1,601	-1,110	-2,630
Initial CE versus Results	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Net Income (Initial CE)	-	-	-2,407	-1,656	-1,926	-1,654	-1,654
Net Income (Results)	-	-	-2,105	-1,733	-1,605	-1,116	-2,632
Initial CE versus Results	**-**	**-**	**-**	**-**	**-**	**-**	**-**

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

Balance sheet

Balance Sheet (JPYmn)	FY12/09 Par.	FY12/10 Par.	FY12/11 Par.	FY12/12 Par.	FY12/13 Par.	FY12/14 Par.	FY12/15 Par.
Assets							
Cash and Equivalents	3,902	2,314	4,559	4,540	6,163	5,692	4,261
Marketable securities	219	1,701	1,953	300	1,100	899	0
Accounts Receivable	-	6	162	148		273	301
Inventories	-	-	207	165	125	245	133
Other Current Assets	97	191	297	268	245	181	131
Total Current Assets	**4,218**	**4,213**	**7,178**	**5,421**	**7,634**	**7,290**	**4,827**
Buildings	3	3	2	3	2	22	22
Equipment, Plant	11	19	15	11	6	27	31
Total Tangible Fixed Assets	**13**	**22**	**17**	**14**	**9**	**49**	**53**
Total Other Fixed Assets	**27**	**27**	**48**	**57**	**37**	**49**	**53**
Software	2	1	10	8	6	62	51
Other	-	-	3	3	2	4	1
Total Intangible Assets	**2**	**1**	**13**	**11**	**8**	**66**	**52**
Total Fixed Assets	**42**	**50**	**78**	**82**	**53**	**164**	**158**
Total Assets	**4,261**	**4,263**	**7,256**	**5,502**	**7,687**	**7,454**	**4,984**
Liabilities							
Accounts Payable	-	1	309	330		306	320
Accrued Amount Payable	182	124	278	196	207	143	184
Short Term Debt	-	-	-	-	-	-	-
Other Current Liabilities	23	52	59	73	44	39	47
Total Current Liabilities	**205**	**178**	**646**	**599**	**251**	**488**	**551**
Long Term Debt	-	-	-	-	-	-	-
Other Fixed Liabilities	2	2	5	4	3	2	2
Total Long Term Liabilities	**2**	**2**	**5**	**4**	**3**	**2**	**2**
Total Interest Bearing Debt	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Total Liabilities	**207**	**180**	**651**	**602**	**254**	**490**	**552**
Shareholder Equity (Net Assets)	4,060	4,083	6,606	4,873	7,336	6,764	4,132
Issued Capital	3,378	3,711	6,025	6,025	8,059	8,331	8,331
Reserves	3,348	3,681	5,995	5,995	8,029	8,301	8,301
Retained Earnings	-2,666	-3,309	-5,413	-7,146	-8,752	-9,868	-12,500
Subscription Rights to Shares	-	-	-	27	97	200	300
Total Shareholder Equity (Net Assets)	**4,054**	**4,083**	**6,606**	**4,900**	**7,433**	**6,964**	**4,432**
Working Capital	-	5	61	-17	125	212	114
Interest Bearing Debt	-	-	-	-	-	-	-
Net Debt (Net Cash)	-3,902	-2,314	-4,559	-4,540	-6,163	-5,692	-4,261

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

Assets

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

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

Liabilities

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

Net assets

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

Cash flow statement

Cash Flow Statement (JPYmn)	FY12/09 Par.	FY12/10 Par.	FY12/11 Par.	FY12/12 Par.	FY12/13 Par.	FY12/14 Par.	FY12/15 Par.
Operating Cash Flow (1)	-211	-754	-2,074	-1,659	-1,677	-1,266	-2,272
Investment Cash Flow (2)	-4	-116	-117	-411	-1,332	314	1,489
Free Cash Flow (1+2)	-215	-870	-2,191	-2,069	-3,010	-952	-783
Financial Cash Flow	2,963	663	4,611	-1	4,057	544	-3
Depreciation & Amortization (A)	4	7	8	9	8	13	24
Capital Expenditures (B)	-3	-14	-12	-3	-	-109	-24
Working Capital Changes (C)	-	5	56	-78	142	86	-98
Simple FCF (NI + A + B - C)	-217	-655	-2,165	-1,650	-1,739	-1,298	-2,534
Cash and Equivalents (year-end)	4,121	3,916	6,311	4,240	5,294	5,092	4,261

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

Cash flow from operations

Cash flow from operations almost matches the company's current net loss before tax.

Cash flow from investment activities

Purchases of tangible fixed assets and intangible assets are limited as SymBio outsources manufacturing, clinical development, and sales and marketing. But investment in time deposits and securities meant outflow from investment 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 flow from financing activities

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

Main sources of funding

Date	Change in shares outstanding	Total shares outstanding	Change in capital/reserves (JPYmn)	Total capital/reserves (JPYmn)	Method
Mar. 2009	7,404	66,017	888	4,643	Paid-in third-party allotment
Nov. 2011	8,334	90,268	500	6,104	Paid-in third-party allotment
Dec. 2009	9,553	100,651	573	6,727	Paid-in third-party allotment
Feb. 2011	11,032	122,769	772	8,164	Paid-in third-party allotment
Feb. 2011	17,368	140,137	1,216	9,380	Paid-in third-party allotment
Oct. 2011	5,100,000	19,130,900	2,628	12,019	Paid-in public offering (price determined by the book building process)
Jan.-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

Source: Shared Research based on company data.

Other information

History

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

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

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

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

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

As of February 2016, Treakisym for relapsed or refractory low-grade NHL and MCL is the company's mainstay product. Clinical trials are also under way toward attaining domestic approval for additional Treakisym indications, anti-cancer drug rigosertib for myelodysplastic syndromes, and SyB P-1501, a patient-controlled analgesia for pain management.

Company history

Date	Details
March 2005	SymBio Pharmaceuticals Limited established with JPY30mn in capital.
December 2005	License Agreement finalized with Astellas Pharma GmbH for SyB L-0501 (bendamustine) development and commercialization rights in Japan.
March 2006	Manufacturer's License (packaging, labeling and storage) obtained from Tokyo Metropolitan Government (License #13AZ200010).
March 2007	Abeille Pharmaceuticals licenses SyB D-0701 (granisetron patch) to SymBio Pharmaceuticals for development & commercialization in Japan, China (HK), Taiwan, Korea and Singapore.
March 2007	License Agreement finalized with Astellas Deutschland GmbH for SyB L-0501 (bendamustine) development & commercialization rights in China (HK), Taiwan, Korea and Singapore.
August 2008	License Agreement finalized with Eisai Co., Ltd. for co-development and commercialization rights of SyB L-0501 (bendamustine) in Japan.
March 2009	SymBio Pharmaceuticals concludes Sublicense Agreement with Cephalon, Inc. for development and commercialization rights of bendamustine hydrochloride in China (HK).
May 2009	License Agreement finalized with Eisai Co., Ltd. for co-development and commercialization rights of SyB L-0501 (bendamustine) in Korea and Singapore.
September 2010	SymBio Pharmaceuticals and Eisai launch SYMBENDA® (bendamustine) in Singapore for the treatment of Low-grade Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukemia.
October 2010	SymBio Pharmaceuticals announces NDA Approval of TREAKISYM® (bendamustine) in Japan.
December 2010	SymBio Pharmaceuticals launches TREAKISYM® in Japan.
July 2011	Onconova and SymBio Pharmaceuticals complete License Agreement for SyB L-1101/SyB C-1101 (rigosertib, a Phase Ⅲ stage multi-kinase inhibitor for Myelodysplastic Syndromes).
October 2011	SymBio Pharmaceuticals launches Symbenda® (bendamustine hydrochloride) in Korea for the treatment of Chronic Lymphocytic Leukemia and multiplemyeloma.
October 2011	Listed on Osaka Securities Exchange JASDAQ Growth Market.
February 2012	SymBio Pharmaceuticals launches Innomustine® (bendamustine hydrochloride) in Taiwan for the treatment of Low-grade Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukemia.
October 2015	SymBio obtained exclusive development and marketing rights to Ionsys (patient-controlled analgesia system) in Japan from The Medicines Company (US).

Source: Company website

News and topics

December 2015

On **December 7, 2015,** the company announced that it has started phase I clinical trials for the use of oral anticancer agent rigosertib in combination with azacytidine for the treatment of higher-risk myelodysplastic syndrome (MDS).

The company has started phase I clinical trials in Japan for the use of the oral anticancer agent rigosertib in combination with azacytidine (Vidaza®, sold in Japan by Nippon Shinyaku Co., Ltd.) for treatment of higher-risk MDS.

The company already completed phase I clinical trials on the monotherapy use of rigosertib in June 2015. Once the combination clinical trials are complete, the company will consider participating in an international joint study for the drug planned by its licenser, Onconova Therapeutics Inc. Onconova Therapeutics has already completed patient enrollment for phase I/II clinical trials of oral rigosertib for the same indication, and was planning to announce results at the American Society of Hematology meeting that started on December 5, 2015. The start of the new clinical study will have no impact on the company's FY12/15 earnings forecasts.

November 2015

On **November 24, 2015,** the company announced the approval of IONSYS® (fentanyl iontophoretic transdermal system) in Europe.

The company announced that The Medicines Company (MEDCO), with which it concluded a license agreement for IONSYS® on October 2, 2015, received marketing authorization from the European Commission for IONSYS® to treat postoperative pain in hospitalized patients on November 20, 2015.

IONSYS® was approved by the US Food and Drug Administration (FDA) on April 4, 2015, and was already being sold in the US.

The company was preparing for early phase III clinical trials in Japan.

October 2015

On **October 30,** the company announced that it had completed phase I clinical trials to use anticancer agent rigosertib (intravenous form) for myelodysplastic syndrome (MDS).

The company plans to participate in global phase III clinical trials already being conducted by US-based Onconova Therapeutics, Inc. (Nasdaq: ONTX) for higher-risk MDS patients whose condition had deteriorated or those who had not responded to previous treatment using hypomethylating agents (HMAs). It intends to begin trials with Japanese patients in 2015, and is targeting simultaneous approval in Japan, the US and Europe. SymBio does not expect completion of the phase I trial to impact its FY12/15 earnings.

On **October 19, 2015**, the company announced the completion of a phase II clinical trial for Treakisym in patients with chronic lymphocytic leukemia (CLL).

The company completed a domestic phase II clinical trial of anti-cancer drug Treakisym (generic: bendamustine hydrochloride) for patients with CLL, which it had been conducting in partnership with Eisai Co. Ltd. (TSE1: 4523). This drug has been approved for the treatment of CLL in Europe and the US. In Japan, this drug was designated as an orphan drug for the CLL indication in June 2012, and the Evaluation Committee on Unapproved or Off-Labeled Drugs with High Medical Needs has submitted a development request to the company. Going forward, SymBio plans to submit an application for manufacturing and marketing approval in Japan in Q1 FY2016 using data from phase III clinical trials

conducted overseas. The company does not expect completion of the phase II trial to impact its FY12/15 earnings.

On **October 5, 2015,** the company announced a strategic partnership for IONSYS® (fentanyl iontophoretic transdermal system).

The Medicines Company (MEDCO) and SymBio concluded a development and commercialization license for IONSYS® (fentanyl iontophoretic transdermal system) on October 2, 2015.

The partnership includes an agreement granting SymBio an exclusive license in Japan to develop and commercialize IONSYS. Sales of IONSYS have started in the US after it was approved by the US Food and Drug Administration (FDA) on April 30, 2015, for the short-term management of acute postoperative pain in adult patients requiring opioid analgesia in the hospital. On September 25, 2015, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) issued a positive opinion recommending marketing authorization for IONSYS, and marketing approval is anticipated in the near future. In Japan, a phase I study for IONSYS targeting healthy Japanese patients has been completed.

IONSYS is a patient-controlled analgesia (PCA) product that enables patients to push a button on a credit-card sized device located on the arm or chest to dispense a certain dose of fentanyl (a synthetic opiate analgesic drug used to control pain after anesthesia, cancer, or surgery, widely used at medical institutions in Japan) transdermally through iontophoresis (a technique of introducing ionic drugs into the body by passing a weak electrical current through the skin) as needed for pain. Transdermally administered fentanyl is absorbed as fast as through intravenous administration, and has analgesic effects. Patient count in Japan is estimated at 1mn per year, and currently standard administration is through epidural or IV PCA pumps. As a needle-free alternative, IONSYS is anticipated to improve treatment satisfaction as it lessens the physical and psychological burden on patients. It is also expected to offer stability and convenience for medical institutions, decreasing the labor and costs required to manage electric pumps.

The company is developing the product with an aim to launch domestic phase III clinical trials from 2016 and receive regulatory approval in 2019. SymBio expects to pay MEDCO an upfront payment and periodic milestones based on development progress, and following product commercialization expects to pay commercial milestones and royalties in line with annual sales targets.

The effect of the upfront payment from this licensing agreement on FY12/15 earnings is expected to be negligible.

November 2014

On **November 14, 2014**, the company announced the issue of second series unsecured convertible bonds with subscription rights to new shares, and series 34 subscription rights to new shares by third-party allotment.

The company expects to receive total funds of about JPY1.5bn, net of expenses. The company plans to use the funds for expenses related to the development of new drug candidates between FY12/14 and FY12/16. As of November 13, 2014, SymBio was negotiating license agreements for two to three new drug candidates with pharmaceutical companies in the US and EU. It has based the amount of funding required on the expected cost of in-licensing these drug candidates.

Overview of the offering

Second series unsecured convertible bonds with subscription rights to new shares

- Payment date: December 1, 2014
- Number of stock subscription rights: 25 units
- Issue price of bonds: JPY20mn (JPY100 per JPY100 par value)
- Issue price of stock subscription rights: Gratis
- Number of potential shares: 1.7mn
- Total funding amount: JPY500mn
- Conversion price: JPY300
- Subscription and allocation method: Issued to Oak Capital Corporation via third-party allotment.

Series 34 subscription rights to new shares

- Allotment date: December 1, 2014
- Number of stock subscription rights: 30,304 units
- Issue price: JPY10.4mn (JPY342 per unit)
- Number of potential shares: 3.0mn
- Total funding amount: JPY1.0bn
  (JPY10.4bn from the issue of subscription rights to new shares; JPY1.0bn from the exercise of subscription rights)
- Exercise price: JPY330
- Subscription and allocation method: Issued to Oak Capital Corporation via third-party allotment.

On **November 13, 2014**, the company announced its revised full-year earnings forecast for FY12/14.

Revisions to the full-year earnings forecast for FY12/14 (previous forecast in parentheses)

- Sales: JPY2.0bn (JPY1.8bn)
- Operating loss: JPY1.3bn (operating loss of JPY1.7bn)
- Recurring loss: JPY1.3bn (recurring loss of JPY1.7bn)
- Net loss: JPY1.3bn (net loss of JPY1.7bn).

Reasons for the revisions

The company expects sales to outperform the initial forecast by JPY205mn, mainly due to an increase in overseas product sales of Treakisym. SG&A expenses are also expected to be lower than in the initial forecast owing to a revision of development costs for clinical trials.

On **November 5, 2014**, the company announced the completion of patient enrollment for the domestic phase II clinical trial of its anticancer agent Treakisym (development code: SyB L-0501; generic: bendamustine hydrochloride) in CLL patients. The company is developing Treakisym in conjunction with partner Eisai Co., Ltd. (“Eisai”). The Ministry of

Health, Labour and Welfare (MHLW) has designated Treakisym as a prioritized unapproved drug having high potential to address the lack of an effective therapy in CLL—Treakisym was designated as an orphan drug for the CLL indication in June 2012.

In October 2010, the company received domestic regulatory approval of Treakisym for the indications of relapsed or refractory NHL and MCL. Since December 2010, Eisai, has been selling the drug in Japan under the product name "Treakisym® 100mg for IV Use."

Major shareholders

Top Shareholders	Amount Held
Fuminori Yoshida	9.6%
Cephalon, Inc.	8.0%
Eisai Co., Ltd.	2.6%
Waseda No. 1 Investment LP	2.1%
Oak Capital Corporation	1.9%
SBI Securities Co., Ltd	1.2%
Matsui Securities Co Ltd	1.0%
Japan Securities Finance Co., Ltd.	1.0%
Rakuten Securities, Inc.	0.7%
Hase Hideyuki	0.6%

Source: Shared Research based on company data.
As of December 31, 2015
Ratio of shares held calculated after subtracting treasury shares from shares outstanding

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 74 employees as of December 31, 2015.

Other

Overview of clinical trials

Development of a new drug takes between 10 and 17 years

The development process of a new drug follows the four stages described below. It usually takes 10 to 17 years for a new

drug to win regulatory approval, according to the company.

Ordinary process and periods of developing new drugs

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

Source: Shared Research based on company data.

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

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

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

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

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

Ethnic factors in the acceptability of foreign clinical data

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

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

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

Glossary

Antigen

Normally, a protein or other substance carrying bacteria and viruses that the body rejects as foreign, causing an

antigen-antibody reaction (AAR). When antigens enter the body, they either stimulate the production of antibodies or combine with them.

Bifidobacterium

Genus of Gram-positive bacteria, and are one of the major genera of bacteria that make up the colon flora in mammals, with probiotic activity limited to anaerobic environments. Bifidobacterium strains are important probiotics and widely used in the food industry (e.g. yogurt). As many types of cancer (specifically solid tumors such as pancreatic cancer) grow in a hypoxic environment, intravenously administered Bifidobacterium expressing the TTR1 nano-agonist molecule will selectively live in cancer tissue and effectively kill cancer cells via TTR1 nano-agonist molecule expression.

Bridging Data

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

Chronic Lymphocytic Leukemia (CLL)

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

Contract Research Organization (CRO)

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

Dose-Responsiveness

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

Fentanyl

A synthetic opioid painkiller used for anesthesia, cancer, and post-operative pain management. It is widely used by Japanese hospitals, and subject to strict control under the Narcotics and Psychotropics Control Act because it is a narcotic.

First-line Drug

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

Immunoglobulin G (IgG)

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

Iontophoresis

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

Key Opinion Leader (KOL)

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

Mantle-Cell Lymphoma (MCL)

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

Monoclonal Antibody

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

Multikinase Inhibitor

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

Myelodysplastic Syndromes

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

Non-Hodgkin's Lymphoma (NHL)

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

Overall Survival (OS)

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

Patient-Controlled Analgesia (PCA)

A pain management method in which patients control the timing of analgesic drug administration.

Progression-Free Survival (PFS)

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

Proof-of-Concept (POC)

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

Rare Disorders

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

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

R-CHOP therapy

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

Special Protocol Assessment (SPA)

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

Standard Therapy

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

TTR1 nano-agonist

Member of the tumor necrosis factor (TNF) family that exerts its apoptotic activity in human cells when it trimerizes by binding to its transmembrane receptors, TRAIL-R1 and TRAIL-R2. It is difficult to form a trimeric structure using conventional anti-TRAIL-R1antibodies, and thus apoptosis-inducing ability is typically weak. Camelids (e.g. camels, alpacas, llamas) produce functional antibodies devoid of light chains of which the single N-terminal domain is fully capable of antigen binding. These single-domain antibody fragments (VHHs or sdAb) have several advantages for biotechnological applications: they are well expressed in microorganisms, have a high stability and solubility, and can penetrate tissues relatively easily. Trivalent anti-TRAIL-R1 single-domain antibodies (TTR1: an abbreviation for Trivalent anti-TRAIL-R1) used in our collaboration have agonistic activities and induce apoptosis, thus we call them TTR1 nano-agonist(s).

Company name

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

Company profile

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

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Chugoku Marine Paints, Ltd.	JIN Co., Ltd.	Star Mica Co., Ltd.
Cocokara Fine, Inc.	Kameda Seika Co., Ltd.	SymBio Pharmaceuticals Limited
Comsys Holdings Corporation	Kenedix, Inc.	Takashimaya Co., Ltd.
CRE, Inc.	KLab Inc.	Takihyo Co., Ltd.
Creek & River Co., Ltd.	LAC Co., Ltd.	Tamagawa Holdings Co., Ltd
Daiseki Corp.	Lasertec Corp.	TEAR Corporation
DIC Corporation	MAC-HOUSE Co.	3-D Matrix, Ltd.
Digital Garage Inc.	Matsui Securities Co., Ltd.	TOKAI Holdings Corp.
Don Qijote Holdings Co., Ltd.	Medinet Co., Ltd.	Verite Co., Ltd.
Dream Incubator Inc.	MEGANESUPER CO., LTD.	WirelessGate, Inc.
Elecom Co.	Milbon. Co., Ltd.	Yellow Hat Ltd.
EMERGENCY ASSISTANCE JAPAN Co.	MIRAIT Holdings Corp.	Yumeshin Holdings
en-Japan Inc.	MONEY SQUARE HOLDINGS, INC.	VOYAGE GROUP, Inc.
FerroTec Corp.	NAGASE & CO., LTD	ZAPPALLAS, INC.
Fields Corp.	NAIGAI TRANS LINE LTD.	ZIGExN Co., Ltd.
FreeBit Co., Ltd.	NanoCarrier Ltd.	

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