SymBio Pharmaceuticals / 4582

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

Executive summary

SymBio in-licenses drugs for development and sale

- SymBio 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 August 2017, the company had received approval for Treakisym (anticancer agent for hematologic malignancies) for the indications of relapsed or refractory low grade NHL and MHL, first-line treatment of relapsed or refractory low grade NHL and MHL, and chronic lymphocytic leukemia (CLL). Drugs in the development pipeline include Treakisym for the indication of relapsed or refractory aggressive NHL, rigosertib (anticancer agent for myelodysplastic syndromes) IV and oral formulations, and SyB P-1501 (patient-controlled analgesia for pain management).

Earnings

- FY12/16 sales were JPY2.4bn (+22.5% YoY). Product sales totaled JPY2.1bn (+10.6% YoY) and milestone payments totaled JPY230mn (no milestone payments in FY12/15). Operating loss totaled JPY2.1bn (loss of JPY2.6bn in FY12/15). The company also reported a recurring loss of JPY2.3bn (loss of JPY2.6bn last year). Net loss was JPY2.3bn (loss of JPY2.6bn).
- As a result of sales growth of Treakisym, SymBio forecasts FY12/17 sales of JPY2.9bn (+22.6% YoY), an operating loss of JPY3.2bn (operating loss of JPY2.1bn in FY12/16), a recurring loss of JPY3.3bn (recurring loss of JPY2.3bn in FY12/16), and a net loss of JPY3.3bn (net loss of JPY2.3bn in FY12/16).
- In its mid-term plan, SymBio projects sales of JPY3.6bn–JPY4.6bn and a net loss of JPY1.9bn–JPY2.3bn in FY12/19. The company obtained regulatory approval for first-line treatment for low-grade NHL and MCL in FY12/16, and aims for additional indication of Treakisym for chronic lymphocytic leukemia (CLL), which will result in higher sales.
- Shared Research thinks sales of JPY10bn and OPM of over 20% is achievable in FY12/21 and beyond. We have identified the following four growth drivers. 1) Sales growth due to progress with market penetration of Treakisym® as a first-line treatment of low-grade non-Hodgkin's lymphoma (NHL) and mantle cell lymphoma (MCL). 2) Sales growth spurred by indication for relapsed or refractory DLBCL going on sale. 3) Profit margin improvement as a result of starting own sales. 4) Establishing a competitive advantage over generics by putting ready-to-dilute (RTD) and rapid infusion (RI) injection products on the market (see Long-term outlook section).

Strengths and weaknesses

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

Key financial data

Income statement (JPYmn)	FY12/09 Par.	FY12/10 Par.	FY12/11 Par.	FY12/12 Par.	FY12/13 Par.	FY12/14 Par.	FY12/15 Par.	FY12/16 Par.	FY12/17 Est.
Sales	**1,191**	**1,450**	**1,883**	**1,955**	**1,532**	**1,955**	**1,933**	**2,368**	**3,583**
YoY	-26.9%	21.7%	29.8%	3.9%	-21.6%	27.6%	-1.1%	22.5%	51.3%
Gross profit	**1,191**	**1,212**	**658**	**593**	**318**	**527**	**583**	**904**	
YoY	-26.9%	1.7%	-45.7%	-9.9%	-46.4%	65.6%	10.7%	55.1%	
GPM	100.0%	83.6%	35.0%	30.3%	20.8%	26.9%	30.2%	38.2%	
Operating profit	**-208**	**-613**	**-2,067**	**-1,700**	**-1,681**	**-1,303**	**-2,552**	**-2,127**	**-3,932**
YoY	-	-	-	-	-	-	-	-	-
OPM	-	-	-	-	-	-	-	-	-
Recurring profit	**-214**	**-638**	**-2,095**	**-1,729**	**-1,601**	**-1,110**	**-2,630**	**-2,317**	**-4,009**
YoY	-	-	-	-	-	-	-	-	-
RPM	-	-	-	-	-	-	-	-	-
Net income	**-218**	**-642**	**-2,105**	**-1,733**	**-1,605**	**-1,116**	**-2,632**	**-2,313**	**-4,009**
YoY	-	-	-	-	-	-	-	-	-
Net margin	-	-	-	-	-	-	-	-	-
Per share data (JPY)									
Shares issued (year end; '000)	101	112	19,131	19,131	30,634	30,634	32,391	46,531	-
EPS	-32.5	-59.3	-143.6	-90.6	-69.3	-36.3	-81.3	-58.8	-82.2
EPS (fully diluted)	-	-	-	-	-	-	-	-	-
Dividend per share	-	-	-	-	-	-	-	-	-
Book value per share	402.8	365.4	345.3	254.7	239.5	208.8	127.6	108.6	-
Balance sheet (JPYmn)									
Cash and cash equivalents	4,121	4,016	6,511	4,840	7,264	6,591	4,261	5,719	
Total current assets	**4,218**	**4,213**	**7,178**	**5,421**	**7,634**	**7,290**	**4,827**	**6,685**	
Tangible fixed assets	13	22	17	14	9	49	53	75	
Investment and other assets	27	27	48	57	37	49	53	77	
Intangible fixed assets	2	1	13	11	8	66	52	42	
Total assets	**4,261**	**4,263**	**7,256**	**5,502**	**7,687**	**7,454**	**4,984**	**6,878**	
Accounts payable	-	1	309	330	-	306	320	322	
Short-term debt	-	-	-	-	-	-	-	-	
Total current liabilities	**205**	**178**	**646**	**599**	**251**	**488**	**551**	**942**	
Long-term debt	-	-	-	-	-	-	-	-	
Total fixed liabilities	**2**	**2**	**5**	**4**	**3**	**2**	**2**	**451**	
Total liabilities	**207**	**180**	**651**	**602**	**254**	**490**	**552**	**1,394**	
Net assets	**4,054**	**4,083**	**6,606**	**4,900**	**7,433**	**6,964**	**4,432**	**5,485**	
Total interest-bearing debt	-	-	-	-	-	-	-	-	
Statement of cash flows (JPYmn)									
Cash flows from operating activities	-211	-754	-2,074	-1,659	-1,677	-1,266	-2,272	-1,960	
Cash flows from investing activities	-4	-116	-117	-411	-1,332	314	1,489	-44	
Cash flows from financing activities	2,963	663	4,611	-1	4,057	544	-3	3,658	
Financial ratios									
ROA (RP-based)	-7.6%	-15.1%	-36.5%	-27.2%	-24.3%	-14.7%	-42.3%	-39.0%	
ROE	-8.1%	-15.8%	-39.4%	-30.2%	-26.3%	-15.8%	-48.3%	-50.4%	
Equity ratio	95.1%	95.8%	91.0%	89.1%	96.7%	93.4%	88.9%	79.7%	

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

Recent updates

Highlights

On **October 16, 2017**, Shared Research updated the report on the company following interviews with SymBio Pharmaceuticals Ltd.

On **October 10, 2017**, the company announced that it had enrolled the first patient in a domestic phase I clinical trial of anticancer agent rigosertib monotherapy for high-risk myelodysplastic syndrome (MDS).

SymBio registered the first patient in its domestic phase I clinical trial of anticancer agent rigosertib (oral formulation) monotherapy for high risk myelodysplastic syndrome (MDS) started in June 2017.

The purpose of the trial is to confirm safety of high-dose oral rigosertib –an additional requirement in the phase II clinical trial conducted by Onconova Therapeutics, Inc. in the US with relapsed and refractory MDS patients. Once safety has been confirmed, SymBio plans to perform a domestic trial of combination therapy with azacitidine and participate in the global phase III study of rigosertib-azacitidine combination therapy with untreated higher-risk MDS patients planned by Onconova.

The company has not made any revisions to its FY12/17 earnings forecast associated with the start of the domestic phase I clinical trial.

On **September 21, 2017**, the company announced revisions to its full-year FY12/17 earnings forecasts.

Revised FY12/17 company earnings forecasts

- ▷ Sales: JPY3.6bn (previous forecast: JPY2.9bn)
- ▷ Operating loss: JPY3.9bn (JPY3.2bn)
- ▷ Recurring loss: JPY4.0bn (JPY3.3bn)
- ▷ Net loss: JPY4.0bn (JPY3.3bn)

Reasons for revisions

The company expects sales of JPY3.6bn, exceeding its previous forecast by JPY680mn, because sales of Treakisym® in Japan grew faster than expected following approval for the new indication of first-line treatment of low-grade non-Hodgkin's lymphoma (NHL) and mantle cell lymphoma (MCL) in December 2016. The company expects operating profit, recurring profit, and net profit to be lower than its previous forecast due to the upfront payment relating to the license agreement with Eagle Pharmaceuticals, Inc., for the liquid formulation products of bendamustine hydrochloride, although SG&A expenses have been solidly controlled within budget.

On **the same day**, the company announced that it had concluded a license agreement with Eagle Pharmaceuticals, Inc., for the bendamustine hydrochloride ready-to-dilute (RTD) and rapid infusion (RI) injection products.

On September 20, 2017, Eagle Pharmaceuticals and SymBio concluded a license agreement that licenses to SymBio rights to develop, market, and sell Eagle's bendamustine hydrochloride RTD and RI injection products (marketed in the US by Teva Pharmaceutical Industries as BENDEKA®) in Japan.

SymBio received approval for the new indication of first-line treatment of low-grade B-cell non-Hodgkin's lymphoma (NHL) and mantle cell lymphoma (MCL) in December 2016. As a result of patent protection conferred by the license agreement with Eagle

Pharmaceuticals for the liquid formulation products of bendamustine hydrochloride, the company will be able to extend the product life cycle of Treakisym® until 2031. Switching from the currently available freeze-dried (FD) powder injection to the RTD product (which is already liquidized) will reduce the dispensing workload. The company also plans to develop a RI product to shorten the administration time from 60 minutes to 10 minutes. SymBio aims to begin selling the RTD product in early 2021, followed by the RI product.

SymBio will pay Eagle a USD12.5mn upfront payment and a milestone payment upon approval. The company will also pay additional milestone payments on the achievement of cumulative sales thresholds and royalties on future sales of licensed bendamustine products.

RTD and RI bendamustine products are marketed in the US by Teva Pharmaceutical Industries as BENDEKA®, which accounts for 97% of the bendamustine market. Teva estimates that the North American market for bendamustine products at around USD600mn–USD660mn.

RTD and RI products: RTD products are ready to dilute, which eliminates the time-consuming process of reconstitution and substantially reduces the workload of healthcare professionals. Rapid infusion (RI) products can be administered by intravenous infusion in 10 minutes instead of 60 minutes, which reduces stress on patients.

Comparison of RTD/RI products and currently available (freeze-dried) product

	RTD and RI products	Currently available products
Generic name	bendamustine hydrochloride	
Dosage form	Liquid	Freeze-dried powder injection
Reconstitution	Not required	Required
Administration time	60 minutes (RTD product) 10 minutes (RI product)	60 minutes
Dosage form	100mg/4mL	100mg/vial 25mg/vial
Storage	Refrigerated storage (2°C–8°C)	Room temperature

On **August 31, 2017**, the company announced the initiation in Japan of the Phase III clinical trial of the anti-cancer drug TREAKISYM® for the indication of relapsed/refractory diffuse large B-cell lymphoma.

The company announced that it initiated a phase III study in Japan of the anti-cancer drug Treakisym® (non-proprietary name: bendamustine hydrochloride) for the indication of relapsed/refractory DLBCL.

Although DLBCL accounts for about one-third of malignant lymphoma in terms of the number of patients, a standard chemotherapy for treatment of DLBCL is currently not available, thus multiple drug therapies are administered. Multiple drug therapies, however, tend to have strong adverse effects, placing a burden on patients, and accordingly a new therapy is much-awaited.

Having completed a phase II study for bendamustine-rituximab (BR) therapy, SymBio obtained clinical trial results for the treatment of patients with relapsed/refractory DLBCL.

Based on the achievements of this clinical study, BR therapy has been recommended in the NCCN (National Comprehensive Cancer Network) Guidelines in the US, the standard for clinical policy in oncology, since 2012. After consultation with Pharmaceuticals and Medical Devices Agency (PMDA) of Japan, SymBio has now initiated a phase III study. The objective of the study is to confirm the efficacy and safety of BR therapy. The disease, relapsed/refractory DLBCL, falls under a therapeutic area with high unmet medical needs, where a new drug therapy is much-awaited, as the strong need for the development of BR therapy has been voiced by a patient group and relevant academic societies.

Swiftly enrolling patients in the study, SymBio aims to file an NDA (new drug application) for relapsed/refractory DLBCL in the second half of 2019. This event will not impact the company's FY12/17 forecasts.

On **August 9, 2017**, the company announced the issuance of the 42nd stock acquisition rights by third-party allotment.

The company resolved to issue its 42nd stock acquisition rights (placement through third-party allotment) as outlined below.

42nd stock acquisition rights

- ▷ Allotment date: August 25, 2017
- ▷ Number of stock acquisition rights issued: 88,000 units
- ▷ Issue price: JPY32,560,000 (JPY370 per unit)
- ▷ Number of underlying shares: 8,800,000 (17.97% of all issued shares)
- ▷ Total funding amount: JPY1,910mn (net of cost)
- ▷ Exercise price and exercise price amendment provisions: Initial exercise price: JPY215

  On February 26, 2018, the exercise price shall be amended to an amount equivalent to 90% of the closing price of SymBio's common shares on February 23, 2018, but in the event that the price falls below the minimum exercise price, the minimum exercise price shall be the exercise price after amendment.

Uses of proceeds to be raised

Specific use of funds to be raised	Amount	Scheduled disbursement timing
Expenses for the development of TREAKISYM® （SyB L-0501） for relapsed/refractory aggressive non-Hodgkin lymphoma (diffuse large B-cell lymphoma, or DLBCL)	JPY900mn	August 2017-December 2018
Expenses related to acquisition of rights and subsequent development of the oral form of TREAKISYM®	JPY1,009mn	August 2017-December 2018

Phase II clinical trials for TREAKISYM (SyB L-0501) for the additional indication of relapsed/refractory aggressive NHL (DLBCL) have been completed with favorable results, and SymBio has considered applying for approval in order to further enhance the product value of TREAKISYM® through additional indications. SymBio is currently formulating the details of a phase III clinical trial plan, and plans to submit a trial plan within 2017 and begin the trials. Of the total development period for these phase III clinical trials, the amount of expenditure expected until the end of December 2018 is stated.

With regard to the acquisition of rights for the oral form of TREAKISYM, SymBio will expand the rights it holds on TREAKISYM® in order to promote indications in addition to blood cancer, such as for solid cancer and autoimmune diseases. Expenses related to the acquisition of rights and expenses related to the implementation of phase I clinical trials currently under consideration are stated.

On **the same day**, the company announced the current status of the domestic phase III clinical trial of the patient-controlled pain management drug SyB P-1501.

On May 11, 2017, SymBio announced temporary suspension of new patient enrollment in the domestic phase III clinical trial of the patient-controlled pain management drug "SyB P-1501." On June 5, 2017, the company announced that The Medicines Company, the licensor of SyB P-1501, had filed a report (Form 8-K) with the US Securities and Exchange Commission.

In an update on the current status of the domestic phase III clinical trial of the drug, SymBio said that it is continuing to discuss with The Medicines Company (MDCO) the effects of MDCO's decision to discontinue and withdraw IONSYS® (the product name for SyB P-1501 in the US) from the US market, in particular on the SyB P-1501 clinical trial and commercialization in Japan. SymBio will make a timely disclosure once it makes a decision pending the results of the ongoing discussions with MDCO.

On **August 3, 2017**, the company announced earnings results for 1H FY12/17; see the results section for details.

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

Trends and outlook

Quarterly trends and results

Cumulative	FY12/16				FY12/17				FY12/17	
(JPYmn)	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	% of FY	FY Est.
Sales	193	1,211	1,408	2,368	870	1,786			49.8%	3,583
YoY	-52.7%	24.0%	5.6%	22.5%	350.2%	47.5%				51.3%
Gross profit	57	405	478	904	239	510				
YoY	-53.1%	43.2%	21.1%	55.1%	323.0%	26.0%				
GPM	29.2%	33.4%	34.0%	38.2%	27.5%	28.5%				
SG&A expenses	575	1,225	2,011	3,031	764	1,746				
YoY	27.0%	31.6%	45.4%	-3.3%	32.9%	42.5%				
SG&A-to-sales ratio	297.6%	101.2%	142.8%	128.0%	87.9%	97.7%				
Operating profit	-518	-820	-1,532	-2,127	-525	-1,236			-	-3,932
YoY	-	-	-	-	-	-				-
OPM	-	-	-	-	-	-				-
Recurring profit	-655	-1,177	-1,917	-2,317	-583	-1,268			-	-4,009
YoY	-	-	-	-	-	-				-
RPM	-	-	-	-	-	-				-
Net income	-653	-1,175	-1,916	-2,313	-583	-1,266			-	-4,009
YoY	-	-	-	-	-	-				-
Net margin	-	-	-	-	-	-				-

Quarterly	FY12/16				FY12/17			
(JPYmn)	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Sales	193	1,018	197	960	870	916		
YoY	-52.7%	79.2%	-44.7%	59.9%	350.2%	-9.9%		
Gross profit	57	348	74	426	239	271		
YoY	-53.1%	114.8%	-34.6%	126.6%	323.0%	-22.2%		
GPM	29.2%	34.2%	37.4%	44.3%	27.5%	29.6%		
SG&A expenses	575	650	786	1,021	764	982		
YoY	27.0%	36.0%	73.8%	-41.7%	32.9%	51.1%		
SG&A-to-sales ratio	297.6%	63.9%	399.2%	106.2%	87.9%	107.1%		
Operating profit	-518	-302	-712	-595	-525	-711		
YoY	-	-	-	-	-	-		
OPM	-	-	-	-	-	-		
Recurring profit	-655	-522	-740	-400	-583	-685		
YoY	-	-	-	-	-	-		
RPM	-	-	-	-	-	-		
Net income	-653	-523	-741	-397	-583	-684		
YoY	-	-	-	-	-	-		
Net margin	-	-	-	-	-	-		

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

1H FY12/17 results

1H FY12/17 sales totaled JPY1.8bn (+47.5% YoY) thanks to sales of Treakisym. Product sales totaled JPY1.8bn (+51.4% YoY) and other sales were JPY0mn (JPY30mn in FY12/16).

In December 2016, Treakisym was approved for the additional indication of first-line treatment for low-grade NHL and MCL. Sales of Treakisym indicated for untreated low-grade NHL and MCL increased in Q2 FY12/17.

Due to the sales increase, gross profit came to JPY510mn (+26.0% YoY). Gross profit margin was 28.5% (-4.9pp).

SG&A expenses rose 42.5% YoY to JPY1.7bn. R&D expenses increased 62.0% to JPY840mn. There were expenses for clinical trials for the intravenous and oral formulations of Rigosertib Sodium and SyB P-1501. SG&A expenses excluding R&D expenses were up 28.3% at JPY906mn.

As a result, operating loss totaled JPY1.2bn (loss of JPY820mn in 1H FY12/16). The company also reported a recurring loss of JPY1.3bn (loss of JPY1.2bn in 1H FY12/16) partly due to non-operating expenses of JPY34mn (mainly on forex losses of JPY27mn). Net loss was JPY1.3bn (loss of JPY1.2bn in 1H FY12/16).

Progress toward the company's full-year forecast was 61.5% for sales (51.1% in 1H FY12/16). Sales volume in 1H FY12/17 was 34,633 vials, exceeding the company's assumption of 30,289 vials. Sales so far in FY12/17 are trending at a pace of 75,000 vials for the full year, ahead of the company's target of 66,000 vials. The company assumes a market penetration rate of 35% for Treakisym indicated for untreated NHL and MCL (first-line treatment), but the actual rate appears to be exceeding this level. Progress made in 1H FY12/17 is as follows.

- ▷ The company announced in August 2017 that it would begin phase III clinical trials in Japan for anticancer agent Treakisym for the additional indication of relapsed or refractory diffuse large-B-cell lymphoma (DLBCL; aggressive NHL).
- ▷ In June 2017, the company restarted domestic phase I clinical trials for oral Rigosertib, because the supply of the study drug had resumed.
- ▷ The Medicines Company had filed a report (Form 8-K) with the US Securities and Exchange Commission in June 2017 stating that it would withdraw the patient-controlled pain management drug IONSYS® (SyB P-1501) from the US market and suspend commercial activities. In May 2017, SymBio announced temporary suspension of new patient enrollment in the domestic phase III clinical trial of SyB P-1501. As of August 2017, SymBio said that it is continuing to discuss with The Medicines Company (MDCO) the effects of MDCO's decision to discontinue and withdraw IONSYS® from the US market, in particular on the SyB P-1501 clinical trial and commercialization in Japan. SymBio will make a timely disclosure once it makes a decision pending the results of the ongoing discussions with MDCO.
- ▷ In August 2017, the company announced the subscription for its 42nd stock acquisition rights by third-party allotment (8,800,000 residual shares corresponding to 17.97% of outstanding shares) to raise JPY1.9bn on an estimated net proceeds basis. The funds are mainly to be used for expenses related to development of Treakisym indicated for relapsed or refractory DLBCL (aggressive NHL) totaling JPY900mn and expenses for obtaining rights to the oral formulation of Treakisym and development after obtaining the rights totaling JPY1.0bn.

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), untreated low-grade NHL and MCL, and chronic lymphocytic leukemia (CLL).

In 1H FY12/17, sales of Treakisym based on the National Health Insurance (NHI) drug price grew 42.9% YoY, and accordingly product sales to Eisai increased 44.6%.

In addition to the above three approved indications, the company is working to gain approval for a fourth indication to help patients who need new treatments and maximize the value of the product.

The company has completed phase II clinical trials for relapsed or refractory diffuse large B-cell lymphoma (DLBCL, or aggressive NHL). In response to strong medical needs, the company finished consultation with the Pharmaceuticals and Medical Devices Agency in June 2017 and announced on August 31, 2017 that it had commenced phase III clinical trials toward the addition of an indication, aiming to file an NDA in 2H 2019.

SymBio is exploring further expansion of the Treakisym business by developing an oral formulation in addition to the injection currently under development or on sale to treat solid tumors and autoimmune diseases.

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

Onconova Therapeutics, Inc., the licensor, is currently conducting a global Phase III trial and SymBio Pharmaceuticals started the Japan trial in December 2015. The global Phase III trial addresses higher risk myelodysplastic syndrome (MDS) patients who do not respond to treatment or relapsed after treatment with hypomethylating agents (HMAs), the current standard of care

("Primary HMA Failure"); the trial is underway in more than ten countries worldwide. The company completed the first patient enrollment in July 2016. Of the total enrollment target of 225, 25 are slated for Japan and as of August 2017, 20 patients have been enrolled.

SymBio started domestic Phase I clinical trials for the oral form of Rigosertib Sodium (used in combination with azacitidine) for higher-risk myelodysplastic syndrome (MDS) in December 2015. Due to delays in the supply of drugs for the joint trials, however, patient enrollment did not make progress. Since Onconova resumed the supply of clinical trial materials, SymBio initiated a phase I clinical trial in Japan in June 2017. The purpose of the Japanese phase I study is to confirm the safety of high-dose oral rigosertib, which was added to the ongoing US phase II study by Onconova in untreated or relapsed/refractory patients with higher-risk MDS. After demonstrating the safety of high-dose oral rigosertib, SymBio intends to immediately recommence an oral rigosertib/azacitidine combination trial in Japan, and participate in the global phase III study in untreated higher-risk MDS patients that Onconova is planning.

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

In June 2016, the company started a domestic phase III clinical trial for SyB P-1501—licensed by The Medicines Company (through its wholly owned subsidiary Incline Therapeutics)by n untreated higher-risk MDS patients that Onconova is planning. y by Onconova i. The company enrolled the first patient in November 2016 and was making progress with case accumulation. However, facts raising concerns about the continuity of SyB P-1501 business at The Medicines Company surfaced, and in the interest of patient welfare, SymBio temporarily suspended further patient enrollment in April 2017. As of August 2017, SymBio said it was in discussions with The Medicines Company, and planned to make a timely disclosure once it determined how the SyB P-1501 clinical trial and commercialization in Japan would be affected.

New drug candidates

From a long-term perspective, SymBio continues to search for and evaluate promising drug candidates, in a bid to acquire global licensing rights for these drugs and grow into a sustainable and profitable biopharmaceutical company with growth potential and profitability. As of August 2017, talks were underway regarding licensing rights for three drug candidates.

In May 2016, the company established SymBio Pharma USA, Inc., a wholly owned US-based subsidiary, as a strategic base for overseas business development. The company looks to leverage this subsidiary to actively acquire rights over new drug development candidates globally, and engage in development and commercialization in major markets including the US, Japan, and Europe to transition to a global specialty pharmaceutical company.

Overseas

The company marketed SyB L-0501 in Korea, Taiwan, and Singapore, and overseas sales were steady.

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

Full-year company forecasts

(JPYmn)	FY12/16 FY Act.	FY12/17 Init. Est.	YoY	FY12/17 Rev. Est.	YoY
Sales	2,368	2,903	22.6%	3,583	51.3%
Milestone revenue	230	0	-	-	-
Product sales	2,137	2,903	35.8%	-	-
Domestic	2,014	2,715	34.8%	-	-
Overseas	123	187	52.0%	-	-
CoGS	1,464	2,080	42.1%	-	-
CoGS ratio (% of product sales)	68.5%	71.7%	-	-	-
Gross profit	904	823	-9.0%	-	-
GPM	38.2%	28.3%	-	-	-
SG&A expensees	3,031	4,061	34.0%	-	-
SG&A-to-sales ratio	128.0%	139.9%	-	-	-
R&D expenses	1,667	2,286	37.1%	-	-
SG&A excluding R&D	1,364	1,775	30.1%	-	-
Operating profit	-2,127	-3,238	-	-3,932	-
OPM	-	-	-	-	-
Recurring profit	-2,317	-3,303	-	-4,009	-
RPM	-	-	-	-	-
Net income	-2,313	-3,306	-	-4,009	-
Net margin	-	-	-	-	-

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

Earnings outlook

The company announced a revision to its FY12/17 earnings forecast on September 21, 2017. The revised forecasts are sales of JPY3.6bn (+51.3% YoY), operating loss of JPY3.9bn (operating loss of JPY2.1bn in FY12/16), recurring loss of JPY4.0bn (JPY2.3bn loss), and net loss of JPY4.0bn (JPY2.3bn loss).

The company expects sales of JPY3.6bn, exceeding its previous forecast by JPY680mn, because sales of Treakisym® in Japan grew faster than expected following approval for the new indication of first-line treatment of low-grade non-Hodgkin's lymphoma (NHL) and mantle cell lymphoma (MCL) in December 2016. The company expects operating profit, recurring profit, and net profit to be lower than its previous forecast due to the upfront payment relating to the license agreement with Eagle Pharmaceuticals, Inc., for the liquid formulation products of bendamustine hydrochloride, although SG&A expenses have been solidly controlled within budget.

The following is based on information obtained before the company's earnings forecast revision. Shared Research plans to update the report after interviewing the company.

Higher sales forecast from Treakisym

Sales are expected to reach JPY2.9bn (+22.6% YoY), attributable to higher sales from Treakisym, breaking down into JPY2.9bn (+35.8% YoY) in product sales and JPY0 in milestone payments (JPY230mn in FY12/16).

For product sales, we assume Treakisym's market share will be 58% (unchanged from FY12/16) for the indications of relapsed or refractory low-grade NHL and MCL and 35% for first-line therapy for low-grade NHL and MCL. We note that approval of Treakisym for the additional indication of first-line therapy for low-grade NHL and MCL in December 2016 will likely make a contribution to sales in FY12/17.

SG&A expense to increase (including R&D expense)

R&D expense is expected to total JPY2.3bn (up from JPY1.7bn in FY12/16), while total SG&A expense–including R&D–is projected to reach JPY4.1bn (up from JPY3.0bn). R&D spending is slated to increase with a global phase III clinical study of rigosertib IV, phase I trials of oral rigosertib azacitidine combination therapy, and phase III trials of SyB P-1501. The company will also consider expanding indications of Treakisym. In a bid to boost its enterprise value for the long term, SymBio plans to consider introducing candidates for newly developed drug products and enhancing the overall value of its pipeline.

Higher losses forecast

As a result, SymBio forecasts an operating loss of JPY3.2bn (operating loss of JPY2.1bn in FY12/16), a recurring loss of JPY3.3bn (recurring loss of JPY2.3bn in FY12/16), and a net loss of JPY3.3bn (net loss of JPY2.3bn in FY12/16).

Pipeline

Treakisym

The company has finished the phase II trial for relapsed or refractory moderate to high-grade non-Hodgkin lymphoma (NHL) and continues considering expansion of indications. In August 2017, SymBio began phase III clinical trials in Japan for anticancer agent Treakisym to add the indication for relapsed or refractory DLBCL (aggressive NHL).

Intravenous and oral rigosertib

The company is moving ahead with the accumulation of cases in Japan in the global phase III trial for the intravenous version of rigosertib. SymBio submitted a clinical trial notification in December 2015, enrolled the first patient in July 2016, and had enrolled 20 patients as of end-August 2017. The company aims to complete enrollment of the target 25 patients by the end of FY12/17.

In December 2016, SymBio began a phase I trial of the oral version of rigosertib for use in combination with azacitidine for the indication of high-risk MDS. However, the company did not begin patient enrollment because of delayed supply of the study drug from Onconova Therapeutics. SymBio restarted the domestic phase I trial in June 2017 after supply of the study drug resumed. The company plans to resume the study of the combination therapy with azacitidine after establishing safety in the phase I trial and plans to participate in an international phase III clinical study planned by Onconova Therapeutics of the combination therapy for the first-line treatment of high-risk MDS. Regarding development with transfusion-dependent 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. The company submitted a clinical trial notification for phase III trials in June 2016 and registered the first patient in November 2016.

In June 2017, The Medicines Company filed a report (Form 8-K) with the US Securities and Exchange Commission, stating that it would withdraw IONSYS® (the product name for SyB P-1501 in the US) from the US market and discontinue commercial activities. Prior to the event, in April 2017 SymBio suspended further enrollment of patients for its domestic phase III clinical trials for SyB P-1501. As of August 2017, SymBio said it was in talks with The Medicines Company, and planned to make a timely disclosure once it determined how the SyB P-1501 clinical trial and commercialization in Japan would be affected.

Long-term outlook

Mid-term Plan (FY12/17–FY12/19)

When it released its FY12/16 results, SymBio also announced a mid-term plan for FY12/17 through FY12/19.

Mid-term Plan

(JPYmn)	FY12/16 Act.	FY12/17 Est.	FY12/18 Target	FY12/19 Target
Sales	1,933	2,339	3,926 to 3,401	4,605 to 3,586
Operating profit (losses)	-2,551	-2,778	-2,309 to -2,509	-1,872 to -2,261
Recurring profit (losses)	-2,630	-2,811	-2,373 to -2,573	-1,936 to -2,325
Net income (losses)	-2,632	-2,815	-2,377 to -2,577	-1,940 to -2,329

Source: Shared Research based on company data.

Main pipeline schedule

Major pipelines	FY12/16	FY12/17	FY12/18	FY12/19	FY12/20
Treakisym® (relapsed or refractory low-grade NHL and MCL)	Obtained approval (Oct-10)				
Treakisym® (first-line treatment of low-grade NHL and MCL)	Obtained approval (Dec-16)				
Treakisym® (CLL)	Obtained approval (Aug-16)				
Treakisym® (relapsed or refractory moderate- and high-grade NHL)	Completed phase II clinical trials				
Rigosertib (IV) (relapsed and refractory high-risk MDS)	Global phase III clinical trials underway		Apply for approval	Obtain approval (planned)	
Rigosertib (oral) (high-risk MDS [in combination with azacitidine])	Phase I clinical trial underway		Complete phase I clinical trials	Phase III clinical trials	
SyB P-1501 Patient-controlled analgesia for pain management	Phase III clinical trials underway		Apply for approval	Obtain approval (planned)	

Source: Shared Research based on company data

Earnings targets of Mid-term Plan (FY12/17–FY12/19)

Sales

Based on the assumptions below, the company's mid-term plan calls for an increase in Treakisym sales by securing a larger market share alongside an expansion of its applications (additional indication for first-line therapy for low-grade NHL and MCL).

SymBio expects Treakisym to maintain the FY12/16 market share of 58% as a treatment for relapsed or refractory low-grade NHL and MCL.

Sales of Treakisym for the indication of first-line low-grade NHL and MCL will likely affect the upper and lower estimates for overall sales in FY12/18 and FY12/19. The company assumes market share of between 50% and 80% in FY12/19. The lower sales estimate is based on a 50% market share and the upper estimate on an 80% share.

SymBio estimates that there are 4,700 patients with relapsed or refractory low-grade NHL and MCL and 7,100 patients with untreated low-grade NHL and MCL. The standard first-line therapy for low-grade NHL and MCL in Japan is a combination of rituximab and CHOP chemotherapy (R-CHOP). CHOP is a combination of four agents (cyclophosphamide, hydroxydaunorubicin (doxorubicin), oncovin (vincristine), and prednisone). However, results of studies in Europe demonstrating that the efficacy of rituximab and Treakisym combination therapy (BR therapy) is significantly higher than R-CHOP as a first-line treatment were

presented at the American Society of Hematology Annual Meeting in 2012. Treatment guidelines in the US and Europe recommend BR therapy as a first-line treatment and an estimated 80% of patients outside Japan now receive BR therapy.

The company targets NDA for post-operative patient-controlled analgesia SyB P-1501 within the medium-term plan period, but has not included any sales in numerical plan targets.

SG&A expenses

SG&A expenses, including R&D costs, are expected to increase in FY12/17 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 expects R&D expenses to decline YoY in FY12/18, because it will complete the case series study in FY12/17. 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, most of which comprises marketing expenses for Treakisym, the company has an agreement with Eisai to share the cost 50/50. Thus SymBio books 50% of the estimated amount as an expense.

Mid-term plan assumptions

Pipeline progress

Treakisym

- Treakisym's market share has reached a high level as a treatment for relapsed or refractory low-grade NHL and MCL. SymBio's medium-term plan assumes that market share will trend at around 58%.
- SymBio received approval for the manufacturing and sale of Treakisym as a first-line treatment for refractory/relapsed low-grade NHL and MCL in December 2016 and for CLL in August 2016. The company is strengthening its marketing partnership with Eisai to grow sales of Treakisym, focusing on increasing market share and optimal use of Treakisym indicated for untreated refractory/relapsed low-grade NHL and MCL to establish its position as a first-line treatment, thereby maximizing its product value. The company's medium-term plan assumes market share of Treakisym for these indications of 35% in FY12/17 and 50–80% in FY12/19.
- 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.
- As of February 2017, patient enrollment for Phase I clinical trials of oral rigosertib for high-risk MDS (in combination with azacitidine) had been interrupted because of delayed supply of the study drug from Onconova Therapeutics. The company plans to resume the trials in FY12/17 for completion in FY12/18 before taking part in global phase III trials planned by Onconova in FY12/19.
- Regarding development with transfusion-dependent low-risk MDS as the target efficacy of oral rigosertib, SymBio will consider it while watching development progress at Onconova Therapeutics.

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

Phase III clinical trials for short-term management of acute postoperative pain began in June 2016 and the first patient was registered in November 2016. The company plans to file NDA in FY12/18.

Plans to establish own sales force

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 under 20%. The company also expects its margin to improve as procurement costs fall in line with higher sales.

As of February 2017, SymBio had not entered into an exclusive domestic sales agreement for SyB P-1501 or rigosertib (IV) 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 SyB P-1501 or rigosertib in IV form and the timing of licensing-in new drug candidates. Labor costs would increase if SymBio were to create its own sales force, but the company could realize a significantly higher profit margin on product supply as well as sales. Assuming the company establishes its own sales force, Shared Research sees potential for a significantly higher profit margin than 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.

Long-term outlook

Shared Research thinks sales of JPY10bn and OPM of over 20% is achievable in FY12/21 after the completion of the current mid-term management plan (FY12/17–FY12/19), and beyond, with additional indications for Treakisym® driving sales growth and OPM improvement. We have identified the following four growth drivers:

- Sales growth due to progress with market penetration of Treakisym® as a first-line treatment of low-grade non-Hodgkin's lymphoma (NHL) and mantle cell lymphoma (MCL)
- Sales growth spurred by Treakisym® indicated for relapsed or refractory DLBCL going on sale
- Profit margin improvement as a result of starting own sales
- Establishing a competitive advantage over generics by putting ready-to-dilute (RTD) and rapid infusion (RI) injection products on the market

Sales growth due to progress with market penetration of Treakisym® as a first-line treatment of low-grade non-Hodgkin's lymphoma (NHL) and mantle cell lymphoma (MCL)

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

Clinical trials conducted overseas have demonstrated that rituximab in combination with bendamustine (BR therapy) was safer and more efficacious than standard R-CHOP therapy in all endpoints including progression-free survival (PFS), time to next treatment, overall survival, and safety. Based on these results, the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines recommend the use of BR therapy as first-line therapy for patients with untreated low-grade NHL and MCL.

SymBio received permission to add first-line low-grade NHL and MCL as indications in December 2016. The company expects market penetration of Treakisym to progress for the new indication in FY12/17 onward. The mid-term plan targets a market penetration rate of 35% for the new indication in FY12/17 and 50–80% in FY12/19. Based on this assumption, SymBio estimates FY12/19 sales of Treakisym (NHI drug reimbursement price basis; total including relapsed or refractory low-grade NHL and MCL indications) at around JPY10bn versus over JPY4bn n FY12/16.

Sales growth due to Treakisym® indicated for relapsed or refractory DLBCL going on sale

In August 2017, SymBio began Phase III clinical trials of Treakisym for an additional indication for relapsed or refractory DLBCL (aggressive NHL). The trials are scheduled to take 24 months. The company plans to file for approval for the additional indication for elapsed or refractory DLBCL (aggressive NHL) in 2H 2019.

The company estimates that there are 6,700 patients with relapsed or refractory DLBCL (aggressive NHL) in Japan. This number is close to the number of patients with untreated NHL and MCL (7,100). We estimate that the company will add around JPY6bn in sales of Treakisym (NHI drug reimbursement price basis) if it can obtain approval for the additional indication.

Profit margin improvement as a result of starting own sales

As of September 2017, SymBio has an exclusive partnership with Eisai for the marketing of Treakisym in Japan. We estimate that Eisai makes roughly 50% profit from sales of the product based on the NHI drug reimbursement price, while SymBio's profit margin on the same basis is slightly under 20%.

SymBio stated in its midterm plan that it would make management decisions to establish its own sales structure. That being said, the company was having problems formulating a strategy based on a long-term sales outlook, because the re-examination term for the currently available freeze-dried (FD) powder injection product ends in 2020.

In September 2017, the company extended the product life cycle of Treakisym (bendamustine hydrochloride) until 2031 by concluding a license agreement with Eagle Pharmaceuticals that grants SymBio rights to develop, market, and sell Eagle's bendamustine hydrochloride RTD and RI injection products in Japan (see below). In our view, the agreement has increased the likelihood of SymBio continuing to expand sales of Treakisym after 2020 and accordingly, that of the company deciding to set up its own sales structure.

If the company does establish its own sales structure, sales-related expenses will increase as the company hires medical reps and other employees. However, it will also allow the company to take a bigger share of profits and is therefore likely to boost profit margins on Treakisym.

SymBio does not yet have its own sales force as of September 2017, but a team of five product managers in the company supports sales at Eisai. We think that in the longer term, SymBio will gradually increase the number of product managers and transition to its own sales structure in or around December 2020, when the exclusive marketing agreement with Eisai comes to an end.

Establishing a competitive advantage over generics by putting RTD and RI bendamustine hydrochloride products on the market

As of September 2017, the company sells bendamustine hydrochloride (brand name in Japan: Treakisym®) as a freeze-dried (FD) powder injection through Eisai. The re-examination term for the product ends in 2020, after which generics can go on the market.

In September 2017, the company concluded a license agreement with Eagle Pharmaceuticals, Inc., for the development and marketing of bendamustine hydrochloride ready-to-dilute (RTD) and rapid infusion (RI) injection products in Japan. Since the RTD and RI products are already liquidized, they do not require the time-consuming process of reconstitution and substantially reduce the workload of healthcare professionals. RI products also do not require reconstitution and can be administered by intravenous infusion in 10 minutes instead of 60 minutes, which reduces stress on patients. The exclusive sales period for these products extends to 2031.

SymBio believes that by selling the RTD and RI products that offer the advantages of reducing healthcare professionals' workload and stress on patients will limit the spread of generics after the re-examination term for Treakisym (FD product) ends. Bendamustine hydrochloride RTD and RI injection products are marketed in the US by Teva Pharmaceutical Industries as BENDEKA®, which has 97% share of the US bendamustine market.

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.

The company received permission to add CLL as an indication for Treakisym in August 2016, followed by permission to add first-line low-grade NHL and MCL as indications in December 2016.

In August 2017, SymBio announced it had commenced phase III clinical trials for an additional indication of relapsed or refractory high-grade DLBCL (aggressive NHL).

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, SymBio is conducting a phase I clinical trial for high-risk MDS (with azacitidine) in Japan. It may participate in global phase III trials that Onconova plans to launch in FY12/20.

SyB P-1501

Patient-controlled analgesia for pain management 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 began phase III clinical trials in June 2016. However, facts raising concerns about the continuity of SyB P-1501 business at The Medicines Company surfaced, and in the interest of patient welfare, SymBio temporarily suspended further patient enrollment in April 2017.

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 FY12/17, the company expects a JPY3.2bn operating loss, JPY3.3bn recurring loss, and net loss of JPY3.3bn. Over the course of the mid-term plan (FY12/16–FY12/18), the company expects to post annual operating losses of JPY1.8–3.3bn.

SymBio expects operating losses of JPY7.4–8.0bn in total between FY12/17 and FY12/19. 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 FY12/16, the company had cash and deposits plus securities of about JPY5.7bn.

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.

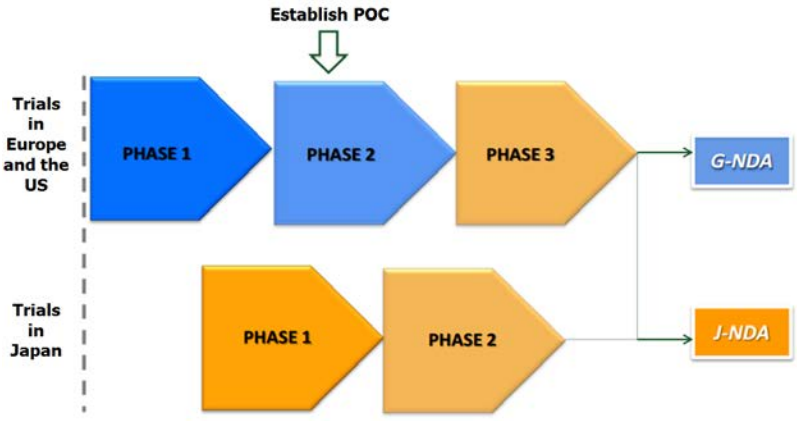
The company focuses on developing drugs that have strong safety and efficacy data in clinical trials, providing an opportunity to develop new drugs more likely to succeed and secure regulatory approval with the use of bridging data whenever possible to shorten development timelines. Because the company 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.

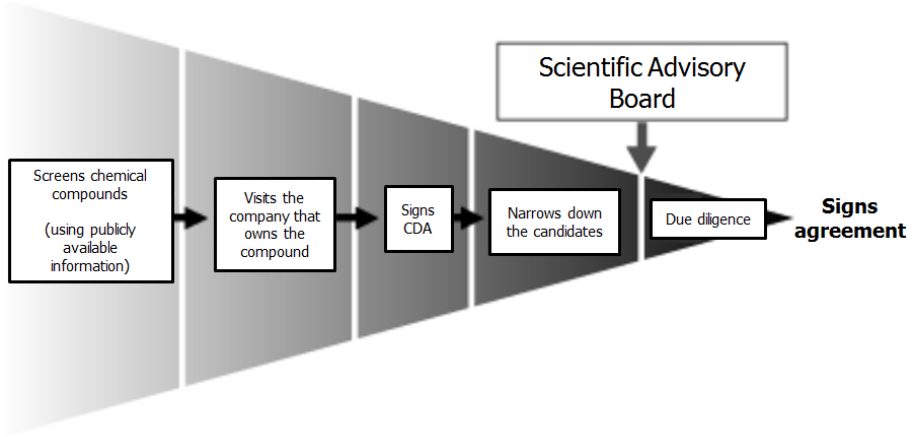
Onsite due diligence

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
Tomomitsu Hotta, M.D.	Honorary President, National Cancer Center Honorary Director, Nagoya Medical Center
Makoto Ogawa, M.D., Ph.D.	Honorary President, Aichi Cancer Center
Tatsutoshi Nakahata, M.D., Ph.D.	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
Koichi Takahashi, M.D.	Assistant Professor, Department of Leukemia, Division of Cancer Medicine, MD Anderson Cancer Center, The University of Texas

Source: Shared Research based on company data.

A fabless strategy with a lean management team

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

Specifically, the company designs clinical trial protocols and whenever possible, will participate in global phase III studies being conducted by its partner(s) overseas with the aim of shortening development timelines in Japan. It may be possible to file NDAs in Japan using foreign data to support or "bridge" data generated in Japanese clinical trials, thereby avoiding the need to complete domestic phase II and/or phase III studies for marketing approval. The company uses its well established network for bendamustine to coordinate with medical professionals, outsourcing routine development duties. Production is also outsourced either to the company that originally granted the product license, or to other domestic or foreign manufacturer(s), but as of February 2017, marketing rights are granted to outside partners.

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

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

According to the company, globally Japan has the third largest oncology market after the US and EU, and the market is expected to continue to expand due to Japan's aging population. However, regarding the type of tumors that anticancer drugs can effectively treat, there is a considerable range of indications with a limited number of patients who will benefit from approved cancer treatments, particularly in the elderly population where the occurrence of serious adverse events can be prohibitive. As a result, barriers to entry are high—developing cancer drugs for niche markets is especially difficult and requires a high level of expertise. Concerns about having sufficient profit margins from marketed drugs to fund large operations means that major pharmaceutical companies may be reluctant to target indications with limited patient numbers for development, presenting an opportunity with fewer competitors in the marketplace for smaller and more specialized pharmaceutical companies such as SymBio. The company can also increase value added of niche disease areas by additional indications and putting new products on the market. For example, its first in-house proprietary drug Treakisym has gained over 50% market share three years after going on sale.

Strategy for global expansion

The company is seeking to develop new drugs that are complementary to Treakisym and rigosertib to sell in China/Hong Kong, Taiwan, South Korea, and Singapore, as well as in Japan. In the medium-term plan announced in February 2016 and updated in February 2017, 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.

Pipeline

Name/Code	Category	Licensed country	Indications	Development stage	Sales partner
Treakisym SyB L-0501	Anti-cancer agent	Japan	Refractory/relapsed low-grade NHL and MCL	Approval obtained (Oct. 2010)	Eisai Co., Ltd. (co-developed: exclusive sales rights granted to Eisai)
			Refractory/relapsed DLBCL (aggressive NHL)	Phase III clinical trials underway	
			Untreated low-grade NHL and MCL	Approval granted (Dec. 2016)	
			CLL	Approval granted (Aug. 2016)	
		Singapore	Low-grade B-cell NHL CLL	Approval granted (Jan. 2010)	Eisai Co., Ltd. (Exclusive development and sales rights granted to Eisai)
		South Korea	CLL MM	Approval granted (May 2011)	Eisai Co., Ltd. (Exclusive development and sales rights granted to Eisai)
			Refractory/relapsed low-grade NHL	Approval granted (Jun. 2014)	
		China	Low-grade NHL	Clinical trials underway	Cephalon, Inc. (US) (Exclusive development and sales rights granted to Eisai)
		Hong Kong	Low-grade NHL	Approval granted (Dec. 2009)	
			CLL		
		Taiwan	Low-grade NHL	Approval granted (Oct. 2011)	InnoPharmax, Inc. (Taiwan) (Exclusive development and sales rights granted to Eisai)
			CLL		
Rigosertib (IV) SyB L-1101	Anti-cancer agent (IV)	Japan	Refractory/relapsed high-risk MDS	Global phase III clinical trials underway	—
Rigosertib (oral) SyB C-1101	Anti-cancer agent (oral)	Japan	High risk MDS (single drug)	Completed phase I clinical trials (Jun. 2015)	—
			High-risk MDS (with azacitidine)	Phase I clinical trials	—
SyB P-1501	Patient-controlled pain management	Japan	Management of acute postoperative pain	Completed phase I clinical trials Phase III clinical trials	—

Source: Shared Research based on the company website
The company is preparing to file for approval of a liquid ready-to-dilute (RTD) formulation and developing a rapid infusion (RI) formulation of Treakisym.

As of September 2017, the main drugs for which SymBio was preparing filing for approval or in the development pipeline were as follows:

▷ Treakisym, targeting indication for refractory or relapsed DLBCL (aggressive NHL)

▷ Treakisym, preparing to file for approval of RTD formulation and developing RI formulation

▷ Rigosertib (intravenous form), targeting indication for relapsed or refractory higher-risk myelodysplastic syndrome (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 (resistance to drugs with a similar structure or action as the study drug) has been shown for this drug, which means it is safer and more 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 has been selling the drug since its launch in December 2010. The company received permission to add CLL as an indication for Treakisym in August 2016, and first-line treatment of low-grade NHL and MCL in December 2016.

In August 2017, the company announced the initiation of phase III clinical studies of Treakisym for an additional indication of relapsed or refractory DLBCL (aggressive NHL).

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

In October 2010, five years after acquiring the right to Treakisym, SymBio received marketing approval in Japan for relapsed or refractory low-grade NHL and MCL. In FY12/16—six years after the domestic launch of the drug in December 2010—Treakisym sales to end users reached JPY4.7bn on a NHI drug price basis.

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

Treakisym: additional indications

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

In December 2016, Treakisym was approved in Japan for first-line treatment of low-grade NHL/MCL and for CLL in August 2016. In August 2017, the company announced the start of phase III clinical studies for relapsed or refractory DLBCL (aggressive NHL) as part of its plans to add indications

Market for Treakisym and number of patients

		Non-Hodgkin's Lymphoma		Chronic Lymphatic Leukemia
		Low-grade B-cell	Moderate- to high-grade	
First-line	Number of patients	7,100		700
	Approval	Obtained		Obtained
	Development status	Dec. 2016 approval obtained		Aug. 2016 approval obtained
Relapsed and refractory	Number of patients	4,700	6,700	
	Approval	Obtained	Completed phase II clinical trials in Japan	
	Development status	Approval obtained in Japan in Oct. 2010 Sales launched in Japan in Dec. 2010	Phase III clinical trials underway in Japan	

Source: Shared Research based on company data.

First-line treatment of low-grade NHL and MCL

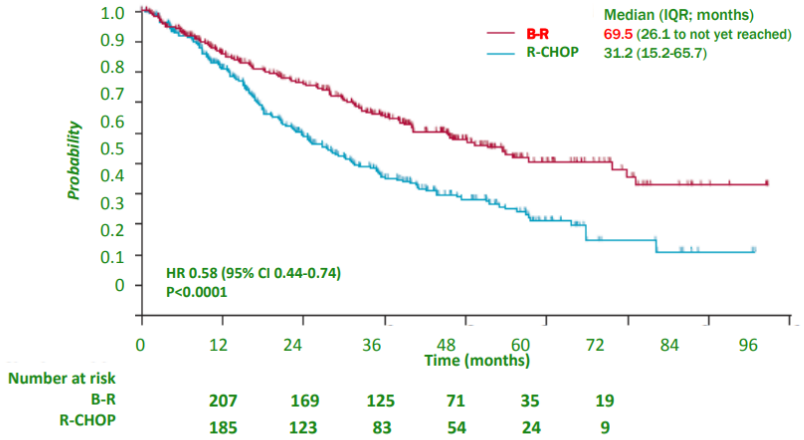
According to the company, R-CHOP therapy—a combination of rituximab with CHOP chemotherapy drugs (cyclophosphamide, doxorubicin, vincristine, and prednisolone)—was standard first-line treatment for low-grade NHL and MCL in Japan prior to December 2016.

Phase III clinical trials conducted overseas have demonstrated that rituximab in combination with bendamustine (BR therapy) was safer and more efficacious than standard R-CHOP therapy for previously untreated low-grade B-cell NHL. These findings were presented at the American Society of Hematology Annual Meeting in December 2012. Based on these results, the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines recommend the use of BR therapy as first-line therapy for patients with untreated low-grade NHL.

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

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

Results of trial comparing B-R and R-CHOP therapies as first-line treatment for patients with low-grade NHL/MCL



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

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

Source: Company data

Treakisym approved in December 2016 for first-line treatment of low-grade NHL and MCL

In December 2016, SymBio received approval to manufacture and sell in Japan Treakisym targeting first-line treatment of low-grade NHL and MCL. The company expects the shift from R-CHOP to BR therapy to progress domestically in the medium term.

Untreated low-grade NHL and MCL: 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–JPY7bn as the Japanese population continues to age.

Treakisym targeting chronic lymphocytic leukemia (CLL)

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

Additional indication for CLL granted in August 2016

In Japan, SymBio completed a pivotal phase II trial for Treakisym in CLL as a joint project with Eisai in October 2015. In August 2016, the company received permission to add CLL as an indication for Treakisym.

Potential patient population, expected sales

SymBio estimates that there are about 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.

Treakisym indicated for relapsed or refractory DLBCL (aggressive NHL)

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

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

R&D status: Began phase III clinical trial of Treakisym to treat relapsed or refractory DLBCL in August 2017

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 as well as clinically manageable side effects in elderly patients.

Following consultations with the Pharmaceuticals and Medical Devices Agency (PMDA), the company commenced Phase III clinical trials using Treakisym in combination with rituximab for relapsed or refractory DLBL. The purpose of the study is to test the efficacy and safety of BR therapy, with the overall response rate (ORR; antitumor effect) as the primary endpoint and an enrollment target of 60 patients. The company plans to conduct the study over 24 months and aims to file NDA in 2H 2019.

Potential patient population

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

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

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

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

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

Comparison of RTD/RI products and currently available (freeze-dried) product

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

Can extend life cycle of Treakisym® until 2031

The re-examination term for the FD product of Treakisym ends in 2020, after which generics can go on the market. SymBio believes that by selling the RTD and RI products that offer the advantages of reducing healthcare professionals' workload and stress on patients after 2020, it can extend the exclusive sales period until 2031. This increases the possibility of prolonging the life cycle of Treakisym and limiting the spread of generics.

Bendamustine hydrochloride RTD and RI injection products are marketed in the US by Teva Pharmaceutical Industries as BENDEKA®, which has 97% share of the US bendamustine market within two years after its sales.

R&D status: Aim to begin selling bendamustine hydrochloride RTD product in 1H 2021

As of September 2017, the schedule for filing for approval of the bendamustine hydrochloride RTD product and development of the RI product were under discussion.

SymBio commented that it is likely to be allowed to file for approval of the RTD product without conducting clinical trials, because the ingredients, efficacy, and administration time are identical to the Treakisym FD product; the only difference being that it does not need reconstitution. The company aims to begin selling the RTD product in 1H 2021, based on the estimated time required to prepare filing documentation and review period from filing to approval.

However, the company expects clinical trials will be required for the RI product, because the administration time is different from the FD product. Given that the trials will only be comparing the safety and efficacy of the RI product and the FD product (which has already been approved) rather than the usual phase III clinical trial of a new drug, SymBio expects that the required number of patients in the study will be small. The company plans to begin preparing for the sale of the RI product after the RTD product goes on sale.

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 2017, 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.

The company had started phase I clinical trials for the oral form of rigosertib for the indications of high-risk MDS (in combination with azacitidine) in December 2015. The supply of the study drug from Onconova had been delayed, but SymBio restarted phase I trials in Japan in June 2017. After establishing safety in phase 1 trials, the company plans to resume the trial of rigosertib in combination with azacitidine and participate in an international phase III study planned by Onconova in FY12/20.

Market for Rigosertib (oral form) and number of patients

		Low-risk MDS	High risk MDS	
		First-line	First-line	Relapsed and refractory
Intravenous	Number of patients			3,200
	Approval			Obtain approval in FY12/19 (expected)
	Development status			Global phase III trials
Oral	Number of patients	7,800	3,200	
	Approval	Obtain approval in FY12/19 or FY12/20 (expected)	TBC	
	Development status	Phase II trials underway in the US	Phase II clinical trials underway in the US Phase I clinical trials underway in Japan (with azacitidine)	

Source: Shared Research based on company data.

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

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

However, some cases of higher-risk MDS show resistance to standard treatment with hypomethylating agents (HMAs) such as Vidaza and Dacogen, including relapse following treatment. The most advanced research being conducted for rigosertib was for the treatment of patients with higher-risk MDS who had progressed on, failed or relapsed after prior therapy with HMAs. According to the company, no drugs have been approved for the treatment of post-HMA higher-risk MDS patients as of February 2017.

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. 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. The first patient was registered in July 2016 and 20 patients had been registered as of end-August 2017 versus the target 25–30. SymBio aims for approval during FY12/19. Onconova is scheduled to perform an interim analysis of the global phase III clinical trials data in Q4 FY12/17.

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

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

Onconova, the anticancer drug rigosertib's licensor, presented Phase 2 clinical trial data on oral rigosertib for patients with higher-risk myelodysplastic syndromes (MDS) at the 58th American Society of Hematology (ASH) Annual Meeting held in December 2016.

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

As of August 2017, Onconova is making efforts toward finalizing the design for a pivotal Phase 3 oral rigosertib/azacitidine combination trial for higher-risk MDS patients.

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. However, patient enrollment had not started because of delayed supply of the study drug from Onconova Therapeutics. After the supply of the study drug resumed in June 2017, the company restarted the domestic phase I clinical trial to confirm the safety of the drug at high doses (an additional requirement for phase III trials conducted by Onconova in the US for the indication of untreated and relapsed/refractory high-risk MDS). After establishing safety in the phase I trial, the company plans to resume the trial of the drug in combination with azacitidine and participate in global phase III trials conducted by Onconova in FY12/20.

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

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 JPY12.4bn for FY03/16 (+14.3% YoY). The company expects to book sales of JPY13.4bn for FY03/17. Shared Research thinks that sales of the intravenous and oral forms of rigosertib could match or exceed sales of Vidaza, used for patients who have not received treatment with Vidaza or in combination therapy with Vidaza.

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

SymBio obtained exclusive development and marketing rights to SyB P-1501 (US product name: Ionsys) in Japan from The Medicines Company (US) in October 2015. SyB P-1501 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.

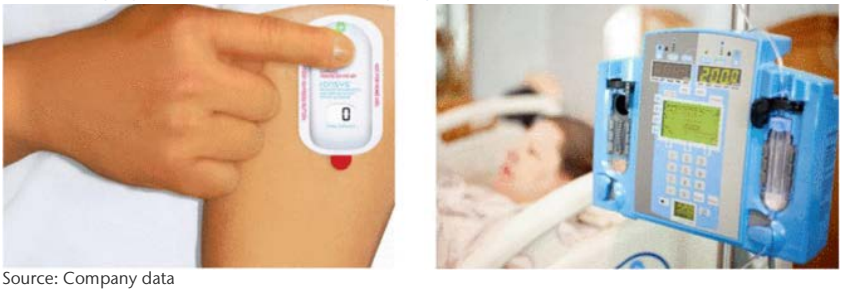
As of February 2017, many hospitals had begun using PCA, which allows patients to control administration of their pain medications based on their own symptoms. The drug is delivered through an electronic pump at the touch of a button. A cassette with diluted fentanyl is connected to an epidural or intravenous 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 temporarily suspended 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 the drug's safety in healthy adults, and SymBio launched phase III trials in June 2016. The company was making progress with enrollment after the first patient was enrolled in November 2016.

The Medicines Company had filed a report (Form 8-K) with the US Securities and Exchange Commission in June 2017 stating that it would withdraw the patient-controlled pain management drug IONSYS® (SyB P-1501) from the US market and suspend commercial activities. In May 2017, SymBio announced temporary suspension of new patient enrollment in the domestic phase III clinical trial of SyB P-1501. As of August 2017, SymBio said it was in talks with The Medicines Company, and planned to make a timely disclosure once it determined how the SyB P-1501 clinical trial and commercialization in Japan would be affected.

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.

Earnings structure

(JPYmn)	FY12/09	FY12/10	FY12/11	FY12/12	FY12/13	FY12/14	FY12/15	FY12/16
Sales	1,191	1,450	1,883	1,955	1,532	1,955	1,933	2,368
Product sales	-	326	1,632	1,955	1,432	1,940	1,933	2,137
Treakisym sales to end users (reference)	-	644	3,390	3,940	4,230	4,320	4,760	4,720
Product sales / Sales to end users	-	50.6%	48.2%	49.6%	33.9%	44.9%	40.6%	45.3%
Royalty revenue	1,191	1,124	250	-	100	15	-	231
Sales to Eisai	1,085	1,446	1,872	1,930	1,486	1,908	1,852	2,265
Non-Eisai sales	106	4	10	26	46	47	81	104
CoGS	-	238	1,224	1,362	1,214	1,428	1,350	1,464
CoGS / Product sales	-	73.1%	75.0%	69.7%	84.8%	73.6%	69.8%	68.5%
CoGS / Sales to end users	-	37.0%	36.1%	34.6%	28.7%	33.1%	28.4%	31.0%
Product procurement	-	238	1,434	1,322	1,175	1,550	1,242	1,606
Gross profit	1,191	1,212	658	593	318	527	583	904
SG&A expenses	1,399	1,825	2,725	2,293	1,999	1,830	3,135	3,031
Personnel expenses	323	343	365	413	441	479	488	628
R&D expenses	817	1,118	1,945	1,438	1,053	774	2,035	1,667
Other	259	364	415	442	505	577	612	737
Operating profit	-208	-613	-2,067	-1,700	-1,681	-1,303	-2,552	-2,127

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 FY12/16, 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. SymBio purchases Treakisym from Astellas Deutschland GmbH. Astellas supplies Treakisym to the company for about 70% of SymBio's wholesale price. Margins may improve as sales increase.

SymBio pays Astellas in euros, with these transactions usually taking place several months apart. Thus, the company faces the risk that euro-yen forex rates will change during this period. The company hedges this risk with forward foreign-exchange contracts, and by reporting gains and losses on forex as a non-operating profit (or loss).

SG&A expenses

Personnel and R&D are the main SG&A expenses. Personnel expenses 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.
- **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 JPY5.7bn at the end of FY12/15. But the company expects a total net loss of JPY7.6–8.2bn over the period of its mid-term plan (FY12/17–FY12/19). 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

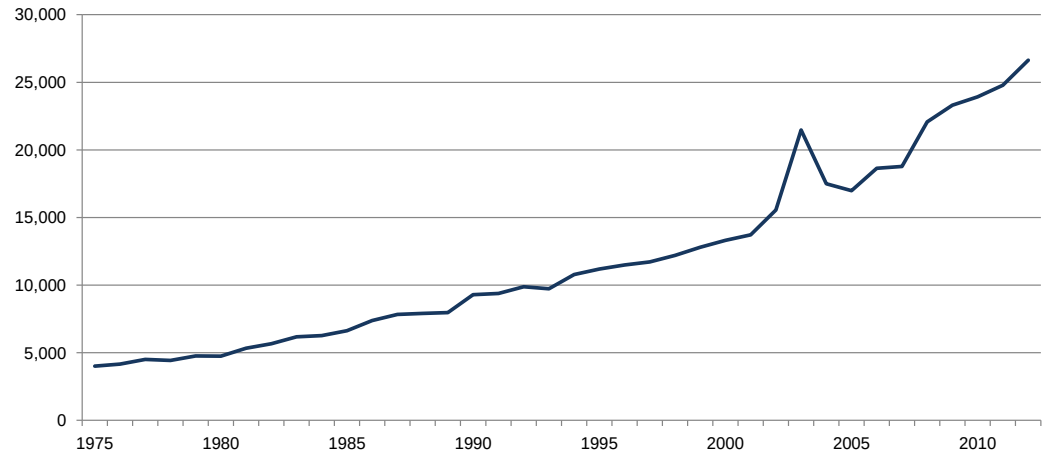
Market strategy

Lymphatic cancer: patient population, market size, drugs

Newly diagnosed patients with lymphatic cancer

In 2012, the number of people diagnosed with lymphatic cancer in Japan was 26,632 (+7.5% YoY; average annual increase in past 10 years is 5.5%), according to the Center for Cancer Control and Information Services. Of these, 20,748 (+8.7%), or 77.9% (77.0% in 2011), were 60 years or older. Of the 865,238 (+1.6%) people diagnosed with cancer, those diagnosed with lymphatic cancer accounted for only 3.1%, but their number increased 71.3% between 2002 and 2012 versus a 51.6% increase in the number of people newly diagnosed with cancer.

Patients newly diagnosed with lymphatic malignancy



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

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

Market for anticancer drugs to expand

According to the Fuji Keizai Group, the domestic market potential for anticancer agents was JPY852.3bn in 2014. The market is growing amid new products going on sale and additional indications, and is expected to hit JPY1.5tn by 2023 (+81.1% from 2014).

Treakisym market potential and patient population

The company estimates that the number of patients being treated for relapsed or refractory low-grade NHL and MCL in Japan is 4,700. Treakisym sales reached JPY4.7bn (-0.8%) in FY12/16.

The company estimates that the number of Japanese patients receiving first-line treatment for low-grade NHL and MCL is about 7,100 (additional indication approved in FY12/16). The number of Japanese patients with CLL is estimated to be about 700. Thus the estimate for total number of users and potential users of Treakisym is 7,800. The company estimates that the number of Japanese patients with relapsed or refractory DLBCL for which the company is considering application for approval of an additional indication is 6,700.

Treakisym indications and number of patients

Indications	Patients	Progress	Notes
Relapsed or refractory low-grade NHL and relapsed or refractory MCL	4,700	Approval granted	Sales: JPY4.7bn (FY12/16)
Untreated low-grade NHL, and untreated MCL	7,100	Approval granted	
Relapsed or refractory moderate- to high-grade NHL	6,700	Clinical trials underway	Consultation on application underway
CLL	700	Approval granted	

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

Drugs competing with Treakisym

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

Rituximab (product name: Rituxan)

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

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

In Japan, Zenyaku Kogyo and Chugai have been jointly selling the drug since September 2001. Chugai's Rituxan sales were JPY32.1bn (+10.7% YoY) in FY12/16.

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 2017, 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 JPY12.4bn in FY03/16 (+14.3% YoY) and expects sales of JPY13.4bn in FY03/17.

Historical performance

Q1 FY12/17 results

Q1 FY12/17 sales totaled JPY870mn (+350.2% YoY) thanks to sales of Treakisym. The company in December 2016 obtained approval of an additional indication for Treakisym for untreated low-grade non-Hodgkin's lymphoma (NHL) and mantle cell lymphoma (MCL). Sales of Treakisym in Q1 FY12/17, just after the approval, sharply increased from Q1 FY12/16.

Due to the sales increase, gross profit came to JPY239mn (+323.0% YoY). Gross profit margin was 27.5% (-1.7pp YoY). The decline in GPM was due to a change in the structure of distribution costs stemming from a change in the product mix.

SG&A expenses rose 32.9% YoY to JPY764mn. R&D expenses increased 76.8% to JPY395mn. There were expenses for clinical trials for the intravenous and oral formulations of Rigosertib Sodium and SyB P-1501. SG&A expenses excluding R&D expenses were up 5.0% at JPY369mn.

As a result, operating loss totaled JPY525mn (loss of JPY518mn in Q1 FY12/16). The company also reported a recurring loss of JPY583mn (loss of JPY655mn in Q1 FY012/16) partly due to non-operating expenses of JPY59mn (mainly on forex losses of JPY55mn). Net loss was JPY583mn (loss of JPY653mn).

Progress in Q1 FY12/17 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).

In Q1 FY12/17, sales of Treakisym based on the National Health Insurance (NHI) drug price grew 28.0% YoY, and accordingly product sales to Eisai increased 312.4%. In December 2016, SymBio obtained approval of an additional indication of Treakisym for untreated low-grade NHL and MCL. In Q1 FY12/17, just after receiving approval, sales of Treakisym sharply increased YoY.

In addition to the above three approved indications, the company has filed an NDA for a fourth indication to help patients who need new treatments and maximize the value of the product. The company has completed phase III clinical trials for relapsed or refractory diffuse large B-cell lymphoma (DLBCL, or aggressive NHL). At the end of FY12/16, the company had said that it was considering an additional indication, and in Q1 FY12/17, in response to strong medical needs, was in consultation with the Pharmaceuticals and Medical Devices Agency and continues to discuss the path forward for approval.

SymBio is exploring further expansion of the Treakisym business by developing an oral formulation in addition to the injection currently under development or on sale to treat solid tumors and autoimmune diseases.

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

Regarding these agents, for which a licensing agreement was entered into in July 2011, the company changed their generic name from "Rigosertib" to "Rigosertib Sodium" in accordance with the notice of decision on its Japanese Accepted Names for Pharmaceuticals (JAN) received in October 2016.

Onconova Therapeutics, Inc., the 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 myelodysplastic syndrome (MDS) patients who do not respond to treatment or relapsed after 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. The company has taken steps to register patients, and completed the first patient enrollment in July 2016. Enrollments are currently accumulating.

SymBio started domestic Phase I clinical trials for the oral (IV) form of Rigosertib Sodium (used in combination with azacitidine) for higher-risk myelodysplastic syndrome (MDS) in December 2015. Due to delays in the supply of drugs for the joint trials, patient enrollment has not started as of May 11, 2017. According to the company, however, it was resolving the issue of delays. The company is looking to start patient registration upon resolution of this issue, and to complete joint trials in line with its plans. SymBio is considering participating in the global clinical trial to be conducted by Onconova.

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

The company started a domestic phase III clinical trial for SyB P-1501—licensed by the Medicines Company (through its wholly owned subsidiary Incline Therapeutics)—for the short-term management of acute post-operative pain during hospitalization in June 2016. The company enrolled the first patient in November 2016 and was making progress with case accumulation. However, in a report submitted to the US Securities and Exchange Commission in May 2017, The Medicines Company said that it intends to consider a business alliance or divestiture regarding SyB P-1501. It also said that if it fails to complete an acceptable deal during Q2 (April–June 2017), it may choose to discontinue the commercialization of SyB P-1501. In the interests of patient welfare, SymBio has suspended further patient enrollment since April 21, 2017 because of the concerns raised about the continuity of The Medicines Company's SyB P-1501 business.

New drug candidates

From a long-term perspective, SymBio will continue to search for and evaluate promising drug candidates, and acquire global rights for these drugs to become a sustainable and profitable pharmaceutical company with growth potential and profitability. Further, in May 2016, the company established SymBio Pharma USA, Inc., a wholly owned US-based subsidiary, as a strategic base for overseas business development. The company looks to leverage this subsidiary to actively acquire rights over new drug development candidates globally, and engage in development and commercialization in major markets including the US, Japan, and Europe to transition to a global specialty pharmaceutical company.

Overseas

The company marketed Treakisym in Korea, Taiwan, and Singapore, and overseas sales were steady.

FY12/16 results

FY12/16 sales totaled JPY2.4bn (+22.5% YoY) thanks to domestic sales of Treakisym (SyB L-0501). Products sales totaled JPY2.1bn (+10.6%). It also booked a royalty revenue of JPY230mn (zero in FY12/15) resulting from achieving the sales milestone of SyB L-0501 in Taiwan.

SG&A expenses fell 3.3% YoY to JPY3.0bn. R&D expenses fell to JPY1.7bn (-18.1% YoY). There were expenses for clinical trials for TREAKISYM®, the intravenous and oral formulations of Rigosertib Sodium, and SyB P-1501 (patient-controlled analgesia for pain management), but declined from FY12/15, when the company booked costs for licensing-in SyB P-1501. The company set an initial R&D expense budget of JPY2.2bn, but spent less than planned because of delays with the development of the oral formulation of rigosertib sodium. SG&A expenses excluding R&D expenses were up 24.0% at JPY1.4bn.

As a result, operating loss totaled JPY2.1bn (loss of JPY2.6bn in FY12/15). The company also reported a recurring loss of JPY2.3bn (loss of JPY2.6bn last year) partly due to non-operating expenses of JPY196mn (mainly on forex losses of JPY159mn). Net loss was JPY2.3bn (loss of JPY2.6bn).

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).
Though product sales based on the National Health Insurance (NHI) drug price declined slightly by 0.8% YoY, product sales to Eisai were largely in line with plan.

Regarding chronic lymphocytic leukemia (CLL), the company filed an NDA in December 2015, and obtained approval for the additional indication in August 2016. The company developed and applied for this indication upon request of the Ministry of Health, Labour and Welfare in Japan as one of the "Unapproved or Off-Labeled Drugs with High Medical Needs." This is the second approval after the approval of an sNDA for the indication of refractory/relapsed low-grade NHL and mantle cell lymphoma which the company has already received in October 2010.

In Japan, the company submitted a new drug application (NDA) to Japan's Pharmaceuticals and Medical Devices Agency (PMDA) in December 2015 for a first-line treatment of low-grade NHL and MCL and obtained approval for the additional indication in December 2016. Meanwhile, in Europe, though the company received notification on January 2016 from Astellas Pharma that its application had been withdrawn, it continued with the domestic approval process upon consulting with the PMDA, resulting in the approval of the additional indication.

Rigosertib Sodium (SyB L-1101 [IV]/SyB C-1101 [oral]; anticancer agent; generic name: Rigosertib Sodium)
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SyB P-1501, a post-operative patient-controlled analgesia
The company started a domestic phase III clinical trial for SyB P-1501—licensed by the Medicines Company (through its wholly owned subsidiary Incline Therapeutics)—for the short-term management of acute post-operative pain during hospitalization in June 2016. The company is looking to complete the phase III clinical trial quickly, and obtain regulatory approval in 2019.

New drug candidates
From a long-term perspective, SymBio will continue to search for and evaluate promising drug candidates, and acquire global rights for these drugs to become a sustainable and profitable pharmaceutical company with growth potential and profitability. Further, in May 2016, the company established SymBio Pharma USA, Inc., a wholly owned US-based subsidiary, as a strategic base for overseas business development. The company looks to leverage this subsidiary to actively acquire rights over new drug development candidates globally, and engage in development and commercialization in major markets including the US, Japan, and Europe to accelerate the process of turning into a global specialty pharmaceutical company.

Overseas
The company marketed Treakisym in Korea, Taiwan, and Singapore, and overseas sales were steady.

Q3 FY12/16 results
Cumulative Q3 FY12/16 sales totaled JPY1.4bn (+5.6% YoY) thanks to domestic sales of Treakisym. Product sales through Eisai were largely in line with forecasts, and products sales rose 3.3%. It also booked a non-recurring revenue resulting from achieving the sales milestone of SyB L-0501 in Taiwan.

In cumulative Q3 FY12/16 sales reached 60.2% of the company's full-year target (vs. 68.9% in the same period the previous year). In Q4 the company expects to generate product sales after gaining approval to add an indication for Treakisym®. In August 2016, the company obtained approval to add chronic lymphocytic leukemia (CLL) as an indication and is in the process of applying for the additional indications as a first-line treatment of low-grade malignant non-Hodgkin's lymphoma and mantle cell lymphoma as indications. Gaining approval for these indications should significantly boost sales.

SG&A expenses rose 45.4% YoY to JPY2.0bn. R&D expenses rose to JPY981mn (+64.1% YoY) primarily due to expenses associated with obtaining the approval for the additional indications of TREAKISYM®, the clinical trial for the intravenous and oral formulations of Rigosertib Sodium, and preparations for the clinical trial of SyB P-1501. SG&A expenses excluding R&D expenses were up 31.2% at JPY1.0bn on expenses for the introduction of new development candidates and expenses for acquisition of companies that own the rights to new drug candidates.

As a result, operating loss totaled JPY1.5bn (loss of JPY988mn in Q3 FY12/15). The company also reported a recurring loss of JPY1.9bn (loss of JPY1.1bn last year) due to non-operating expenses of JPY391mn (mainly on forex losses of JPY356mn). Net loss was JPY1.9bn (loss of JPY1.1bn).

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). In Q3, product sales to Eisai were largely in line with plan.

In Japan, the company submitted a new drug application (NDA) to Japan's Pharmaceuticals and Medical Devices Agency (PMDA) in December 2015 for a first-line treatment of low-grade NHL and MCL. Meanwhile, in Europe, though the company received notification on January 2016 from Astellas Pharma that its application had been withdrawn, it plans to continue with the domestic approval process upon consulting with the PMDA.

On November 24, 2016, the Ministry of Health, Labour and Welfare hosted a meeting for Drug Section Two of the Pharmaceutical Affairs and Food Sanitation Council. One topic at the meeting was on setting the re-examination period and on whether to allow partial modifications to the approved manufacturing and marketing of drug products TREAKISYM® Intravenous Infusion 25 mg and 100 mg. Shared Research understands that the council discussed the approval of additional indications and that if it is approved, SymBio will be notified after a predetermined period of time.

According to the company, over 7,100 people have low-grade malignant non-Hodgkin's lymphoma and mantle cell lymphoma for first-line treatment, and over 4,700 people suffer from relapsed or refractory low-grade malignant non-Hodgkin's lymphoma and mantle cell lymphoma. With these numbers, we believe that adding indications as first-line treatment of low-grade malignant non-Hodgkin's lymphoma and mantle cell lymphoma to Treakisym® would significantly boost product sales.

Regarding chronic lymphocytic leukemia (CLL), the company filed an NDA in December 2015, and obtained approval for the additional indication in August 2016. The company developed and applied for this indication upon request of the Ministry of Health, Labour and Welfare in Japan as one of the "Unapproved or Off-Labeled Drugs with High Medical Needs." This is the second approval after the approval of an sNDA for the indication of refractory/relapsed low-grade NHL and mantle cell lymphoma which the company has already received in October 2010. According to the company, there are 700 people suffering from chronic lymphocytic leukemia (CLL).

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

Regarding these agents, for which a licensing agreement was entered into in July 2011, the company changed their generic name from "Rigosertib" to "Rigosertib Sodium" in accordance with the notice of decision on its Japanese Accepted Names for Pharmaceuticals (JAN) received in October 2016. Onconova Therapeutics, Inc., the 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

myelodysplastic syndrome (MDS) patients who do not respond to treatment or relapsed after 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. The company has taken steps to register patients, and completed the first patient enrollment in July 2016. Enrollments are currently accumulating.

SymBio started domestic Phase I clinical trials for the oral (IV) form of Rigosertib Sodium (used in combination with azacitidine) for higher-risk myelodysplastic syndrome (MDS) in December 2015. Due to delays in the supply of drugs for the joint trials, patient enrollment has not started as of November 11, 2016. The company is looking to start patient registration upon resolution of this issue, and complete joint trials in line with its plans. SymBio is considering participating in the global clinical trial to be conducted by Onconova.

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

The company started a domestic phase III clinical trial for SyB P-1501—licensed by the Medicines Company (through its wholly owned subsidiary Incline Therapeutics)—for the short-term management of acute post-operative pain during hospitalization in June 2016. In November 2016, the first patient completed registration. The company is looking to complete the phase III clinical trial quickly, and obtain regulatory approval in 2019.

New drug candidates

From a long-term perspective, SymBio will continue to search for and evaluate promising drug candidates, and acquire global rights for these drugs to become a sustainable and profitable pharmaceutical company with growth potential and profitability. Further, in May 2016, the company established SymBio Pharma USA, Inc., a wholly owned US-based subsidiary, as a strategic base for overseas business development. The company looks to leverage this subsidiary to actively acquire rights over new drug development candidates globally, and engage in development and commercialization in major markets including the US, Japan, and Europe to accelerate the process of turning into a global specialty pharmaceutical company.

Overseas

The company marketed Treakisym in Korea, Taiwan, and Singapore, and saw overseas sales progress largely in line with plans in Q1 because shipments to overseas clients are planned from Q3 and after.

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.

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.	FY12/16 Par.
Total sales	**1,191**	**1,450**	**1,883**	**1,955**	**1,532**	**1,955**	**1,933**	**2,368**
YoY	-26.9%	21.7%	29.8%	3.9%	-21.6%	27.6%	-1.1%	22.5%
CoGS	0	238	1,224	1,362	1,214	1,428	1,350	1,464
Gross profit	**1,191**	**1,212**	**658**	**593**	**318**	**527**	**583**	**904**
GPM	100.0%	83.6%	35.0%	30.3%	20.8%	26.9%	30.2%	38.2%
SG&A expenses	1,399	1,825	2,725	2,293	1,999	1,830	3,135	3,031
SG&A-to-sales ratio	117.5%	125.8%	144.8%	117.3%	130.4%	93.6%	162.1%	128.0%
Operating profit	**-208**	**-613**	**-2,067**	**-1,700**	**-1,681**	**-1,303**	**-2,552**	**-2,127**
YoY	-	-	-	-	-	-	-	-
OPM	-	-	-	-	-	-	-	-
Non-operating income	20	13	56	7	114	215	17	7
Non-operating expenses	26	38	85	37	35	22	96	196
Recurring profit	**-214**	**-638**	**-2,095**	**-1,729**	**-1,601**	**-1,110**	**-2,630**	**-2,317**
YoY	-	-	-	-	-	-	-	-
RPM	-	-	-	-	-	-	-	-
Extraordinary gains	-	-	-	-	-	2	3	9
Extraordinary losses	-	0	5	0	-	3	1	1
Tax charges	4	4	4	4	4	4	4	4
Implied tax rate	-	-	-	-	-	-	-	-
Net income	**-218**	**-642**	**-2,105**	**-1,733**	**-1,605**	**-1,116**	**-2,632**	**-2,313**
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.	FY12/16 Par.
Sales (Initial CE)	-	-	1,933	2,338	1,927	1,785	1,785	2,339
Sales (Results)	-	-	1,883	1,955	1,532	1,955	1,933	2,368
Initial CE versus Results	**-**	**-**	**-2.6%**	**-16.4%**	**-20.5%**	**9.5%**	**8.3%**	**1.2%**
Operating profit (Initial CE)	-	-	-2,351	-1,625	-1,889	-1,654	-1,654	-2,778
Operating profit (Results)	-	-	-2,067	-1,700	-1,681	-1,303	-2,552	-2,127
Initial CE versus Results	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Recurring profit (Initial CE)	-	-	-2,398	-1,652	-1,922	-1,650	-1,650	-2,811
Recurring profit (Results)	-	-	-2,095	-1,729	-1,601	-1,110	-2,630	-2,317
Initial CE versus Results	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Net income (Initial CE)	-	-	-2,407	-1,656	-1,926	-1,654	-1,654	-2,815
Net income (Results)	-	-	-2,105	-1,733	-1,605	-1,116	-2,632	-2,313
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.	FY12/16 Par.
Assets								
Cash and deposits	3,902	2,314	4,559	4,540	6,163	5,692	4,261	5,719
Marketable securities	219	1,701	1,953	300	1,100	899	0	0
Accounts receivable	0	6	162	148	0	273	301	487
Inventories	0	0	207	165	125	245	133	273
Other current assets	97	191	297	268	245	181	131	205
Total current assets	**4,218**	**4,213**	**7,178**	**5,421**	**7,634**	**7,290**	**4,827**	**6,685**
Buildings (net)	3	3	2	3	2	22	22	31
Tools, furniture, and fixtures (net)	11	19	15	11	6	27	31	43
Total tangible fixed assets	**13**	**22**	**17**	**14**	**9**	**49**	**53**	**75**
Total other fixed assets	**27**	**27**	**48**	**57**	**37**	**49**	**53**	**77**
Software	2	1	10	8	6	62	51	42
Other	0	0	3	3	2	4	1	0
Total intangible fixed assets	**2**	**1**	**13**	**11**	**8**	**66**	**52**	**42**
Total fixed assets	**42**	**50**	**78**	**82**	**53**	**164**	**158**	**193**
Total assets	**4,261**	**4,263**	**7,256**	**5,502**	**7,687**	**7,454**	**4,984**	**6,878**
Liabilities								
Accounts payable	0	1	309	330	0	306	320	322
Accounts payable–other	182	124	278	196	207	143	184	553
Short-term debt	0	0	0	0	0	0	0	0
Other current liabilities	23	52	59	73	44	39	47	68
Total current liabilities	**205**	**178**	**646**	**599**	**251**	**488**	**551**	**942**
Long-term debt	0	0	0	0	0	0	0	0
Other fixed liabilities	2	2	5	4	3	2	2	451
Total long-term liabilities	**2**	**2**	**5**	**4**	**3**	**2**	**2**	**451**
Total interest bearing debt	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Total liabilities	**207**	**180**	**651**	**602**	**254**	**490**	**552**	**1,394**
Net assets	4,060	4,083	6,606	4,873	7,336	6,764	4,132	5,054
Capital stock	3,378	3,711	6,025	6,025	8,059	8,331	8,331	9,948
Capital surplus	3,348	3,681	5,995	5,995	8,029	8,301	8,301	9,918
Retained earnings	-2,666	-3,309	-5,413	-7,146	-8,752	-9,868	-12,500	-14,813
Subscription rights to shares	0	0	0	27	97	200	300	431
Total net assets	**4,054**	**4,083**	**6,606**	**4,900**	**7,433**	**6,964**	**4,432**	**5,485**
Working capital	0	5	61	-17	125	212	114	438
Total interest-bearing debt	0	0	0	0	0	0	0	0
Net debt	-3,902	-2,314	-4,559	-4,540	-6,163	-5,692	-4,261	-5,719

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. Booked liabilities are accounts payable and arrears. In FY12/16, the company booked corporate bonds totaling JPY450mn under fixed liabilities. This is the unexercised portion of its third unsecured bonds with convertible bond type stock acquisition rights (issued in April 2016, total value: JPY3.0bn, no interest on bonds).

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.	FY12/16 Par.
Cash flows from operating activities (1)	-211	-754	-2,074	-1,659	-1,677	-1,266	-2,272	-1,960
Cash flows from investing activities (2)	-4	-116	-117	-411	-1,332	314	1,489	-44
Free cash flow (1+2)	-215	-870	-2,191	-2,069	-3,010	-952	-783	-2,004
Cash flows from financing activities	2,963	663	4,611	-1	4,057	544	-3	3,658
Depreciation and amortization (A)	4	7	8	9	8	13	24	26
Capital expenditures (B)	-3	-14	-12	-3	-	-109	-24	-28
Working capital change (C)	-	5	56	-78	142	86	-98	324
Simple FCF (NI + A + B - C)	-217	-655	-2,165	-1,650	-1,739	-1,298	-2,534	-2,640
Cash and cash equivalents (year-end)	4,121	3,916	6,311	4,240	5,294	5,092	4,261	5,719

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

Cash flows from operating activities

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

Cash flows from investing activities

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 investing activities widened in FY12/12 and FY12/13. SymBio booked an inflow of JPY1.5bn in FY12/15 due to payments from time deposits and the redemption of securities.

Cash flows from financing activities

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

Main sources of funding

Date	Change in shares issued	Total shares issued	Change in capital stock and capital surplus (JPYmn)	Capital stock and capital surplus (JPYmn)	
Mar. 2009	7,404	66,017	888	4,643	Paid-in private placement
Nov. 2009	8,334	90,268	500	6,104	Paid-in private placement
Dec. 2009	9,553	100,651	573	6,727	Paid-in private placement
Feb. 2011	11,032	122,769	772	8,164	Paid-in private placement
Feb. 2011	17,368	140,137	1,216	9,380	Paid-in private placement
Oct. 2011	5,100,000	19,130,900	2,628	12,019	Paid-in public offering (price determined by the book building process)
Jan. to Dec. 2013	3,921,257	23,052,157	1,244	13,263	Exercise of stock options attached to convertible corporate bonds and other stock options
Dec. 2013	6,720,200	29,772,357	2,504	15,767	Paid-in public offering (price determined by the book building process)
Dec. 2014	1,756,666	32,390,923	544	16,632	Exercise of stock options attached to convertible corporate bonds and other stock options
Jan. to Dec. 2016	14,139,901	46,530,824	3,235	19,867	Exercise of stock options attached to convertible corporate bonds and other stock options

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 2017, 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.

March 2005	SymBio Pharmaceuticals Limited established with JPY30mn in capital.
December 2005	License Agreement finalized with Astellas Pharma GmbH for SyB L-0501 (bendamustine) development and commercialization rights in Japan.
March 2006	Manufacturer's License (packaging, labeling and storage) obtained from Tokyo Metropolitan Government (License #13AZ200010).
March 2007	Abeille Pharmaceuticals licensed SyB D-0701 (granisetron patch) to SymBio Pharmaceuticals for development & commercialization in Japan, China (HK), Taiwan, 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 concluded Sublicense Agreement with Cephalon, Inc. for development and commercialization rights of bendamustine hydrochloride in China (HK).
May 2009	License Agreement finalized with Eisai Co., Ltd. for co-development and commercialization rights of SyB L-0501 (bendamustine) in Korea and Singapore.
September 2010	SymBio Pharmaceuticals and Eisai launch SYMBENDA® (bendamustine) in Singapore for the treatment of Low-grade Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukemia.
October 2010	Announced NDA Approval of TREAKISYM® (bendamustine) in Japan.
December 2010	Launched TREAKISYM® in Japan.
July 2011	Onconova and SymBio Pharmaceuticals completed License Agreement for SyB L-1101/SyB C-1101 (rigosertib, a Phase III stage multi-kinase inhibitor for Myelodysplastic Syndromes).

October 2011	Launched Symbenda® (bendamustine hydrochloride) in Korea for the treatment of Chronic Lymphocytic Leukemia and multiplemyeloma.
October 2011	Listed on Osaka Securities Exchange JASDAQ Growth Market.
February 2012	Launched Innomustine® (bendamustine hydrochloride) in Taiwan for the treatment of Low-grade Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukemia.
October 2015	Obtained exclusive development and marketing rights to Ionsys (patient-controlled analgesia system) in Japan from The Medicines Company (US).
August 2016	Received approval for Chronic Lymphocytic Leukemia to be added as indication for TREAKISYM®.
December 2016	Announced approval of the anti-cancer drug TREAKISYM® for the additional indication of first-line treatment of low-grade non-Hodgkin's lymphoma and mantle cell lymphoma.

News and topics

June 2017

On **June 30, 2017**, the company announced that it has initiated in Japan a phase I clinical trial of single-agent oral rigosertib in higher-risk myelodysplastic syndromes (MDS).

The company initiated the phase I clinical trial since Onconova Therapeutics, Inc., the licensor for oral rigosertib, resumed the supply of clinical trial materials after completing a change of manufacturing sites.

The purpose of the Japanese phase I study is to confirm the safety of high-dose oral rigosertib, which was added to the ongoing overseas phase II study by Onconova in untreated or relapsed/refractory patients with higher-risk MDS. After demonstrating the safety of high-dose oral rigosertib, SymBio intends to immediately recommence an oral rigosertib/azacitidine combination trial in Japan, and participate in the global phase III study in untreated higher-risk MDS patients that Onconova is planning. In initiating the subject phase I study, SymBio has terminated the phase I combination study for oral rigosertib/azacitidine.

The enrollment of patients is currently underway in the global phase III clinical trial for the intravenous version of rigosertib in relapsed/refractory patients with higher-risk MDS, which SymBio has been taking part in.

The initiation of this phase I study will not impact the company’s FY12/17 forecasts.

On **June 5, 2017**, the company announced a US SEC filing (Form 8-K) by The Medicines Company as the licensor of the patient-controlled pain management drug SyB P-1501.

On May 11, 2017, the company announced it has suspended further registration of new patients in a domestic phase III clinical trial of SyB P-1501 indicated for the short-term management of acute post-operative pain during hospitalization. In relation to this, the Medicines Company, the licensor of this product, filed a Form 8-K with the US Securities and Exchange Commission on June 2, 2017.

The Form 8-K states that The Medicines Company commenced implementation of a workforce reduction on June 1, 2017 in connection with the discontinuation and market withdrawal of IONSYS® (US product name of SyB P-1501) in the US and the cessation of related commercialization activities, while the New Drug Application for IONSYS® is to remain open until December 31, 2017.

SymBio will discuss with The Medicines Company the effects of the 8-K filing on the clinical trial plan of SyB P-1501 and plans to make timely disclosures accordingly.

May 2017

On **May 11, 2017**, the company announced that it has suspend further patient enrollment for the phase III trial of SyB P-1501 (patient-controlled analgesia for pain management).

SymBio decided to suspend further registration of new patients in a domestic phase III trial of SyB P-1501 indicated for the short-term management of acute post-operative pain during hospitalization.

In a quarterly report submitted to the US Securities and Exchange Commission (SEC) in May 2017, The Medicines Company, the licensor of SyB P-1501, stated that it was considering a business alliance or company split for the SyB P-1501 business and that it may suspend commercialization of the agent unless an acceptable agreement is concluded by Q2 FY12/17 (April–June 2017).

SymBio started the domestic phase III trial of SyB P-1501 in June 2016, enrolled the first patient in November, and has made progress with case accumulation. However, on April 21, 2017, The Medicines Company notified the company of its intentions as outlined in the quarterly report. SymBio, which is committed to the primacy of patient welfare, interrupted patient enrollment on the same day given concerns about the continuity of The Medicines Company's SyB P-1501 business. Accordingly, SymBio notified medical institutions participating in the study and the Pharmaceuticals and Medical Devices Agency (PMDA) that it would suspend further patient enrollment.

SymBio will not register new patients in the trial until The Medicines Company makes a further announcement about the commercialization of SyB P-1501. The company intends to disclose without delay any impact on the implementation plan of the trial if an announcement is made.

February 2017

On **February 24, 2017**, the company announced a notice concerning the appointment of a representative director.

At a Board of Directors' meeting held on the same day, the company decided to formally propose the approval of the appointment of a new representative director at its ordinary general meeting of shareholders to be held on March 29, 2017, and at a Board of Directors' meeting to be held immediately following the shareholders meeting.

Change of positions

Name	New position	Current position
Kazuo Asakawa	Representative Director, Executive Vice President, COO, and Head of the Japan Business Unit	Corporate Officer, Executive Vice President, COO, and Head of the Japan Business Unit

January 2017

On **January 31, 2017**, the company announced the sales launch in Japan of the anti-cancer drug TREAKISYM® Intravenous Infusion 25 mg.

The company, through Eisai Co., Ltd. (Eisai), launched sales in Japan on January 31, 2017 of TREAKISYM® Intravenous Infusion 25 mg, a standard low-dose product (non-proprietary name: bendamustine hydrochloride) for the treatment of low-grade B-cell non-Hodgkin's lymphoma and mantle cell lymphoma, and chronic lymphocytic leukemia. Based on a license agreement between the company and Eisai, Eisai will be exclusively in charge of marketing the drug.

December 2016

On **December 19, 2016**, the company announced approval of the anti-cancer drug TREAKISYM® for the additional indication of first-line treatment of low-grade non-Hodgkin's lymphoma and mantle cell lymphoma.

SymBio obtained approval for the additional indication of first-line treatment of this disease after filing a new drug application on previously untreated patients in December 2015, based on the results of a domestic Phase 2 clinical trial and the outcome of an overseas Phase 3 clinical trial. The company made no changes to its forecast of FY12/16 earnings based on this approval for manufacturing and marketing of the drug.

On **December 9, 2016**, Shared Research updated the report following interviews with the company.

On **December 6, 2016**, the company announced that Onconova presented Phase 2 clinical trial data on oral rigosertib at the 2016 American Society of Hematology (ASH).

SymBio began handling the anticancer drug rigosertib in July 2011. Onconova Therapeutics, Inc., the drug's licensor, presented Phase 2 clinical trial data on oral rigosertib for patients with higher-risk myelodysplastic syndromes (MDS) at the 58th American Society of Hematology (ASH) Annual Meeting in San Diego, California. The meeting lasted from December 3 to 6.

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

The international joint Phase 3 clinical trial is currently underway for patients with relapsed or refractory higher-risk MDS. Onconova is also making efforts toward finalizing the design for a pivotal Phase 3 oral rigosertib/azacitidine combination trial for higher-risk MDS patients.

November 2016

On **November 10, 2016**, the Ministry of Health, Labour and Welfare announced it will host a meeting of the Drug Section Two of the Pharmaceutical Affairs and Food Sanitation Council on November 24, 2016. One topic at the meeting will be on setting the re-examination period and on whether to allow partial modifications to the approved manufacturing and marketing of drug products TREAKISYM® Intravenous Infusion 25 mg and 100 mg.

As was announced in December 2015, the company applied for approval of the anti-cancer drug TREAKISYM® for additional expected indications of mantle cell lymphoma and low-grade malignant non-Hodgkin's lymphoma for first-line treatment.

September 2016

On **September 28, 2016**, the company announced that anti-cancer drug TREAKISYM® Intravenous Infusion 100 mg received approval for manufacturing and marketing in Japan.

The company received approval to manufacture and market TREAKISYM® Intravenous Infusion 25 mg, a standard low-dose product of the anti-cancer drug TREAKISYM® (non-proprietary name: bendamustine hydrochloride) in Japan. It received approval to manufacture and market TREAKISYM® Intravenous Infusion 100 mg for the indication of recurrent/refractory low-grade malignant non-Hodgkin's lymphoma and mantle cell lymphoma in October 2010, which has been marketed through Eisai Co., Ltd. since December 2010. Also, the additional indication of chronic lymphocytic leukemia was granted in August 2016.

There are no changes in the earnings forecasts for FY12/16 based on this approval.

August 2016

On **August 26, 2016**, the company announced that it had obtained the approval for additional indications of anti-cancer drug Treakisym in chronic lymphocytic leukemia (CLL).

SymBio had applied for approval for the additional indication in response to a request from the Ministry of Health, Labour and Welfare for its development as one of the "unapproved or off-labeled drugs with high medical needs." The company had already received approval in October 2010 for manufacturing and marketing of Treakisym for the indication of relapsed or refractory low-grade non-Hodgkin's lymphoma (NHL) and mantle cell lymphoma (MCL). Treakisym, marketed by Eisai Co., Ltd. (Eisai) since

December 2010, has obtained about 60% market share for the indication of relapsed or refractory low-grade NHL and MCL, according to the company's estimation. The company expects Treakisym to be a new treatment option for many CLL patients.

The company also applied for approval for additional indications of Treakisym in first-line treatment for low-grade NHL and MCL in December 2015, and the application is currently being reviewed. Further, the company has completed phase II clinical trial for relapsed or refractory Diffuse large B-cell lymphoma (DLBCL, or aggressive NHL). The company looks to expand the indication of Treakisym and pursue the full range of its use, aiming to maximize the value of the product.

There are no changes in the earnings forecasts for FY12/16 based on this additional approval.

July 2016

On **July 11, 2016**, the company announced the achievement of a sales milestone in Taiwan for the anti-cancer drug bendamustine and the receipt of a milestone payment.

InnoPharmax has exclusive development and marketing rights for bendamustine in Taiwan, and sells bendamustine under the brand name Innomustine (Japanese brand name: Treakisym Injection). Since the launch of the product in 2012, total net sales have exceeded EUR2.4mn, which will result in a milestone payment from InnoPharmax to SymBio. In October 2011, the Taiwan Food and Drug Administration granted InnoPharmax manufacturing and marketing authorization for bendamustine for the indication of low-grade malignant non-Hodgkin's lymphoma and chronic lymphocytic leukemia. InnoPharmax has been selling the product in Taiwan since February 2012.

This will have no impact on SymBio's earnings forecast for FY12/16.

June 2016

On **June 13, 2016,** the company announced the start of phase III clinical trials for the patient-controlled analgesia, SyB P-1501.

The company started phase III clinical trials for SyB P-1501—a patient controlled analgesia for the short-term management of acute postoperative pain during hospitalization.

The company obtained exclusive development and commercialization rights for the drug in Japan from the Medicines Company in October 2015. The product, launched in the US, was approved by the US Food and Drug Administration (FDA) in April 2015, and also approved by the European Medicines Agency (EMA) in November 2015.

SymBio will proceed with phase III clinical trials, and hopes to obtain manufacturing and marketing approval for the drug in Japan in 2019.

April 2016

On **April 6, 2016**, the company announced the issue of a third series unsecured convertible bonds with subscription rights to new shares, and series 39 subscription rights to new shares by third-party allotment.

The company expects to receive total funds of about JPY3.9bn, net of expenses. The company plans to use the funds for expenses related to the development of new drug candidates between April 2016 and December 2018. As of April 6, 2016, SymBio was negotiating license agreements for several new drug candidates with client companies. The amount of funding required is based on costs to acquire rights to new drug candidates or to acquire companies with new drug candidates, as well as estimated developments costs, primarily those required to conduct clinical trials upon acquiring companies with new drug candidates or acquiring rights to new drug candidates.

Overview of the offering

Third series of unsecured convertible bonds with subscription rights to new shares

▷ Payment date: April 22, 2016

▷ Number of stock subscription rights:	40 units
▷ Issue price of bonds:	JPY75mn (JPY100 per JPY100 par value)
▷ Issue price of stock subscription rights:	Gratis
▷ Number of potential shares:	14,218,000
▷ Total funding amount:	JPY3.0bn
▷ Conversion price:	JPY211
▷ Subscription and allocation method:	Issued to Whiz Healthcare Japan 2.0 Investment Limited Partnership via third-party allotment.

Series 39 subscription rights to new shares

▷ Allotment date:	April 22, 2016
▷ Number of stock subscription rights:	104 units
▷ Issue price:	JPY10mn (JPY94,000 per unit)
▷ Number of potential shares:	4,472,000
▷ Total funding amount:	JPY953mn (JPY10mn from the issue of subscription rights to new shares; JPY944mn from the exercise of subscription rights)
▷ Exercise price:	JPY211
▷ Subscription and allocation method:	Issued to Whiz Healthcare Japan 2.0 Investment Limited Partnership via third-party allotment.

February 2016

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.

December 2015

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 of the 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.

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 azacitidine 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 azacitidine (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.

Major shareholders

Top Shareholders	Amount Held
Fuminori Yoshida	6.7%
Cephalon, Inc.	5.6%
SBI Securities Co., Ltd	4.1%
Japan Securities Finance Co., Ltd.	1.8%
Eisai Co., Ltd.	1.8%
Nomura Securities Co., Ltd.	1.5%
Waseda No. 1 Investment LLP	1.5%
Daiwa Securities Co., Ltd.	1.5%
Matsui Securities Co., Ltd.	1.4%
Rakuten Securities, Inc.	0.9%

Source: Shared Research based on company data.
As of December 31, 2016
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 77 employees as of December 31, 2016.

Other

Overview of clinical trials

Development of a new drug takes between 10 and 17 years

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

Ordinary process and periods of developing new drugs

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

Source: Shared Research based on company data.

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

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

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

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

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

Ethnic factors in the acceptability of foreign clinical data

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

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

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

Glossary

Antigen

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

Bridging Data

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

Chronic Lymphocytic Leukemia (CLL)

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

Contract Research Organization (CRO)

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

Dose-Responsiveness

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

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.

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

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