# 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.

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# Executive summary

## SymBio in-licenses drugs for development and sale

- SymBio Pharmaceuticals Ltd. is a specialty pharmaceutical company that buys the right to develop and commercialize drug candidates 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 rare diseases, the company typically seeks in-licensing opportunities for niche markets from pharmaceutical and biotech companies based in the US or EU.
- Notably, the company does not conduct basic research and outsources preclinical/clinical development, employing a fabless in-licensing approach. Using its proprietary in-house "search engine," the company identifies, assesses and in-licenses only quality drug candidates having proof-of-concept established in human subjects. The company first screens third-party drug candidates being tested in clinical trials, then presents the in-licensing opportunities to its Scientific Advisory Board for further assessment of the science behind each molecule, preclinical/clinical data, target market, and the feasibility of receiving marketing approval from Japanese regulatory authorities.
- According to the company, the typical development timeline of an oncology drug in Japan from preclinical studies to marketing approval is about 10 to 17 years. However, the company secured marketing approval for its first oncology drug under development in Japan, Treakisym®, in only four years after the first clinical trial was initiated, with product launch only two years after US marketing approval and around the same time that approval was granted in Europe. Within three years of its launch, Treakisym® captured more than 50% of the non-Hodgkin's lymphoma (NHL) and mantle cell lymphoma (MCL) market in Japan.
- As of February 2020, the company had obtained approval for and launched Treakisym® (anticancer agent for hematologic malignancies) for the indications of relapsed or refractory low-grade NHL and MCL, untreated (first-line treatment) and relapsed or refractory low-grade NHL and MCL, and chronic lymphocytic leukemia (CLL). Treakisym® is listed in the Practical Guidelines for Hematological Malignancies 2018 edited and published by Japanese Society of Hematology as the standard treatment for relapsed or refractory low-grade B-cell NHL, MCL, and CLL, and as a treatment option for untreated low-grade NHL.
- Drugs in the development pipeline include Treakisym® for the indication of relapsed or refractory diffuse large B-cell lymphoma (DLBCL), liquid formulations (RTD and RI products) of Treakisym®, rigosertib (anticancer agent for myelodysplastic syndromes) IV and oral formulations, and the antiviral drug brincidofovir.

## Earnings

- FY12/19 sales were JPY2.8bn (-26.0% YoY). Product sales totaled JPY2.8bn (-26.2% YoY) and royalty revenue totaled JPY26mn (JPY26mn in FY12/18). The operating loss totaled JPY4.3bn (loss of JPY2.7bn). The company also reported a recurring loss of JPY4.4bn (loss of JPY2.7bn). Net loss was JPY4.4bn (loss of JPY2.8bn).
- SymBio forecasts FY12/20 sales of JPY3.4bn (+20.0% YoY), an operating loss of JPY5.1bn (operating loss of JPY4.3bn in FY12/19), a recurring loss of JPY5.1bn (recurring loss of JPY4.4bn), and a net loss of JPY4.8bn (net loss of JPY4.4bn).
- In its medium-term plan, with the aims of achieving sales growth and higher profit margins, SymBio projects sales of JPY10.8bn and a net income of JPY1.7bn in FY12/22. The company expects higher sales from increased market penetration of Treakisym® for approved indications, as well as anticipated approval of additional indication of Treakisym® for relapsed or refractory diffuse large B-cell lymphoma (DLBCL). The company projects a significant increase in profit on higher sales as well as on higher GPM attributed to profit generated from the sale of Treakisym® following the shift to in-house sales of the product. The company has factored the cost of establishing and operating its own sales structure into its forecast, but Shared Research thinks the increase in GPM driven by the shift to in-house sales structure will easily offset the increase in costs. The company's own sales structure is specialized to the area of hematologic disorders, and will also handle the sale of rigosertib in addition to Treakisym®.

## 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) | FY12/10 Par. | FY12/11 Par. | FY12/12 Par. | FY12/13 Par. | FY12/14 Par. | FY12/15 Par. | FY12/16 Par. | FY12/17 Par. | FY12/18 Par. | FY12/19 Par. | FY12/20 Est. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Sales** | **1,450** | **1,883** | **1,955** | **1,532** | **1,955** | **1,933** | **2,368** | **3,444** | **3,836** | **2,838** | **3,404** |
| YoY | 21.7% | 29.8% | 3.9% | -21.6% | 27.6% | -1.1% | 22.5% | 45.4% | 11.4% | -26.0% | 20.0% |
| **Gross profit** | **1,212** | **658** | **593** | **318** | **527** | **583** | **904** | **1,031** | **1,173** | **865** | |
| YoY | 1.7% | -45.7% | -9.9% | -46.4% | 65.6% | 10.7% | 55.1% | 14.1% | 13.7% | -26.3% | |
| GPM | 83.6% | 35.0% | 30.3% | 20.8% | 26.9% | 30.2% | 38.2% | 29.9% | 30.6% | 30.5% | |
| **Operating profit** | **-613** | **-2,067** | **-1,700** | **-1,681** | **-1,303** | **-2,552** | **-2,127** | **-3,947** | **-2,656** | **-4,302** | **-5,090** |
| YoY | - | - | - | - | - | - | - | - | - | - | - |
| OPM | - | - | - | - | - | - | - | - | - | - | - |
| **Recurring profit** | **-638** | **-2,095** | **-1,729** | **-1,601** | **-1,110** | **-2,630** | **-2,317** | **-3,977** | **-2,749** | **-4,377** | **-5,134** |
| YoY | - | - | - | - | - | - | - | - | - | - | - |
| RPM | - | - | - | - | - | - | - | - | - | - | - |
| **Net income** | **-642** | **-2,105** | **-1,733** | **-1,605** | **-1,116** | **-2,632** | **-2,313** | **-3,978** | **-2,753** | **-4,376** | **-4,803** |
| YoY | - | - | - | - | - | - | - | - | - | - | - |
| Net margin | - | - | - | - | - | - | - | - | - | - | - |
| **Per share data (JPY)** | | | | | | | | | | | |
| Shares issued (year-end; '000) | 112 | 19,131 | 19,131 | 30,634 | 30,634 | 32,391 | 46,531 | 54,049 | 20,560 | 26,438 | |
| EPS | -59.3 | -143.6 | -90.6 | -69.3 | -36.3 | -81.3 | -58.8 | -79.8 | -165.5 | -189.0 | -181.8 |
| EPS (fully diluted) | - | - | - | - | - | - | - | - | - | - | |
| Dividend per share | - | - | - | - | - | - | - | - | - | - | - |
| Book value per share | 365.4 | 345.3 | 254.7 | 239.5 | 208.8 | 127.6 | 108.6 | 50.0 | 212.2 | 143.1 | |
| **Balance sheet (JPYmn)** | | | | | | | | | | | |
| Cash and cash equivalents | 4,016 | 6,511 | 4,840 | 7,264 | 6,591 | 4,261 | 5,719 | 2,947 | 4,821 | 3,911 | |
| **Total current assets** | **4,213** | **7,178** | **5,421** | **7,634** | **7,290** | **4,827** | **6,685** | **4,037** | **6,038** | **4,887** | |
| Tangible fixed assets | 22 | 17 | 14 | 9 | 49 | 53 | 75 | 47 | 57 | 75 | |
| Investments and other assets | 27 | 48 | 57 | 37 | 49 | 53 | 77 | 100 | 73 | 70 | |
| Intangible fixed assets | 1 | 13 | 11 | 8 | 66 | 52 | 42 | 69 | 71 | 241 | |
| **Total assets** | **4,263** | **7,256** | **5,502** | **7,687** | **7,454** | **4,984** | **6,878** | **4,252** | **6,239** | **5,274** | |
| Accounts payable | 1 | 309 | 330 | - | 306 | 320 | 322 | 604 | 726 | 121 | |
| Short-term debt | - | - | - | - | - | - | - | - | - | - | |
| **Total current liabilities** | **178** | **646** | **599** | **251** | **488** | **551** | **942** | **1,011** | **1,336** | **872** | |
| Long-term debt | - | - | - | - | - | - | - | - | - | - | |
| **Total fixed liabilities** | **2** | **5** | **4** | **3** | **2** | **2** | **451** | **1** | **1** | **2** | |
| **Total liabilities** | **180** | **651** | **602** | **254** | **490** | **552** | **1,394** | **1,013** | **1,338** | **874** | |
| **Net assets** | **4,083** | **6,606** | **4,900** | **7,433** | **6,964** | **4,432** | **5,485** | **3,239** | **4,902** | **4,400** | |
| Total interest-bearing debt | - | - | - | - | - | - | - | - | - | - | |
| **Statement of cash flows (JPYmn)** | | | | | | | | | | | |
| Cash flows from operating activities | -754 | -2,074 | -1,659 | -1,677 | -1,266 | -2,272 | -1,960 | -3,817 | -2,325 | -4,351 | |
| Cash flows from investing activities | -116 | -117 | -411 | -1,332 | 314 | 1,489 | -44 | -78 | -26 | -216 | |
| Cash flows from financing activities | 663 | 4,611 | -1 | 4,057 | 544 | -3 | 3,658 | 1,164 | 4,272 | 3,740 | |
| **Financial ratios** | | | | | | | | | | | |
| ROA (RP-based) | -15.1% | -36.5% | -27.2% | -24.3% | -14.7% | -42.3% | -39.0% | -71.5% | -52.5% | -76.0% | |
| ROE | -15.8% | -39.4% | -30.2% | -26.3% | -15.8% | -48.3% | -50.4% | -102.6% | -77.8% | -107.4% | |
| Equity ratio | 95.8% | 91.0% | 89.1% | 96.7% | 93.4% | 88.9% | 79.7% | 76.2% | 78.6% | 83.4% | |

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

# Recent updates

## Highlights

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

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

The primary endpoint of the trial was overall survival, comparing IV rigosertib plus best supportive care to PC plus best supportive care. Onconova also analyzed a pre-specified subgroup of very high risk (VHR-MDS) patients.

Results of INSPIRE demonstrated that in the intent-to-treat analysis patients given IV rigosertib achieved overall survival of 6.4 months, versus 6.3 months for PC (p=0.33) in the overall HR-MDS population. There was also no significant difference in overall survival between the two study arms in the VHR-MDS subgroup. Onconova is conducting further analysis.

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

On **August 5, 2020**, the company announced earnings results for 1H FY12/20; see the results section for details.

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

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

### Summary of arbitration judgment

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

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

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

On June 29, 2020, Chugai Pharmaceutical Co., Ltd. filed for approval for a combination of polatuzumab vedotin-piiq with bendamustine and rituximab (BR therapy) for the treatment of r/r DLBCL, based on clinical trials in Japan and overseas.

Prior to this application, in May 2020, SanBio filed a partial change application for the use of BR therapy in r/r DLBCL based on favorable results from its phase III trial, in which the overall response rate (the primary endpoint) exceeded expectations. As of July 2020, the Pharmaceuticals and Medical Devices Agency (PMDA) was reviewing the application.

Once the applications from SanBio and Chugai Pharmaceutical are approved, and polatuzumab vedotin-piiq is listed on the National Health Insurance (NHI) drug price list, it will be possible to use Treakisym® in combination with polatuzumab vedotin-piiq in BR therapy.

On **June 16, 2020**, Shared Research updated the report following interviews with the company.

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

# Trends and outlook

## Quarterly trends and results

| Cumulative | FY12/19 | | | | FY12/20 | | | | FY12/20 | |
|---|---|---|---|---|---|---|---|---|---|---|
| (JPYmn) | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | % of Est. | FY Est. |
| Sales | 1,611 | 2,005 | 2,008 | 2,838 | 551 | 1,361 | | | 40.0% | 3,404 |
| YoY | 81.4% | 4.0% | -33.8% | -26.0% | -65.8% | -32.1% | | | | 20.0% |
| Gross profit | 609 | 529 | 563 | 865 | 128 | 330 | | | | |
| YoY | 144.0% | -7.7% | -39.1% | -26.3% | -79.0% | -37.7% | | | | |
| GPM | 37.8% | 26.4% | 28.0% | 30.5% | 23.2% | 24.2% | | | | |
| SG&A expenses | 1,205 | 2,545 | 4,099 | 5,166 | 1,090 | 2,170 | | | | |
| YoY | 25.0% | 34.1% | 44.8% | 34.9% | -9.6% | -14.7% | | | | |
| SG&A ratio | 74.8% | 126.9% | 204.1% | 182.1% | 197.6% | 159.5% | | | | |
| Operating profit | -596 | -2,015 | -3,536 | -4,302 | -962 | -1,840 | | | - | -5,090 |
| YoY | - | - | - | - | - | - | | | | - |
| OPM | - | - | - | - | - | - | | | | - |
| Recurring profit | -616 | -2,069 | -3,642 | -4,377 | -991 | -1,883 | | | - | -5,134 |
| YoY | - | - | - | - | - | - | | | | - |
| RPM | - | - | - | - | - | - | | | | - |
| Net income | -617 | -2,070 | -3,641 | -4,376 | -992 | -1,885 | | | - | -4,803 |
| YoY | - | - | - | - | - | - | | | | - |
| Net margin | - | - | - | - | - | - | | | | - |

| Quarterly | FY12/19 | | | | FY12/20 | | | |
|---|---|---|---|---|---|---|---|---|
| (JPYmn) | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 |
| Sales | 1,611 | 394 | 3 | 830 | 551 | 809 | | |
| YoY | 81.4% | -62.2% | -99.7% | 3.3% | -65.8% | 105.7% | | |
| Gross profit | 609 | -79 | 33 | 302 | 128 | 202 | | |
| YoY | 144.0% | - | -90.5% | 21.4% | -79.0% | - | | |
| GPM | 37.8% | - | - | 36.4% | 23.2% | 25.0% | | |
| SG&A expenses | 1,205 | 1,340 | 1,555 | 1,067 | 1,090 | 1,080 | | |
| YoY | 25.0% | 43.4% | 66.5% | 7.0% | -9.6% | -19.4% | | |
| SG&A ratio | 74.8% | 340.4% | - | 128.6% | 197.6% | 133.5% | | |
| Operating profit | -596 | -1,419 | -1,521 | -765 | -962 | -878 | | |
| YoY | - | - | - | - | - | - | | |
| OPM | - | - | - | - | - | - | | |
| Recurring profit | -616 | -1,453 | -1,573 | -735 | -991 | -892 | | |
| YoY | - | - | - | - | - | - | | |
| RPM | - | - | - | - | - | - | | |
| Net income | -617 | -1,453 | -1,571 | -736 | -992 | -893 | | |
| YoY | - | - | - | - | - | - | | |
| Net margin | - | - | - | - | - | - | | |

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

### Breakdown of SG&A expenses

| Cumulative | FY12/19 | | | | FY12/20 | | | |
|---|---|---|---|---|---|---|---|---|
| (JPYmn) | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 |
| SG&A expenses | 1,205 | 2,545 | 4,099 | 5,166 | 1,090 | 2,170 | | |
| YoY | 25.0% | 34.1% | 44.8% | 34.9% | -9.6% | -14.7% | | |
| R&D expenses | 472 | 963 | 1,972 | 2,442 | 438 | 834 | | |
| YoY | 13.4% | 14.8% | 52.5% | 33.2% | -7.1% | -13.4% | | |
| SG&A expenses excl. R&D | 733 | 1,582 | 2,127 | 2,725 | 651 | 1,336 | | |
| YoY | 33.8% | 49.3% | 38.3% | 36.5% | -11.1% | -15.5% | | |

| Quarterly | FY12/19 | | | | FY12/20 | | | |
|---|---|---|---|---|---|---|---|---|
| (JPYmn) | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 |
| SG&A expenses | 1,205 | 1,340 | 1,555 | 1,067 | 1,090 | 1,080 | | |
| YoY | 25.0% | 43.4% | 66.5% | 7.0% | -9.6% | -19.4% | | |
| R&D expenses | 472 | 491 | 1,009 | 470 | 438 | 396 | | |
| YoY | 13.4% | 16.2% | 122.1% | -13.0% | -7.1% | -19.4% | | |
| SG&A expenses excl. R&D | 733 | 849 | 546 | 597 | 651 | 685 | | |
| YoY | 33.8% | 66.0% | 13.8% | 30.6% | -11.1% | -19.3% | | |

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

## 1H FY12/20 results

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

Sales fell YoY. The company booked sales of Treakisym®.

SG&A expenses fell 14.7% YoY to JPY2.2bn and R&D expenses declined 13.4% YoY to JPY834mn. This included expenses for conducting clinical trials of intravenous and oral formulations of Treakisym® and rigosertib. Excluding R&D expenses, SG&A expenses fell by 15.5% YoY to JPY1.3bn. The company incurred development costs for its in-house sales organization.

**Domestic**

Preparations for in-house sales organization begin

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

In Q2, the company completed setting up its nationwide internal sales organization as planned, hiring and training additional Treakisym® sales representatives and regional sales managers who will form the core of its nationwide in-house marketing network. In addition, SymBio continued building its distribution and logistics capabilities with logistics centers in East and West Japan and in-house infrastructure including a new IT system with ERP, which is also now in the final stages.

Substandard products

SymBio imports lyophilized Treakisym® for injection from Astellas Deutschland (consolidated subsidiary of Astellas Pharma). Some batches of Treakisym® 100mg vials imported from Astellas Deutschland for domestic sales in FY12/19 had impurities and appearance defects in a significantly higher percentage than stipulated in the supply agreement. In order to prevent a recurrence of such product quality issues, the company objected to Astellas Deutschland, and demanded steps such as corrective and preventive action (CAPA) processes to fulfil its responsibilities as the supplier. Nonetheless, there was no improvement in 1H, with persistent supply issues. Several batches from Astellas Deutschland had high defect ratios and deliveries were irregular. Q2 sales fell YoY as Treakisym® inventory levels were low compared with Q2 FY12/19.

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

Treakisym® (SyB L-0501[lyophilized injection]/SyB L-1701 [RTD]/SyB L-1702 [RI]/SyB C-0501 [oral]; anticancer agent; generic name: bendamustine hydrochloride)

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

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

Also, SymBio obtained approval for the partial revision to the marketing authorization of Treakisym® in July 2018. Treakisym® can now be used in combination with new anti-CD20 antibodies and not just rituximab for the treatment of CD20-positive follicular

lymphoma, the most common histological type of low-grade NHL. This allows the company to provide patients a new treatment option: combination therapy with obinutuzumab (launched in August 2018). In March 2019, SymBio obtained approval for the partial revision to its application to use Treakisym® as a pretreatment agent in tumor-specific T cell infusion therapy. This allows Treakisym® to be used as a pretreatment agent for Kymriah® intravenous infusion, which was the first chimeric antigen receptor T-cell (CAR-T) therapy approved in Japan and on the NHI drug price list from May 2019.

Following on from the above approved indications, the company conducted a phase III clinical study for the fourth indication of relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL), with Treakisym® administered in combination with rituximab (BR therapy). The response rate (primary endpoint) in the test results released in November 2019 was better than expected. In May 2020, the company applied for a partial revision to manufacture and marketing approval. After Chugai Pharmaceutical Co., Ltd. applied for manufacture and marketing approval of polatuzumab vedotin-piiq in combination with BR therapy to treat r/r DLBCL in June 2020, the company made a partial change to its application for approval of Treakisym® in combination with polatuzumab vedotin-piiq and rituximab therapy. If the new drug applications by Chugai and SymBio are approved and polatuzumab vedotin-piiq is added to the NHI drug price list, Treakisym® can be used with polatuzumab vedotin-piiq in combination with BR therapy. At present there are no effective treatments for the additional indication of r/r DLBCL, which is usually treated by a combination of anticancer agents as salvage chemotherapy. An effective new drug with few side effects is sought, however, because salvage chemotherapy produces severe adverse effects. Since BR therapy is already being used in the West to treat r/r DLBCL, patient organizations and related academic societies have petitioned MHLW so that it can be used in Japan as soon as possible.

The company concluded an exclusive licensing agreement in Japan with Eagle Pharmaceuticals (based in New Jersey, US) in September 2017 for the RTD and RI formulations of Treakisym®. The company filed for approval of the RTD formulation in September 2019, and plans to launch it in Q1 FY12/21. SymBio launched clinical trials for the RI formulation in November 2018 primarily to confirm safety and completed patient enrollment in March 2020. The company will apply for approval without delay after the end of the clinical trials of the RI formulation and aims to begin sales in 2H FY12/22. The RI formulation can be administered in just 10 minutes versus 60 minutes for the current lyophilized injection and RTD formulation. This reduces the burden on patients and healthcare professionals, providing significant value added. Multiple patent protections in the form of a liquid product license will enable the extension of the product life of Treakisym® to 2031.

Rigosertib Sodium (SyB L-1101 [IV]/SyB C-1101 [oral]; anticancer agent; generic name: Rigosertib Sodium)
Onconova Therapeutics, Inc., the licensor, is currently conducting a global phase III trial (INSPIRE trial), with SymBio performing the Japan trial. The global phase III trial addresses higher-risk myelodysplastic syndromes (higher-risk MDS), which do not respond to the current standard treatment with hypomethylating agents, which relapse after treatment under the current standard of care, or which are intolerant to hypomethylating agents, and is under way at clinical trial sites in more than 20 countries worldwide. Onconova announced that it had reached its target of enrolling 360 patients worldwide as of March 2020 and achieved the required number of survival events in July 2020. Onconova said the primary endpoint results would become clear in Q3 2020, and that it planned to announce trial results at an academic conference by the end of the year. Based on these trial results, the company plans to apply for approval in Japan at the same time as in the US and Europe.

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

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

After concluding the exclusive global license agreement, SymBio held discussions with Japanese and overseas infectious disease experts to examine the scientific and medical validity of BCV and progress its feasibility study. The company concluded that it would prioritize global development of BCV IV (mainly in Japan, the US, and Europe) to treat adenovirus (AdV) infections in patients receiving hematopoietic stem cell transplantation to address an unmet medical need. Based on safety and efficacy data acquired from its study, the company plans to extend its target disease area to multivirus infections in patients receiving hematopoietic stem cell transplantation. By exploring the potential for expanding target disease areas to organ transplants (including kidney transplants) to grow the market for, and maximize the business value of BCV, the company aims to transform itself into a global specialty pharmaceutical company with an integrated structure to supply quality pharmaceutical products. Clinical trials by Chimerix have demonstrated superior, broad-spectrum antivirus activity of BCV Oral against dsDNA viruses, raising expectations for its potential as a safe and effective therapy to prevent and treat a range of viral infections in patients receiving hematopoietic stem cell transplantation.

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

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

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

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

## Full-year company forecasts

| | FY12/19 | | | FY12/20 | | |
|---|---|---|---|---|---|---|
| (JPYmn) | 1H Act. | 2H Act. | FY Act. | 1H Act. | 2H Est. | FY Est. |
| Sales | 2,005 | 833 | 2,838 | 1,361 | 2,043 | 3,404 |
| Gross profit | 529 | 335 | 865 | 330 | 816 | 1,146 |
| GPM | 26.4% | 40.3% | 30.5% | 24.2% | 39.9% | 33.7% |
| SG&A expenses | 2,545 | 2,622 | 5,166 | 2,170 | 4,066 | 6,236 |
| SG&A ratio | 126.9% | 314.8% | 182.1% | 159.5% | 199.0% | 183.2% |
| Operating profit | -2,015 | -2,287 | -4,302 | -1,840 | -3,250 | -5,090 |
| OPM | - | - | - | - | - | - |
| Recurring profit | -2,069 | -2,307 | -4,377 | -1,883 | -3,251 | -5,134 |
| RPM | - | - | - | - | - | - |
| Net income | -2,070 | -2,306 | -4,376 | -1,885 | -2,918 | -4,803 |
| Net margin | - | - | - | - | - | - |

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

## Earnings outlook

- ▷ Sales: JPY3.4bn (+20.0% YoY)
- ▷ Operating loss: JPY5.1bn (loss of JPY4.3bn in FY12/19)
- ▷ Recurring loss: JPY5.1bn (loss of JPY4.4bn in FY12/19)
- ▷ Net loss: JPY4.8bn (loss of JPY4.4bn in FY12/19)

SymBio expects sales growth primarily on rising domestic product sales for Treakisym® Sales of Treakisym® should recover after the postponement of shipments in FY12/19. That said, sales are expected to fall below the FY12/18 level as Eisai shrinks its inventories.

- ▷ Recovery of Treakisym® following postponed shipments: In FY12/19, lyophilized injection formulations of Treakisym® imported from Astellas Deutschland GmbH, a consolidated subsidiary of Astellas Pharma, were found to contain impurities and appearance defects. Consequently, shipments of Treakisym® 100mg to Japan distributor Eisai were delayed and the booking of some product sales was postponed until FY12/20. Once the shipment system is restored, sales should benefit from the postponed amount.
- ▷ Lower sales due to shrinkage of Eisai inventories: From FY12/21 SymBio will conduct sales of Treakisym® in-house rather than entrusting them to Eisai. With this, the company will be shipping Treakisym® to pharmaceutical wholesalers instead of to Eisai. Therefore, Eisai needs to shrink inventories by end-2020 to accommodate this change. SymBio plans to end shipments to Eisai from the end of 1H even though NHI price-based sales of Treakisym® remain firm reflecting market demand; this is why the company expects FY12/20 Treakisym® sales to decline (compared to the FY12/18 level).

The company estimates gross profits will increase 32.5% YoY to JPY1.1bn while the GPM rises 3.2pp to 33.7%. The higher GPM is attributable to an improved product mix and cost reductions.

- ▷ The weighting of domestic sales of Treakisym®, which has a relatively high gross margin, declined in the previous fiscal year, but is projected to increase in FY12/20, thus lifting the overall GPM.
- ▷ SymBio also incurred costs as a result of impurities and appearance defects in Treakisym® 100mg injection formulations, but these costs are expected to diminish in FY12/20.

The company forecasts SG&A expenses of JPY6.2bn (+20.7% YoY).

- ▷ SymBio plans R&D expenses of JPY2.7bn (+9.7% YoY) to continue developing Treakisym® for relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL) and liquid formulations of Treakisym® (RTD and RI formulations), oral and intravenous rigosertib products, and new drug brincidofovir, an antiviral drug to treat infections. An upfront fee (JPY540mn) incurred in

FY12/19 for the in-licensing of antiviral drug brincidofovir will not be repeated while the expected Q4 FY12/20 approval of Treakisym® RTD formulation will incur a milestone payment.

▷ The company forecasts SG&A expenses excluding R&D at JPY3.6bn (+30.5% YoY). Personnel expenses and sales promotion expenses are expected to increase; In particular, personnel expenses are slated to increase as SymBio looks to expand the workforce from 106 (FY12/19) to 152 employees. The number of sales representatives will increase from 39 to 70. Eisai's exclusive marketing rights to Treakisym® ends in 2020 and SymBio will take over marketing from 2021. The company aims to build up the nationwide sales force with 62 sales representatives by Q2 and is also considering using about 30 of the 62 sales representatives for joint marketing activities with co-promotion partners (in collaboration with sales representatives of pharmaceutical companies).

Consequently, profits below the operating level are expected to decline YoY.

The main pipeline development plans are as follows.

### Treakisym®

▷ For r/r DLBCL, the company plans to continue preparations to apply for drug approval

▷ SymBio is preparing to begin sales of the RTD formulation (which has been approved) in Q1 FY12/21 and progressing with clinical trials of the RI formulation mainly to confirm safety for Treakisym® in-licensed from Eagle Pharmaceuticals

### Oral and intravenous rigosertib products

▷ SymBio is continuing to develop intravenous rigosertib formulation, and is enrolling patients in Japan as part of global phase III clinical trials

▷ For oral rigosertib, SymBio is preparing for participation in global phase III trials of rigosertib azacitidine combination therapy that Onconova Therapeutics is planning

# Long-term outlook

## Medium-term plan (FY12/20–FY12/22)

SymBio announced a three-year medium-term plan for FY12/20 through FY12/22 along with the FY12/19 results announcement. The company reduced the Treakisym® sales target compared to the previous medium-term plan after reassessing market share assumptions and accordingly revised down operating and recurring profit estimates. In contrast, the company revised up net income estimates to reflect tax effect accounting.

The main goals of the medium-term plan are to build an in-house sales structure, grow sales of Treakisym® from already approved indications, expand indications for Treakisym®, and extend the product lifecycle for Treakisym®. The two main changes in the medium-term plan were a reduction in the end-2020 Treakisym® market share assumption for first-line treatment of low-grade non-Hodgkin's lymphoma from 70% to 64% and a more accelerated pace of market penetration for Treakisym® liquid formulations.

- Build in-house sales structure: The business alliance agreement with Eisai expires in December 2020, and the company has been making preparations to sell Treakisym® in-house from the start of 2021, after the agreement expires. To prepare for the start of in-house sales and the later launch of rigosertib IV formulation, SymBio plans to increase the number of medical representatives as necessary, build a sales and marketing organization specializing in the area of blood cancers, and set up a sophisticated and dedicated training system by 1H FY12/20.
- Grow sales of Treakisym® from already approved indications: The company seeks to increase market share to 64% by the end of FY12/20 by further promoting penetration in first-line treatment of low-grade non- Hodgkin's lymphoma.
- Expand indications for Treakisym®: SymBio aims to complete the phase III clinical trial for the indication of relapsed or refractory diffuse large B-cell lymphoma, with the aim of filing a new drug application in Q2 FY12/20 and launching in Q3 FY12/21.
- Extend the product lifecycle for Treakisym®: The company looks to launch the RTD formulation in Q1 FY12/21 and the RI formulation in 1H FY12/22, proceeding 95% of the way toward a switch from the current lyophilized powder formulation to a liquid formulation by the end of 2021 and 100% by the beginning of 2022.

## Targets in medium-term plan (FY12/20–FY12/22)

Under the action plan outlined above, SymBio seeks to achieve profitability in FY12/21 and realize sustainable profit growth thereafter, with the following as earnings objectives. The company expects higher sales from increased market penetration of Treakisym® for approved indications and anticipated approval of additional indication of Treakisym® for relapsed or refractory diffuse large B-cell lymphoma (DLBCL). The company projects a significant increase in profit on higher sales as well as on higher GPM attributed to profit generated from the sale of Treakisym® following the shift to in-house sales of the product. The company has factored the cost of establishing and operating its own sales structure into its forecast, but Shared Research thinks the increase in GPM driven by the shift to in-house sales structure will easily offset the increase in costs. The company's own sales structure is specialized to the area of hematologic disorders, and will also handle the sale of rigosertib in addition to Treakisym®.

**Medium-term plan**

| (JPYmn) | FY12/19 Act. | FY12/20 Est. | FY12/21 MTP | FY12/22 MTP |
|---|---|---|---|---|
| Sales | 2,811 | 3,404 | 9,008 | 10,816 |
| Operating profit (loss) | -4,302 | -5,090 | 1,031 | 1,482 |
| Recurring profit (loss) | -4,377 | -5,134 | 987 | 1,438 |
| Net income (loss) | -4,376 | -4,803 | 1,356 | 1,717 |

Source: Shared Research based on company data.

### Medium-term plan sales target

SymBio expects product sales of Treakisym® to account for the bulk of sales. Product sales targets reflect the recent pace of market penetration and sales trends, which feed into the company's revised sales growth rates calculated over the medium-term plan period. As of February 2020, sales are booked based on product shipment sales to the sales distributor, Eisai. From FY12/21 onward, sales will be booked on product shipment sales to pharmaceutical wholesalers from the company's own in-house sales organization.

In estimating sales in FY12/21 and FY12/22, SymBio disclosed targets assuming increased product sales of Treakisym® as it expects to gain approval of the drug as a treatment for relapsed or refractory diffuse large B-cell lymphoma (DLBCL) in Q2 FY12/21.

### Greater market penetration in first-line treatment of low-grade non-Hodgkin's lymphoma

In December 2016, Treakisym® was approved in Japan for the additional indication of first-line treatment of low-grade non-Hodgkin's lymphoma (NHL), and in Q3 FY12/18 Treakisym® accounted for 56% of drugs used for the first-line treatment of low-grade NHL. On an NHI drug reimbursement price basis, Treakisym® sales have increased from JPY4.8bn in FY12/16 to JPY8.5bn in FY12/18. According to SymBio, the indication of first-line treatment of low-grade NHL has accounted for most of that JPY3.7bn increase.

SymBio aims to further promote uptake of Treakisym® as first-line treatment of low-grade non-Hodgkin's lymphoma, with a view to raising market share to 64% as of end-FY12/20. The following factors are seen contributing to market share expansion.

- ▷ 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 mantle cell lymphoma (MCL) in Japan prior to December 2016. In July 2018, Treakisym® was newly included as a standard treatment option for low-grade NHL and MCL in the Guidelines for Tumors of Hematopoietic and Lymphoid Tissues 2018 issued by the Japan Society of Hematology.
- ▷ 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 NHL. These findings were presented at the American Society of Hematology Annual Meeting in December 2012 (see the Business section).
- ▷ SymBio plans to increase the number of Treakisym® product managers from 10 in FY12/18 to 20 in FY12/19, and 62 in Q2 FY12/20, in doing so contributing to further market penetration for Treakisym®.

### Transition to in-house sales structure

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

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

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

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

As reference for the anticipated impact of adding the indication of r/r DLBCL, the company estimates that the number of patients being treated for relapsed or refractory low-grade NHL and MCL in Japan is 9,336 and the number of patients with untreated low-grade NHL and MCL is 6,967, for a total of 16,303. For these indications, SymBio targets FY12/19 sales of JPY10.1bn on an NHI drug price basis. By comparison, the company estimates that the number of Japanese patients with r/r DLBCL is 18,672.

**Gross profit under medium-term plan**

Based on historical performance, Shared Research estimates a gross profit margin of about 30% for Treakisym® shipments to Eisai. As outlined earlier, from FY12/21 SymBio will conduct sales of Treakisym® in-house rather than entrusting them to Eisai. With this, the company will be shipping Treakisym® to pharmaceutical wholesalers instead of to Eisai. The gross profit earned thus far will remain, but will be augmented by the gross profit that hitherto had gone Eisai's way (difference between the procurement price paid by Eisai and the price on shipments from Eisai to wholesalers). Shared Research believes that the transition to in-house sales will lift SymBio's gross profit margin to 60–70%.

Shared Research also sees potential for SymBio to further boost the gross profit margin by procuring Treakisym® from a different source. The company procures Treakisym® in lyophilized powder form from Astellas Deutschland GmbH, but procures the RTD and RI formulations from Eagle Pharmaceuticals. SymBio looks to launch the RTD formulation in Q1 FY12/21 and the RI formulation in 1H FY12/22, proceeding 90% of the way toward a switch from the current lyophilized powder formulation to a liquid formulation by the end of 2021 and 100% by the end of 2022.

**SG&A expenses under the medium-term plan**

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

- The company calculated R&D expenses based on the latest development plans for its existing pipeline comprising Treakisym®, rigosertib IV and oral formulations, and brincidofovir, an antiviral drug for the treatment of infections.
- The company has not factored in upfront payments for in-licensing drug candidates outside its existing pipeline after brincidofovir, an antiviral drug for the treatment of infections, although it will continue to evaluate and investigate them.

R&D expenses

- For FY12/20, the company forecasts R&D spending will increase 9.7% YoY to JPY2.7bn centered on Treakisym® for treatment of relapsed and refractory diffuse large B-cell lymphoma (r/r DLBCL), Treakisym® liquid formulations (RTD and RI), intravenous and oral formulations of rigosertib, and development of new antiviral agent brincidofovir. The upfront licensing fee (JPY540mn) paid in FY12/19 for in-licensing antiviral agent brincidofovir will not be repeated, but it expects to make a milestone payment in Q4 FY12/20 in line with approval of Treakisym® RTD.
- In FY12/21, the R&D budget is expected to decline YoY while the milestone payment for Treakisym® RTD should diminish. In FY12/22, R&D spending is expected to increase YoY due to some one-time costs.

Other SG&A expenses

Other SG&A expenses comprise primarily Treakisym® sales and marketing, production and distribution, business development, d management related costs. SymBio is factoring in costs associated with building and operating its own sales organization from FY12/20 onward ahead of the move to sell Treakisym® in-house from FY12/21. It forecasts an increase primarily in personnel costs due to a higher medical representative headcount and higher costs due to more activities.

- In FY12/20, other SG&A expenses, excluding R&D spending, are projected to increase 30.5% YoY to JPY3.6bn on higher personnel expenses and sales promotion expenses. The company aims to expand its workforce from 106 to 152 employees, so personnel expenses are expected to rise. SymBio plans to increase the number of sales representatives from 39 to 70. Eisai's marketing agreement for exclusive distribution rights to Treakisym® ends in 2020 and SymBio will take over marketing from 2021. Management looks to build a nationwide marketing force of 62 sales representatives by Q2 FY12/20 and is considering

joint marketing activities with co-promotion partners (collaborating with sales representatives from pharmaceutical companies) for about 30 of the 62 sales representatives.

▷ It looks like the company will maintain other SG&A expenses at FY12/20 levels from FY12/21 onward. Large changes to the in-house sales force are not expected after it is expanded to 62 sales representatives in Q2.

### Net income

The company forecasts net income exceeding recurring profit in FY12/21 and FY20/22 to reflect the reduction of loss carried over from the previous fiscal year from FY12/21 (when it is expected to turn profitable) onward on tax effect accounting.

# 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 rare diseases—and smaller patient populations. Larger pharmaceutical companies may be reluctant to develop drugs in niche markets due to limited sales potential—SymBio sees an opportunity to avoid intense competition in the marketplace by focusing on the development of orphan or 'orphan-like' drugs.
- **Global expansion 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..."

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

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

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

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

### Treakisym® (FD)

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

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

As of February 2020, phase III clinical trials for the fourth indication of relapsed or refractory diffuse large B-cell lymphoma (DLBCL) were under way. In November 2019, the trial confirmed a positive overall response rate (the primary endpoint of the study) exceeding expectations and the company is currently preparing for an approval filing in 1H FY12/20.

### Treakisym® (RTD and RI)

In September 2017, Eagle Pharmaceuticals and SymBio concluded a license agreement that licenses to SymBio rights to develop, market, and sell Eagle's bendamustine hydrochloride ready-to-dilute (RTD) and rapid infusion (RI) products in Japan. Securing products to replace existing freeze-dried (FD) product (whose exclusive sales rights in Japan expire in 2H 2020) had been a priority for the company. SymBio looks to gain approval for the RTD formulation in Q4 FY12/20 and win approval for and launch the RI formulation in FY12/22. With this, it aims to promote a switch in clinical settings from the current lyophilized powder formulation to RTD and RI formulations that lighten the workload for medical professionals, at the same time curtailing uptake of Treakisym® generics (filing for approval of generics will be possible from 2H 2020, although Shared Research believes that even if generics launch it will not be until around 2022). Because it has the exclusive rights to sell the RTD and RI formulations in Japan, SymBio will be able to extend the Treakisym®'s product lifecycle until 2031.

### Rigosertib

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

In February 2014, Onconova completed phase III clinical trials 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) in more than 20 countries. Within Japan, the company has been conducting joint global phase III clinical trials in cooperation with Onconova. On the basis of results of an interim analysis performed in January 2018, Onconova decided to continue with the trial with a larger patient population based on pre-planned statistical criteria. Based on these results, the company plans to apply for approval in Japan at the same time as in the US and Europe.

For the oral form of the drug, SymBio initiated the phase I clinical trial for higher-risk MDS in Japan to evaluate safety from June 2017 and completed enrollments in June 2019. The company plans to begin a clinical trial in combination with azacitidine after confirming safety in the phase I clinical trials, and participate in global phase III trials of rigosertib azacitidine combination therapy targeting first-line treatment of higher-risk MDS that Onconova plans to launch.

### Brincidofovir

Brincidofovir is an antiviral drug formed by conjugating a lipid chain (hexadecyloxypropyl, or HDP) of specified length to cidofovir (an antiviral drug already approved and marketed in the EU and the US, but not approved in Japan). It has a novel

mechanism of action, which is attributed to its being a lipid conjugate, and can be taken up into cells with enhanced efficiency compared to cidofovir (i.e., brincidofovir has higher cell membrane permeability). Once inside a cell, brincidofovir transforms into a direct-acting agent and inhibits viral replication, demonstrating high antiviral effect. It is also easy to use as it has a low risk of nephrotoxicity, which is a side effect of cidofovir, hence making brincidofovir a novel, highly active anti-multiviral drug. It is expected to become an effective treatment for a wide spectrum of infectious diseases caused by DNA viruses, including cytomegalovirus (CMV) and other herpes viruses, adenoviruses, BK virus, papillomaviruses, and smallpox virus.

In September 2019, SymBio entered an exclusive global license agreement with Chimerix Inc. for brincidofovir. As a result, the company acquired exclusive worldwide rights to develop, market, and manufacture brincidofovir for all indications except smallpox.

The company will initially develop brincidofovir for the indications of viral hemorrhagic cystitis (vHC) and HHV-6 encephalitis (HHV-6) after hematopoietic stem cell transplantation and kidney transplantation, areas with high unmet medical needs, with the goal of commercializing the product in Japan by mid 2020s.

### Revenue: milestone payments and Treakisym®

Revenue comes from milestone payments and product sales. Operating losses have persisted since the company's founding 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®.

For FY12/20, the company expects a JPY5.1bn operating loss, JPY5.1bn recurring loss, and net loss of JPY4.8bn. Over the course of the medium-term plan (FY12/20–FY12/22), the company expects to post an operating profit of JPY1.0bn in FY12/21 and JPY1.5bn in FY12/22 and plans to remain in the black thereafter.

# Business strategy

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

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

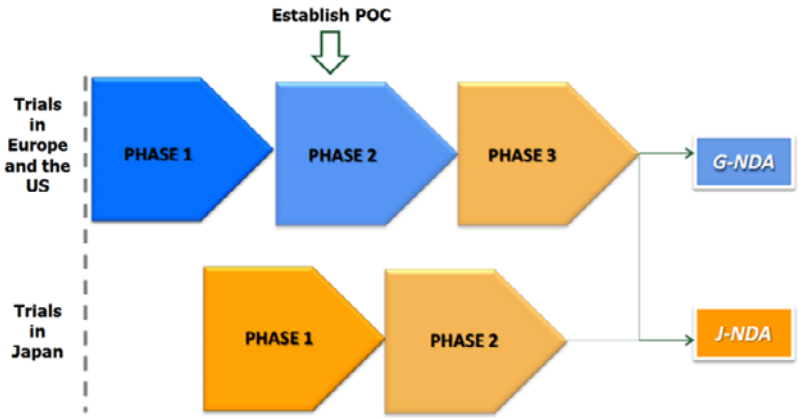
The overall aim is to reduce development risk, streamline expenses, and expand revenue opportunities. This hinges on the following five strategies, namely post proof-of-concept, screening, fabless, niche market, and global expansion.

## SymBio targets compounds with an established proof-of-concept

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

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

**Post-proof-of-concept strategy**




Source: Shared Research based on company data

## Screening: independent search network plus evaluation experience

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

### Onsite due diligence

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

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

The company had screened several hundred new drug candidates since its foundation, of which it has in-licensed only a few that have met its stringent criteria. The first was Treakisym®, which Eisai Co., Ltd. (TSE1: 4523) currently sells in Japan (as of February 2020). Clinical trials for additional Treakisym® indications are underway, as are preparations to file for approval of, and begin clinical trials of RTD and RI Treakisym® products. In addition, the company is also developing intravenous and oral versions of rigosertib and antiviral agent brincidofovir.

### Scientific Advisory Board

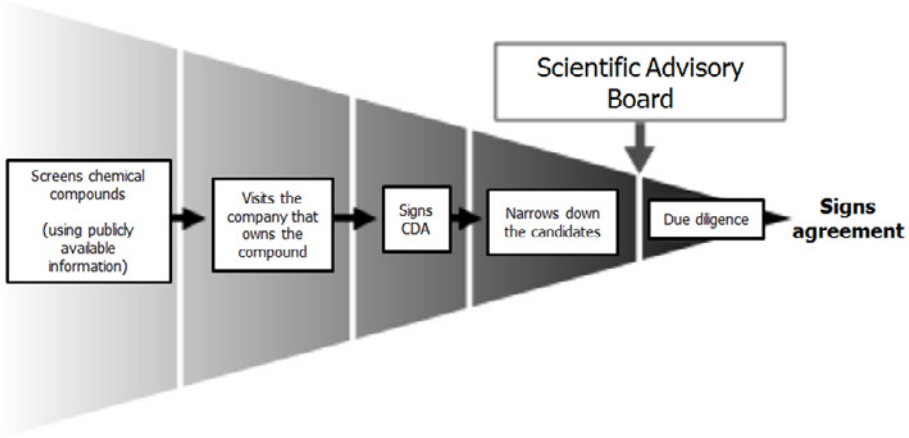
The Scientific Advisory Board is comprised of former directors of pharmaceutical companies, researchers, and doctors, and meets three times a year. Typically, the SAB panel evaluates two to three drug candidates that have been selected via the company's in-house screening process. This in-house screening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

**Scientific Advisory Board members**

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

Source: Shared Research based on company data

**Drug candidate selection process**




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

## 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). The company is preparing to establish its own sales organization to start in-house sales from FY12/21, but as of February 2020, marketing rights are granted to outside partners.

## Focusing on niche markets: oncology, hematology, and rare diseases

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

According to the company, globally Japan has the third largest oncology market after the US and EU, and the market is expected to continue to expand due to Japan's aging population. However, regarding the type of tumors that anticancer drugs can effectively treat, there is a considerable range of indications with a limited number of patients who will benefit from approved cancer treatments, particularly in the elderly population where the occurrence of serious adverse events can be prohibitive. As a result, barriers to entry are high—developing cancer drugs for niche markets is especially difficult and requires a high level of expertise. Concerns about having sufficient profit margins from marketed drugs to fund large operations means that major pharmaceutical companies may be reluctant to target indications with limited patient numbers for development, presenting an opportunity with fewer competitors in the marketplace for smaller and more specialized pharmaceutical companies such as SymBio. The company can also increase value added of niche disease areas by additional indications and putting new products on the market. For example, its first in-house proprietary drug Treakisym® has gained over 50% market share three years after going on sale. In July 2018, Treakisym® was newly included as a standard option for first-line treatment of low-grade NHL and mantle cell lymphoma in the Guidelines for Hematological Malignancies 2018 issued by the Japan Society of Hematology in July 2018.

## Strategy for global expansion

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

## Pipeline

| Name/Code | Licensed country | Indications | Development stage | Sales partner |
|---|---|---|---|---|
| Treakisym®<br>SyB L-0501<br>(FD) | Japan | Relapsed or refractory low-grade NHL and MCL | Approval obtained (Oct. 2010) | Eisai Co., Ltd.<br>(co-developed: exclusive sales rights granted to Eisai) |
| | | Relapsed or refractory DLBCL (aggressive NHL) | Preparing for approval filing | |
| | | Untreated low-grade NHL and MCL | Approval granted (Dec. 2016) | |
| | | CLL | Approval granted (Aug. 2016) | |
| | Singapore | Low-grade B-cell NHL | Approval granted (Jan. 2010) | Eisai Co., Ltd.<br>(Exclusive development and sales rights granted to Eisai) |
| | | CLL | | |
| | South Korea | CLL<br>MM | Approval granted (May 2011) | Eisai Co., Ltd.<br>(Exclusive development and sales rights granted to Eisai) |
| | | Relapsed or refractory low-grade NHL | Approval granted (Jun. 2014) | |
| | China | Low-grade NHL | Clinical trials underway | Cephalon, Inc. (US)<br>(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)<br>(Exclusive development and sales rights granted to Eisai) |
| | | CLL | | |
| Treakisym®<br>SyB L-1701<br>(RTD) | Japan | All indications | Filed for approval (Sep 2019) | — |
| Treakisym®<br>SyB L-1702<br>(RI) | Japan | All indications | Clinical trials underway | — |
| Treakisym®<br>SyB C-0501<br>(oral) | Japan | Systemic lupus erythematosus (SLE) | Phase I clinical trials completed | — |
| Rigosertib<br>(IV)<br>SyB L-1101 | Japan | Relapsed or refractory higher-risk MDS | Global phase III clinical trials underway | — |
| Rigosertib<br>(oral)<br>SyB C-1101 | Japan | Relapsed or refractory higher-risk MDS (single drug) | Phase I clinical trials underway | — |
| | | Untreated higher-risk MDS (with azacitidine) | Preparing for phase I clinical trials<br>Preparing for global phase III clinical trials | — |
| Brincidofovir<br>SyB V-1901 | Worldwide | Viral hemorrhagic cystitis (vHC) and HHV-6 encephalitis (HHV-6) after hematopoietic stem cell and kidney transplantation | — | — |

Source: Shared Research based on the company website

As of February 2020, the main drugs for which SymBio was preparing filing for approval or in the development pipeline were as follows:

- Treakisym®, for the indication of relapsed or refractory DLBCL (aggressive NHL): Completed enrollment of patients for the phase III clinical trial (April 2019). Preparing to file approval application in 1H FY12/20
- Treakisym®, preparing to file for approval of RTD formulation and conducting clinical trials on RI formulation: Filed for approval for RTD formulation in September 2019, and clinical trials on RI formulation initiated in November 2018
- Rigosertib (intravenous formulation), for the indication of relapsed or refractory higher-risk myelodysplastic syndrome (MDS): Enrolling patients for global phase III clinical trials
- Rigosertib (oral formulation), for the indication of higher-risk MDS: Completed patient enrollment for the phase I clinical trial in June 2019, in preparations for the phase I clinical trial of the combination therapy with azacitidine, in preparations for global clinical trials of the combination therapy with azacitidine
- Antiviral drug brincidofovir: Acquired exclusive global rights to develop, market, and manufacture brincidofovir for all indications except smallpox from Chimerix, Inc. in September 2019

## 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 efficacious than existing treatments for target indications. In October 2010, SymBio received regulatory approval in Japan to market the drug for relapsed or refractory low-grade NHL and MCL. Eisai has been selling the drug since its launch in December 2010. The company received permission to add CLL as an indication for Treakisym® in August 2016, and first-line treatment of low-grade NHL and MCL in December 2016.

As of February 2020, the company initiated phase III clinical studies of Treakisym® for an additional indication of relapsed or refractory DLBCL (aggressive NHL) and is preparing for a label expansion filing in 1H FY12/20.

### Lymphatic cancer

**Lymphatic cancer a malignant growth of lymphatic corpuscles in white blood cells**

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

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

**Lymphatic malignancy: frequency by type**

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

Source: Japanese Society for Lymphoreticular Tissue Research (JSLTR)

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

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

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

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

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

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

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

## 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 reached JPY4.7bn on an NHI drug price basis.

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

# Treakisym®: additional indications, RTD, RI, and oral forms

## 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.

As of February 2020, the company is preparing to file for the expanded approval of Treakisym® to treat relapsed or refractory DLBCL (aggressive NHL) in 1H 2020.

**Market for Treakisym® and number of patients**

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

Source: Shared Research based on company data

## First-line treatment of low-grade NHL and MCL

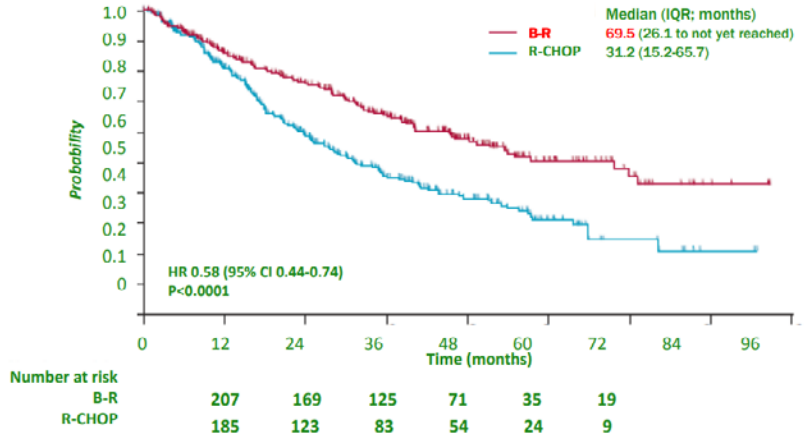
According to the company, R-CHOP therapy—a combination of rituximab with CHOP chemotherapy drugs (cyclophosphamide, doxorubicin, vincristine, and prednisolone)—was standard first-line treatment for low-grade NHL and MCL in Japan prior to December 2016. In December 2016, Treakisym® won approval for the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

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. Shared Research believes this shift will gain support from the aforementioned data demonstrating that BR therapy is more efficacious than R-CHOP therapy, and inclusion of BR therapy as a standard treatment option in the Guidelines for Tumors of Hematopoietic and Lymphoid Tissues 2018.

### Untreated low-grade NHL and MCL: Patient population

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

## Treakisym® targeting chronic lymphocytic leukemia (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 656 CLL patients in Japan. Shared Research estimates that sales could reach JPY300mn–JPY350mn. This estimate is based on Treakisym® sales per patient with relapsed or refractory low-grade NHL or MCL.

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

Diffuse large B-cell lymphoma (DLBCL), or aggressive NHL, progresses rapidly but recovery may be expected in patients for whom anticancer drugs are effective. R-CHOP is the standard 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 efficacious method of treatment such as Treakisym®.

**R&D status: Preparing for filing of Treakisym® to treat relapsed or refractory DLBCL**

Phase II clinical trial data demonstrates potential for improved prognosis in patients with relapsed or refractory DLBCL (aggressive NHL)

In March 2012, the company completed final analysis and evaluation of data from its phase II clinical trials 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.

Planning to file for approval in FY12/20 for indication of relapsed or refractory DLBCL

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 DLBCL. 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. Enrollment of 60 patients was completed in April 2019. SymBio aims to file for approval in Q2 FY12/20 with a view to launching in Q3 FY12/21.

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

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

**Potential patient population**

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

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

In September 2017, Eagle Pharmaceuticals and SymBio concluded a license agreement that licenses to SymBio rights to develop, market, and sell Eagle'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 | Dilute with 50ml physiological | Dilute with 250ml physiological |

| | | | |
|---|---|---|---|
| | saline | saline | saline |
| Administration time | 60 minutes | 10 minutes | 60 minutes |
| Dosage form | 100mg/4mL | | 100mg/vial<br>25mg/vial |
| Storage | Refrigerated storage (2–8°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 be manufactured and sold. 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: Aiming to obtain approval in FY12/20 for bendamustine hydrochloride RTD product**

As of February 2020, the company is respectively preparing to file for approval and conducting clinical trials for the bendamustine hydrochloride RTD and RI products.

SymBio was allowed to file for approval of the RTD product without conducting clinical trials, because its ingredients, efficacy, and administration time are identical to those of the Treakisym® freeze-dried (FD) product; the only difference being that it does not need reconstitution. After consultations with PMDA, the company completed the approval filing in September 2019. Based on the time needed to prepare the documents required for this application, and subsequent period between filing and approval, SymBio aims to submit an application in FY12/19, obtain approval in FY12/20, and launch in Q1 FY12/21.

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

## Treakisym® (oral) SyB C-0501

SymBio explored the possibility of expanding the business by progressing development of the oral form of Treakisym® targeting new indications such as solid tumors and autoimmune diseases. As part of this project, the company completed a phase I clinical trial to confirm efficacy against progressive solid tumors and pre-clinical studies for systemic lupus erythematosus (SLE), but development was halted even though the studies achieved their initial objectives. This is because SymBio has decided to maximize management resources by concentrating on domestic and overseas development of antiviral drug brincidofovir.

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

In September 2018, the company applied for approval of a partial revision to manufacture and marketing approval of anticancer drug Treakisym® to enable its use as a pretreatment agent for regenerative medical products.

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

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

## SyB L-1101 (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.

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

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

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

### Myelodysplastic Syndromes (MDS)

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

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

### Acquired rights from Onconova to develop and sell rigosertib in Japan, South 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 2020, SymBio is developing the IV form of rigosertib for the indication of relapsed or refractory higher-risk MDS, and the oral form for higher-risk MDS.

Onconova has been conducting joint global phase III clinical trials in over 20 countries since August 2015 for the intravenous form of rigosertib in higher-risk MDS patients who had failed 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 higher-risk MDS (in combination with azacitidine) in December 2015. The supply of the study drug from Onconova had been delayed, but with resumption of study drug supply SymBio restarted phase I clinical trials in Japan in June 2017 and completed patient enrollment in June 2019, to verify the tolerability and safety of the oral formulation of rigosertib among Japanese patients. After establishing safety in phase I clinical trials, the company plans to resume the trial of rigosertib in combination with azacitidine and participate in global phase III clinical trials planned by Onconova in higher-risk MDS patients, and in combination with azacitidine.

**Market for Rigosertib (oral form) and number of patients**

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

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 2020.

### R&D status: ongoing joint global phase III clinical trials in patients with relapsed higher-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 anticancer agent was approximately 60%. With rigosertib, toxicity of Grade 3 or above did not exceed 7%, and non-hematological toxicity did not exceed 3%, confirming safety of the drug.

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**

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 48 patients had been registered as of end December 2019 versus the target of 50. Onconova decided to proceed with the clinical trial on the basis of results of an interim analysis performed in January 2018 by increasing the number of patients registered from 225 to 360 based on preplanned statistical criteria. According to a press release by Onconova made in December 2019, worldwide patient enrollment had exceeded 90% of the 360 target. Top-line (primary endpoint) results are slated for release in 1H 2020.

## Oral form of rigosertib for first-line higher-risk MDS

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

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

The data on the efficacy and safety of oral rigosertib and azacitidine combination for 33 MDS patients (20 HMA naïve; 13 HMA resistant) was presented at the poster presentation, "Combination of Oral Rigosertib and Injectable Azacitidine in Patients with Myelodysplastic Syndromes (MDS): Results from a Phase II Study." The complete remission (CR) rate 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 February 2020, Onconova is making efforts toward finalizing the design for a pivotal phase III oral rigosertib/azacitidine combination trial for the first-line treatment of higher-risk MDS.

**Domestic phase I clinical trials**

In FY12/16, the company launched phase I clinical trials to confirm the safety of the drug in combination with azacitidine for treatment of higher-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 clinical trials conducted by Onconova in the US for the indication of untreated and relapsed or refractory higher-risk MDS). The patient enrollment for the study was completed in June 2019. After establishing safety in the phase I clinical trial, the company plans to resume the trial of the drug in combination with azacitidine and participate in global phase III clinical trials conducted by Onconova. In December 2019, Onconova issued a press release announcing it was considering a phase II/III adaptive trial for untreated high-risk MDS patients based on data presented at the 61st American Society of Hematology Annual Meeting and Exposition in December 2019.

**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 JPY14.5bn for FY03/19 (+11.1% YoY) and forecast to reach JPY15.4bn in FY03/20. Shared Research thinks that sales of the intravenous and oral forms of rigosertib could

match or exceed sales of Vidaza, used for patients who have not received treatment with Vidaza or in combination therapy with Vidaza.

## SyB V-1901 (antiviral drug brincidofovir)

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

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

### Mechanism of action and indications of brincidofovir

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

> Cidofovir (CDV): Approved by FDA in 1996 as a treatment for cytomegalovirus retinitis in AIDS patients. It inhibits replication of multiple families of DNA viruses other than herpes viruses, including adenoviruses, papillomaviruses, and polyomaviruses.
>
> CDV is taken up by renal tubular epithelial cells through organic anion transporter 1 (OAT1), and its accumulation in the cells cause nephrotoxicity. Brincidofovir is expected to have a low risk of nephrotoxicity as its lipid chain prevents it from being taken up by OAT1 and accumulating in renal tubular epithelial cells.

### Development status: targeting commercialization by mid-2020s

The US-based phase I clinical trial of intravenous formulation of brincidofovir has been completed. It has been reported that no serious side effects were observed in the study.

SymBio will initially develop brincidofovir toward commercialization in Japan for treatment of viral hemorrhagic cystitis (vHC)*[1] and HHV-6 encephalitis*[2] occurring after hematopoietic stem cell and kidney transplantation, which have high unmet medical demand. The company also looks to expand its business in Europe, the US, and Asia (including China), where organ transplant markets are large. It will also consider forming partnerships that take advantage of regional characteristics of these target diseases. The company will explore all options for maximizing business value, including the utilization of wholly-owned subsidiary SymBio Pharma USA, Inc. established in May 2016. It aims to commercialize the product by mid 2020s.

Hematopoietic stem cell transplantation is one of the therapies aimed at completely curing diseases such as blood cancer and immunodeficiency disorders that are difficult to treat with conventional chemotherapy. In Japan, there are about 4,000 patients who have undergone allogeneic hematopoietic stem cell transplantation, and about 60% of them have contacted viral

hemorrhagic cystitis (vHC) or HHV-6 encephalitis. For vHC, cidofovir is used as first-line treatment in the EU and US. For encephalitis, foscavir and denocin are designated as the first-line drugs, and cidofovir as the second-line drug.

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

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

**Number of patients and estimated sales**

As previously mentioned, the company will initially develop brincidofovir for the indications of viral hemorrhagic cystitis (vHC) and HHV-6 encephalitis after hematopoietic stem cell and kidney transplantation toward commercialization in Japan. In Japan, there are about 4,000 patients who have received allogeneic hematopoietic stem cell transplants, and about 60% of them have contracted vHC or HHV-6 encephalitis.

In addition to vHC and HHV-6 encephalitis after hematopoietic stem cell transplantation in Japan, the company expects indications of brincidofovir to be expanded to include infectious diseases that occur after kidney transplantation (about 40% of patients suffer from infectious diseases caused by BK virus or cytomegalovirus after kidney transplantation) in China, the EU, and the US. Based on such factors, the company estimates global sales of brincidofovir, including sales from emerging markets, to reach JPY100.0bn.

## Earnings structure

| (JPYmn) | FY12/10 | FY12/11 | FY12/12 | FY12/13 | FY12/14 | FY12/15 | FY12/16 | FY12/17 | FY12/18 | FY12/19 |
|---|---|---|---|---|---|---|---|---|---|---|
| Sales | 1,450 | 1,883 | 1,955 | 1,532 | 1,955 | 1,933 | 2,368 | 3,444 | 3,836 | 2,838 |
| YoY | 21.7% | 29.8% | 3.9% | -21.6% | 27.6% | -1.1% | 22.5% | 45.4% | 11.4% | -26.0% |
| Product sales | 326 | 1,632 | 1,955 | 1,432 | 1,940 | 1,933 | 2,137 | 3,444 | 3,810 | 2,811 |
| YoY | - | 401.3% | 19.8% | -26.8% | 35.5% | -0.3% | 10.6% | 61.1% | 10.6% | -26.2% |
| Treakisym sales (NHI price basis; reference) | 644 | 3,390 | 3,940 | 4,230 | 4,320 | 4,760 | 4,720 | 7,600 | 8,500 | - |
| Product sales / Sales (NHI price basis) | 50.6% | 48.2% | 49.6% | 33.9% | 44.9% | 40.6% | 45.3% | 45.3% | 44.8% | - |
| Royalty revenue | 1,124 | 250 | - | 100 | 15 | - | 231 | - | 26 | 26 |
| Sales to Eisai | 1,446 | 1,872 | 1,930 | 1,486 | 1,908 | 1,852 | 2,265 | 3,382 | 3,648 | 2,831 |
| YoY | 33.2% | 29.5% | 3.1% | -23.0% | 28.4% | -2.9% | 22.3% | 49.4% | 7.9% | -22.4% |
| Sales to other partners | 4 | 10 | 26 | 46 | 47 | 81 | 104 | 62 | 187 | 6 |
| CoGS | 238 | 1,224 | 1,362 | 1,214 | 1,428 | 1,350 | 1,464 | 2,413 | 2,663 | 1,973 |
| CoGS / Product sales | 73.1% | 75.0% | 69.7% | 84.8% | 73.6% | 69.8% | 68.5% | 70.1% | 69.9% | 70.2% |
| CoGS / Sales (NHI price basis) | 37.0% | 36.1% | 34.6% | 28.7% | 33.1% | 28.4% | 31.0% | 31.7% | 31.3% | - |
| Product procurement | 238 | 1,434 | 1,322 | 1,175 | 1,550 | 1,242 | 1,606 | 2,589 | 2,969 | 1,684 |
| Gross profit | 1,212 | 658 | 593 | 318 | 527 | 583 | 904 | 1,031 | 1,173 | 865 |
| Product gross profit | 87 | 408 | 593 | 218 | 512 | 583 | 673 | 1,031 | 1,147 | 838 |
| Gross profit margin | 26.9% | 25.0% | 30.3% | 15.2% | 26.4% | 30.2% | 31.5% | 29.9% | 30.1% | 29.8% |
| Royalty revenue | 1,124 | 250 | - | 100 | 15 | - | 231 | - | 26 | 26 |
| SG&A expenses | 1,825 | 2,725 | 2,293 | 1,999 | 1,830 | 3,135 | 3,031 | 4,978 | 3,829 | 5,166 |
| Personnel expenses | 343 | 365 | 413 | 441 | 479 | 488 | 541 | 554 | 504 | 506 |
| R&D expenses | 1,118 | 1,945 | 1,438 | 1,053 | 774 | 2,035 | 1,667 | 3,018 | 1,833 | 2,442 |
| Other | 364 | 415 | 442 | 505 | 577 | 612 | 823 | 1,406 | 1,492 | 2,219 |
| Operating profit | -613 | -2,067 | -1,700 | -1,681 | -1,303 | -2,552 | -2,127 | -3,947 | -2,656 | -4,302 |

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 anticancer agent in December 2010. ThroughFY12/16, the company booked sales of Treakisym® indicated for relapsed or refractory low-grade NHL and MCL.

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

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

### Royalty revenue

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

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

## SG&A expenses

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

### Personnel expenses

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

### R&D expenses

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

Eisai pays half of the development costs for the Treakisym® freeze-dried (FD) product in Japan. In its income statement, SymBio accordingly books total R&D expense less the portion of R&D expenditure borne by Eisai.

# Strengths and weaknesses

## Strengths

- **Unique candidate selection process**: SymBio makes decisions on in-licensing new drug candidates based on an initial assessment and screening process by its in-house search and evaluation team. The final decision is made by the company after evaluation by a team of medical experts—the Scientific Advisory Board (SAB). President Yoshida's extensive range of contacts in the pharmaceutical industry built during his tenure at Amgen Japan and Amgen Inc. is a significant hurdle for competitors attempting to emulate the quality of the company's search and evaluation team, SAB panel and selection process.
- **Strong product development**: Treakisym® (bendamustine hydrochloride)—the first drug the company developed—received marketing approval in Japan just five years after the license agreement was signed with Astellas. Treakisym®, launched by the company in December 2010, is being used by a number of Japanese physicians and is considered to be an essential drug for the treatment of relapsed or refractory low-grade NHL and MCL. The company's success with Treakisym® demonstrates its strong product development capabilities and nimbleness.
- **Strong share in niche markets**: SymBio focuses on niche markets for rare oncologic and hematologic diseases and rare diseases. The company takes advantage of a less competitive environment by developing drugs for indications that serve a limited number of patients and require a high degree of in-house expertise. Thus, the company has succeeded in securing more than 50% of the target market for Treakisym® in relapsed or refractory low-grade NHL and MCL in the third year after launch.

## Weaknesses

- **Lack of sales force:** The company does not currently have its own sales force, thus Treakisym® is being sold through Eisai, an alliance partner. Eisai will be responsible for sales of Treakisym® in Japan through FY12/20. At end-FY12/20, though, the sales agreement with Eisai expires. At this point the company will switch to in-house sales, likely triggering improvement in profit margins.
- **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 JPY3.9bn at end-FY12/19, but the company expects a total net loss of JPY4.8bn for FY12/20. SymBio aims to secure a total of JPY5.5bn through its February 2020 issue of the 50th and 51st stock acquisition rights with exercise price revision clauses. The company's operations could be affected, though, if it fails to secure additional funding as planned.
- **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

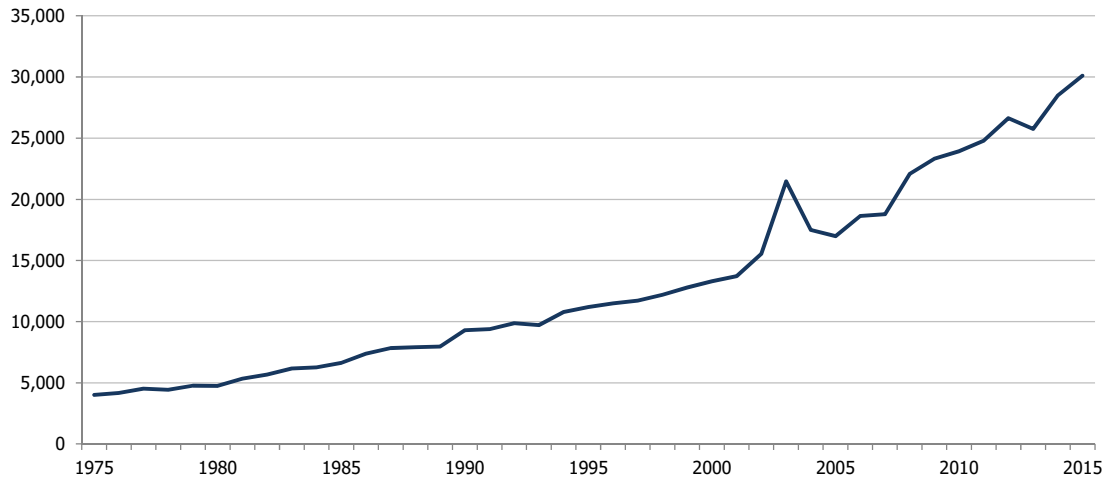
## Market overview

### Lymphatic cancer: patient population, market size, drugs

#### Newly diagnosed patients with lymphatic cancer

In 2015, the number of people diagnosed with lymphatic cancer in Japan was 30,103 (+5.7% YoY; average annual increase in past 10 years is 5.9%), according to the Center for Cancer Control and Information Services. Of these, 23,782 (+5.4% YoY), or 79.0% (79.2% in the previous year), were 60 years or older. Of the 903,914 (+3.1% YoY) people diagnosed with cancer, those diagnosed with lymphatic cancer accounted for only 3.3% (3.2% in 2014), but their number increased 77.2% between 2005 and 2015 versus a 39.8% increase in the number of people newly diagnosed with cancer.

**Patients newly diagnosed with lymphatic malignancy**




| | 1975 | 1980 | 1985 | 1990 | 1995 | 2000 | 2005 | 2010 | 2015 |
|---|---|---|---|---|---|---|---|---|---|
| Number of patients | 4,013 | 4,741 | 6,635 | 9,297 | 11,195 | 13,307 | 16,991 | 23,919 | 30,103 |
| Incidence rate (per 100,000) | 3.6 | 4.1 | 5.5 | 7.5 | 8.9 | 10.5 | 13.3 | 18.7 | 23.7 |

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

#### Treakisym® market potential and patient population

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

The company estimates that the number of Japanese patients with relapsed or refractory DLBCL for which the company is considering application for approval of an additional indication is 18,672.

**Treakisym® indications and number of patients**

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

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

## Drugs competing with Treakisym®

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

### Rituximab (product name: Rituxan)

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

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

In Japan, Zenyaku Kogyo and Chugai have been jointly selling the drug since September 2001. Chugai's Rituxan sales were JPY11.9bn (-44.1% YoY) in FY12/19.

### 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 efficacious treatment available.

**Rigosertib indications and number of patients**

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

Source: Shared Research based on company data

## Drugs competing with rigosertib

According to the company, as of February 2020, 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 efficacious after use for three to six months, with bone marrow suppression as the main side effect (a decline in white blood cells and platelets). However, while the use of

hypomethylating agents such as azacitidine and decitabine (Dacogen) in the treatment of MDS has improved the outcome of patients who tend to have very poor survival, about half of MDS patients do not respond, progress, or relapse at different times after their response on these HMAs, followed by an extremely poor prognosis.

According to Nippon Shinyaku, Vidaza is the only approved drug in Japan for the first-line treatment of higher-risk MDS, with no efficacious treatment available once patients treated with Vidaza relapse. Nippon Shinyaku booked Vidaza sales of JPY14.5bn in FY03/19 and expects sales of JPY15.4bn in FY03/20.

# Historical performance

## Q1 FY12/20 results

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

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

According to disclosure by Eisai, the sales agent for Treakisym®, FY03/20 sales of the product increased 6.2% YoY to JPY8bn. On a quarterly basis, Q4 (Jan–Mar 2020) Treakisym® sales were JPY1.6bn, up from JPY1.5bn a year earlier.

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

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

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

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

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

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

### Domestic

Preparations for in-house sales organization begin

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

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

### Substandard products

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

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

### Treakisym® (SyB L-0501[lyophilized injection]/SyB L-1701 [RTD]/SyB L-1702 [RI]/SyB C-0501 [oral]; anticancer agent; generic name: bendamustine hydrochloride)

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

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

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

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

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

<By gene activity pattern>

▷ GCB type: Overall Response Rate (ORR) of 83%, Complete Response Rate (CR) of 67%

▷ Non-GCB type: ORR of 78%, CR of 39%

| |
|---|
| Divided into GCB or non-GCB type DLBCL<br>GCB type: Geminal center B-cell type<br>Non-GCB type: non Geminal center B-cell type |

<By age group>

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

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

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

The company concluded an exclusive licensing agreement in Japan with Eagle Pharmaceuticals (based in New Jersey, US) in September 2017. Following consultations with the PMDA, the company filed for approval of the RTD formulation in September 2019, and plans to launch it in Q1 FY12/21. SymBio launched clinical trials for the RI formulation in November 2018 primarily to confirm safety and completed patient enrollment in March 2020. The company will apply for approval without delay after the end of the clinical trials of the RI formulation and aims to begin sales in 2H FY12/22. The RI formulation can be administered in just 10 minutes versus 60 minutes for the current lyophilized injection and RTD formulation. This reduces the burden on patients and healthcare professionals, providing significant value added. Multiple patent protections in the form of a liquid product license extended the product life of Treakisym® to 2031.

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 (50 patients enrolled as of April 2020). The global phase III trial addresses higher-risk myelodysplastic syndromes (higher-risk MDS), which do not respond to the current standard treatment with hypomethylating agents, which relapse after treatment under the current standard of care, or which are intolerant to hypomethylating agents, and is under way at clinical trial sites in more than 20 countries worldwide. Onconova announced that it had reached its target of enrolling 360 patients worldwide as of March 2020. Onconova said the primary endpoint results would become clear in 2H 2020, and that it planned to announce trial results at an academic conference by the end of the year. Based on these trial results, the company plans to apply for approval in Japan at the same time as in the US and Europe.

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

Antiviral drug for the treatment of infections SyB V-1901 (generic name: Brincidofovir)

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

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

The company will initially develop BCV-IV for treatment of viral hemorrhagic cystitis (vHC) occurring after hematopoietic stem cell transplantation for the domestic market, which has high unmet medical needs. It plans to conduct clinical studies and gain

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

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

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

**Overseas**

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

**In-licensing of drug candidates**

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

## Full-year FY12/19 results

- ▷ Sales: JPY2.8bn (-26.0% YoY)
- ▷ Operating loss: JPY4.3bn (loss of JPY2.7bn in FY12/18)
- ▷ Recurring loss: JPY4.4bn (loss of JPY2.7bn in FY12/18)
- ▷ Net loss: JPY4.4bn (loss of JPY2.8bn in FY12/18)

Sales declined YoY. As per the reason for earnings forecast revisions announced in August 2019, foreign matter contamination and appearance defects were discovered in lyophilized injection agents imported from Astellas Deutschland GmbH, a subsidiary of Astellas Pharma Inc. The extent of contamination and defects significantly exceeded limits permitted by quality standards stipulated in the supply agreement, and as a result, the shipments of Treakisym® 100mg vials to its domestic distributor Eisai was delayed with some product sales expected to be booked in FY12/19 postponed to the next fiscal year. Reviewing the quarterly sales trend, sales increased 81.4% YoY to JPY1.6bn in Q1 (January–March 2019), declined 62.2% YoY to JPY394mn in Q2 (April–June), dropped 99.7% YoY to JPY3mn in Q3 (July–September), and increased 3.3% YoY to JPY830mn in Q4 (October–December). There were practically no sales in Q3 due to the aforementioned factors, but the company posted sales in Q4 once shipments to Eisai resumed following rigorous quality inspections.

Gross profit declined 26.3% YoY to JPY865mn while the gross profit margin declined 0.3pp to 29.8%.

SG&A expenses rose 34.9% YoY to JPY5.2bn and R&D expenses increased 33.2% YoY to JPY2.4bn. This included upfront payments (JPY540mn) for new drug brincidofovir (an antiviral drug for the treatment of infections), and expenses for conducting clinical trials of intravenous and oral formulations of Treakisym® and rigosertib. Excluding R&D expenses, SG&A expenses increased by 36.5% YoY to JPY2.7bn.

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

Major progress in cumulative Q3 FY12/19 was as follows:

- ▷ In November 2019, the company announced that in the phase III study of the anticancer drug Treakisym® administered in combination with rituximab (BR therapy) targeting relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL), the response rate, which was the primary endpoint of the study, exceeded expectations. The company plans to compile final analysis results of the study and apply for approval during 1H FY12/20.
- ▷ In October 2019, Onconova Therapeutics, Inc. announced that it was approaching enrollment of 90% of the target 360 patients for its INSPIRE trial evaluating intravenous formulation of rigosertib in higher-risk myelodysplastic syndrome (MDS) patients who had failed to respond to or relapsed after previous treatment with a hypomethylating agent, the current standard of care for MDS, and that it planned to report primary endpoint results of the study during 1H 2020. Further, regarding the oral formulation of rigosertib, Onconova announced that based on the result of its consultation with the FDA on Special Protocol Assessment (SPA), it would consider conducting a phase II clinical trial targeting untreated higher-risk MDS patients. The purpose of the trial would be to compare the combination therapy of rigosertib and azacitidine with the azacitidine monotherapy.
- ▷ In October 2019, the company entered a global license agreement with the US-based Chimerix Inc. to acquire exclusive worldwide rights to the antiviral drug brincidofovir. Under the terms of the agreement, Chimerix will grant global exclusive rights to develop, market, and manufacture brincidofovir for all indications except smallpox to the company.
- ▷ In September 2019, the company filed for manufacturing and marketing approval of the ready-to-dilute (RTD) liquid formulation of Treakisym®. The application covers all indications for which Treakisym® has already been approved; if the RTD formulation is approved for the additional indication of r/r DLBCL, which is currently in a clinical trial stage, it can also be used to treat r/r DLBCL. Once the company obtains approval for the RTD formulation, it plans to launch the product in Q1 FY12/21.
- ▷ In June 2019, the US Food and Drug Administration (FDA) granted accelerated approval to polatuzumab vedotin-piiq, a CD79b-directed antibody-drug conjugate, in combination with bendamustine (product name: Treakisym®) and rituximab (BR therapy) for patients with relapsed or refractory DLBCL who are not eligible for transplant. Polatuzumab vedotin-piiq was discovered by Roche Group company Genentech and is being developed in Japan by Chugai Pharmaceutical, another member of the Roche Group.
- ▷ In April 2019, the first patient was enrolled in the clinical trial of the liquid formulation of Treakisym® (rapid infusion [RI] formulation), whose primary goal was to confirm safety of the drug.
- ▷ In March 2019, the company obtained approval to partially revise the marketing approval of anticancer drug Treakisym® as a pretreatment agent in antigen-specific T cell infusion therapy. This enabled the use of Treakisym® as a pretreatment agent for the chimeric antigen receptor T-cell (CAR-T) therapy Kymriah® intravenous infusion.

**Domestic**

Preparations for in-house sales organization begin

The business alliance agreement between SymBio and Eisai Co., Ltd. under which Eisai acts as a sales agent expires in December 2020. SymBio started to build an in-house sales organization for Treakisym® in the domestic market in October 2018. Key management priority is to move into the black in FY12/21 and ongoing profit growth thereafter. The company is therefore laying the groundwork for a shift to an internal sales organization to drive future business development.

The company increased Treakisym® sales representatives (highly specialized sales representatives) and conducted training to form the core of its in-house marketing network. Information provision activities were started from July 2019 by the Treakisym®

sales representatives dispatched to each region to promote the shift to a nationwide operation with close local ties. The company made progress toward completing the formation of its nationwide sales structure (planned in 1H FY12/20). In Q4 FY12/19 (October to December 2019) it hired additional regional sales managers and Treakisym® managers necessary to complete the sales structure, as well as moving ahead with business alliances with pharmaceutical wholesalers and establishing logistics centers in East and West Japan to provide a distribution and logistics function. It also prepared a new IT system that includes ERP to upgrade its IT infrastructure.

Treakisym® (SyB L-0501[lyophilized injection]/SyB L-1701 [RTD]/SyB L-1702 [RI]/SyB C-0501 [oral]; 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 untreated low-grade non-Hodgkin's lymphoma and mantle cell lymphoma (marketing approval obtained in December 2016), refractory or relapsed low-grade non-Hodgkin's lymphoma and mantle cell lymphoma (October 2010), and chronic lymphocytic leukemia (August 2016).

The combination therapy of Treakisym® and rituximab (BR therapy) was newly included in the Practical Guidelines for Hematological Malignancies 2018 edited and published by Japanese Society of Hematology as a standard treatment option, which applies to all of the approved indications. This has seen Treakisym® establish its position as a standard treatment for lymphatic cancer. By switching to its own sales structure in 1H FY12/20, the company plans to attain a large market share as in markets in Europe and the US.

In addition to the above three approved indications, the company is conducting a phase III clinical trial for the fourth indication of relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL). The response rate (primary endpoint) in the test results released in November 2019 was better than expected. As of February 2020, the company is preparing to apply for approval in 1H FY12/20.

SymBio is targeting a transition to Treakisym® liquid formulation (RTD and RI formulations), for which it concluded an exclusive licensing agreement in Japan with Eagle Pharmaceuticals (based in New Jersey, US) in September 2017. The company has already consulted with PMDA and filed for approval of the RTD formulation in September 2019 with an eye towards commercialization by Q1 FY12/21. SymBio launched clinical trials for the RI formulation in November 2018 primarily to confirm safety, and has made steady progress with patient enrollments since enrolling the first patient in April 2019, having enrolled 31 patients as of end January 2020. The company will apply for approval without delay after the end of the clinical trials of the RI formulation and aims to begin sales in 1H FY12/22. Liquid formulations of Treakisym® will offer significant value added (reduced burden) to patients and healthcare professionals, and patent protection in the form of a liquid product license makes it possible to extend the product life of Treakisym® until 2031.

In July 2018, SymBio obtained approval for the partial revision to the marketing authorization of Treakisym®. As a result, Treakisym® can now be used in combination with not only rituximab but new anti-CD20 antibodies as well. This will allow combination therapy with obinutuzumab (launched in August 2018) for the treatment of CD 20-positive follicular lymphoma (FL), the most common histological type of low-grade NHL, enabling the company to provide patients with a new treatment therapy. In March 2019, the company obtained approval for the partial revision to its application concerning the use of Treakisym® as a pretreatment agent in tumor-specific T cell infusion therapy. This will allow Treakisym® to be used as a pretreatment agent for Kymriah® intravenous infusion, which was approved as the first chimeric antigen receptor T-cell (CAR-T) therapy in Japan and listed on the NHI drug price list in May 2019.

The Phase I clinical trial of Treakisym® as a treatment for progressive solid tumors and preclinical study to verify the efficacy of Treakisym® in the treatment of systemic lupus erythematosus (SLE), which were conducted to explore further potential indications of the drug, have been completed. However, the company decided to suspend development despite the initial objectives of the studies being met. Its policy is to prioritize development in Japan and overseas of antiviral drug candidate brincidofovir (for which it has obtained a license) to utilize its management resources most effectively.

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 (48 patients enrolled as of December 2019). The global phase III trial addresses higher-risk myelodysplastic syndromes (higher-risk MDS), which do not respond to the current standard treatment with hypomethylating agents, which relapse after treatment under the current standard of care, or which are intolerant to hypomethylating agents, and is under way at clinical trial sites in more than 20 countries worldwide. In December 2019, Onconova announced that it had reached over 90% of its target of enrolling 360 patients worldwide as of November 2019. The company plans to report top-line (primary endpoint) results in 1H 2020. Based on these trial results, the company plans to apply for approval in Japan at the same time as in the US and Europe.

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

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

The company will initially develop BCV-IV for treatment of viral hemorrhagic cystitis (vHC) occurring after hematopoietic stem cell transplantation, which have high unmet medical demand. It also plans to market BCV IV globally after conducting international joint clinical trials in countries including the US and Europe. As well, the company plans clinical development of BCV IV as an antiviral treatment of infections after kidney transplants, because it is likely to be effective for transplants other than hematopoietic stem cell transplants, including organ transplants. The company looks to expand its business in Europe, the US and Asia (including China), where organ transplant markets are large. It will also consider forming partnerships that take advantage of regional characteristics of these target diseases. The company will explore all options for maximizing business value, including the strategic utilization of wholly-owned subsidiary SymBio Pharma USA, Inc. established in May 2016. The company is working on a development plan (including improvement of the formulation) for BCV Oral. BCV Oral has demonstrated a strong, broad-spectrum antiviral effect in clinical trials in Europe and the US by Chimerix. The company will design a global clinical trial based on these findings.

**SyB P-1501, a post-operative patient-controlled analgesia**
Regarding SyB P-1501 licensed by The Medicines Company (through its wholly owned subsidiary Incline Therapeutics, Inc.) in October 2015, SymBio learned of an event that raised concerns about the continuity of its business, and in the interests of patient welfare, it suspended further patient enrollment in April 2017.

The company initiated an arbitration against The Medicines Company, under the rules of the International Chamber of Commerce, seeking damages of USD82mn (approximately JPY9.0bn) arising from The Medicines Company's repudiation of the license agreement. SymBio argued that The Medicine Company's failure to provide sufficient assurance to the company regarding the performance of obligations under on the license agreement in light of its decision to suspend and withdraw from business activities relating to SyB P-1501in the European and US markets was a material breach of the license agreement. Arbitration proceedings against The Medicines Company are still ongoing, and an arbitration ruling is expected in 1H FY12/20. On January 6, 2020, Swiss company Novartis AG announced that it had acquired The Medicines Company.

**Overseas**

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

## Q3 FY12/19 results

- ▷ Sales: JPY2.0bn (-33.8% YoY)
- ▷ Operating loss: JPY3.5bn (loss of JPY1.9bn in Q3FY12/18)
- ▷ Recurring loss: JPY3.6bn (loss of JPY1.9bn in Q3 FY12/18)
- ▷ Net loss: JPY3.6bn (loss of JPY1.9bn in Q3 FY12/18)

Cumulative Q3 sales fell YoY. By quarter, sales increased 81.4% YoY to JPY1.6bn in Q1 (Jan–Mar 2019), but fell 62.2% YoY to JPY394mn in Q2 (Apr–Jun 2019) and dropped again by 99.7% YoY to JPY3mn in Q3 (Jul–Sep 2019). As the company explained as its reason for earnings forecast revisions announced in August 2019, foreign matter contamination and appearance defects were discovered in lyophilized injection agents imported from Astellas Deutschland GmbH, a subsidiary of Astellas Pharma Inc. The extent of contamination and defects significantly exceeded limits permitted by quality standards stipulated in the supply agreement, and as a result, the initially scheduled shipment of Treakisym® 100mg vials to its domestic distributor Eisai was delayed.

Gross profit was JPY563mn (-39.1% YoY), with the GPM down 2.5pp YoY to 28.0%. By quarter, while gross profit jumped 144.0% YoY to JPY609mn and GPM rose 9.7pp YoY to 37.8% in Q1, gross profit plunged to -JPY79mn in Q2. The sharp decline in gross profit was attributed to weak sales in Q2, combined with a JPY188mn loss on valuation of inventories due to quality defects found in some batches of Treakisym® 100mg. In Q3, gross profit declined 90.5% YoY to JPY33mn.

SG&A expenses rose 44.8% YoY to JPY4.1bn and R&D expenses increased 52.5% YoY to JPY2.0bn. This included upfront payments for new antiviral drug candidate brincidofovir, and expenses for conducting clinical trials of intravenous and oral formulations of Treakisym® and rigosertib. Excluding R&D expenses, SG&A expenses increased by 38.3% YoY to JPY2.1bn.

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

Major progress in cumulative Q3 FY12/19 was as follows:

- ▷ In November 2019, the company announced that in the phase III study of the anticancer drug Treakisym® administered in combination with rituximab (BR therapy) targeting relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL), the response rate, which was the primary endpoint of the study, exceeded expectations. The company plans to compile final analysis results of the study and apply for approval during 1H FY12/20.
- ▷ In October 2019, Onconova Therapeutics, Inc. announced that it was approaching enrollment of 90% of the target 360 patients for its INSPIRE trial evaluating intravenous formulation of rigosertib in higher-risk myelodysplastic syndrome (MDS) patients who had failed to respond to or relapsed after previous treatment with a hypomethylating agent, the current standard of care for MDS, and that it planned to report primary endpoint results of the study during 1H 2020. Further, regarding the oral formulation of rigosertib, Onconova announced that based on the result of its consultation with the FDA on Special Protocol Assessment (SPA), it would consider conducting a phase II clinical trial targeting untreated higher-risk MDS patients. The purpose of the trial would be to compare the combination therapy of rigosertib and azacitidine with the azacitidine monotherapy.
- ▷ In October 2019, the company entered a global license agreement with the US-based Chimerix Inc. to acquire exclusive worldwide rights to the antiviral drug brincidofovir. Under the terms of the agreement, Chimerix will grant global exclusive rights to develop, market, and manufacture brincidofovir for all indications except smallpox to the company.

- In September 2019, the company filed for manufacturing and marketing approval of the ready-to-dilute (RTD) liquid formulation of Treakisym®. The application covers all indications for which Treakisym® has already been approved; if the RTD formulation is approved for the additional indication of r/r DLBCL, which is currently in a clinical trial stage, it can also be used to treat r/r DLBCL. Once the company obtains approval for the RTD formulation, it plans to launch the product in Q1 FY12/21.
- In August 2019, SymBio announced a revision to its FY12/19 earnings forecast. In Q2 FY12/19, impurities and appearance defects were found in Treakisym® 100mg vials imported from Astellas Deutschland, which led to the company returning the whole batch. Thus only a fraction of the batches scheduled for shipment in 2Q FY12/19 onward can be shipped by the end of the year, with shipments possibly being delayed until Q1 FY12/20. The company therefore revised down its FY12/19 earnings forecast.
- In June 2019, the US Food and Drug Administration (FDA) granted accelerated approval to polatuzumab vedotin-piiq, a CD79b-directed antibody-drug conjugate, in combination with bendamustine (product name: Treakisym®) and rituximab (BR therapy) for patients with relapsed or refractory DLBCL who are not eligible for transplant. Polatuzumab vedotin-piiq was discovered by Roche Group company Genentech and is being developed in Japan by Chugai Pharmaceutical, another member of the Roche Group.
- In 1H FY12/19, capital stock and capital surplus each increased by JPY1.3bn YoY, reflecting proceeds from the issuance of shares resulting from exercise of the 46th stock acquisition rights.
- In April 2019, the first patient was enrolled in the clinical trial of the liquid formulation of Treakisym® (rapid infusion [RI] formulation), whose primary goal was to confirm safety of the drug.
- In March 2019, the company obtained approval to partially revise the marketing approval of anticancer drug Treakisym® as a pretreatment agent in antigen-specific T cell infusion therapy. This enabled the use of Treakisym® as a pretreatment agent for the chimeric antigen receptor T-cell (CAR-T) therapy Kymriah® intravenous infusion.

**Introduction of new pipeline candidate**

SymBio concluded an exclusive global license agreement with Chimerix Inc. for the antiviral drug brincidofovir (SyB V-1901, hereafter BCV)*[1]. The company acquired exclusive global rights to develop, manufacture, and market BCV for all diseases except smallpox.

The company will initially develop BCV for treatment of viral hemorrhagic cystitis (vHC)*[2] and HHV-6 encephalitis*[3] occurring after hematopoietic stem cell and kidney transplantation, which have high unmet medical demand. The company also looks to expand its business in Europe, the US and Asia (including China), where organ transplant markets are large. It will also consider forming partnerships that take advantage of regional characteristics of these target diseases. The company will explore all options for maximizing business value, including the strategic utilization of wholly-owned subsidiary SymBio Pharma USA, Inc. established in May 2016.

1. Brincidofovir (BCV) has a structure in which cidofovir (CDV, an antiviral drug already approved and marketed in the US and Europe but not approved in Japan) is bound to a lipid chain (hexadecycloxypropyl, HDP). It is absorbed into the lipid bilayer membrane and transferred into cells, where the bound lipid chain (HDP) is metabolized and separated from the structure by intracellular phospholipases. This process generates an activator (CDV diphosphate [CDV-PP]) that is retained in the cells for a long period of time, raising the compound's antiviral activity. Furthermore, BCV avoids nephrotoxicity, a fundamental issue plaguing CDV, since HDP conjugation prevents the accumulation of the compound in renal tubular epithelial cells through organic anion transporter 1 (OAT 1) and CDV is released at low levels into the bloodstream.

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

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

**Domestic**

Preparations for in-house sales organization begin

The business alliance agreement between SymBio and Eisai Co., Ltd. under which Eisai acts as a sales agent expires in December 2020. SymBio started to build an in-house sales organization for Treakisym® in the domestic market in October 2018. Key management priority is to move into the black in FY12/21 and ongoing profit growth thereafter. The company is therefore laying the groundwork for a shift to an internal sales organization to drive future business development.

The company increased Treakisym® sales representatives and conducted training needed to form the core of its in-house marketing network. Information provision activities were started from July 2019 by the Treakisym® sales representatives dispatched to each region to promote the shift to a nationwide operation with close local ties. The company also made steady progress with preparation of infrastructure such as logistics, distribution, and information systems.

Treakisym® (SyB L-0501[lyophilized injection]/SyB L-1701 [RTD]/SyB L-1702 [RI]/SyB C-0501 [oral]; 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 untreated low-grade non-Hodgkin's lymphoma and mantle cell lymphoma (marketing approval obtained in December 2016), refractory or relapsed low-grade non-Hodgkin's lymphoma and mantle cell lymphoma (October 2010), and chronic lymphocytic leukemia (August 2016).

As a result of additional indications, Treakisym® is steadily increasing its market share in the area of first-line treatment in medical settings by replacing R-CHOP, the conventional standard treatment. The combination therapy of Treakisym® and rituximab (BR therapy) was newly included in the Practical Guidelines for Hematological Malignancies 2018 edited and published by Japanese Society of Hematology as a standard treatment option, which applies to all of the approved indications. This has seen Treakisym® establish its position as a standard treatment for lymphatic cancer. According to the company, market share in the area of first-line treatment increased to 55%.

In addition to the above three approved indications, the company is conducting a phase III clinical trial for the fourth indication of relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL), and the trial is progressing well with an aim to obtain approval. In response to strong medical needs, the company began a phase III clinical trial in August 2017. With the enrollment of the first patient in January 2018, the company made steady progress and completed enrollments in April 2019. The observational period for all patients (Last Patient Last Visit, LPLV) was completed in September 2019. Results of the trial indicated that the primary endpoint of response rate exceeded initial expectations. Going forward, the company will prepare for the approval filing, projected for Q2 2020.

SymBio is targeting a transition to Treakisym® liquid formulation (RTD and RI formulations), for which it concluded an exclusive licensing agreement in Japan with Eagle Pharmaceuticals (based in New Jersey, US) in September 2017. The company has already consulted with PMDA and filed for approval of the RTD formulation in September 2019 with an eye towards commercialization by Q1 2021. SymBio launched clinical trials for the RI formulation in November 2018 primarily to confirm safety, and has made steady progress with patient enrollments since enrolling the first patient in April 2019, having enrolled 26 patients as of end

October 2019. Liquid formulations of Treakisym® will offer significant value added (reduced burden) to patients and healthcare professionals, and liquid formula patent protection makes it possible to extend the product life of Treakisym® until 2031.

In July 2018, SymBio obtained approval for the partial revision to the marketing authorization of Treakisym®. As a result, Treakisym® can now be used in combination with not only rituximab but new anti-CD20 antibodies as well. This will allow combination therapy with obinutuzumab (launched in August 2018) for the treatment of CD 20-positive follicular lymphoma (FL), the most common histological type of low-grade NHL, enabling the company to provide patients with a new treatment therapy. In March 2019, the company obtained approval for the partial revision to its application concerning the use of Treakisym® as a pretreatment agent in tumor-specific T cell infusion therapy. This will allow Treakisym® to be used as a pretreatment agent for Kymriah® intravenous infusion, which was approved as the first chimeric antigen receptor T-cell (CAR-T) therapy in Japan and listed on the NHI drug price list in May 2019.

To reinforce the position of Treakisym® at the core of its business to strengthen its business foundation, SymBio is looking at the possibility of developing Treakisym® for other disorders such as solid tumors and autoimmune diseases. The company commenced a phase I clinical trial for progressive solid tumors in January 2018, with the aim of examining the recommended dosage and schedule as well as tolerability and safety of the oral formulation of Treakisym®, and narrowing down the types of potential target tumors. With the enrollment of the first patient in May 2018, the company is currently working on enrolling more patients for the trial. To evaluate the effect of oral administration of Treakisym® on the immune system, the company concluded a joint research agreement with Keio University in May 2018 and performed a preclinical study to verify the efficacy of the oral formulation of Treakisym® in treating systemic lupus erythematosus (SLE), a form of autoimmune disease. The company is currently compiling study results and after evaluating the findings will consider the next stage of this research project (including clinical trials).

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 (48 patients enrolled as of October 2019). The global phase III trial addresses higher-risk myelodysplastic syndromes (higher-risk MDS), which do not respond to the current standard treatment with hypomethylating agents, which relapse after treatment under the current standard of care, or which are intolerant to hypomethylating agents, and is under way at clinical trial sites in more than 20 countries worldwide. In October 2019, Onconova announced that it had reached 90% of its target of enrolling 360 patients worldwide. The company plans to report top-line (primary endpoint) results in 1H 2020. Based on these trial results, the company plans to apply for approval in Japan at the same time as in the US and Europe.

Regarding the oral formulation of rigosertib, Onconova has completed phase I/II clinical trials for the drug used in combination with azacitidine as first-line treatment for higher-risk MDS and phase II clinical trials for transfusion-dependent lower-risk MDS in the US. To verify the tolerability and safety of the oral formulation of rigosertib among Japanese patients, SymBio began phase I clinical trials in Japan in June 2017, enrolled the first patients in October 2017, and completed patient enrollment in June 2019. After completing the phase I trials, the company will consider phase I clinical trials for rigosertib used in combination with azacitidine, participate in global clinical trials of the drug used in combination with azacitidine as first-line treatment for higher-risk MDS currently planned by Onconova, and apply for approval of the oral formulation of the drug in Japan at the same time as in the US and Europe. In December 2018, Onconova submitted a Special Protocol Assessment (SPA) request to the US Food and Drug Administration (FDA) to speed up the approval review for the global trials. Onconova announced in October 2019 that it was considering a phase II controlled study comparing rigosertib + azacitidine to azacitidine stand-alone therapy for untreated patients with higher-risk MDS. In regards to development of rigosertib for transfusion-dependent lower-risk MDS, the company is considering participating from Japan while monitoring Onconova's development progress.

**SyB P-1501, a post-operative patient-controlled analgesia**
Regarding SyB P-1501 licensed by The Medicines Company (through its wholly owned subsidiary Incline Therapeutics, Inc.) in October 2015, SymBio learned of an event that raised concerns about the continuity of its business, and in the interests of patient welfare, it suspended further patient enrollment in April 2017.

The company initiated an arbitration against The Medicines Company, under the rules of the International Chamber of Commerce, seeking damages of USD82mn (approximately JPY9.0bn) arising from The Medicines Company's repudiation of the license agreement. SymBio argued that The Medicine Company's failure to provide sufficient assurance to the company regarding the performance of obligations under on the license agreement in light of its decision to suspend and withdraw from business activities relating to SyB P-1501in the European and US markets was a material breach of the license agreement. Arbitration proceedings against The Medicines Company are still ongoing.

**Overseas**

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

## 1H FY12/19 results

- Sales: JPY2.0bn (+4.0% YoY)
- Operating loss: JPY2.0bn (loss of JPY1.3bn in 1H FY12/18)
- Recurring loss: JPY2.1bn (loss of JPY1.4bn in 1H FY12/18)
- Net loss: JPY2.1bn (loss of JPY1.4bn in 1H FY12/18)

Sales rose on domestic product sales of Treakisym®.

On a quarterly basis, sales grew 81.4% YoY to JPY1.6bn in Q1 (Jan–Mar 2019), but fell 62.2% YoY to JPY394mn in Q2 (Apr–Jun 2019). In Q2, impurities and appearance defects were found in Treakisym® 100mg vials imported from Astellas Deutschland, which led to the company returning the whole batch. For this reason, Q2 sales were low relative to Q1 as well as Q2 FY12/18. In order to resolve this problem, SymBio says that all parties involved are working to return supplies to normal; it has requested that Astellas Deutschland take steps to improve its manufacturing and quality control arrangements for Treakisym® 100mg.

Gross profit fell 7.7% YoY to JPY529mn, and the gross profit margin narrowed by 3.3pp YoY to 26.4%. On a quarterly basis, gross profit was 144.0% higher YoY at JPY609mn in Q1, for a gross profit margin of 37.8% (+9.7pp YoY), but dropped to a loss of JPY79mn in Q2. In addition to weak sales in Q2, SymBio booked a JPY188mn inventory valuation loss under CoGS, in connection with the aforementioned quality issues associated with a particular batch of Treakisym® 100mg.

SG&A expenses rose 34.1% YoY to JPY2.5bn and R&D expenses increased 14.8% YoY to JPY963mn, which included expenses for conducting clinical trials of intravenous and oral formulations of Treakisym® and rigosertib. Excluding R&D expenses, SG&A expenses increased by 49.3% YoY to JPY1.6bn. Fees and commissions paid for expert consultations rose 85.5% YoY to JPY542mn. On the other hand, personnel expenses (total for directors' remuneration and salaries) were 3.0% lower YoY at JPY248mn, as although the company hired more Treakisym® managers in the process of building an in-house sales organization, some administrative staff retired.

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

Major progress in 1H FY12/19 was as follows:

- In August 2019, SymBio announced a revision to its FY12/19 earnings forecast. In Q2 FY12/19, impurities and appearance defects were found in Treakisym® 100mg vials imported from Astellas Deutschland, which led to the company returning the whole batch. Thus only a fraction of the batches scheduled for shipment in 2Q FY12/19 onward can be shipped by the end of the year, with shipments possibly being delayed until Q1 FY12/20. The company therefore revised down its FY12/19 earnings forecast.

- Progress was made in Q2 in the company's arbitration against The Medicines Company, and SymBio expects a conclusion to be reached by the end of 2019.
- In July 2019, the company agreed upon basic terms for a new license.
- In June 2019, the US Food and Drug Administration (FDA) granted accelerated approval to polatuzumab vedotin-piiq, a CD79b-directed antibody-drug conjugate, in combination with bendamustine (product name: Treakisym®) and rituximab (BR therapy) for patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who are not eligible for transplant. Polatuzumab vedotin-piiq was discovered by Roche Group company Genentech and is being developed in Japan by Chugai Pharmaceutical, another member of the Roche Group.
- In 1H FY12/19, capital stock and capital surplus each increased by JPY1.3bn YoY, reflecting proceeds from the issuance of shares resulting from exercise of the 46th stock acquisition rights.
- In April 2019, the first patient was enrolled in the clinical trial of the liquid formulation of Treakisym® (rapid infusion [RI] formulation), whose primary goal was to confirm safety of the drug.
- In April 2019, patient enrollment was completed for the phase III clinical trial of anticancer drug Treakisym® as a treatment for relapsed or refractory diffuse large B-cell lymphoma (DLBCL). Once the follow-up period is over, the company plans to statistically analyze the efficacy and safety of the drug with an aim of filing for approval for the additional indication of relapsed or refractory DLBCL in Q2 FY12/20.
- In March 2019, the company obtained approval to partially revise the marketing approval of anticancer drug Treakisym® as a pretreatment agent in antigen-specific T cell infusion therapy. This enabled the use of Treakisym® as a pretreatment agent for the chimeric antigen receptor T-cell (CAR-T) therapy Kymriah® intravenous infusion.

**Domestic**

Preparations for in-house sales organization begin

The business alliance agreement between SymBio and Eisai Co., Ltd. under which Eisai acts as a sales agent expires in December 2020. SymBio started to build an in-house sales organization for Treakisym® in the domestic market in October 2018. Key management priority is to move into the black in FY12/21 and ongoing profit growth thereafter. The company is therefore laying the groundwork for a shift to an internal sales organization to drive future business development.

Twenty Treakisym® managers are to form the core of the marketing team in the internal sales organization. The company conducted the necessary recruitment and training activities, and prepared for deployment to each region of responsibility as planned by the end of 1H. In Q3, SymBio intends to deploy Treakisym® managers across Japan. The company is also making steady progress with preparation of infrastructure such as logistics, distribution, and information systems.

Treakisym® (SyB L-0501[lyophilized injection]/SyB L-1701 [RTD]/SyB L-1702 [RI]/SyB C-0501 [oral]; 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 untreated low-grade non-Hodgkin's lymphoma and mantle cell lymphoma (marketing approval obtained in December 2016), refractory or relapsed low-grade non-Hodgkin's lymphoma and mantle cell lymphoma (October 2010), and chronic lymphocytic leukemia (August 2016).

As a result of additional indications, Treakisym® is steadily increasing its market share in the area of first-line treatment in medical settings by replacing R-CHOP, the conventional standard treatment. The combination therapy of Treakisym® and rituximab (BR therapy) was newly included in the Practical Guidelines for Hematological Malignancies 2018 edited and published by Japanese Society of Hematology as a standard treatment option, which applies to all of the approved indications. This has seen Treakisym® establish its position as a standard treatment for lymphatic cancer. According to the company, market share in the area of first-line treatment increased to 55% (from 52% in Q2 FY12/18). SymBio expects market share in the area of first-line treatment to grow further from 2H FY12/19, as the aforementioned Treakisym® managers become fully operational.

In addition to the above three approved indications, the company is conducting phase III clinical trials for the fourth indication of relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL) and these are progressing well with an aim to obtain approval. In response to strong medical needs, the company began phase III clinical trials in August 2017, and with the enrollment of the first patient in January 2018, is working on enrolling patients. The company has made steady progress in enrollments following the first patient in January 2018, completing enrollments in April 2019. Going forward, after completing the follow-up period for enrolled cases, it will prepare to file an application for regulatory approval.

SymBio is targeting a transition to Treakisym® liquid formulation (RTD and RI formulations), for which it concluded an exclusive licensing agreement in Japan with Eagle Pharmaceuticals (based in New Jersey, US) in September 2017. The company has already consulted with PMDA and is preparing to file for approval of the RTD formulation in 2H FY12/19. SymBio launched clinical trials for the RI formulation in November 2018 primarily to confirm safety, and has made steady progress with patient enrollments since enrolling the first patient in April 2019. Liquid formulations of Treakisym® will offer significant value added (reduced burden) to patients and healthcare professionals, and liquid formula patent protection makes it possible to extend the product life of Treakisym® until 2031.

In July 2018, SymBio obtained approval for the partial revision to the marketing authorization of Treakisym®. As a result, Treakisym® can now be used in combination with not only rituximab but new anti-CD20 antibodies as well. This will allow combination therapy with obinutuzumab (launched in August 2018) for the treatment of CD 20-positive follicular lymphoma (FL), the most common histological type of low-grade NHL, enabling the company to provide patients with a new treatment therapy. In March 2019, the company obtained approval for the partial revision to its application concerning the use of Treakisym® as a pretreatment agent in tumor-specific T cell infusion therapy. This will allow Treakisym® to be used as a pretreatment agent for Kymriah® intravenous infusion, which was approved as the first chimeric antigen receptor T-cell (CAR-T) therapy in Japan and listed on the NHI drug price list in May 2019.

To reinforce the position of Treakisym® at the core of its business to strengthen its business foundation, SymBio is developing an oral formulation of the drug in addition to the injection currently under development or on sale. The company commenced a phase I clinical trial for progressive solid tumors in January 2018, with the aim of examining the recommended dosage and schedule as well as tolerability and safety of the oral formulation of Treakisym®, and narrowing down the types of potential target tumors. With the enrollment of the first patient in May 2018, the company is currently working on enrolling more patients for the trial. To evaluate the effect of oral administration of Treakisym® on the immune system, the company concluded a joint research agreement with Keio University in May 2018 and performed a preclinical study to verify the efficacy of the oral formulation of Treakisym® in treating systemic lupus erythematosus (SLE), a form of autoimmune disease. The company will consider the next stage of this research project (including clinical trials) after evaluating the results of the preclinical study.

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 (44 patients enrolled as of July 2019, versus a target of 50). The global phase III trial addresses higher-risk myelodysplastic syndromes (higher-risk MDS), which do not respond to the current standard treatment with hypomethylating agents, which relapse after treatment under the current standard of care, or which are intolerant to hypomethylating agents, and is under way at clinical trial sites in more than 20 countries worldwide. As of March 2019, the company had reached 75% of its target of enrolling 360 patients worldwide. Based on these trial results, the company plans to apply for approval in Japan at the same time as in the US and Europe.

Regarding the oral formulation of rigosertib, Onconova has completed phase I/II clinical trials for the drug used in combination with azacitidine as first-line treatment for higher-risk MDS and Phase II clinical trials for transfusion-dependent lower-risk MDS in the US. To verify the tolerability and safety of the oral formulation of rigosertib among Japanese patients, SymBio began phase I clinical trials in Japan in June 2017, enrolled the first patients in October 2017, and completed patient enrollment in June 2019. After completing the phase I trials, the company plans to start phase I clinical trials for rigosertib used in combination with azacitidine, participate in global phase III clinical trials of the drug used in combination with azacitidine as first-line treatment for

higher-risk MDS currently planned by Onconova, and apply for approval of the oral formulation of the drug in Japan at the same time as in the US and Europe. In December 2018, Onconova submitted a Special Protocol Assessment (SPA) request to the US Food and Drug Administration (FDA) to speed up the approval review for the global trials, and plans to begin phase III clinical trials as soon as it receives approval from the FDA. In regards to development of rigosertib for transfusion-dependent lower-risk MDS, the company is considering participating from Japan while monitoring Onconova's development progress.

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

Regarding SyB P-1501 licensed by The Medicines Company (through its wholly owned subsidiary Incline Therapeutics, Inc.) in October 2015, SymBio learned of an event that raised concerns about the continuity of its business, and in the interests of patient welfare, it suspended further patient enrollment in April 2017. The license agreement was terminated in November 2017, and the development of the drug was terminated in February 2018.

In October 2017, SymBio initiated an arbitration against The Medicines Company, under the rules of the International Chamber of Commerce, seeking damages of USD82mn (approximately JPY9.0bn) arising from The Medicines Company's repudiation of the license agreement. Arbitration proceedings against The Medicines Company are still ongoing. According to SymBio, progress was made in Q2 in the company's arbitration against The Medicines Company, and the company expects that a conclusion will be reached by end-2019.

**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. The company is considering licensing rights for several drug candidates. In July 2019, the company agreed upon basic terms for a new license.

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 licensing 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 South Korea, Taiwan, and Singapore, and product sales were in line with the company's plans.

## Income statement

| Income statement (JPYmn) | FY12/10 Par. | FY12/11 Par. | FY12/12 Par. | FY12/13 Par. | FY12/14 Par. | FY12/15 Par. | FY12/16 Par. | FY12/17 Par. | FY12/18 Par. | FY12/19 Par. |
|---|---|---|---|---|---|---|---|---|---|---|
| **Sales** | **1,450** | **1,883** | **1,955** | **1,532** | **1,955** | **1,933** | **2,368** | **3,444** | **3,836** | **2,838** |
| YoY | 21.7% | 29.8% | 3.9% | -21.6% | 27.6% | -1.1% | 22.5% | 45.4% | 11.4% | -26.0% |
| CoGS | 238 | 1,224 | 1,362 | 1,214 | 1,428 | 1,350 | 1,464 | 2,413 | 2,663 | 1,973 |
| **Gross profit** | **1,212** | **658** | **593** | **318** | **527** | **583** | **904** | **1,031** | **1,173** | **865** |
| GPM | 83.6% | 35.0% | 30.3% | 20.8% | 26.9% | 30.2% | 38.2% | 29.9% | 30.6% | 30.5% |
| SG&A expenses | 1,825 | 2,725 | 2,293 | 1,999 | 1,830 | 3,135 | 3,031 | 4,978 | 3,829 | 5,166 |
| SG&A ratio | 125.8% | 144.8% | 117.3% | 130.4% | 93.6% | 162.1% | 128.0% | 144.5% | 99.8% | 182.1% |
| **Operating profit** | **-613** | **-2,067** | **-1,700** | **-1,681** | **-1,303** | **-2,552** | **-2,127** | **-3,947** | **-2,656** | **-4,302** |
| YoY | - | - | - | - | - | - | - | - | - | - |
| OPM | - | - | - | - | - | - | - | - | - | - |
| Non-operating income | 13 | 56 | 7 | 114 | 215 | 17 | 7 | 5 | 2 | 4 |
| Non-operating expenses | 38 | 85 | 37 | 35 | 22 | 96 | 196 | 34 | 95 | 79 |
| **Recurring profit** | **-638** | **-2,095** | **-1,729** | **-1,601** | **-1,110** | **-2,630** | **-2,317** | **-3,977** | **-2,749** | **-4,377** |
| YoY | - | - | - | - | - | - | - | - | - | - |
| RPM | - | - | - | - | - | - | - | - | - | - |
| Extraordinary gains | - | - | - | - | 2 | 3 | 9 | 17 | 10 | 4 |
| Extraordinary losses | 0 | 5 | 0 | - | 3 | 1 | 1 | 15 | 10 | - |
| Tax charges | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| Implied tax rate | - | - | - | - | - | - | - | - | - | - |
| **Net income** | **-642** | **-2,105** | **-1,733** | **-1,605** | **-1,116** | **-2,632** | **-2,313** | **-3,978** | **-2,753** | **-4,376** |
| YoY | - | - | - | - | - | - | - | - | - | - |
| Net margin | - | - | - | - | - | - | - | - | - | - |

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

See the Earnings Structure section for more information about specific items (from total sales to recurring profit) on the company's income statement. There are no matters requiring special mention regarding non-operating profit/loss, extraordinary profit/loss, corporate income tax, etc.

## Historical forecast accuracy

| Results vs. Initial Est. (JPYmn) | FY12/10 Par. | FY12/11 Par. | FY12/12 Par. | FY12/13 Par. | FY12/14 Par. | FY12/15 Par. | FY12/16 Par. | FY12/17 Par. | FY12/18 Par. | FY12/19 Par. |
|---|---|---|---|---|---|---|---|---|---|---|
| Sales (Initial Est.) | - | 1,933 | 2,338 | 1,927 | 1,785 | 1,785 | 2,339 | 2,903 | 4,201 | 4,465 |
| Sales (Results) | - | 1,883 | 1,955 | 1,532 | 1,955 | 1,933 | 2,368 | 3,444 | 3,836 | 2,838 |
| **Results vs. Initial Est.** | **-** | **-2.6%** | **-16.4%** | **-20.5%** | **9.5%** | **8.3%** | **1.2%** | **18.6%** | **-8.7%** | **-36.4%** |
| Operating profit (Initial Est.) | - | -2,351 | -1,625 | -1,889 | -1,654 | -1,654 | -2,778 | -3,238 | -2,981 | -3,587 |
| Operating profit (Results) | - | -2,067 | -1,700 | -1,681 | -1,303 | -2,552 | -2,127 | -3,947 | -2,656 | -4,302 |
| **Results vs. Initial Est.** | **-** | **-** | **-** | **-** | **-** | **-** | **-** | **-** | **-** | **-** |
| Recurring profit (Initial Est.) | - | -2,398 | -1,652 | -1,922 | -1,650 | -1,650 | -2,811 | -3,303 | -3,044 | -3,612 |
| Recurring profit (Results) | - | -2,095 | -1,729 | -1,601 | -1,110 | -2,630 | -2,317 | -3,977 | -2,749 | -4,377 |
| **Results vs. Initial Est.** | **-** | **-** | **-** | **-** | **-** | **-** | **-** | **-** | **-** | **-** |
| Net income (Initial Est.) | - | -2,407 | -1,656 | -1,926 | -1,654 | -1,654 | -2,815 | -3,306 | -3,056 | -3,612 |
| Net income (Results) | - | -2,105 | -1,733 | -1,605 | -1,116 | -2,632 | -2,313 | -3,978 | -2,753 | -4,376 |
| **Results vs. Initial Est.** | **-** | **-** | **-** | **-** | **-** | **-** | **-** | **-** | **-** | **-** |

Source: Shared Research based on company data
Note: Figures may differ from company materials due to differences in rounding methods.
Note: The company listed its common shares in October 2011, so the forecasts are from FY12/11 onward.

## Balance sheet

| Balance sheet (JPYmn) | FY12/10 Par. | FY12/11 Par. | FY12/12 Par. | FY12/13 Par. | FY12/14 Par. | FY12/15 Par. | FY12/16 Par. | FY12/17 Par. | FY12/18 Par. | FY12/19 Par. |
|---|---|---|---|---|---|---|---|---|---|---|
| **Assets** | | | | | | | | | | |
| Cash and deposits | 2,314 | 4,559 | 4,540 | 6,163 | 5,692 | 4,261 | 5,719 | 2,947 | 4,821 | 3,911 |
| Marketable securities | 1,701 | 1,953 | 300 | 1,100 | 899 | - | - | - | - | |
| Accounts receivable | 6 | 162 | 148 | - | 273 | 301 | 487 | 490 | 412 | 549 |
| Inventories | - | 207 | 165 | 125 | 245 | 133 | 273 | 363 | 534 | 1 |
| Other current assets | 191 | 297 | 268 | 245 | 181 | 131 | 205 | 237 | 271 | 427 |
| **Total current assets** | **4,213** | **7,178** | **5,421** | **7,634** | **7,290** | **4,827** | **6,685** | **4,037** | **6,038** | **4,887** |
| Buildings (net) | 3 | 2 | 3 | 2 | 22 | 22 | 31 | 28 | 37 | 47 |
| Tools, furniture, and fixtures (net) | 19 | 15 | 11 | 6 | 27 | 31 | 43 | 18 | 20 | 19 |
| **Total tangible fixed assets** | **22** | **17** | **14** | **9** | **49** | **53** | **75** | **47** | **57** | **75** |
| **Total other fixed assets** | **27** | **48** | **57** | **37** | **49** | **53** | **77** | **100** | **73** | **70** |
| Software | 1 | 10 | 8 | 6 | 62 | 51 | 42 | 66 | 51 | 95 |
| Other | - | 3 | 3 | 2 | 4 | 1 | - | 3 | 20 | 146 |
| **Total intangible fixed assets** | **1** | **13** | **11** | **8** | **66** | **52** | **42** | **69** | **71** | **241** |
| **Total fixed assets** | **50** | **78** | **82** | **53** | **164** | **158** | **193** | **216** | **201** | **386** |
| **Total assets** | **4,263** | **7,256** | **5,502** | **7,687** | **7,454** | **4,984** | **6,878** | **4,252** | **6,239** | **5,274** |
| **Liabilities** | | | | | | | | | | |
| Accounts payable | 1 | 309 | 330 | - | 306 | 320 | 322 | 604 | 726 | 121 |
| Accounts payable–other | 124 | 278 | 196 | 207 | 143 | 184 | 553 | 331 | 504 | 639 |
| Short-term debt | - | - | - | - | - | - | - | - | - | - |
| Other | 52 | 59 | 73 | 44 | 39 | 47 | 68 | 76 | 107 | 112 |
| **Total current liabilities** | **178** | **646** | **599** | **251** | **488** | **551** | **942** | **1,011** | **1,336** | **872** |
| Long-term debt | - | - | - | - | - | - | - | - | - | - |
| Corporate bonds | | | | | | - | 450 | - | - | - |
| Other fixed liabilities | 2 | 5 | 4 | 3 | 2 | 2 | 1 | 1 | 1 | 2 |
| **Total fixed liabilities** | **2** | **5** | **4** | **3** | **2** | **2** | **451** | **1** | **1** | **2** |
| Total interest-bearing debt | - | - | - | - | - | - | - | - | - | - |
| **Total liabilities** | **180** | **651** | **602** | **254** | **490** | **552** | **1,394** | **1,013** | **1,338** | **874** |
| **Net assets** | | | | | | | | | | |
| Capital stock | 3,711 | 6,025 | 6,025 | 8,059 | 8,331 | 8,331 | 9,948 | 10,762 | 12,973 | 14,871 |
| Capital surplus | 3,681 | 5,995 | 5,995 | 8,029 | 8,301 | 8,301 | 9,918 | 10,732 | 12,943 | 14,841 |
| Retained earnings | -3,309 | -5,413 | -7,146 | -8,752 | -9,868 | -12,500 | -14,813 | -18,791 | -21,543 | -25,919 |
| Treasury stock | - | -0 | -0 | -0 | -0 | -0 | -0 | -0 | -0 | -15 |
| Subscription rights to shares | - | - | 27 | 97 | 200 | 300 | 431 | 537 | 530 | 621 |
| **Total net assets** | **4,083** | **6,606** | **4,900** | **7,433** | **6,964** | **4,432** | **5,485** | **3,239** | **4,902** | **4,400** |
| Working capital | 5 | 61 | -17 | 125 | 212 | 114 | 439 | 249 | 220 | 429 |
| Total interest-bearing debt | - | - | - | - | - | - | - | - | - | - |
| Net debt | -2,314 | -4,559 | -4,540 | -6,163 | -5,692 | -4,261 | -5,719 | -2,947 | -4,821 | -3,911 |

Source: Shared Research based on company data
Note: 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.

### Net assets

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

# Cash flow statement

| Cash flow statement (JPYmn) | FY12/10 Par. | FY12/11 Par. | FY12/12 Par. | FY12/13 Par. | FY12/14 Par. | FY12/15 Par. | FY12/16 Par. | FY12/17 Par. | FY12/18 Par. | FY12/19 Par. |
|---|---|---|---|---|---|---|---|---|---|---|
| Cash flows from operating activities (1) | -754 | -2,074 | -1,659 | -1,677 | -1,266 | -2,272 | -1,960 | -3,817 | -2,325 | -4,351 |
| Cash flows from investing activities (2) | -116 | -117 | -411 | -1,332 | 314 | 1,489 | -44 | -78 | -26 | -216 |
| Free cash flow (1+2) | -870 | -2,191 | -2,069 | -3,010 | -952 | -783 | -2,004 | -3,894 | -2,351 | -4,567 |
| Cash flows from financing activities | 663 | 4,611 | -1 | 4,057 | 544 | -3 | 3,658 | 1,164 | 4,272 | 3,740 |
| Depreciation and good will amortization (A) | 7 | 8 | 9 | 8 | 13 | 24 | 26 | 30 | 35 | 38 |
| Capital expenditures (B) | -14 | -12 | -3 | - | -109 | -24 | -28 | -57 | -40 | -217 |
| Working capital change (C) | 5 | 56 | -78 | 142 | 86 | -98 | 325 | -190 | -29 | 209 |
| Simple FCF (NI + A + B - C) | -655 | -2,165 | -1,650 | -1,739 | -1,298 | -2,534 | -2,640 | -3,815 | -2,729 | -4,764 |
| Cash and cash equivalents (year-end) | 3,916 | 6,311 | 4,240 | 5,294 | 5,092 | 4,261 | 5,719 | 2,947 | 4,821 | 3,911 |

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

## Cash flows from operating activities

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

## Cash flows from investing activities

Outlays on the purchase of tangible fixed assets and intangible assets are limited as SymBio outsources 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.

### 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 |
| Jan. to Dec. 2017 | 7,518,400 | 54,049,224 | 1,627 | 21,493 | Exercise of stock options attached to convertible corporate bonds and other stock options |
| Apr. to Dec. 2018 | 28,349,700 | 82,398,924 | 4,422 | 25,915 | Exercise of stock options |
| Jan. to Dec. 2019 | 1,726,800 | 26,437,681 | 3,796 | 29,711 | Exercise of stock options |

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

# Other information

## Claim for damages

### SymBio initiated arbitration against The Medicines Company, seeking damages of USD82mn

The license agreement the SymBio entered with The Medicines Company (MDCO) on October 5, 2015 for the exclusive rights to develop and commercialize the patient-controlled pain management drug SyB P-1501 (IONSYS in the US) has terminated effective November 30, 2017, pursuant to the terms of the subject agreement.

As disclosed in MDCO's Form 10-Q filing of November 9, 2017, the company initiated an arbitration against MDCO on October 11, 2017, under the rules of the International Chamber of Commerce, seeking damages of USD82mn (approximately JPY9bn) arising from MDCO's repudiation of the license agreement. In the Request for Arbitration, SymBio claims that MDCO failed to provide SymBio with adequate assurances of performance of MDCO's contractual obligations under the license agreement in the light of MDCO's decision to (1) discontinue and withdraw the drug (IONSYS®) from the markets in the US and EU and (2) cease related commercialization activities. SymBio claims such failure by MDCO to be a repudiation and material breach of the license agreement, resulting in its termination.

SymBio claims that when MDCO decided to suspend or withdraw its business related to SyB P-1501 in Europe and the US it failed to provide sufficient guarantees to fulfill its obligations under the license agreement, which was a material breach. Arbitration proceedings with MDCO are still ongoing, and an arbitration ruling is expected in 1H FY12/20. Novartis AG (Switzerland) announced on January 6, 2020 that it has completed the acquisition of MDCO.

> The International Chamber of Commerce, a Paris-based international organization, has around 130 participating countries including Japan. Its flagship institution, the International Court of Arbitration, aims to solve disputes arising from international commercial agreements not by lawsuits, but by arbitration. When one party does not obey the court's judgment, the other party may perform compulsory execution.

## History

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

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

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

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

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

As of February 2020, Treakisym® for relapsed or refractory low-grade NHL and MCL is the company's mainstay product. Clinical trials are also in preparation or under way toward attaining domestic approval for additional Treakisym® indications, RTD and RI formulations of Treakisym®, and anticancer drug rigosertib for myelodysplastic syndromes. In addition, after acquiring exclusive worldwide rights from Chimerix in September 2019 to develop, manufacture, and market brincidofovir for all indications except smallpox, SymBio looks to commercialize it by the mid-2020s.

| | |
|---|---|
| March 2005 | SymBio Pharmaceuticals Limited established with JPY30mn in capital. |
| December 2005 | License Agreement finalized with Astellas Pharma GmbH for SyB L-0501 (bendamustine) development and commercialization rights in Japan. |
| March 2006 | Manufacturer's License (packaging, labeling and storage) obtained from Tokyo Metropolitan Government (License #13AZ200010). |
| March 2007 | Abeille Pharmaceuticals licensed SyB D-0701 (granisetron patch) to SymBio Pharmaceuticals for development & commercialization in Japan, China (HK), Taiwan, South Korea and Singapore. |
| March 2007 | License Agreement finalized with Astellas Deutschland GmbH for SyB L-0501 (bendamustine) development & commercialization rights in China (HK), Taiwan, South Korea and Singapore. |
| August 2008 | License Agreement finalized with Eisai Co., Ltd. for co-development and commercialization rights of SyB L-0501 (bendamustine) in Japan. |
| March 2009 | SymBio Pharmaceuticals concluded Sublicense Agreement with Cephalon, Inc. for development and commercialization rights of bendamustine hydrochloride in China (HK). |
| May 2009 | License Agreement finalized with Eisai Co., Ltd. for co-development and commercialization rights of SyB L-0501 (bendamustine) in South Korea and Singapore. |
| September 2010 | SymBio Pharmaceuticals and Eisai launch SYMBENDA® (bendamustine) in Singapore for the treatment of Low-grade Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukemia. |
| October 2010 | Announced NDA Approval of Treakisym® (bendamustine) in Japan. |
| December 2010 | Launched Treakisym® in Japan. |
| July 2011 | Onconova and SymBio Pharmaceuticals 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 South 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 anticancer drug Treakisym® for the additional indication of first-line treatment of low-grade non-Hodgkin's lymphoma and mantle cell lymphoma. |
| September 2017 | Concluded license agreement with Eagle Pharmaceuticals, Inc. (US), granting SymBio exclusive rights to develop, market, and sell Eagle's bendamustine hydrochloride RTD and RI products in Japan. |
| September 2019 | Concluded license agreement with Chimerix Inc. (US), granting SymBio exclusive worldwide rights to develop, manufacture, and market antiviral brincidofovir for all indications except smallpox. |

## News and topics

### May 2020

On **May 11, 2020**, the company announced the completion of approval filing regarding the combination therapy of Treakisym® and rituximab for the treatment of relapsed or refractory diffuse large B-cell lymphoma.

The company filed for approval of partial change to the manufacturing and marketing authorization of anticancer drug Treakisym® (generic name: bendamustine), which will allow the drug to be used in combination with rituximab to treat relapsed or refractory diffuse large B-cell lymphoma.

### March 2020

On **March 25, 2020**, the company announced the completion of patient enrollment for the global phase III INSPIRE study concerning anticancer agent rigosertib.

On March 24, 2020, Onconova Therapeutics, Inc., which provides licenses for rigosertib, an anticancer agent currently being developed by SymBio, announced the achievement of the target number of 360 patient enrollments for rigosertib's global phase III INSPIRE study.

Out of the 360 patient enrollments, 48 were enrolled in Japan. The company expects that the fulfillment status of the study's primary endpoints will become clear in Q3 or Q4 FY12/20 and plans to announce the study's results at an academic conference within 2020.

### February 2020

On **February 27, 2020**, the company announced the issuance of the 50th and 51st stock acquisition rights with exercise price revision clauses and the conclusion of a third-party allotment agreement (commit issue program).

The company agreed with EVO FUND (the allottee) to issue the 50th and 51st stock acquisition rights and to enter with the allottee into a third-party allotment agreement on stock acquisition rights (commit issue program), on condition of becoming effective via notification in accordance with the Financial Instruments and Exchange Act.

**Summary of subscription**

| | |
|---|---|
| Date of allotment | March 16, 2020 |
| Number of stock acquisition rights | 10,000,000 units<br>(50th stock acquisition rights: 7,000,000 units; 51st stock acquisition rights: 3,000,000 units) |
| Issue price | JPY11mn<br>(50th stock acquisition rights: JPY1.06 per unit; 51st stock acquisition rights: JPY1.04 per unit) |
| Number of dilutive shares from the issuance | 10,000,000 shares (one share per unit; corresponds to a dilution rate of 37.8% against total number of shares outstanding as of December 31, 2019)<br>No maximum exercise price.<br>While the minimum exercise price is JPY291, even at the minimum exercise price, the number of dilutive shares is 10,000,000. |
| Amount of funding | JPY5,450mn |
| Exercise price and conditions for revising the exercise price | The initial price is set at JPY547.<br>The initial revision of the exercise price on the 50th and 51st stock acquisition rights will take place on March 17, 2020, and further revisions will take place after the passage of each subsequent five trading-day period. In the event the exercise price is revised, on the next trading day following the fifth trading day counted from the date on which the exercise price was previously revised (the revision date), the exercise price will be revised to an amount obtained by multiplying the simple average value of the volume weighted average price (VWAP) of SymBio's common shares in regular trading announced by the Tokyo Stock Exchange on each trading day for the five consecutive trading days prior to the revision date by 94%. However, the price will be revised to the minimum exercise price if such price falls below the minimum exercise price. |
| Method for subscription or | All of the stock acquisition rights will be allotted to EVO FUND through third-party allotment. |

| | |
|---|---|
| allotment (allottee) | |

Characteristics of the 50th and 51st stock acquisition rights and specific uses of the funds to be raised

- ▷ 50th stock acquisition rights: The exercise period begins on the trading day immediately following issuance. Once the exercise period begins, the allottee shall in principle exercise all of the 50th stock acquisition rights (7,000,000 shares) within 106 trading days. Furthermore, the allottee commits in principle to the exercise of the 50th stock acquisition rights, a number corresponding to 2,800,000 shares or more, within 56 trading days on or after the trading day following the issuance date.
- ▷ 51st stock acquisition rights: The allottee shall in principle exercise all of the 51st stock acquisition rights up to the maximum amount issued within 46 trading days starting from the trading day immediately following the date the company gives an instruction to exercise. The 51st Stock acquisition rights are designed so that it cannot be exercised until the company issues an instruction to exercise. Conditions for issuing an instruction to exercise are that SymBio does not continue to possess undisclosed insider information at the time it issues an instruction to exercise and at the start of the exercise period, and that no portion of the 50th Stock Acquisition Rights is remaining.

| | 50th stock acquisition rights | 51st stock acquisition rights |
|---|---|---|
| Number of stock acquisition rights issued | 7,000,000 units | 3,000,000 units |
| Total issue price | JPY7mn | JPY3mn |
| Total exercise price | JPY3,829mn | JPY1,641mn |
| Expected exercise period (in principle, except if reasons for extension of commitment period occur) | Approximately five months after issuance | Roughly two months from the date specified by SymBio after it issues an instruction to exercise |
| Number of revisions (revised every five trading days in principle) | Total of 21 (planned) | Total of nine (planned) |
| Exercise price | 94% of simple average value of VWAP of SymBio's common shares in regular trading over five consecutive trading days | |
| Commitment | Commitment, in principle, to exercise all of the stock acquisition rights issued within 106 trading days (full commitment)<br>Commitment, in principle, to exercise at least 40% of the stock acquisition rights issued within 56 trading days (first-half commitment) | Commitment, in principle, to exercise the complete number of stock acquisition rights specified within 46 trading days |
| Expected start date of initial exercise | March 17, 2020 | To be determined |
| Expected final date of commitment | Full commitment: August 21, 2020<br>First-half commitment: June 9, 2020 | To be determined |

**Specific uses of the funds to be raised**

| (JPYmn) | Funds to be raised through the 50th stock acquisition rights | Funds to be raised through the 51st stock acquisition rights | Total amount of funds to be raised | Expected timing of expenditure |
|---|---|---|---|---|
| Development of in-licensed drugs | 2,375 | 55 | 2,430 | March 2020 to June 2021 |
| Establishment of the company's own salesforce | 1,431 | 54 | 1,485 | March 2020 to June 2021 |
| Investment in new in-licensing and M&A | 0 | 1,535 | 1,535 | October 2020 to June 2021 |
| Total | 3,806 | 1,644 | 5,450 | |

### Duty to discuss in case of change in funding requirements due to arbitration award

SymBio initiated an arbitration against The Medicines Company on October 11, 2017 under the rules of the International Chamber of Commerce, seeking damages of USD82mn (equivalent to approximately JPY9.0bn), arising out of The Medicines Company's repudiation of the license agreement. This arbitration is ongoing.

Hearing procedures commenced in New York in June 2019, and both parties had finished submitting their final documents as of the end of December 2019. Currently, a panel comprising three arbitrators is preparing an arbitration judgment. Assuming typical submission procedures, SymBio expects to receive an arbitration judgment between March and June 2020. The company intends to establish a provision to the effect that it will be able to request the allottee, after discussions with the allottee, not to exercise more stock acquisition rights than a number specified by the company, in case of an award by the arbitration panel, and that the allottee will discuss any such request with SymBio in good faith.

On **February 6, 2020**, the company announced a medium-term plan covering FY12/20–FY12/22.

**Medium-term plan targets**

| (JPYmn) | FY12/19 Act. | FY12/20 Est. | FY12/21 MTP | FY12/22 MTP |
|---|---|---|---|---|
| Sales | 2,811 | 3,404 | 9,008 | 10,816 |
| Operating profit (loss) | -4,302 | -5,090 | 1,031 | 1,482 |
| Recurring profit (loss) | -4,377 | -5,134 | 987 | 1,438 |
| Net income (loss) | -4,376 | -4,803 | 1,356 | 1,717 |

Source: Shared Research based on company data

## Targets in medium-term plan (FY12/20–FY12/22)

### Sales

SymBio expects product sales of Treakisym® to account for the bulk of sales. Product sales targets reflect the recent pace of market penetration and sales trends, which feed into the company's revised sales growth rates calculated over the medium-term plan period. Currently sales are booked based on product shipment sales to the sales distributor, Eisai. From FY12/21 onward, sales will be booked on product shipment sales to pharmaceutical wholesalers from the company's own in-house sales organization.

In estimating sales in FY12/21 and FY12/22, SymBio disclosed targets assuming increased product sales of Treakisym® as it expects to gain approval of the drug as a treatment for relapsed or refractory diffuse large B-cell lymphoma (DLBCL) in Q2 FY12/21.

### SG&A expenses

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

- The company calculated R&D expenses based on the latest development plans for its existing pipeline comprising Treakisym®, rigosertib IV and oral formulations, and brincidofovir, an antiviral drug for the treatment of infections.
- The company has not factored in upfront payments for in-licensing drug candidates outside its existing pipeline after brincidofovir, an antiviral drug for the treatment of infections, although it will continue to evaluate and investigate them.
- Other SG&A expenses comprise primarily Treakisym® sales and marketing, production and distribution, business development, and management related costs. SymBio is factoring in costs associated with building and operating its own sales organization from FY12/20 onward ahead of the move to sell Treakisym® in-house from FY12/21. It forecasts an increase primarily in personnel costs due to a higher medical representative headcount and higher costs due to more activities.

### Net income

The company forecasts net income exceeding recurring profit in FY12/21 and FY20/22 to reflect the reduction of loss carried over from the previous fiscal year from FY12/21 (when it is expected to turn profitable) onward on tax effect accounting.

### Personnel plans

SymBio assumes it will complete the formation of its 62-member nationwide sales structure by Q2 FY12/20 and transition to operating its own sales force in FY12/21. It plans to allocate the bare minimum of necessary personnel in other parts of the organization and is budgeting for personnel expenses accordingly. Regarding plans to increase personnel expenses for global expansion of brincidofovir, an antiviral drug to treat infections, the company noted that as of February 2020, it was considering a clinical trial plan and would not need extra personnel during the plan period. Accordingly, it has not booked related personnel expenses.

### Funding plans

In April 2018, the company decided to issue its 45th through 47th stock acquisition rights to secure funds needed to operate.

## November 2019

On **November 12, 2019**, the company announced that it would bring forward the exercise date of its 47th stock acquisition rights and that it had concluded an amendment agreement to this effect.

The company decided to instruct the bringing forward of the exercise date of its 47th stock acquisition rights with exercise price revision clauses, which were issued in April 2018 by third-party allotment to EVO FUND, under the terms of the third-party allotment agreement between the two companies. On the same day, the company and EVO FUND also concluded an agreement to amend the third-party allotment agreement. As a result of concluding the amendment agreement, the company can specify the date on which the rights can be exercised and the start date of the full commitment period.

The company's business is progressing more or less on track to turn profitable in FY12/21, but profits in FY12/19 will likely fall short of the company forecast at the time the 47th stock acquisition rights were issued. The expected shortfall is due to delayed product shipments caused by defects discovered in lyophilized injection agents imported from Astellas Deutschland GmbH. The company must purchase and build up inventory in order to begin sales of its own products in FY12/20. It also decided that it needed additional funds to in-license (on a global license agreement) and develop brincidofovir

### Name of issue: SymBio Pharmaceuticals 47th stock acquisition rights

- Number of rights issued: 15,000,000
- Number of shares issued: 3,750,000
- Date of instruction to bring forward exercise date: November 12, 2019
- Exercise start date: November 14, 2019

On **November 5, 2019,** the company announced that primary endpoints (response rates) were met in its phase III study of the anticancer drug Treakisym® targeting relapsed/refractory diffuse large B-cell lymphoma ("r/r DLBCL").

The company stated that the results of the phase III study, the objective of which was to confirm the efficacy and safety of Treakisym used in combination with rituximab (bendamustine-rituximab combination therapy or BR therapy) for treatment of patients with r/r DLBCL, exceeded expected primary endpoints for response rate. The company will compile the results of this study's final analyses and plans to submit an application for the treatment's approval in 1H FY12/20.

## October 2019

On **October 25, 2019,** the company announced an update on the global phase III INSPIRE study of the anticancer agent rigosertib, and on future clinical trial plans.

On October 24, 2019, the licensor for the anticancer agent rigosertib sodium (hereafter, rigosertib), Onconova Therapeutics, Inc. (hereafter, Onconova), provided an update on the global phase III INSPIRE study of rigosertib, and on future clinical trial plans.

The INSPIRE trial is investigating the efficacy of rigosertib in higher-risk myelodysplastic syndrome ("HR-MDS") patients who had progressed on, failed to respond to, or relapsed after previous treatment with a hypomethylating agent, the standard of care for MDS (such patients are described as "HMA-refractory"). Onconova is approaching enrollment of 90% of the required 360 patients for the INSPIRE trial, and anticipates reporting top-line data in the first half of 2020.

Regarding the development of oral rigosertib, as a result of Onconova's consultations with the FDA on SPA (Special Protocol Assessment), Onconova plans to conduct a randomized controlled phase II trial with a control arm of single agent azacitidine for the continued development of oral rigosertib plus azacitidine in untreated HR-MDS patients.

On **October 1, 2019,** the company announced the signing of an exclusive global license agreement for the highly active antiviral drug, brincidofovir (BCV).

On October 1, SymBio said it had entered into a license agreement with US-based Chimerix Inc., for the purpose of acquiring global rights for the antiviral drug, brincidofovir (BCV). Under the terms of the agreement, Chimerix has granted SymBio exclusive worldwide rights to develop, manufacture, and commercialize BCV in all human indications, excluding the prevention and treatment of smallpox. Acquiring the exclusive worldwide license to BCV will aid SymBio in its transition into a global business.

> Chimerix Inc. (NASDAQ: CMRX) is headquartered in the US state of North Carolina, and has developed two types of nucleotide compounds using its own lipid technology. Chimerix was developing brincidofovir (CMX001) as the world's first drug with strong and broad activity against viral diseases (such as AdV, BKV, EBV, and HHV-6) for which there is currently no effective treatment. In order to concentrate on businesses centering on the oncology field, however, Chimerix out-licensed a global license excluding smallpox to SymBio in September 2019.

Based on BCV's strong data, SymBio will initially target treatment of viral hemorrhagic cystitis (vHC) and HHV-6 encephalitis (HHV-6) after allogeneic hematopoietic stem cell transplantation and kidney transplantation, to address critically underserved therapeutic areas. Although other antiviral drugs are currently used for these diseases, there is a long-standing and significant medical need for a treatment that is both effective and safe.

BCV is a lipid conjugate of cidofovir (CDV), which is an antiviral drug already approved and marketed in the US and the EU, but unapproved in Japan. As BCV has not only higher antiviral activity, but also a superior safety profile in comparison with CDV, the company expects BCV to be an effective treatment against a wide spectrum of infectious diseases caused by DNA viruses, including herpes viruses (including CMV), adenovirus, BK virus, papilloma virus, and smallpox virus. BCV's innovative mechanism of action, which is based on conjugating a lipid chain of specified length to a CDV base, dramatically improves efficiency of uptake into the cells where BCV is converted into a direct-acting agent in the cell, resulting in high antiviral effect. Furthermore, BCV is easy to use due to its low risk of nephrotoxicity, which is a serious side effect of CDV. This makes BCV a novel highly active anti-multiviral drug.

## September 2019

On **September 26, 2019,** the company announced filing of an approval application for the RTD formulation of Treakisym®.

The company applied for approval to manufacture and market the ready-to-dilute (RTD) liquid formulation of Treakisym®. If approved, the RTD formulation can be used for the indication of relapsed or refractory diffuse large B-cell lymphoma (DLBCL), for which clinical trial is currently under way, in addition to all previously approved indications. The company plans to launch the product in Q1 FY12/21 after obtaining approval.

On **September 18, 2019,** the company announced achievement of LPLV in phase III clinical trials of anticancer agent Treakisym® targeting relapsed or refractory diffuse large B-cell lymphoma (DLBCL).

The company announced completion of Last Patient Last Visit (LPLV) in its phase III clinical trials of anticancer agent Treakisym® (generic name: bendamustine hydrochloride) for the additional indication of relapsed or refractory DLBCL.

The company plans to announce topline data of the drug's efficacy in Q4 FY12/19 (October–December 2019). Having received the topline results, the company will prepare to file for approval for the additional indication of relapsed or refractory DLBCL in Q2 FY12/20 (April–June 2020).

## Major shareholders

| Top shareholders | Shares held | Shareholding ratio |
|---|---|---|
| Fuminori Yoshida | 862,750 | 3.30% |
| Cephalon, Inc. | 647,250 | 2.50% |
| SMBC Nikko Securities Co., Ltd. | 538,300 | 2.00% |
| Daiwa Securities Co., Ltd. | 293,350 | 1.10% |
| Eisai Co., Ltd. | 208,350 | 0.80% |
| Matsui Securities Co., Ltd. | 189,300 | 0.70% |
| Goldman Sachs International | 185,075 | 0.70% |
| Japan Securities Finance Co., Ltd. | 183,900 | 0.70% |
| Kazuyuki Ota | 157,700 | 0.60% |
| Nomura Securities Co., Ltd. | 155,622 | 0.60% |
| SUM | 3,421,597 | 13.00% |

Source: Shared Research based on company data
As of December 31, 2019
Note: Shareholding ratio calculated excluding treasury shares from shares issued.

## Top management

Representative Director, President and CEO, Fuminori Yoshida established SymBio Pharmaceuticals Limited, his third company, in March of 2005. As founding president of two other major healthcare companies, Nippon BioRad Laboratories (1980) and Amgen Japan (1993), he has earned high visibility and credibility within Japan's healthcare and academic communities. Following his graduation from Gakushuin University in 1971 with a B.S. in Organic Chemistry, he went on to receive an M.S. in Molecular Biology from MIT (1973) and M.S. in Health Policy and Management from Harvard University Graduate School (1975). He possesses dual experience and expertise in the management of major Japanese and American corporations due to his prior work experience at various companies, including Mitsubishi Corporation and AHS Japan, Syntex Japan (1993) as President and CEO, and Amgen Inc. where he served concurrently as Corporate Vice-President, President and CEO of Amgen Japan, for 12 years.

## Employees

SymBio had a total of 107 employees as of December 31, 2019.

| Employees | FY12/10 Par. | FY12/11 Par. | FY12/12 Par. | FY12/13 Par. | FY12/14 Par. | FY12/15 Par. | FY12/16 Par. | FY12/17 Par. | FY12/18 Par. | FY12/19 Par. |
|---|---|---|---|---|---|---|---|---|---|---|
| No. of employees | 56 | 71 | 76 | 72 | 69 | 74 | 77 | 78 | 90 | 107 |
| YoY change | 4 | 15 | 5 | -4 | -3 | 5 | 3 | 1 | 12 | 17 |

Source: Shared Research based on company data

# Other

## Overview of clinical trials

### Development of a new drug takes between 10 and 17 years

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

**Ordinary process and periods of developing new drugs**

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

Source: Shared Research based on company data

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

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

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

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

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

## Ethnic factors in the acceptability of foreign clinical data

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

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

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

## Glossary

**Antigen**

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

**Bridging Data**

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

**Chronic Lymphocytic Leukemia (CLL)**

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

**Contract Research Organization (CRO)**

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

**Dose-Responsiveness**

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

**First-line Drug**

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

**Immunoglobulin G (IgG)**

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

**Mantle-Cell Lymphoma (MCL)**

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

**Monoclonal Antibody**

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

**Multikinase Inhibitor**

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

**Myelodysplastic Syndromes**

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

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

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

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

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

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

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

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

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

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

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

## Company name

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

## Company profile

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

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Daiseki Co., Ltd.
Demae-Can CO., LTD
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Digital Garage Inc.
DIP Corporation
Doshisha Corporation
Dream Incubator Inc.
Earth Corporation
Edion Corporation
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en-Japan Inc.
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GameWith, Inc.
GCA Corporation
Good Com Asset Co., Ltd.
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Hamee Corp.
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HOUSEDO Co., Ltd.
H2O Retailing Corporation
IDOM Inc.
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i-mobile Co.,Ltd.
Inabata & Co., Ltd.
Infocom Corporation
Infomart Corporation
Intelligent Wave, Inc.
ipet Insurance CO., Ltd.
Itochu Enex Co., Ltd.
JMDC Inc.
JSB Co., Ltd.
JTEC Corporation
J Trust Co., Ltd
Japan Best Rescue System Co., Ltd.
JINS HOLDINGS Inc.
JP-HOLDINGS, INC.
KAMEDA SEIKA CO., LTD.
Kanamic Network Co.,LTD
Kawanishi Holdings, Inc.
KFC Holdings Japan, Ltd.
KI-Star Real Estate Co., Ltd.
Kondotec Inc.
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Lasertec Corporation
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Media Do Co., Ltd.
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MedPeer,Inc.
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MIRAIT Holdings Corporation
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Takihyo Co., Ltd.
TEAR Corporation
Tenpo Innovation Inc.
3-D Matrix, Ltd.
TKC Corporation
TKP Corporation
Tsuzuki Denki Co., Ltd.
TOCALO Co., Ltd.
TOKAI Holdings Corporation
Tokyu Construction Co., Ltd.
TOYOBO CO., LTD.
Toyo Ink SC Holdings Co., Ltd
Toyo Tanso Co., Ltd.
Tri-Stage Inc.
TSURUHA Holdings
VISION INC.
VISIONARY HOLDINGS CO., LTD.
WirelessGate, Inc.
YELLOW HAT LTD.
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**Contact Details**
Shared Research Inc.
3-31-12 Sendagi Bunkyo-ku Tokyo, Japan
https://sharedresearch.jp
Phone: +81 (0)3 5834-8787
Email: info@sharedresearch.jp