EDISON

SymBio Pharmaceuticals

Corporate outlook

Looking forward to Treakisym Phase III data

Pharma & biotech

Treakisym continues to generate double-digit sales growth, although 2018 sales were below our expectations. A temporary dip in revenue is expected in 2020 as inventory held by Eisai is wound down, ahead of SymBio establishing its own sales organisation in Japan at the end of that year. The ongoing Phase III study of Treakisym in diffuse large B-cell lymphoma (DLBCL) is on track to allow a potential filing in Q220; we estimate that the DLBCL indication could double peak sales, if approved. SymBio reaffirmed its key goal to become profitable in 2021, the first full year of Treakisym self-commercialisation. Our valuation is ¥26.8bn or ¥308/share.

Year end	Revenue (¥m)	PBT* (¥m)	EPS* (¥)	DPS (¥)	P/E (x)	Yield (%)
12/17	3,444	(3,977)	(79.8)	0.0	N/A	N/A
12/18	3,836	(2,749)	(41.4)	0.0	N/A	N/A
12/19e	4,109	(3,679)	(41.0)	0.0	N/A	N/A
12/20e	3,293	(5,303)	(54.5)	0.0	N/A	N/A

Note: *PBT and EPS (diluted) are normalised, exceptional items.

Guidance adjusted for lower sales, lower costs

Treakisym sales reported by partner Eisai rose by ~12% to ~¥7.6bn in 2018. SymBio's revenue from Eisai and other partners rose by 11.4% to ¥3.8bn, but was 9% below guidance and our forecasts. Net loss declined by 31% to ¥2.8bn. The company's updated mid-range plan forecasts sales to decline by 26% in 2020 to ~¥3.3bn, as it transitions the product shipment destination from Eisai to wholesalers, ahead of the switch to the company's own salesforce in 2021. Its 2021 sales target is lowered by about 17% to ¥9.1bn. However, lower anticipated costs mean that targeted net profit in 2021, the first full year of self-commercialisation, is virtually unchanged at ¥1.0bn.

First Treakisym liquid formulation to file Q121

SymBio is on track to launch its ready-to-dilute (RTD) liquid Treakisym formulation in Q121 and is preparing a marketing application for filing. A trial to confirm the safety of the rapid-infusion (RI) product enrolled the first subject in April 2019, with a market launch targeted in H122. SymBio aims to transition at least 90% of patients from currently marketed freeze dried (FD) powder to liquid formulations by the end of 2021, and 100% by end 2022. This strategy could prevent FD generics from gaining significant market share (generics not expected before June 2022).

Treakisym on track for DLBCL filing in Q220

The Phase III study of Treakisym in DLBCL recently completed recruitment; if the trial is successful, filing is planned for Q220, allowing a potential launch in Q321.

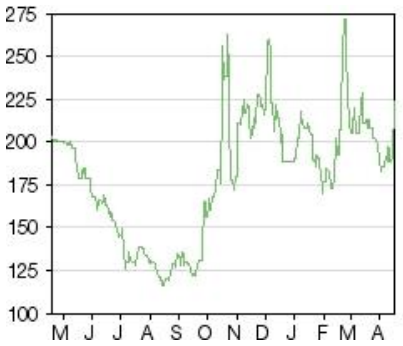
Valuation: rNPV of ¥26.8bn ($237m) or ¥308/share

Our updated SymBio risk-adjusted valuation is vs ¥26,828m ($237m) or ¥308/share (vs ¥25,469m). The increase results from the ¥4.3bn net capital raised in 2018 and rolling forward the model, partly offset by lower peak sales in currently approved Treakisym indications and the sales dip in 2020 due to inventory run-off.

17 April 2019

Price	**¥224**
Market cap	**¥19,555m**
	¥113/$
Net cash (¥m) at end December 2018	4,821
Shares in issue	87.3m
Free float	84%
Code	4582
Primary exchange	Japan
Secondary exchange	OTC US

Share price performance



%	1m	3m	12m
Abs	6.2	8.2	11.4
Rel (local)	4.6	2.3	19.0
52-week high/low		¥272	¥116

Business description

SymBio Pharmaceuticals is a Japanese specialty pharma company with a focus on oncology and haematology. The Treakisym powder formulation was in-licensed from Astellas in 2005; liquid Treakisym was in-licensed from Eagle Pharmaceuticals in 2017. Rigosertib was in-licensed from Onconova.

Next events

Treakisym sales update	Q219
DLBCL top-line data	H219
RTD liquid formulation filing	2019

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Edison profile page

Investment summary

Company description: Japanese specialty pharma company

SymBio is a Japanese specialty pharma company that was established in 2005 and is based in Tokyo. It in-licenses assets with proof-of-concept data for development and commercialisation in Asia-Pacific, removing the need for investment in early-stage R&D. SymBio has two main assets: Treakisym (bendamustine) for blood cancers, with Asia-Pacific marketing rights out-licensed to various commercial partners; and rigosertib for a rare blood cancer, which is being investigated in a global Phase III trial in which SymBio is participating. SymBio plans to commercialise Treakisym and rigosertib via its own salesforce after 2020 in Japan. SymBio is exploring opportunities to in-license further assets during 2019. It is also looking to expand globally and it established a US-based subsidiary in 2016.

Exhibit 1: SymBio main product pipeline

Product	Indication(s)	Stage	Comments
Treakisym (SyB L-0501)	r/r lg NHL/MCL	Marketed	First approved indication in Japan. Partner Eisai reported 2018 sales of ¥7.6bn.
	CLL; first-line lg NHL/MCL	Marketed	Both indications were approved in Japan during 2016 launched by partner Eisai in 2017.
	r/r DLBCL	Phase III	Phase III initiated Q317, fully recruited Q219; targeting filing Q220, launch Q321.
Rigosertib iv (SyB L-1101)	r/r HR-MDS	Phase III	Global Phase III ongoing with SymBio participating; trial expanded after cleared interim analysis in Q118; full recruitment expected H219; SymBio targeting filing in 2021.
Rigosertib oral (SyB C-1101)	First-line HR-MDS (combo) and LR-MDS	Phase I	New Phase I single agent study of oral high-dose rigosertib initiated Q217, to be followed by Phase I in combination with Vidaza; SymBio intends to participate in partner Onconova's planned Phase III combo trial in first-line HR-MDS.

Source: Edison Investment Research. Note: NHL: non-Hodgkin's lymphoma; MCL: mantle cell lymphoma; CLL: chronic lymphocytic leukaemia; lg: low grade; r/r: relapsed/refractory; DLBCL: diffuse large B-cell lymphoma; HR-MDS: higher-risk myelodysplastic syndromes; LR-MDS: lower-risk myelodysplastic syndromes.

Valuation: Risk-adjusted NPV of ¥26.8bn ($237m) or ¥308/share

We value SymBio at ¥26,828m ($237m) or ¥308/share, which is based on a risk-adjusted NPV analysis and includes ¥4.8bn ($43m) net cash at end December 2018. Our valuation includes Treakisym, where we assume sales can continue to grow for the next two years supported by additional indications that were approved in 2016, as well as risk-adjusted contributions for the relapsed/refractory (r/r) DLBCL indication for Treakisym (Phase III ongoing) and for rigosertib. Our valuation assumes that liquid Treakisym formulations will allow SymBio to maintain a greater than 75% share of the market until at least 2031 in the face of competition from powder generics from 2022 onwards.

Financials: Cash runway to H120

We estimate that end December 2018 net cash of ¥4.8bn should be sufficient to fund operations into H120. We model ¥4.2bn of indicative debt in FY20, and note that the company may require additional funding over and above these amounts for investment in new in-licensing or M&A opportunities.

Sensitivities: Treakisym sales growth and pipeline progress

The main sensitivities for SymBio relate to the main assets and SymBio's ability to in-license additional products in the future. For Treakisym, our estimates assume that partner Eisai can continue to grow sales over the next two years in the indications that were approved in 2016. We also expect top-line data from Treakisym in r/r DLBCL during 2019, which will be critical in shaping the future development pathway. SymBio plans to establish its own salesforce to market Treakisym and rigosertib (if approved), which will require investment into a commercial infrastructure from 2019 onwards. We estimate sales organisation costs to be ¥1.7bn per year.

Maximising Treakisym's potential

SymBio acquired the rights to develop and commercialise Treakisym from Astellas in Japan (2005) and subsequently in China/Hong Kong, Korea, Taiwan and Singapore (April 2007). In 2008, SymBio out-licensed the marketing of Treakisym to various commercial partners (an overview of the main agreements is shown in Exhibit 2). Although precise deal terms have not been disclosed, we estimate that SymBio earns an average net margin of around 10–12% on top-line reported Treakisym sales in Asia-Pacific. SymBio intends to establish its own sales organisation to market Treakisym in Japan after the current marketing arrangement with Eisai expires in December 2020.

Exhibit 2: Summary of SymBio's Treakisym commercial out-licensing deals

Region	Partner	Date	Terms
Taiwan	InnoPharmax	March 2008	Development and launch; SymBio receives upfront, milestones and double-digit royalty.
Japan	Eisai	August 2008	Co-development and commercialisation rights; Eisai and SymBio share development costs equally, with Eisai funding 100% of sales and marketing.
South Korea, Singapore	Eisai	May 2009	Development and marketing rights (financials not disclosed).
China (including Hong Kong)	Cephalon (Teva)	April 2009	Development and commercialisation rights (financials not disclosed).

Source: Edison Investment Research, SymBio

SymBio moved to extend the lifecycle of Treakisym when it in-licensed rights to patent-protected liquid formulations of Treakisym from Eagle in September 2017. The liquid formulations are protected by patents that extend to 2031.Treakisym is likely to face competition from generic versions of the marketed FD powder formulation from June 2022, but the company expects to switch the majority of patients to the more convenient liquid formulations following the intended launch of the RTD formulation in Q121.

Encouraged by the longer Treakisym lifecycle, SymBio is investing in a Phase III study of Treakisym in r/r DLBCL patients, an indication where it reported promising results from a Phase II study in 2012. DLBCL comprises around 45% of non-Hodgkin's lymphoma (NHL) cases in Japan, and we estimate that approval in this indication could double the sales potential of Treakisym.

Taken together, the patented liquid formulations and the DLCBL Phase III justify SymBio investing in establishing its own sales organisation to market Treakisym and other drugs such as rigosertib (if approved), in our view. We estimate that SymBio could earn an operating profit margin of 50% of net sales of Treakisym under a self-commercialisation model, compared to an estimated margin of 10–12% of in-market top-line sales under the arrangement with Eisai. We expect the higher margin from self-commercialisation of Treakisym to make SymBio profitable in 2021.

New products could leverage own sales organisation

Having its own sales organisation should enable SymBio to better understand and respond to market needs, positioning it to deliver the benefits of Treakisym to healthcare providers and patients. Treakisym is used in the haematology departments of approximately 900 institutions across Japan, with the top 400 institutions accounting for ~90% of sales. If rigosertib is approved for treating myelodysplastic syndromes (MDS), the top 400 institutions would similarly be expected to account for the majority of use. Therefore, SymBio would be in a position to market rigosertib (if approved) through its own sales organisation for minimal additional cost. The same operation leverage would apply were SymBio to in-licence or develop other haematological drugs. Establishing its own sales organisation will be an important step towards achieving SymBio's vision of establishing itself as a leading speciality pharma company.

Pipeline progress

Exhibit 3 summarises the status of SymBio's product pipeline. The main areas of focus are:

- Obtaining approval for the two liquid formulations of Treakisym to extend the product lifecycle out to 2031.
- Completion of the Phase III study of Treakisym in DLBCL, which could potentially double the sales potential of Treakisym.
- Participating in the global Phase III study of intravenous (iv) rigosertib in MDS, which could become SymBio's second product for haematological cancers.
- Completion of ongoing Phase I studies of oral formulations of Treakisym and rigosertib, which could lead to development of additional indications for both drugs.

Exhibit 3: Status of Treakisym development program

Project	Indication	Phase 1	Phase 2	Phase 3	NDA Filing	Approval
TREAKISYM® FD	2nd line low-grade NHL and MCL	Approved in Oct, 2010				
	CLL	Approved in Aug, 2016				
	1st line low-grade NHL and MCL	Approved in Dec, 2016				
	r/r DLBCL	P3 study started from Aug, 2017				
TREAKISYM® RTD	All approved indications	Preparation for NDA Filing in Progress				
TREAKISYM® RI	All approved indications	Study started from Nov, 2018				
TREAKISYM® Oral	Progressive Solid Tumors	P1 study started from Jan, 2018 Patients Enrollment in Progress				
TREAKISYM® Oral	SLE	Pre-clinical study started from Jul, 2018				

Source: SymBio

Exhibit 4: Rigosertib development program

Project	Indication		Phase 1	Phase 2	Phase 3	NDA Filing	Approval
Rigosertib IV	2nd line higher-risk MDS		Global Phase 3 study in progress				
Rigosertib Oral	2nd line higher-risk MDS	Mono	Japan	Patient enrollment in progress			
	1st line higher-risk MDS	Combo w AZA	Japan	Under preparation			
	1st line higher-risk MDS	Combo w AZA	Global Phase 3 study	Under preparation			

Source: SymBio

Key news anticipated for SymBio in 2019 includes:

- Top-line data from the DLBCL Phase III study.
- Filing for approval of the RTD liquid Treakisym formulation.
- Update on the clinical study of the rapid infusion Treakisym formulation.
- Reaching full recruitment in the rigosertib Phase III study.

Liquid formulations extend Treakisym lifecycle

The new liquid formulations of Treakisym that SymBio in-licensed from Eagle are more convenient for healthcare workers and for patients.

The first in-licensed product is an RTD liquid formulation that will significantly reduce dose preparation time, making it easier and safer for health professionals. This compares to the FD Treakisym, which has to be reconstituted before administration, a time-consuming process that carries the risk of exposing healthcare workers to cytotoxic powders and vapours.

The second in-licensed product is an RI formulation that will cut drug infusion time to 10 minutes from 60 for the current Treakisym product (and the RTD formulation).

Liquid formulations aim to maintain SymBio's market share

We expect the approval pathway for the RTD Treakisym formulation to be relatively straightforward, as the same dose of drug is administered to patients in the same way, with the only difference being the way the dose is prepared. SymBio has consulted with regulators the approval pathway for the RTD formulation and is preparing a filing application. It has narrowed down the timing of the anticipated launch of the RTD product to Q121, which is towards the earlier end of its previous target of H121. A launch at this time would allow it the RTD formulation to be well established in the marketplace before the potential entry of the first FD generics in June 2022.

The RI product represents a greater change to the current treatment protocols, so approval of this product is expected to take longer. SymBio announced on 4 April 2019 that it had enrolled the first of the planned 32 patients in a clinical trial primarily aimed at confirming the safety of the RI formulation; market launch targeted in H122. We conservatively model a 95% chance of a launch of the RI product by the start of 2023.

SymBio aims to transition at least 90% of patients from currently marketed FD powder to liquid formulations by the end of 2021, and 100% by the end of 2022. We take a slightly more conservative view and model 95% of patients being switched to these products.

DLBCL indication could double Treakisym sales

SymBio is seeking to add another indication for Treakisym, in the treatment of r/r DLBCL, an intermediate or high-risk form of NHL. It commenced a Phase III trial to confirm the safety and efficacy of Treakisym plus rituximab in r/r DLBCL in August 2017 and announced on 8 April 2019 that it had completed enrolment. SymBio's mid-range plan aims to file an NDA in Q220 and is targeting a market launch in Q321, if approved, so we expect top-line data to be reported in H219. We model Phase III costs of ¥2bn and a potential launch in H221.

DLBCL is a rapidly growing, intermediate or high-risk form of NHL, in contrast to the slower-growing indolent or low-risk lymphomas that are included in the current approvals for Treakisym.

DLBCL is the most common form of NHL and is estimated to represent 45% of NHL cases in Japan.[1] Based on epidemiology studies[1] and Globocan data, we estimate there will be 35,500 new cases of NHL and 16,000 new cases of DLBCL in Japan in 2020. Assuming that 70% of DLBCL patients progress to receive second-line therapy, we forecast a target market of 11,200 second-line (r/r) DLBCL patients per year in Japan by 2020.

The market of 11,200 r/r DLBCL patients in Japan is almost as large as the combined market of ~12,500 patients for the currently approved indications for Treakisym in chronic lymphocytic leukaemia (CLL) and first-line and r/r low-grade NHL and mantle cell lymphoma (MCL). Given the

1 Chihara et al; British Journal of Haematology, 2014, 164, 536–545.

high unmet need for this patient group, we model a 50% market penetration and peak sales (net sales after discounts) of ¥9.6bn for DLBCL vs ¥9.3bn for the currently approved indications.

Treakisym sales forecasts trimmed after slower 2018

Japan accounts for about 95% of Treakisym sales. Japanese in-market sales of Treakisym estimated from prescription numbers and expressed on a National Health Insurance price basis grew by 11.6% to ~¥8.5bn in 2018, from ¥7.6bn in the previous year. Partner Eisai reports sales on a net sales after discounts basis; on this basis Eisai reported Treakisym sales revenue of ¥7.3bn in Japan itself for the 2018 calendar year (up ~12%) and total net Treakisym revenue of ¥7.6bn when sales in other territories (South Korea and Singapore) were included.

SymBio books revenue equal to about 50% of net in-market Treakisym sales under the marketing agreement with Eisai. While total sales reported by SymBio in 2018 increased by 11.4% to ¥3.8bn, these sales were 9% below guidance and our forecasts.

Treakisym sales have grown by ~80% over the period from 2016 to 2018, supported by approvals for two new indications for Treakisym in Japan that were received in 2016:

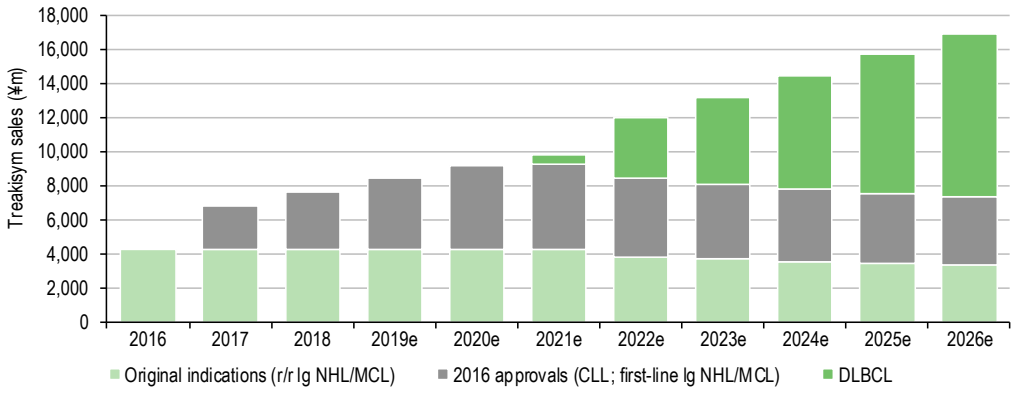
- CLL, approved in August 2016; and
- first-line low-grade NHL and MCL (first-line lg NHL/MCL), approved in December 2016.

SymBio attributed the shortfall in 2018 sales to slower than expected market penetration in first-line treatment of low-grade NHL. As a result, it has reduced its targeted market penetration in first-line lg NHL to 70% by 2020, from its previous target of 75%.

We have adjusted our forecasts of net in-market sales of Treakisym in currently approved indications, adjusted for discounts (the form reported by Eisai), to grow by ¥0.6bn in 2019 (75% of the Treakisym sales growth reported by Eisai for the 2018 calendar year) and by ¥0.6bn in 2020. We forecast Treakisym sales in existing indications to peak at ¥8.6bn (previously ¥9.5bn) in 2021, as shown in Exhibit 5.

We model in-market Treakisym sales (net sales after discounts) in DLBCL in 2021 to be ¥0.5bn, if launched in Q321 in line with the company's targets. We estimate that sales in DLBCL could exceed the currently marketed indications by 2025, and peak at ¥9.6bn in 2026, if approved (Exhibit 5).

Exhibit 5: Treakisym in-market net sales forecasts



Source: Eisai, SymBio, Edison Investment Research. Note: SymBio records royalties on in-market Treakisym sales; sales estimates are net in-market sales, after discounts.

Plans for self-commercialisation starting to take shape

In February, SymBio released an updated four-year plan along with its results for the 2018 financial year. The plan provides a clearer outline of the pathway to self-commercialisation in 2021.

Previously, in February 2018 the company foreshadowed that it was giving serious consideration to moving to self-commercialisation of Treakisym, and at that time prepared its 2021 targets on the assumption that it would proceed with self-commercialisation. On 16 October 2018 it announced that it had begun preparations to establish its own sales organisation to sell Treakisym in Japan.

The rationale for self-commercialisation is underpinned by the in-license of liquid formulations of Treakisym from Eagle Pharmaceuticals. We expect the launch of liquid formulations (if approved) to allow SymBio to maintain a dominant share of the bendamustine hydrochloride market in the face of FD powder generic which could be launched as early as June 2022.

Exhibit 6 compares the targets in the most recent four-year plan announced in February 2019 to the targets announced 12 months earlier. For 2021, we compare the new targets to the median of the old high and low targets.

The most notable revision is that the sales target for 2020 has been reduced by 23% to ¥3.3bn, due to its expectation that it will discontinue shipments to Eisai around the end of H120 as it transitions the product shipment destination from Eisai to wholesalers.

Furthermore, targeted sales for 2021 are 17% below the median point of the old sales target range. The twin contributors for this are, firstly, an anticipated launch date of the DLBCL indication now three months later (Q321) and, secondly, a 5% reduction in the peak uptake of Treakisym in the first-line l/g NHL indications approved in 2016.

For the first time the company has provided performance targets for 2022. These provide the first insights as to the company's expectations of the full-year sales potential and the costs of promoting the DLBCL indication and liquid formulations for Treakisym. We calculate targeted operating expenses to be ¥9.3bn in 2022 vs ¥7.9bn in 2021, with lower R&D costs due to the completion of the DLBCL Phase III trial likely partly offsetting the cost of supporting its own sales force.

Exhibit 6: Old and new forecasts and performance targets

	2019	2019		2020	2020		2021*	2021		2022**	2022	2022*
	Old (¥m)	New (¥m)	% Change	Old (¥m)	New (¥m)	% Change	Old (median, ¥m)	New (¥m)	% Change	Low (¥m)	High (¥m)	Median (¥m)
Revenue	4,238	4,465	+5%	4,238	3,282	-23%	10,975	9,132	-17%	11,282	11,809	11,546
Operating income	(3,786)	(3,587)	-5%	(3,786)	(5,180)	+37%	1,328	1,225	-8%	2,084	2,464	2,274
Ordinary income	(3,849)	(3,612)	-6%	(3,849)	(5,224)	+36%	1,275	1,181	-7%	2,040	2,420	2,230
Net income	(3,853)	(3,616)	-6%	(3,853)	(5,228)	+36%	1,085	1,005	-7%	1,736	2,060	1,898
Implied OpEx	(8,024)	(8,052)	+0%	(8,024)	(8,462)	+5%	(9,647)	(7,907)	-18%			(9,272)

Source: SymBio, Edison Investment Research. Note: *Median values calculated by Edison from high and low range data; ** 2022 performance targets have been provided or the first time in the current four-year mid-range plan; OpEx= operating expenses – calculated by Edison as revenue minus operating profit.

IV rigosertib: A potential second product for SymBio

SymBio in-licensed rigosertib (iv and oral formulations, Japan and Korean rights) from Onconova in 2011 for MDS, a rare blood cancer. SymBio is contributing patients from Japan to the global Phase III INSPIRE trial of *iv* rigosertib for the treatment of second-line higher-risk MDS (HR-MDS).

Onconova announced on 25 March 2019 that enrolment in the Phase III study has passed 75% (ie 270 patients), and that it is on track to fully enrol the target of 360 patients in H219. Onconova also expect to report top-line results of the overall survival analysis after 288 events will be available in H219. SymBio has previously said it aims to file for approval in Japan in 2021.

As of December 2018 SymBio had already reached its target of enrolling 40 patients in Japan, but it has stated that enrolment is proceeding.

Onconova said that the Independent Data Monitoring Committee had observed a promising survival signal at the interim analysis conducted in early 2018. The committee recommended that the trial

continue with an expansion in enrolment to 360 patients (from 225 patients) based on a pre-planned sample size re-estimation.

Development of IONSYS pain patch terminated

SymBio in-licensed the exclusive rights to develop the IONSYS (SyB P-1501) pain patch in Japan from The Medicines Company (MDCO) in October 2015 and initiated a Phase III trial in Japan in June 2016. SymBio suspended enrolment in the trial in April 2017 due to concerns over the continuity of MDCO's business regarding the product. The licence agreement between SymBio and MDCO was terminated effective 30 November 2017 and SymBio completed the process of terminating the development of SyB P-1501 in February 2018. SymBio is seeking damages of at least $82m (¥9bn) arising from MDCO's repudiation of the licence agreement. We do not include any potential damages in our valuation or forecasts.

Continued focus on in-licensing new drugs

SymBio is actively seeking new drug candidates and in-licensing opportunities globally, targeting drug candidates with clinically confirmed efficacy and safety. Discussions with multiple potential licensors are ongoing. If the company proceeds with its plans to establish its own salesforce in Japan then there will be increased incentive to in-license additional products that could be marketed by the salesforce.

The company has established a US-based subsidiary, SymBio Pharma USA, as a strategic base for overseas business development. It may look to in-license or develop drugs it can commercialise on a global basis as part of a continued transformation to a global specialty pharma company.

Reverse stock split to take effect on 1 July

On 28 March, shareholders voted to approve a one-for-four consolidation of the company's common stock, which will take effect on 1 July 2019. We will not incorporate the reverse stock split into our forecasts until after it takes effect on 1 July.

Sensitivities

SymBio is subject to the usual drug development risks, including clinical development delays or failures, regulatory risks, competitor successes, partnering setbacks, financing and commercial risks. The main sensitivities include rigosertib and DLBCL clinical trial success or failure, the ability to execute future in-licensing deals and successfully establishing its own salesforce to self-commercialise Treakisym after 2020.

For Treakisym, key risks relate to the outcome of the DLBCL Phase III trial, obtaining regulatory approval for the liquid Treakisym formulations and success in migrating patients to the liquid formulation to stave off competition from generic copies of Treakisym powder after 2021. It will have to bear the cost of establishing a salesforce before the marketing arrangement with Eisai expires.

SymBio is seeking damages from The Medicines Company arising from its repudiation of the IONSYS licence agreement. We do not model any compensation payments for IONSYS, so if SymBio was to receive any compensation, this would represent the potential to recover some of the value we have now written off.

The main sensitivity for rigosertib is the outcome of the Phase III INSPIRE trial of iv rigosertib in second-line HR-MDS. Onconova may need additional cash to complete the trial and report top-line data. If it is unable to secure any additional funds that may be required, this could delay trial completion and therefore timelines. If the outcome of the trial is negative, then not only would this impact the development of iv rigosertib, but there could also be read-across to oral rigosertib.

SymBio is reliant on in-licensing further assets to fill its pipeline. We believe the CEO's network is crucial to securing future deals, although we have limited visibility on the potential terms and timing of any such agreements.

Valuation

Our valuation of SymBio is increased to ¥26,828m ($237m), or ¥308/share, based on a risk-adjusted NPV analysis, which includes ¥4.8bn net cash at end December 2018 vs ¥2.9bn at the end of the previous year. We use a 10% discount rate for approved products and 12.5% elsewhere. Our valuation includes Treakisym approved indications and the new r/r DLBCL indication, plus rigosertib. We have rolled our valuation model forward to the new financial year and reduced forecast peak sales for approved Treakisym indications by 9% to ¥8.6bn, following below-expectations growth in 2018.

The higher cash balance due to ¥4.3bn (net) raised from the issue of shares and share acquisition rights in 2018, combined with rolling forward the model to the new financial year, has more than offset the negative impact of reduced peak sales forecast for the approved Treakisym indications.

Our main assumptions are summarised in Exhibit 7 below.

Exhibit 7: SymBio rNPV valuation

Product	Indication	Launch	Peak sales (¥m)**	NPV (¥m)	Probability (%)	rNPV (¥m)	NPV/share (¥/share)
Treakisym	LG NHL/MCL (r/r and 1st line); CLL	2010*	8,600	16,515	95-100	15,818	181.3
Treakisym (DLBCL)	r/r DLBCL	2021	9,600	9,544	60	5,046	57.8
Rigosertib (IV)	r/r HR-MDS	2023	3,800	2,218	50	894	10.3
Rigosertib (oral)	First-line HR-MDS (combo)	2025	7,500	3,586	15	248	2.8
Net cash at 31 December 2018				4,821	100	4,821	55.3
Valuation				36,684		26,828	307.5

Source: Edison Investment Research. Note: *Treakisym was launched in 2010 in r/r low-grade NHL/MCL; it received approvals in Japan in CLL in August 2016 and in first-line, low-grade NHL/MCL in December 2016; **we present Treakisym peak sales estimates net of discounts, to align with sales reporting by Eisai.

We model a 95% likelihood that the RI Treakisym formulation will be launched before the end of 2022, thereby minimising the penetration of generic copies of the FD Treakisym formulation. We model branded Treakisym market share gradually declining from 96% in 2022 to 75% in 2031, followed by a more rapid decline from 2032 after the liquid formulation patents expire.

Our Treakisym valuation assumes that SymBio earns an average net margin of 10–12% on top-line reported Treakisym sales until 2020. We assume that after 2020 the net operating margin gradually increases to reach 50% in 2024 and subsequent years as SymBio switches to self-commercialisation of Treakisym via its own salesforce and the liquid formulations in-licensed from Eagle gain market share vs powder formulations.

We model ¥1.5bn of development costs to achieve approval for the RTD and RI liquid formulations. We estimate that a salesforce of 60 would be needed to market Treakisym in Japan. At a fully-loaded cost of $250,000 per person, this would cost US$15m or approximately ¥1.7bn per year.

Scenario analysis

In a scenario where the Treakisym market share declines to 50% by 2031 (vs 75% for the base case), our valuation would fall by around ¥2.0bn (¥23/share) to around ¥24.8bn (¥284/share). We currently assume stable Treakisym pricing apart from a 5% price cut in 2022 when FD powder generics are expected to enter the market. However, an additional price cut to Treakisym in the future could represent downside to our forecasts; a 10% price cut in 2020 would remove around ¥2.5bn from our Treakisym rNPV, or ¥30/share.

Financials

Our financial forecasts have been updated to reflect FY18 reported financials and SymBio's updated financial guidance for 2019 and targets for 2020–2022. The main changes to our forecasts are summarised in Exhibit 8.

We have reduced forecast revenue in 2019 because 2018 sales were 9% below our expectations, and our decision to reduce our peak sales forecast for Treakisym in the approved indications to ¥8.6bn from ¥9.5bn (expressed as net in-market sales after discounts). We have reduced forecast revenue in 2020 by 27%, reflecting the anticipated winding down of Eisai inventory in H220 in the lead up the end of the marketing arrangement in December 2020.

We have increased R&D expenditure and reduced SG&A forecasts in 2019, broadly in line with SymBio's guidance (Exhibit 9). We have increased forecast R&D expenditure in 2020 in line with the three-month delay in anticipated completion of the DLBCL Phase III, and have further increased forecast SG&A spend as SymBio begins to build its own salesforce in Japan.

SymBio raised ¥4.3bn (net) from the issue of shares and share acquisition rights in 2018, lifting net cash at 31 December 2018 to ¥4.8bn vs ¥2.9bn at the end of the previous year. We estimate that the cash of ¥4.8bn should be sufficient to fund operations into H120. We model ¥4.2bn of indicative debt in FY20. The company may require additional funding over and above these amounts for investment in new in-licensing or M&A opportunities.

Exhibit 8: Main changes to our financial forecasts

¥m	2019 Old	2019 New	% change	2020 Old*	2020 New	% change
Revenue	4,325	4,109	-5	4,502	3,293	-27
Research and development	(2,200)	(2,500)	+14	(1,767)	(2,623)	+48
Selling, general and administration	(2,720)	(2,436)	-10	(3,180)	(3,680)	+16
Operating profit (reported)	(3,640)	(3,703)	+2	(3,614)	(5,315)	+47
Profit before tax (reported)	(3,617)	(3,679)	+2	(3,602)	(5,303)	+47
Profit after tax (reported)	(3,621)	(3,683)	+2	(3,606)	(5,307)	+47

Source: Edison Investment Research. Note: *We have not previously published our 2020 forecasts.

Exhibit 9: SymBio's 2018 outlook and 2019 targets versus our estimates

	2019 guidance	2019 estimates	2020 targets	2020 estimates
Revenue	¥4,465m	¥4,109m	¥3,282m	¥3,293m
R&D	¥2,508m	¥2,500m	N/A	¥2,623m
SG&A (including R&D)	¥5,053m	¥4,936m	N/A	¥6,303m
Operating loss	¥3,587m	¥3,703m	¥5,180m	¥5,315m
Ordinary loss	¥3,612m	¥3,679m	¥5,224m	¥5,303m
Net loss	¥3,616m	¥3,683m	¥5,228m	¥5,307m

Source: Edison Investment Research. Note: We have not previously published 2020 forecasts.

Exhibit 10: Financial summary

Accounts: JPN GAAP, year-end: 31 December; ¥m	2016	2017	2018	2019e	2020e	2021e
Total revenues	2,368	3,444	3,836	4,109	3,293	9,159
Cost of sales	(1,464)	(2,413)	(2,663)	(2,876)	(2,305)	(1,790)
Gross profit	904	1,031	1,173	1,233	988	7,370
SG&A (expenses)	(1,364)	(1,961)	(1,996)	(2,436)	(3,680)	(5,537)
R&D costs	(1,667)	(3,018)	(1,833)	(2,500)	(2,623)	(750)
Other income/(expense) included in adjusted	0	0	0	0	0	0
Other income/(expense) excluded from adjusted	0	0	0	0	0	0
Reported EBIT	(2,127)	(3,947)	(2,656)	(3,703)	(5,315)	1,083
Finance income/ (expense)	5	3	1	24	12	8
Other income/(expense) included in adjusted	7	3	(0)	0	0	0
Other income/(expense) excluded from adjusted	(195)	(33)	(93)	0	0	0
Reported PBT	(2,309)	(3,974)	(2,749)	(3,679)	(5,303)	1,090
Income tax expense	(4)	(4)	(4)	(4)	(4)	(91)
Reported net income	(2,313)	(3,978)	(2,753)	(3,683)	(5,307)	999
Average number of shares - basic (m)	39.3	49.9	66.5	89.9	97.4	97.4
Basic EPS	(58.82)	(79.78)	(41.38)	(40.97)	(54.49)	10.26
Adjusted EBITDA	(2,101)	(3,917)	(2,621)	(3,664)	(5,273)	1,130
Adjusted EBIT	(2,127)	(3,947)	(2,656)	(3,703)	(5,315)	1,083
Adjusted PBT	(2,317)	(3,977)	(2,749)	(3,679)	(5,303)	1,090
Adjusted EPS	(59.00)	(79.84)	(41.38)	(40.97)	(54.49)	10.26
Adjusted diluted EPS	(59.00)	(79.84)	(41.38)	(40.97)	(54.49)	8.60
BALANCE SHEET						
Property, plant and equipment	75	47	57	71	74	117
Goodwill	0	0	0	0	0	0
Intangible assets	42	69	71	59	50	44
Other non-current assets	77	100	73	73	73	73
Total non-current assets	193	216	201	203	197	234
Cash and equivalents	5,719	2,947	4,821	1,172	500	983
Inventories	273	363	534	236	189	147
Trade and other receivables	487	490	412	473	361	1,004
Other current assets	205	237	272	272	272	272
Total current assets	6,685	4,037	6,038	2,153	1,322	2,406
Non-current loans and borrowings	450	0	0	0	4,235	4,235
Trade and other payables	0	0	0	0	0	0
Other non-current liabilities	1	1	1	1	1	1
Total non-current liabilities	451	1	1	1	4,236	4,236
Trade and other payables	322	604	726	402	515	513
Current loans and borrowings	0	0	0	0	0	0
Other current liabilities	620	407	610	610	610	610
Total current liabilities	942	1,011	1,336	1,013	1,125	1,123
Equity attributable to company	5,485	3,239	4,902	1,342	(3,842)	(2,720)
Non-controlling interest	0	0	0	0	0	0
CASH FLOW STATEMENT						
Profit before tax	(2,309)	(3,974)	(2,749)	(3,679)	(5,303)	1,090
Depreciation and Amortisation	26	30	35	40	41	47
Share based payments	137	121	123	123	123	123
Other adjustments	197	42	85	(24)	(12)	(8)
Movements in working capital	(13)	(35)	184	(87)	271	(602)
Interest paid / received	6	3	1	24	12	8
Income taxes paid	(4)	(4)	(4)	(4)	(4)	(91)
Cash from operations (CFO)	(1,960)	(3,817)	(2,325)	(3,608)	(4,871)	567
Capex	(28)	(57)	(40)	(42)	(35)	(84)
Acquisitions & disposals net	0	0	0			
Other investing activities	(16)	(20)	14	0	0	0
Cash used in investing activities (CFIA)	(44)	(78)	(26)	(42)	(35)	(84)
Net proceeds from issue of shares	3,226	1,164	4,272	0	0	0
Movements in debt	450	0	0	0	4,235	0
Other financing activities	(18)	0	0	0	0	0
Cash from financing activities (CFF)	3,658	1,164	4,272	0	4,235	0
Currency translation differences and other	(196)	(42)	(47)	0	0	0
Increase/(decrease) in cash and equivalents	1,458	(2,772)	1,874	(3,650)	(672)	483
Cash and equivalents at end of period	5,719	2,947	4,821	1,172	500	983
Net (debt) cash	5,269	2,947	4,821	1,172	(3,735)	(3,252)

Source: Edison Investment Research and SymBio accounts

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Management team

President and CEO: Fuminori Yoshida	Corporate Officer and CFO: Kenji Murata
Mr Yoshida founded SymBio in March 2005. He has held senior management positions in the healthcare industry in both the US and Japan, including founding director of both Nippon BioRad Laboratories (1980) and Amgen Japan (1993) in addition to Amgen Inc as corporate VP. Mr Yoshida has a BS in organic chemistry (Gakushin University), an MS in molecular biology (MIT) and an MS in health policy and management (Harvard Grad School).	Mr Murata was the CFO for Japan at Novartis Pharma and, most recently before joining SymBio, at Elanco Japan. He has also held managerial roles at Novartis Japan Sourcing and Sumitomo Life Insurance.
Corporate Officer, Executive VP and COO: Kazuo Asakawa	**Corporate Officer and CDO: Nobuo Ishida**
Mr Asakawa is a SymBio corporate officer, executive VP and COO, as well as GM of SymBio's Japan business unit. He was formerly MD and head of the Oncology division at Novartis Pharma KK, as well as being the company's corporate officer, head of the Transplantation & Immunology business division, and GM of the marketing department. He has also held managerial roles at Nippon Roche and Sandoz Japan.	Mr Ishida is a SymBio corporate officer and chief development officer, as well as being head of R&D and director of R&D Support and Data Science. He was formerly oncology project head, Japan development, at AbbVie GK; also formerly global project leader, Oncology, R&D, at Bayer Healthcare.

Principal shareholders	(%)
Yoshida Fuminori	4.2
Cephalon	3.1
Matsui Securities	1.5
Japan Securities Finance Co.	1.5
Eisai Co., Ltd.	1.0

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