EDISON

SymBio Pharmaceuticals

Corporate outlook

Self-commercialisation gains favour

Pharma & biotech

With the lifecycle of Treakisym extended through the in-licensing of liquid formulations from Eagle in 2017, SymBio is refining its plans to establish its own salesforce to market Treakisym (and other drugs) in Japan. While the company has not yet made a final decision, we think it is highly likely to move to self-commercialisation in order to improve operating margins after its marketing arrangement with Eisai expires. Therefore, we now model self-commercialisation in our base-case valuation. This more than offsets the later anticipated filing date for rigosertib iv and lower peak penetration for Treakisym in first-line non-Hodgkin's lymphoma and lifts our valuation to ¥23.8bn.

Year end	Revenue (¥m)	PBT* (¥m)	EPS* (¥)	DPS (¥)	P/E (x)	Yield (%)
12/16	2,368	(2,317)	(59.0)	0.0	N/A	N/A
12/17	3,444	(3,977)	(79.8)	0.0	N/A	N/A
12/18e	4,203	(3,030)	(54.2)	0.0	N/A	N/A
12/19e	4,325	(3,636)	(62.9)	0.0	N/A	N/A

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

Eagle, DLBCL and Eisai expiry favour own salesforce

Treakisym in-market sales reported by partner Eisai grew by 61% to ¥7.6bn in 2017 (NHI price basis), supported by two new indications approved in 2016. The extension of Treakisym's lifecycle through the in-license of liquid formulations from Eagle Pharmaceuticals and the potential for the r/r diffuse large B-cell lymphoma (DLBCL) Phase III to drive further sales growth from 2021 (if successful), provide a strong case for SymBio to establish its own salesforce to market Treakisym and other drugs after its existing marketing arrangement with Eisai expires in December 2020; in-licensing opportunities could complement this strategy. The company expects to decide in 2018 whether to adopt a self-commercialisation strategy.

iv rigosertib trial expanded after interim analysis

Partner Onconova expanded the recruitment target from 225 to 360 patients in the global Phase III trial of iv rigosertib in r/r higher-risk MDS (myelodysplastic syndromes), following an interim analysis in January. SymBio has increased targeted enrolment in Japan to 40 patients, and now aims to file in 2021, vs a prior 2018 target. While it is positive news that the trial cleared the interim analysis, we consider this a higher-risk study and maintain a 50% probability of success.

Valuation: rNPV of ¥23.8bn ($211m) or ¥412/share

Our updated SymBio risk-adjusted valuation is ¥23,823m ($211m) or ¥412/share (vs ¥19,672m). We have: reduced peak market penetration for recently approved Treakisym indications from 42% to 37% in line with modest near-term Treakisym sales growth implied by SymBio's performance targets; deferred market launch for iv and oral rigosertib by three years; and assumed that the Treakisym price is cut by 5% in 2022 when the first freeze dried powder generics are launched. However, the higher 50% operating profit margin anticipated from self-commercialisation of Treakisym (and other products) in Japan has more than offset these other factors.

6 April 2018

Price	**¥229**
Market cap	**¥13,236m**
	¥113/$
Net cash (¥m) at end December 2017	2,947
Shares in issue	57.8m
Free float	84%
Code	4582
Primary exchange	Japan
Secondary exchange	OTC US

Share price performance

%	1m	3m	12m
Abs	10.6	4.1	10.1
Rel (local)	8.7	13.5	(4.0)
52-week high/low	¥311.0		¥200.0

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	Q218
In-licensing activities	2018
Decision on self-commercialisation	2018

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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. 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 currently has two main assets: (1) Treakisym (bendamustine) for blood cancers, with Asia-Pacific marketing rights out-licensed to various commercial partners; and (2) rigosertib for a rare blood cancer, which is currently being investigated in a global Phase III trial in which SymBio is participating. SymBio is evaluating plans to commercialise Treakisym (after 2020) and rigosertib via its own salesforce in Japan. SymBio is aiming to in-license further assets during 2018. It is also looking to expand globally and it established a US-based subsidiary in 2016. SymBio has circa 78 employees and is based in Tokyo.

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 2016 sales of ¥4,200m.
	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; targeting filing H120, approval H121.
Rigosertib iv (SyB L-1101)	r/r HR-MDS	Phase III	Global Phase III ongoing with SymBio participating; trail expanded after cleared interim analysis in Q118; top-line data 2019; 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 ¥23.8bn ($211m) or ¥412/share

We value SymBio at ¥23,823m ($211m) or ¥412/share, which is based on a risk-adjusted NPV analysis and includes ¥2,947m ($26m) net cash at end December 2017. Our valuation includes Treakisym, where we assume sales can continue to grow in the future supported by approvals in 2016 in new indications, in addition to 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 Q119

We estimate that end December 2017 net cash of ¥2,947m plus estimated proceeds of ¥0.7bn from the issue of ~3.8m shares so far in 2018 should be sufficient to fund operations into Q119. We model ¥3.4bn of indicative debt in FY19, 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 following approvals in new indications during 2016. We also expect top line data from Treakisym in r/r DLBCL and from rigosertib iv data during 2019, which will be critical in shaping the future development pathway. SymBio is evaluating plans to establish its own salesforce to market Treakisym and rigosertib (if approved) which would require investment into a commercial infrastructure from 2019 onwards.

Key goal is to maximise 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. The 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 added significant value to its Treakisym franchise when it in-licensed rights to patent-protected liquid formulations of Treakisym from Eagle in September 2017. These improved formulations will extend the lifecycle of Treakisym. Treakisym is likely to face competition from generic versions of the currently marketed freeze dried (FD) powder formulation from 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 H121.

The longer Treakisym lifecycle has prompted SymBio to invest 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. We estimate that the r/r DLBCL indication could double the peak sales potential for Treakisym, if approved.

The combination of the extended Treakisym lifecycle, ongoing growth in Treakisym sales driven by new indications approved in 2016, and the potential for an approval in DLBCL to further boost sales, has set the scene for SymBio to improve profit margins on Treakisym sales by establishing its own salesforce to market Treakisym and potentially also rigosertib (if approved) and other in-licensed products.

Sales in new indications may peak below our initial estimates

Japan accounts for about 95% of Treakisym sales. SymBio books revenue equal to about 50% of net in-market Treakisym sales under the marketing agreement with Eisai. Japanese in-market sales of Treakisym by partner Eisai grew by 61% in 2017 to ¥7.6bn on a NHI price basis. On a net sales after discounts basis, Eisai reported Treakisym sales revenue of ¥6.5bn in Japan itself for the calendar year, and total net Treakisym revenue of ¥6.8bn when sales in other territories (South Korea and Singapore) were included.

The sales growth was supported by approvals for two new indications for Treakisym in Japan achieved in 2016:

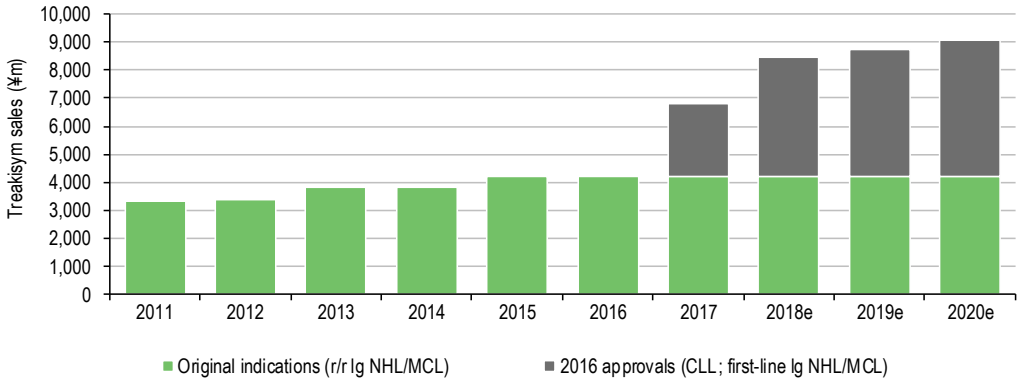
- chronic lymphocytic leukaemia (CLL), approved in August 2016, and
- first-line low-grade NHL and MCL (first-line lg NHL/MCL), approved in December 2016.

These two indications represent patient markets of about 7,800 in Japan, compared to around 4,700 patients for the r/r lg NHL/MCL indications which were the subject of the earlier Treakisym approvals.

SymBio expects Treakisym to approach the upper limit of market penetration for first-line lg NHL/MCL in 2018. This is reflected in its guidance issued in February 2018 for 22% growth in

Treakisym sales in 2018, with its performance targets implying further 1% growth in 2019 and 4% in 2020. We had previously assumed that it would take longer to reach peak market penetration and we had modelled 12% sales growth in 2019 and 6% growth in 2020. We have reduced our forecast peak market penetration in the two indications approved in 2016 from 42% to 37%, in order to align our sales forecasts more closely with the company's targets. However, even with this lower peak market penetration we still forecast the two new indications to comprise over 50% of Treakisym sales by 2020, with in-market Treakisym sales (net sales after discounts) reaching ¥9.1bn in that year as shown in Exhibit 3.

Exhibit 3: 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.

DLBCL Phase III could give peak sales a further boost

SymBio is seeking to add an additional indication for 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 (bendamustine HCl) plus rituximab in r/r DLBCL in August 2017. SymBio's mid-range plan aims to file an NDA in H120; we now model a potential launch in H221 vs our prior assumption of a launch in H121.

SymBio completed a Phase II study for Treakisym plus rituximab in r/r DLBCL in 2012. An analysis of 59 cases in the Phase II study showed an encouraging ORR of 62.7% and CR of 37.3%. The fact that the branded Treakisym liquid formulations are expected to maintain over 75% of the market out to 2031 has increased the potential value of the DLBCL indication to SymBio, and has made the expense of the DLBCL Phase III trial worthwhile (we model Phase III costs of ¥2bn).

Overview of DLBCL

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 approval for Treakisym. There is currently no standard chemotherapy for the treatment of DLBCL. Patients are typically treated with multiple drug therapies including:

- CHOP – Cyclophosphamide, doxorubicin (hydroxydaunorubicin), vincristine, and prednisone;
- R-CHOP – CHOP plus rituximab; and
- Dose-adjusted EPOCH-R – etoposide, prednisone, vincristine [Oncovin], cyclophosphamide, doxorubicin, plus rituximab.

Although DLBCL is an aggressive lymphoma, the rapidly growing cells are often susceptible to chemotherapy and a significant proportion of patients can be cured by first-line chemotherapy treatments. Unfortunately, a majority of patients relapse, typically within two years of the initial

treatment. Patients who relapse or are refractory to first-line treatment have an extremely poor prognosis. A range of salvage chemotherapy regimens are used in relapse therapy.

DLBCL indication could double Treakisym peak sales potential

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 that 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 patient 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 CLL and first-line and r/r low-grade NHL and MCL patients. Given the 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 ¥9.5bn for the currently approved indications.

Liquid formulations extend Treakisym lifecycle

SymBio has in-licensed two liquid formulations of bendamustine HCl (Treakisym) from Eagle Pharmaceuticals (Eagle). The new formulations will be an important component of Treakisym life cycle management, as they are protected by patents that extend to 2031, whereas orphan exclusivity on the company's currently marketed FD powder Treakisym product expires in October 2020. The new formulations are more convenient for healthcare workers and patients and will be important advantages as SymBio seeks to switch users away from the FD formulations.

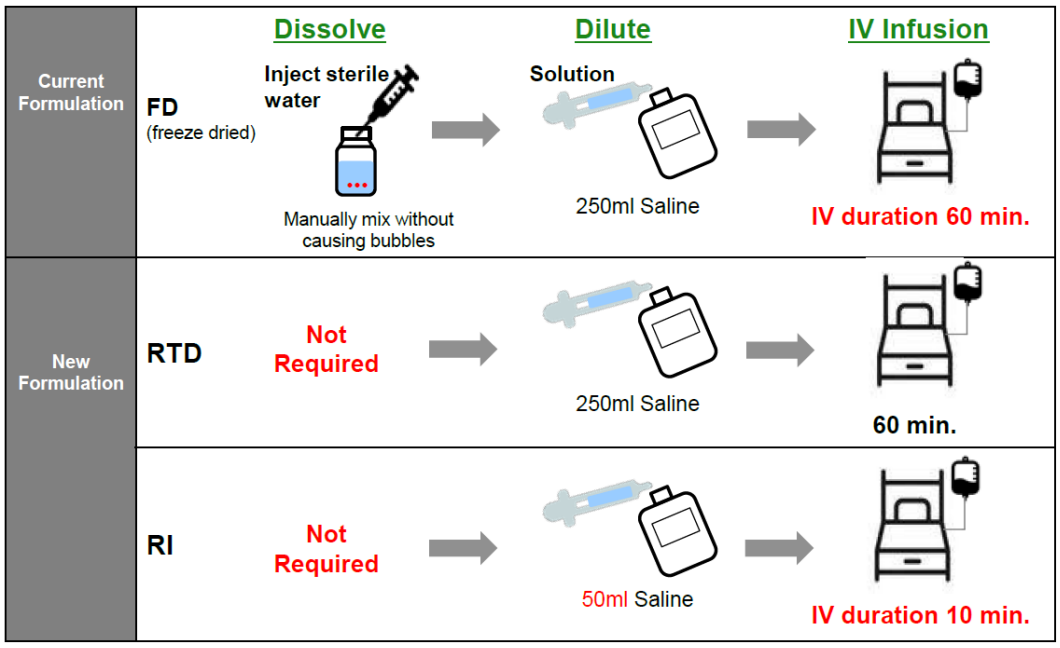
The first in-licensed product is a ready-to-dilute (RTD) liquid formulation that will significantly reduce dose preparation time, making it easier and safer for health professionals. This compares to the FD Treakisym which has to be reconstituted before administration, is time consuming and carries the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

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

Exhibit 4 illustrates the differences in usage between the current FD Treakisym and the new liquid RTD and RI formulations.

1 Chihara et al; British Journal of Haematology, 2014, 164, 536–545; doi: 10.1111/bjh.12659

Exhibit 4: Comparison of the current FD powder and new liquid formulations



Source: SymBio

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 in the way the dose is prepared. SymBio is aiming to launch the RTD product in H121, which would allow the product to be well established in the marketplace before the expected entry of the first FD generics in 2022.

The RI product represents a greater change to the current treatment protocols, so approval of this product is expected to take longer – we model a 95% chance of a launch by the start of 2023. Given the greater convenience for patients of the rapid 10-minute infusion with the RI formulation, we expect over 95% of patients to be switched to this product.

SymBio is pursuing a similar strategy to that adopted by Teva in the US, where it markets bendamustine HCl under the brand names Treanda and Bendeka. Teva in-licensed the RI bendamustine HCl formulation from Eagle and now markets it as Bendeka.

Teva launched an RTD liquid formulation of Treanda in November 2014; it launched the Bendeka RI product in January 2016. FD Treanda powder for injection is still available, but its use has substantially declined in favour of Bendeka. Eagle disclosed in a corporate presentation in September 2017 that Bendeka has achieved a 97% market share in the US, which is testament to the appeal of the short infusion time.

Orphan exclusivity for SymBio's Treakisym expires in October 2020, so the first generic copies of the FD Treakisym powder could be launched as early as the start of 2022. This means that SymBio may have less than 12 months to convert clinicians to using the liquid Treakisym formulations before the launch of the first FD Treakisym generics. This shorter time period creates additional uncertainty as to how large a market share the RTD and RI products will be able to gain before they potentially face competition from FD generics.

In our forecasts we model SymBio's strategy being quite successful at maintaining market share, with dry powder Treakisym generics slowly growing market share from 2022 onwards to reach 25%

market share by 2031, in line with company guidance. We model the growth in Treakisym generics' market share accelerating in 2032 after the patents on the liquid formulations expire.

In our scenario analysis on page 10, we note that if Treakisym generics were to gain a 50% market share by 2031 (vs 25%), this would reduce our valuation by around ¥2.2bn (¥38/share).

Self-commercialisation after 2020 preferred for Treakisym

Treakisym is currently marketed by Eisai under a business partnership agreement which expires in December 2020. SymBio's mid-range plan is to shift Treakisym sales to its own salesforce from 2021 in order to improve profitability, which it rates as a top priority. We estimate that SymBio could earn an operating profit margin of 50% of net sales of Treakisym under a self-commercialisation model.

SymBio intends to make a decision regarding the establishment of its salesforce in 2018, after considering the progress of development of rigosertib IV, as well as the timing of introducing new drug candidates for development. It has included an allowance for expenses related to the establishment and operation of its own salesforce in its performance targets from 2019 onwards, with hiring expected to begin in 2019 so that the salesforce can be fully operational from the start of 2021.

While the company has not yet made a final decision, we have formed the view that establishing its own salesforce is the most likely strategy that SymBio will pursue. In light of this assessment we have now adopted the self-commercialisation of Treakisym after 2020 in our base-case forecasts (we previously considered this option in scenario analysis).

iv rigosertib Phase III expanded after interim analysis

SymBio in-licensed rigosertib (iv and oral formulations, Japan and Korean rights) from Onconova in 2011 for MDS (myelodysplastic syndromes), 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 HR-MDS (higher-risk MDS), and has already enrolled 30 patients in the study.

Onconova announced in January that it is moving forward with the study as it had been cleared to continue following an interim analysis by the independent data monitoring committee (DMC). Following a pre-planned sample size re-estimation conducted by the DMC as part of the interim analysis, the target enrolment was expanded from 225 to 360 patients, with the aim of increasing the power of the trial. SymBio will continue to collaborate with Onconova on the study and plans to increase the total enrolment in Japan to 40 patients. With the trial having been expanded by 135 patients, Onconova is guiding for top-line results of the overall survival analysis after 288 events to be available in 2019. SymBio now aims to file for approval in 2021, vs the prior target of a 2018 filing.

The INSPIRE trial has been designed following analysis of the failed Phase III ONTIME trial of iv rigosertib in HR-MDS. In the ONTIME trial, iv rigosertib failed to meet the primary endpoint, although it did show improved survival in certain subgroups.

In order to improve the likelihood of success, patient recruitment in INSPIRE has been refined to focus on the subgroup of HR-MDS patients who: have failed HMA[2] (hypomethylating agent) treatment within nine months of HMA initiation; are younger than 82 years of age; and received their last HMA dose within the six months prior to entering the INSPIRE trial. In the ONTIME trial, iv

[2] HMA failures are defined as patients who have progressed, failed or relapsed following treatment with either Vidaza (azacitidine) or Dacogen (decitabine), the US approved HMAs. Only Vidaza is approved in Japan.

rigosertib was able to improve survival in this particular patient group (data summarised in Exhibit 5).

Exhibit 5: Median overall survival (OS) in the ONTIME trial

		Median OS	N	Hazard ratio	p value
ONTIME trial	rigosertib	8.2 months	199	0.87	0.33
	BSC*	5.9 months	100	(95% CI: 0.67-1.14)	
ONTIME subset (as per INSPIRE inclusion criteria)	rigosertib	7.9 months	77	0.48	0.0008
	BSC	4.1 months	39	(95% CI: 0.31-0.74)	

Source: Onconova, *The Lancet Oncology* 2016 (17): 496–508. *BSC = best supportive care

Onconova had $7.6m cash at 30 September and raised net proceeds of $8.7m from a capital raise in February. With a current cash burn rate of ~$6.5m per quarter, Onconova will need to raise additional funds to complete the INSPIRE trial in 2019. With a market capitalisation of ~$20m, there is a risk that Onconova may not be able to raise sufficient funds to complete the study.

Phase I studies in preparation for oral rigosertib Phase III

rigosertib is also available in an oral formulation. There are two main potential indications within MDS that could be pursued for oral rigosertib:

- combination with the hypo-methylating agent (HMA) azacitidine (Vidaza) as first-line treatment for HR-MDS; and
- monotherapy for treatment of LR-MDS

Vidaza combination the main development priority for oral rigosertib

SymBio initiated a Phase I trial of oral rigosertib as a single agent in HR-MDS in Japan in June 2017. The company will conduct an oral rigosertib/Vidaza combination trial in HR-MDS in Japan after demonstrating the safety of oral rigosertib. SymBio intends to participate in the global Phase III study in untreated HR-MDS that Onconova is currently planning.

Data from the initial expansion phase of Onconova's Phase II open-label trial of oral rigosertib in combination with Vidaza are summarised in Exhibit 6. Data were available from 33 evaluable MDS patients (from 40 MDS patients recruited into the trial). The median duration of remission was eight months. The combination appeared to have a similar side effect profile to monotherapy Vidaza, as reported in other studies (there was no control monotherapy Vidaza arm in this Phase II trial).

Onconova is currently recruiting an additional ~40 patients in a further extension to the Phase II study, to explore dose and schedule optimisation and gain additional efficacy and safety data.

Exhibit 6: Overview of data from a Phase II trial of oral rigosertib in combination with Vidaza

Outcome	Total (n=33)	HMA naïve (n=20)	HMA resistant (n=13)
Response rate	76% (n=25)	85% (n=17)	62% (n=8)
Complete remission (CR)	24% (n=8)	35% (n=7)	8% (n=1)

Source: Edison Investment Research, Onconova. Note: Response rate was as defined by IWG criteria.[3]

While Onconova has indicated that it expects to initiate a global Phase III study of oral rigosertib in untreated HR-MDS in 2018, we take a more conservative approach and assume that the study does not commence until 2020, after the INSPIRE iv rigosertib Phase III is completed. We model a market launch of the oral rigosertib/Vidaza combination in untreated HR-MDS in 2025.

[3] Cheson BD, Greenberg PL, Bennett JM, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood 2006; 108:419-25.

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 as to 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.

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 we 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 that it can commercialise on a global basis as part of a continued transformation to a global specialty pharma company.

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 if it decides to pursue self-commercialisation of 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. The commercialisation arrangements for Treakisym after 2020 (licence vs self-commercialise) will influence profit margins on the product. If it decides to self-commercialise Treakisym, it will have to bear the cost of establishing a salesforce before the marketing arrangement with Eisai expires.

With a recent focus on oncology drug prices in Japan, Treakisym pricing could come under scrutiny. Our current forecasts assume stable pricing; any price cuts could therefore adversely affect our sales projections.

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

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 continue funding the trial until 2019 when it expects to report top-line data. If Onconova is unable to secure additional funds, this could also delay trial completion and therefore timelines. If the outcome of the trial is negative, then not

only would this have an impact on 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 ¥23,823m ($211m), or ¥412/share, based on a risk-adjusted NPV analysis, which includes ¥2,947m ($26m) net cash at end December 2017. 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 in time and have made a number of adjustments to our main assumptions. We have:

- adopted self-commercialisation of Treakisym from 2021 onwards as our base case (50% operating margin on Treakisym sales by 2024), vs our prior assumption of commercialisation by a partner with operating margins peaking at 25% in 2023).
- reduced forecast peak sales for currently approved Treakisym indications by 20%, in line with modest growth in Treakisym sales in 2019 and 2020 implied by SymBio's performance targets, and a quicker ramp up in 2017 than we had originally expected. We now model 37% peak penetration for the CLL and first-line lg NHL/MCL indications that were approved in 2016, vs 42% previously (we estimate that penetration in this indication was 19% in 2017).
- assumed that the Treakisym price is cut by 5% in 2022 when the first powder generics are launched. We assume that the price cut applies to the RTD and RI formulations as well as to FD-branded Treakisym.
- delayed market launch of rigosertib iv and rigosertib oral by three years to 2023 and 2025 respectively, due to the expansion in patient numbers and consequent later reporting of top line data from the Phase III INSPIRE trial.
- Reduced the probability of success for rigosertib oral from 25% to 15% due to uncertainty as to whether Onconova will be able to fund a global Phase III trial in this indication.

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*	9,500	16,178	100-95%	15,519	268.4
Treakisym (DLBCL)	r/r DLBCL	2021	9,600	8,697	60%	4,447	76.9
Rigosertib (IV)	r/r HR-MDS	2023	3,800	1,839	50%	642	11.1
Rigosertib (oral)	First-line HR-MDS (combo)	2025	7,500	3,037	15%	267	4.6
Net cash at 30 December 2017				2,947	100%	2,947	51.0
Valuation				32,699		23,823	412.0

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 have changed to presenting 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 by the start of 2023, 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 continues to assume that SymBio earns an average net margin of 10-12% on top-line reported Treakisym sales until 2020. However, we now 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 of Treakisym. We estimate that a salesforce of 60 reps would be needed to market Treakisym in Japan. At a fully-loaded cost of $250,000 per rep this would cost US$15m or approximately ¥1.6bn per year.

Scenario analysis

SymBio has not yet made a final decision whether to establish its own salesforce to self-commercialise Treakisym and other products in Japan. Should SymBio choose to market Treakisym through a marketing partner, we estimate that it could achieve an operating margin of 25% on Treakisym. Under this scenario our valuation would fall by around ¥9.8bn (¥171/share) to around ¥14.0bn (¥241/share).

On the other hand, 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 ¥2.2bn (¥38/share) to around ¥21.6bn (¥374/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, should Treakisym be subject to an additional price cut in the future, this could represent downside to our forecasts; a 10% price cut in 2019 would remove around ¥2.2bn from our Treakisym rNPV, or ¥39/share.

Financials

Our financial forecasts have been updated to reflect FY17 reported financials and SymBio's updated financial guidance for 2018 and targets for 2019-2021. The main changes to our forecasts are summarised in Exhibit 8. Our sales forecasts previously assumed a 55% market penetration by 2021 for the approximately 7,800 additional patients in Japan in the new Treakisym indications that were approved in 2016 (first-line lg NHL/MCL and CLL). However, these forecasts have now been refined to a 40% peak penetration, to align our sales forecasts more closely to the growth in in-market sales implied by the company's revised performance targets. Our previous forecasts assumed a 42% penetration in 2018, which we have revised to 34%.

We have made only minor changes to our SG&A forecasts in 2018, which are broadly in-line with SymBio's guidance (Exhibit 9), but forecast SG&A spend to increase in 2019 as SymBio begins to build its own salesforce in Japan. SymBio anticipates R&D spend of ¥2,311m in 2018, compared to ¥3,018m in 2017, which included the $12.5m (¥1.4bn) upfront payment relating to the licence agreement with Eagle Pharmaceuticals. We expect R&D spend to stay above 2016 levels for the next few years due the cost of the DLBCL Phase III trial and development costs to achieve approval for the liquid Treakisym formulations.

We estimate that current cash of ¥2.9bn plus estimated proceeds of ¥0.7bn from the issue of ~3.8m shares so far in 2018 should be sufficient to fund operations into Q119. We model ¥3.4bn of indicative debt in FY19. 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	2018 Old	2018 New	% Change	2019 Old	2019 New	% Change
Revenue	4,248	4,203	-1%	4,738	4,325	-9%
Research and development	(1,350)	(2,250)	+67%	(1,450)	(2,200)	+52%
Selling, general and administration	(1,924)	(2,039)	+6%	(2,001)	(2,720)	+36%
Operating profit (reported)	(2,017)	(3,045)	+51%	(2,049)	(3,640)	+78%
Profit before tax (reported)	(2,003)	(3,030)	+51%	(2,043)	(3,636)	+78%
Profit after tax (reported)	(2,006)	(3,034)	+51%	(2,046)	(3,640)	+78%

Source: Edison Investment Research

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

	2018 Guidance	2018 Estimates	2019 Targets	2019 Estimates
Revenue	¥4,201m	¥4,203m	¥4,238m	¥4,325m
R&D	¥2,311m	¥2,250m	N/A	¥2,200m
SG&A (including R&D)	¥4,350m	¥4,289m	N/A	¥4,920m
Operating loss	¥2,981m	¥3,045m	¥3,786m	¥3,640m
Ordinary loss	¥3,044m	¥3,030m	¥3,849m	¥3,636m
Net loss	¥3,056m	¥3,034m	¥3,853m	¥3,640m

Source: Edison Investment Research

Exhibit 10: Financial summary

Accounts: JPN GAAP, Yr end: 31 December; ¥m	2014	2015	2016	2017	2018e	2019e
Total revenues	1,955	1,933	2,368	3,444	4,203	4,325
Cost of sales	(1,428)	(1,350)	(1,464)	(2,413)	(2,959)	(3,045)
Gross profit	527	583	904	1,031	1,244	1,280
SG&A (expenses)	(1,056)	(1,100)	(1,364)	(1,961)	(2,039)	(2,720)
R&D costs	(774)	(2,035)	(1,667)	(3,018)	(2,250)	(2,200)
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	(1,303)	(2,552)	(2,127)	(3,947)	(3,045)	(3,640)
Finance income/ (expense)	25	16	5	3	15	4
Other income/(expense) included in adjusted	(2)	2	7	3	0	0
Other income/(expense) excluded from adjusted	168	(95)	(195)	(33)	0	0
Reported PBT	(1,112)	(2,628)	(2,309)	(3,974)	(3,030)	(3,636)
Income tax expense	(4)	(4)	(4)	(4)	(4)	(4)
Reported net income	(1,116)	(2,632)	(2,313)	(3,978)	(3,034)	(3,640)
Average number of shares - basic (m)	30.8	32.4	39.3	49.9	55.9	57.8
Basic EPS	(36.26)	(81.26)	(58.82)	(79.78)	(54.23)	(62.92)
Adjusted EBITDA	(1,291)	(2,527)	(2,101)	(3,917)	(3,004)	(3,591)
Adjusted EBIT	(1,303)	(2,552)	(2,127)	(3,947)	(3,045)	(3,640)
Adjusted PBT	(1,110)	(2,630)	(2,317)	(3,977)	(3,030)	(3,636)
Adjusted EPS	(36.20)	(81.33)	(59.00)	(79.84)	(54.23)	(62.92)
Adjusted diluted EPS	(36.20)	(81.33)	(59.00)	(79.84)	(54.23)	(62.92)
Balance sheet						
Property, plant and equipment	49	53	75	47	48	49
Goodwill	0	0	0	0	0	0
Intangible assets	66	52	42	69	86	96
Other non-current assets	49	53	77	100	100	100
Total non-current assets	164	158	193	216	235	245
Cash and equivalents	5,092	4,261	5,719	2,947	423	500
Inventories	245	133	273	363	324	250
Trade and other receivables	273	301	487	490	576	498
Other current assets	1,681	132	205	237	237	237
Total current assets	7,290	4,827	6,685	4,037	1,560	1,485
Non-current loans and borrowings	0	0	450	0	0	3,402
Trade and other payables	0	0	0	0	0	0
Other non-current liabilities	2	2	1	1	1	1
Total non-current liabilities	2	2	451	1	1	3,404
Trade and other payables	306	320	322	604	349	400
Current loans and borrowings	0	0	0	0	0	0
Other current liabilities	182	231	620	407	407	407
Total current liabilities	488	551	942	1,011	756	807
Equity attributable to company	6,964	4,432	5,485	3,239	1,037	(2,481)
Non-controlling interest	0	0	0	0	0	0
Cash flow statement						
Profit before tax	(1,112)	(2,628)	(2,309)	(3,974)	(3,030)	(3,636)
Depreciation and Amortisation	13	24	26	30	40	49
Share based payments	95	103	137	121	121	121
Other adjustments	(207)	26	197	42	(15)	(4)
Movements in working capital	(78)	190	(13)	(35)	(303)	203
Interest paid / received	27	18	6	3	15	4
Income taxes paid	(4)	(4)	(4)	(4)	(4)	(4)
Cash from operations (CFO)	(1,266)	(2,272)	(1,960)	(3,817)	(3,175)	(3,266)
Capex	(109)	(24)	(28)	(57)	(59)	(60)
Acquisitions & disposals net	0	0	0	0	0	
Other investing activities	423	1,513	(16)	(20)	0	0
Cash used in investing activities (CFIA)	314	1,489	(44)	(78)	(59)	(60)
Net proceeds from issue of shares	544	(2)	3,226	1,164	711	0
Movements in debt	0	0	450	0	0	3,402
Other financing activities	(1)	(1)	(18)	0	0	0
Cash from financing activities (CFF)	544	(3)	3,658	1,164	711	3,402
Currency translation differences and other	206	(45)	(196)	(42)	0	0
Increase/(decrease) in cash and equivalents	(202)	(831)	1,458	(2,772)	(2,524)	77
Cash and equivalents at end of period	5,092	4,261	5,719	2,947	423	500
Net (debt) cash	5,092	4,261	5,269	2,947	423	(2,902)
Movement in net (debt) cash over period	(202)	(831)	1,008	(2,322)	(2,524)	(3,326)

Source: Edison Investment Research and SymBio accounts

Contact details	Revenue by geography
Toranomon 30 Mori Bldg 3-2-2 Toranomon Minato-ku Tokyo 105-0001 Japan +81 3 5472-1125 www.symbiopharma.com	N/A

Management team

President and CEO: Fuminori Yoshida	Corporate Officer, Legal/Licensing & Global Alliance: Tsutomu Abe
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 Abe is the former director of the legal departments of KOKUYO Co and Fast Retailing Co. His former positions also include legal manager of Mitsubishi Corporation's European headquarters, GM of International Legal Affairs at NTT DoCoMo, Inc, before his role at DoCoMo Europe in France as executive director and chief legal officer.
Corporate Officer, Executive VP and COO: Kazuo Asakawa	**Corporate Officer, Head of Finance & Accounting and CFO: Kenji Murata**
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 KK and Sandoz Japan KK.	Mr. Murata was the CFO for Japan at Novartis Pharma K.K. and, most recently before joining SymBio, at Elanco Japan K.K. He has also held managerial roles at Novartis Japan Sourcing and Sumitomo Life Insurance.

Principal shareholders	(%)
Whiz Partners Inc	7.2
Yoshida Fuminori	6.7
Cephalon	5.6
SBI Holdings Inc	1.8
Eisai	1.8
Matsui Securities	1.6
Weru Investment	1.5

Companies named in this report

Eisai (4523 JP), Onconova (ONTX US), The Medicines Company (MDCO US)

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