SymBio Pharmaceuticals

Corporate outlook

Moving ahead on all fronts

Pharma & biotech

During 2017 we expect updates on all three of SymBio's main assets. We expect Treakisym sales growth via partner Eisai following approvals during 2016 in new indications, which could more than double the current levels (¥4.7bn/$42m). For pipeline assets IONSYS and rigosertib, data from ongoing trials could become available during H217, which will shape the future development pathways. We also expect SymBio to remain focused on in-licensing further opportunities to complement its existing pipeline. This could help drive future operating leverage if SymBio evolves into a commercial entity, possibly from 2020. We value SymBio at $175m.

Year end	Revenue (US$m)	PTP (US$m)	EPADR ($)	DPADR ($)	P/E (x)	Gross yield (%)
12/15	17.1	(23.3)	(0.72)	0.0	N/A	N/A
12/16	21.0	(20.5)	(0.52)	0.0	N/A	N/A
12/17e	25.7	(28.9)	(0.61)	0.0	N/A	N/A
12/18e	33.8	(20.2)	(0.42)	0.0	N/A	N/A

Note: Converted at ¥113 to US$1. Dividend yield excludes withholding tax. Investors should consult their tax advisor regarding the application of any domestic and foreign tax laws.

On track to maximize Treakisym's potential

During 2016 SymBio received additional approvals for Treakisym in chronic lymphocytic leukemia (CLL) and first-line low-grade non-Hodgkin's lymphoma (NHL) and mantle cell lymphoma (MCL). These represent patient markets in Japan of around 7,800, compared to around 4,700 patients with relapsed or refractory (r/r) low-grade NHL/MCL, where sales have been generated to date (¥4,200m/$37m in 2016) via partner Eisai. Hence, we believe these additional indications could more than double current Treakisym sales and we expect an uplift during 2017.

Rigosertib iv interim data expected H217

SymBio continues to participate in the global Phase III trial of iv rigosertib for the treatment of r/r higher-risk MDS (myelodysplastic syndromes). Partner Onconova expects interim data from the trial to become available during H217. These data will be key in our view, not just for rigosertib's future, but also for Onconova's ability to raise additional capital, which may be needed to complete the trial.

SymBio could choose to market IONSYS alone

IONSYS is in a Phase III trial in Japan for the treatment of post-operative pain. IONSYS is already approved in the US and Europe, hence we believe this trial is a formality, prior to potential approval in 2019. Although SymBio has not announced definitive plans for IONSYS, SymBio may elect to market IONSYS alone, potentially propelling SymBio to the next phase with a commercial infrastructure.

Valuation: rNPV of $175m or $3.6/ADR

Our updated SymBio risk-adjusted valuation is $175m or $3.6/ADR (based on an increased share count following majority conversion of a bond issued in 2016) which includes $47m net cash at end December 2016. Our rNPV suggests the current price is underpinned by Treakisym and cash.

27 February 2017

Price	**US$2.08***
Market cap	**US$100m**

*underlying ¥ price converted at ¥113/US$ ADR/Ord conversion ratio 1:1

Net cash (US$m) at end December 2016	47
ADRs in issue	48.0m
ADR Code	SYMQY
ADR exchange	OTC
Underlying exchange	Tokyo
Depository	BNY

Business description

SymBio Pharmaceuticals is a Japanese specialty pharma company with a focus on oncology, hematology and pain management. Treakisym was in-licensed from Astellas in 2005. Rigosertib was in-licensed from Onconova and IONSYS was in-licensed from The Medicines Company.

Next events

IONSYS Phase III data	Q317
Rigosertib iv Phase III interim data	H217
In-licensing activities	2017

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Edison profile page

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Investment summary

Company description: Japanese specialty pharma company

SymBio is a Japanese specialty pharma company that was established in 2005. It is focused on addressing high unmet medical needs within the oncology, hematology and pain management fields. SymBio in-licenses assets with proof-of-concept data for development and commercialization in Asia-Pacific, removing the need for investment in early-stage R&D. SymBio currently has three main assets: (1) Treakisym (bendamustine) for blood cancers, with Asia-Pacific marketing rights out-licensed to various commercial partners; (2) IONSYS for post-operative, patient-controlled pain management, which is approved in the US and Europe and SymBio is conducting a Phase III trial in Japan; and (3) rigosertib for a rare blood cancer, which is currently being investigated in a global Phase III trial in which SymBio is participating. SymBio may elect to commercialize IONSYS and rigosertib alone. SymBio has an active New Drug Search Engine and is aiming to in-license at least one further asset during 2017. SymBio is also looking to expand globally. It has around 85 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	Approved	Both indications were approved in Japan during 2016 and we expect partner Eisai to launch during Q117. We expect these new indications to be a significant sales driver.
	r/r aggressive NHL	Phase II	Phase II completed. Discussing route to approval with regulators.
IONSYS (SyB P-1501)	Post-operative pain	Phase III	Phase III ongoing; we expect top-line data Q317. SymBio aiming for approval during 2019.
Rigosertib iv (SyB L-1101)	r/r HR-MDS	Phase III	Global Phase III ongoing with SymBio participating; interim data H217; top-line data H118.
Rigosertib oral (SyB C-1101)	First-line HR-MDS (combo) and LR-MDS	Phase I	Phase I in combination with Vidaza ongoing; partner Onconova is planning a Phase III combo trial to start during 2017; SymBio may elect to participate.

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

Valuation: Risk-adjusted NPV of $175m or $3.6/ADR

We value SymBio at $175m or $3.6/ADR, which is based on a risk-adjusted NPV analysis and includes $47m net cash at end December 2016. Our valuation includes Treakisym, where we assume sales can grow in the future with recent approvals in new indications, in addition to risk-adjusted contributions for IONSYS and rigosertib. Our valuation suggests that the current share price is underpinned by Treakisym and cash.

Financials: Cash runway to end 2018

SymBio has net cash of ¥5,269m/$46.6m (consisting of ¥5,719m/$50.6m gross cash and ¥450m/$4.0m of long-term debt related to the convertible bond issued during 2016). We estimate that this should provide a cash runway through to the end of 2018, by which point clinical trials for both rigosertib iv and IONSYS should be complete.

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 successfully grow sales following approvals in new indications during 2016. We also expect interim rigosertib iv data during H217, which will be critical in shaping the future development pathway. Finally, IONSYS is also undergoing a Phase III trial in Japan, which we expect to be successful, potentially leading to approval during 2019. IONSYS could represent the first asset that SymBio elects to commercialize alone, requiring investment into a commercial infrastructure.

Maximising Treakisym's potential

SymBio recently received approvals for Treakisym in additional indications. We believe that these indications could materially expand Treakisym's market potential (2016 sales were c ¥4.7bn), and expect to see an acceleration from current levels during 2017 via main partner Eisai. We believe these new indications should help to maximize Treakisym's potential ahead of expiry of the orphan drug exclusivity in Dec 2020, with new indications potentially more than doubling current sales.

Recent approvals could more than double current sales

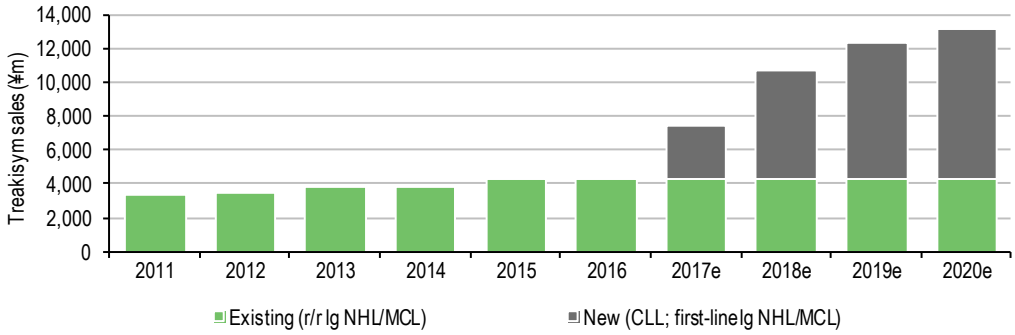
In December 2015 SymBio filed three supplemental NDAs (new drug applications) for Treakisym in Japan, including a lower dose (25mg vial versus the original 100mg vial) and two new indications:

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

SymBio has generally waited to file for approvals in Japan once an indication has been approved by US and/or European regulators. However, partner Astellas withdrew its application for first-line lg NHL/MCL in Europe in January 2016 following numerous delays; approval was initially expected in late 2014/early 2015. Despite this setback in Europe, SymBio's decision to proceed in Japan was rewarded during 2016, with approval granted for all three sNDAs.

We believe these new indications could materially expand Treakisym's potential, given the size of the patient market, particularly in first-line lg NHL/MCL. SymBio estimates that this is a patient market of 7,100 in Japan, which is c 50% larger than r/r lg NHL/MCL (4,700 patients). SymBio estimates that CLL is a patient market of around 700 in Japan. With generally more treatment cycles per patient (six cycles in first-line lg NHL versus four to five cycles in r/r lg NHL), we estimate sales in these new indications could reach nearly ¥9bn ($80m) by 2020 if Treakisym can achieve a similar 50-60% market share as in r/r lg NHL. Our Treakisym sales forecasts are shown in Exhibit 2.

Exhibit 2: Treakisym in-market sales forecasts



Source: Eisai, SymBio, Edison Investment Research. Note: SymBio records royalties on in-market Treakisym sales.

Current Treakisym sales of around ¥4.7bn ($42m)

SymBio acquired the rights to develop and commercialize Treakisym from Astellas in Japan (2005) and subsequently in China/Hong Kong, Korea, Taiwan and Singapore (April 2007). In 2008, SymBio out-licensed marketing of Treakisym to various commercial partners (an overview of the main agreements is shown in Exhibit 3). The agreements call for royalties and milestones. 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. We also believe that the bulk of development-related milestones both due and owed to partners has now been

received/paid. SymBio could be due sales-related milestones in the future, although we do not include any further significant milestones in our forecasts or valuation.

Exhibit 3: 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 commercialization 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 commercialization rights (financials not disclosed)

Source: Edison Investment Research, SymBio

Treakisym was approved in Japan in October 2010 for the treatment of relapsed or refractory (r/r) low-grade non-Hodgkin's lymphoma (lg NHL) and mantle cell lymphoma (MCL). It has also been approved in a number of other indications and countries, summarized in Exhibit 4. The bulk of current sales are generated by partner Eisai, predominantly in Japan; Eisai reported 2016 sales of ¥4.2bn; SymBio estimates total market sales from partners of around ¥4.7bn. SymBio estimates that Treakisym has captured around a 60% share of the c 4,700 r/r lg NHL/MCL patients in Japan.

Exhibit 4: Treakisym approvals in Asia-Pacific

Country	Brand name	Indication(s)	Approval	Launch	Partner
Japan	Treakisym	r/r lg NHL; MCL CLL First-line lg NHL; MCL	October 2010 August 2016 December 2016	December 2010	Eisai
South Korea	Symbenda	CLL; MM r/r lg NHL	May 2011 June 2014	October 2011 (CLL; MM)	Eisai
Singapore	Symbenda	r/r lg NHL; CLL	January 2010	September 2010	Eisai
Hong Kong	Treanda	r/r lg NHL; CLL	December 2009	2010	Cephalon (Teva)
Taiwan	Innomustine	r/r lg NHL; CLL	October 2011	February 2012	InnoPharmax

Source: Edison Investment Research, SymBio. Note: lg NHL: low grade non-Hodgkin's lymphoma; CLL: chronic lymphocytic leukemia; r/r: relapsed/refractory; MCL: mantle cell lymphoma; MM: multiple myeloma.

We do not expect patient penetration in r/r lg NHL/MCL to expand materially beyond current levels, given the already high share achieved in this market. Assuming stable pricing for Treakisym going forwards, our in-market sales forecasts therefore remain broadly constant in r/r lg NHL/MCL through to 2020, when the orphan drug exclusivity expires. Beyond 2020, we include a gradual decline in sales, with genericization in Japan generally not as abrupt as in other markets. If SymBio and partners are able to maintain sales beyond 2020, potentially through new formulations or extended patent protection, this could provide upside to our forecasts.

SymBio has also completed development in r/r aggressive NHL (a patient population of 6,700 in Japan) in 2012. However, filing has been delayed owing to discussions with regulators, which are still ongoing. It is possible that approval will only be granted subject to conducting an additional trial. However, we believe it is unlikely that SymBio will invest in further Treakisym development owing to expiry of market exclusivity in December 2020. Hence we do not include a contribution from Japanese r/r aggressive NHL patients in our valuation. If it can be approved, we estimate it could add ¥5.0-8.5bn (c $45-75m) in sales.

Japan drug pricing in focus; expect Treakisym to remain stable

There have recently been a number of high-profile price cuts in Japan, including 50% to Opdivo (nivolumab) in cancer and Sovaldi (sofosbuvir) for hepatitis C. These have been instigated owing to a focus on rising healthcare costs in the face of an ageing population. Drug prices in Japan are typically reviewed every other year. To date, to our knowledge, Treakisym has not been subject to a price cut and our current forecasts assume that pricing remains stable through to 2020. We believe that the recent 50% cuts have been for drugs that exceed ¥150bn, with 25% cuts for drug sales of ¥100-150bn. Hence, Treakisym should not be subject to such aggressive measures. However, if there are future cuts to Treakisym's price, this could represent downside to our current forecasts.

IONSYS on track towards approval in 2019

In October 2015 SymBio acquired an exclusive license in Japan to develop and market IONSYS (SyB P-1501) for the short-term management of acute post-operative pain from The Medicines Company. SymBio initiated a Phase III trial in Japan in June, with the first patient recruited in November 2016. We expect top-line data could become available during Q317. This should allow for regulatory filings during 2018 and approval during 2019, in line with SymBio's expectations.

Phase III data during Q317

IONSYS received US FDA approval in April 2015 and EU approval in November 2015. SymBio is now conducting a Phase III bridging study to confirm efficacy in Japanese patients. The Phase III trial, which will recruit around 312 patients, was initiated in June 2016 and the first patient was recruited in November 2016. Top-line data are anticipated during Q317.

Assuming positive data, which we believe is likely given approvals already in the US and Europe, we believe SymBio could file a new drug application in Japan in 2018, which should therefore allow for approval during 2019, assuming at least a year for regulatory reviews. We now assume first sales in Japan from early 2020 (we previously included some sales in 2019). While SymBio has not announced definitive plans, we expect that SymBio will seek to market IONSYS through its own salesforce.

SymBio estimates that around 700k patients in Japan require post-operative, patient-controlled pain management. With each patient potentially using up to three IONSYS systems, depending on the length of pain management required, this suggests a total market for IONSYS of ¥8,400m-¥25,200m (assuming pricing is similar to the US). Our peak sales remain ¥6,500m (c $58m) for IONSYS in Japan, which represents only a fraction of this total market. This is based on the rate of post-surgical patient-controlled analgesia use in the US, discounted to reflect studies from the European Society of Medical Oncologists (ESMO) suggesting that post-surgical opioid use is much lower in Japan than other developed countries.

To date, The Medicines Company has not broken out specific sales of IONSYS since its approval in April 2015 (IONSYS sales are grouped together with other products). With its most recent financial results to end September 2016, $7.4m was recorded for potential inventory expiry related to IONSYS components, which are expected to reach expiration prior to projected sales.

Patient-controlled pain patch

IONSYS is a patient-controlled fentanyl iontophoretic transdermal system for the short-term management of acute post-operative pain. Patient-controlled analgesia (PCA) infusion pumps have been widely used since the late 1980s. The pumps are used primarily to alleviate pain for a day or two following inpatient surgery. The pumps contain a syringe of pain medication (usually an opioid) and are connected to a patient's iv line. The pump is programmed to allow patients to administer a dose of medication whenever they feel pain. The pumps include several safety features to prevent an overdose. Intravenous PCA pumps have a number of downsides including high equipment and nursing costs and risks of medical errors and patient infection.

The IONSYS fentanyl iontophoretic transdermal system does not require needles, pumps, catheters or intravenous (iv) pump stands to manage post-operative pain. Being needle-free, this treatment eliminates the risk of needle-stick injuries and infection due to analgesic administration with iv PCA. This system has the potential to make the administration of post-operative pain management a less time-consuming task for healthcare professionals and less invasive for patients.

IONSYS is applied to the patient (usually on the upper arm or chest) by a healthcare professional. The patient is then able to activate drug delivery on demand, according to their own needs. A dose

of opioid is administered transdermally over 10 minutes, and each subsequent dose cannot be initiated until delivery is complete.

Exhibit 5: IONSYS vs PCA pumps

	Iv PCA	IONSYS
Effectiveness		Superior performance of fentanyl compared with SOC Equal to or superior to iv PCA Fewer analgesic gaps
Safety	Programming skill required (error prone) Drug dilution required Medication refill errors	Simplified pre-programming/minimal setup Smaller overall opioid-related adverse event burden No drug dilution required
Simplicity	Time consuming set up (power cable/tubing)	No set up (two components snap together) No hardware or maintenance
Mobility	May require nursing help Iv can be dislodged	Improved post-operative mobility
Infection risk	Invasive	Needle-free and disposable

Source: Edison Investment Research

IONSYS diversifies SymBio's pipeline

IONSYS reflects an expansion in SymBio's original focus on oncology and hematology and into the broader market of pain management. The acquisition diversifies SymBio's portfolio into a large, well-established market with a product that is highly differentiated and has significant cost and clinical advantages over existing technology.

Management has indicated in the past that it is open to new therapeutic classes as long as a prospective in-licensing opportunity meets the company's undisclosed screening criteria. We believe SymBio views IONSYS as a market-changing product due to its credit-card sized, needle-free design that does not require the patient to be tethered to an iv line and other equipment. We also believe IONSYS will help reinforce SymBio's presence as a strong development and commercial partner for Asia-Pacific, in addition to diversifying risk.

Rigosertib interim analysis in H217 will be key

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 participating in the global Phase III INSPIRE trial of iv rigosertib for the treatment of second-line HR-MDS (higher-risk MDS) and an interim analysis is expected during H217. If this is positive, then partner Onconova may need to seek additional financing to complete the INSPIRE trial; this follows partner Baxter, which was funding half the trial costs, returning all rigosertib rights in March 2016. The INSPIRE trial has been designed following analysis of the failed Phase III ONTIME trial of iv rigosertib in HR-MDS. During 2017 partner Onconova is also planning to start a pivotal Phase III oral rigosertib trial in combination with Vidaza for first-line HR MDS; SymBio may elect to participate in this trial.

Iv rigosertib: Interim Phase III analysis expected during H217

Partner Onconova enrolled the first patient into the global Phase III INSPIRE trial in December 2015. SymBio is contributing patients from Japan to the trial. The trial has been designed with input from regulators including the FDA and EMA, and the patient eligibility criteria have been refined following a detailed analysis of the previous Phase III ONTIME trial. In the ONTIME trial, iv rigosertib failed to meet the primary endpoint, although did show benefits in certain subgroups; the Phase III INSPIRE trial has been designed following a detailed review of the ONTIME data to try to maximize the chance of success. Onconova expects a pre-planned interim analysis of the INSPIRE trial to occur during H217, with top-line data from the full analysis in H118.

Patient recruitment in INSPIRE has been refined to HR-MDS patients who meet all of the following criteria: (1) patients who have failed HMA[1] (hypomethylating agent) treatment within nine months of HMA initiation; (2) patients younger than 82 years of age; and (3) patients who received their last HMA dose within the six months prior to entering the INSPIRE trial. These criteria have been selected following a subset analysis of the ONTIME trial, in which iv rigosertib was able to improve survival in this particular patient group (data summarized in Exhibit 6). Hence, the trial design and recruitment criteria have been selected to try to improve the likelihood of INSPIRE trial success.

Exhibit 6: 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

The INSPIRE trial will recruit around 225 HR-MDS patients, with SymBio expected to contribute 20-25 from Japan. SymBio enrolled the first patient from Japan in July 2016 and we expect SymBio to complete patient enrolment in Japan by YE17. The trial is randomized 2:1 and will compare iv rigosertib in combination with best supportive care (BSC) to physician's choice with BSC. The primary efficacy endpoint is overall survival. According to Onconova, the interim analysis will be performed after 88 events (deaths) have occurred, and will examine overall survival in the intent to treat population (ITT). For a trial to be stopped for efficacy at an interim analysis would usually require a much higher statistical hurdle than at the full analysis (ie generally p>0.05). The full analysis will occur at 176 events. For the full analysis, overall survival will be examined in the ITT population, and if the outcome in this group is not successful, an analysis of the subgroup of patients classified at entry as IPSS-R very high risk (revised International Prognostic Scoring System) will be conducted. Hence, the trial can succeed if the survival endpoint is achieved in either group.

Oral rigosertib: Combination with Vidaza the main priority

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

- monotherapy for treatment of LR-MDS, and
- combination with HMAs (Vidaza) as first-line treatment for HR-MDS

SymBio has already completed a Phase I trial as monotherapy in LR-MDS, and a Phase I trial in combination with Vidaza as first-line treatment for HR-MDS has been initiated.

Vidaza combination the main development priority for oral rigosertib

SymBio initiated a Phase I trial in Japan in December 2015 to investigate the combination of oral rigosertib with Vidaza for the treatment of first-line HR-MDS. The first patient has yet to be enrolled as, according to SymBio, the supply of oral rigosertib (which is provided by partner Onconova) has been interrupted. SymBio is hopeful that recruitment efforts can resume during Q317.

Onconova has been in discussions with the FDA regarding the trial design for a Phase III trial to investigate oral rigosertib in combination with Vidaza for the treatment of first-line HR-MDS. The precise trial design is still being finalized with input from regulators, but is likely to focus on the combination of oral rigosertib with Vidaza compared to Vidaza alone and will assess overall response rate (ORR), rather than survival, which should reduce the trial's length. Onconova plans

[1] 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.

to launch this study during 2017; SymBio is considering participating in this trial, which could involve SymBio recruiting patients from Japan into the trial (as per INSPIRE).

Updated data from the final expansion phase of Onconova's fully recruited Phase II open-label trial of oral rigosertib in combination with Vidaza were recently presented at the ASH meeting (American Society of Hematology) in December 2016 and are summarized in Exhibit 7. These data formed the basis of pivotal trial design discussions with the FDA. Data were available from 33 evaluable MDS patients (from 40 MDS patients recruited into the trial). The median duration of remission was 8 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).

Exhibit 7: 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.[2]

Uncertain future for oral rigosertib in LR-MDS

Both SymBio and partner Onconova have completed early stage trials of oral rigosertib as a treatment for first-line LR-MDS (lower-risk MDS). However, the future development of this program is uncertain, and has effectively been on hold since Onconova's European partner Baxter elected not to pursue further development in LR-MDS in January 2015. In March 2016 Baxter also decided to return all rigosertib rights to Onconova, leaving Onconova with only enough cash to fund activities through 2017 (under the terms of the deal, Baxter was funding 50% of the costs of the INSPIRE trial, capped at $15m). These include continued funding of the Phase III INSPIRE iv rigosertib trial to the planned interim analysis, expected in H217, and start of the planned pivotal Phase III oral rigosertib combination trial. If Onconova does decide to pursue oral rigosertib in LR-MDS, then SymBio could choose to mirror and follow Onconova's approach. However, until there is clarity from Onconova on the future development of oral rigosertib in LR-MDS, we do not expect any trial initiations in LR-MDS in the near future.

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 IONSYS clinical trial success or failure, expansion of Treakisym to additional indications and the ability to execute future in-licensing deals.

For Treakisym, now that approval has been granted in additional indications, successful penetration and uptake in these new patient markets will be key to driving sales beyond current levels. We believe partner Eisai is well placed to maximize Treakisym's potential in these additional indications. With a recent focus on oncology drug prices in Japan, Treakisym pricing could come under scrutiny. Our current forecasts assume stable pricing until expiry of the orphan drug exclusivity in December 2020; any price cuts could therefore adversely affect our sales projections.

IONSYS has already been approved in the US and Europe and hence we expect a positive outcome from the ongoing Phase III trial being conducted in Japan; we expect data in Q317. Assuming these are positive and that IONSYS is successfully approved in Japan during 2019, then IONSYS could represent the first asset that SymBio chooses to commercialize alone. This

[2] 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.

introduces an element of execution risk and uncertainty, as SymBio has limited experience in building out a commercial infrastructure.

The main sensitivity for rigosertib in 2017 will be the outcome of the pre-planned interim analysis of the Phase III INSPIRE trial of iv rigosertib in second line HR-MDS, which partner Onconova expects during H217. If the outcome is positive and the trial proceeds as planned, Onconova may need additional cash to continue funding the trial beyond the end of 2017; top-line data are expected in H118. If Onconova is unable to secure additional funds, this could delay trial completion and therefore timelines. If the outcome of the interim analysis is negative, then not only would this have an impact on iv rigosertib development, but there could also be read-across to oral rigosertib. This may reduce Onconova's ability to secure funds to run a pivotal Phase III trial for oral rigosertib and could also therefore affect SymBio's future trials.

SymBio is reliant on in-licensing 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

We value SymBio at $175m, shown in Exhibit 8, or $3.6/ADR (with the increased share count following issuance of a convertible bond in 2016), based on a risk-adjusted NPV analysis, which includes $47m net cash at end December 2016. We use a 10% discount rate for approved products and 12.5% elsewhere. Our valuation includes Treakisym, IONSYS and rigosertib. We have rolled our valuation model forward in time and have made a number of adjustments to our main assumptions, which are summarized below.

Exhibit 8: SymBio rNPV valuation

Product	Indication	Launch	Peak sales ($m)	NPV ($m)	Probability	rNPV ($m)	NPV/ADR ($/ADR)
Treakisym	Low grade NHL/MCL (r/r and 1st line); CLL	2010*	119	50.5	100%	50.5	1.1
Rigosertib (iv)	r/r HR-MDS	2020	30	33.3	50%	14.7	0.3
Rigosertib (oral)	LR-MDS (monotherapy) or First-line HR-MDS (combo)	2022	66	55.4	25%	10.5	0.2
IONSYS	Pain management	2020	58	55.7	95%	52.4	1.1
Net cash (at end 2016)				46.6	100%	46.6	1.0
Valuation				**241.5**		**174.7**	**3.6**

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.

For Treakisym, with the new indications now approved we have combined the sales potential from these with the sales potential from the previous indications into one Treakisym valuation. Hence, we now include our future sales forecasts from the expanded indications with 100% probability and a 10% discount rate, as these are now approved indications (previously sales from the new indications were included with a 90% probability and a 12.5% discount rate). We currently assume stable Treakisym pricing. However, should Treakisym be subject to a price cut in the future, this could represent downside to our forecasts; a 10% price cut in 2018 would remove around $4.4m from our Treakisym rNPV, or $0.1/ADR. Our forecasts continue to exclude any sales potential in r/r aggressive NHL, as described earlier in this report. Our Treakisym valuation continues to assume that SymBio earns an average net margin of 10-12% on top-line reported Treakisym sales.

We have maintained our peak sales assumptions and probabilities of success for rigosertib (iv and oral). However, we have delayed our initial launch expectations for both programs. This is based on the most recent trial timing expectations, with top-line data from the ongoing Phase III INSPIRE trial of iv rigosertib expected in H118. Assuming that SymBio files in Japan in parallel with Onconova's filings in the US/Europe potentially during H218, and allowing around a year for regulatory processes, approval could therefore be possible during H219. Hence, we now assume initial launch

of iv rigosertib in Japan in early 2020 (from 2019 when we last published). For oral rigosertib, we now assume initial launches from 2022, two years after the iv, as this has not yet entered Phase III development in the US/Europe (conducted by partner Onconova) and SymBio still needs to complete the interrupted Phase I combination trial with Vidaza. Our rigosertib oral peak sales estimate of ¥7.5bn ($65m) assume development and launch in either HR-MDS in combination with Vidaza (Nippon Shinyaku reported 2016 Vidaza sales in Japan of ¥13.4bn) or in LR-MDS as monotherapy. If both indications are developed, this could provide upside to our forecasts.

For IONSYS, SymBio is working towards an approval during 2019. Hence, we now assume initial launch from 2020, allowing time to build out a commercial infrastructure. Our peak sales and probability are unchanged.

Financials

Our financial forecasts have been updated to reflect FY16 reported financials and SymBio's updated financial guidance for 2017 and targets for 2018. The main changes to our forecasts are summarized in Exhibit 9. Our sales forecasts did previously include a contribution from expansion to the now approved additional indications (first-line lg NHL/MCL and CLL). However, these have now been refined following formal approvals during 2016. Our forecasts assume that in 2017 partner Eisai can achieve around a 20% penetration of the c 7,800 additional patients in Japan in these new indications (our last published forecasts assumed a <10% penetration in 2017). Our Treakisym forecasts have also increased in 2018 given the higher base in 2017.

We have made only minor changes to our R&D and SG&A forecasts in 2017, which are broadly in-line with SymBio's guidance (Exhibit 10). SymBio anticipates R&D spend of ¥2,286m/$20m in 2017, compared to ¥1,667m/$14.7m in 2016. We believe this uptick may be due to inclusion of at least one milestone payment for any prospective in-licensing activity in 2017. Hence, in 2018, we expect R&D spend to revert to 2016 levels.

During 2016 SymBio issued a convertible bond, raising ¥3,000m/$26.5m (40 units, equivalent to 14.2m shares with a conversion price of ¥211). To date, 13.5m shares have converted (12.1m during 2016 and a further 1.4m so far in 2017). This cash boost in 2016 resulted in net cash at the end of 2016 of ¥5,269m/$46.6m (consisting of ¥5,719m/$50.6m gross cash and ¥450m/$4.0m of long-term debt related to the convertible bond). We estimate current cash should be sufficient to fund operations through to the end of 2018, by which point clinical trials for both rigosertib iv and IONSYS should be complete.

Exhibit 9: Main changes to our financial forecasts; ¥-based future financial forecasts

¥m	2017 Old	2017 New	% Change	2018 Old	2018 New	% Change
Revenue	2,290	2,902	+27%	2,897	3,820	+32%
Research and development	(2,163)	(2,300)	+6%	(2,686)	(1,600)	-40%
Selling, general and administration	(1,831)	(1,750)	-4%	(1,964)	(1,837)	-6%
Operating profit (reported)	(3,316)	(3,191)	-4%	(3,793)	(2,306)	-39%
Profit before tax (reported)	(3,316)	(3,261)	-2%	(3,793)	(2,284)	-40%
Profit after tax (reported)	(3,320)	(3,264)	-2%	(3,797)	(2,288)	-40%

Source: Edison Investment Research

Exhibit 10: SymBio's 2017 outlook and 2018 targets versus our estimates; ¥-based future financial forecasts

	2017 Guidance	2017 Estimates	2018 targets Low	2018 targets High	2018 Estimates
Revenue	¥2,903m	¥2,902m	¥3,401m	¥3,926m	¥3,820m
R&D	¥2,286m	¥2,300m	N/A	N/A	¥1,600m
SG&A (including R&D)	¥4,062m	¥4,050m	N/A	N/A	¥3,437m
Operating loss	¥3,239m	¥3,191m	¥2,509m	¥2,309m	¥2,306m
Ordinary loss	¥3,303m	¥3,261m	¥2,573m	¥2,373m	¥2,284m
Net loss	¥3,307m	¥3,264m	¥2,577m	¥2,377m	¥2,288m

Source: SymBio and Edison Investment Research

Exhibit 11: Financial summary

Accounts: JPN GAAP, year-end: December, $'000s		2013	2014	2015	2016	2017e	2018e
Total revenues		13,558	17,301	17,108	20,957	25,683	33,806
Cost of sales		(10,744)	(12,641)	(11,949)	(12,955)	(18,081)	(23,799)
Reported gross profit		2,814	4,661	5,159	8,002	7,602	10,007
SG&A (expenses)		(8,369)	(9,343)	(9,734)	(12,072)	(15,484)	(16,259)
R&D costs		(9,317)	(6,850)	(18,006)	(14,753)	(20,354)	(14,159)
Other (includes exceptionals)		0	0	0	0	0	0
Adjusted EBIT		(14,872)	(11,533)	(22,581)	(18,823)	(28,236)	(20,411)
Reported EBIT		(14,872)	(11,533)	(22,581)	(18,823)	(28,236)	(20,411)
Finance income/ (expense)		89	219	144	48	(619)	201
Other income (expense) (includes exceptionals)		612	1,473	(822)	(1,663)	0	0
Adjusted PTP		(14,172)	(9,826)	(23,278)	(20,503)	(28,856)	(20,210)
Reported PTP		(14,172)	(9,841)	(23,259)	(20,437)	(28,856)	(20,210)
Income tax expense		(34)	(34)	(34)	(34)	(34)	(34)
Adjusted net income		(14,206)	(9,859)	(23,311)	(20,536)	(28,889)	(20,244)
Reported net income		(14,206)	(9,875)	(23,293)	(20,471)	(28,889)	(20,244)
Earnings per ADR							
Basic EPADR	USD	(0.61)	(0.32)	(0.72)	(0.52)	(0.61)	(0.42)
Diluted EPADR	USD	(0.61)	(0.32)	(0.72)	(0.52)	(0.61)	(0.42)
Adjusted diluted EPADR	USD	(0.61)	(0.32)	(0.72)	(0.52)	(0.61)	(0.42)
Average number of ADRs - basic	millions	23.2	30.8	32.4	39.3	47.2	48.0
Balance sheet							
Property, plant and equipment		76	434	469	660	782	947
Goodwill		0	0	0	0	0	0
Intangible assets		69	585	460	372	277	177
Other non-current assets		324	430	465	680	680	680
Total non-current assets		469	1,449	1,394	1,711	1,739	1,804
Cash and equivalents		46,851	45,063	37,712	50,613	20,006	272
Inventories		1,107	2,164	1,177	2,413	2,477	2,608
Trade and other receivables		0	2,413	2,661	4,314	4,574	4,631
Other current assets		19,600	14,874	1,164	1,818	1,818	1,818
Assets classified for sale		0	0	0	0	0	0
Total current assets		67,557	64,514	42,715	59,159	28,875	9,329
Non-current loans and borrowings		0	0	0	3,982	1,327	0
Trade and other payables		0	0	0	0	0	0
Other non-current liabilities		27	20	14	12	12	12
Total non-current liabilities		27	20	14	3,995	1,340	12
Trade and other payables		0	2,708	2,831	2,848	2,924	2,475
Current loans and borrowings		0	0	0	0	0	1,327
Other current liabilities		2,221	1,610	2,045	5,489	5,489	5,489
Liabilities of assets held for sale		0	0	0	0	0	0
Total current liabilities		2,221	4,318	4,876	8,337	8,413	9,291
Equity attributable to company		65,779	61,625	39,220	48,539	20,862	1,830
Non-controlling interest		0	0	0	0	0	0
Cash flow statement							
Profit before tax		(14,172)	(9,841)	(23,259)	(20,437)	(28,856)	(20,210)
Depreciation and Amortization		72	112	215	227	265	309
Share based payments		589	838	911	1,212	1,212	1,212
Other adjustments		(236)	(1,830)	231	1,744	619	(201)
Movements in working capital		(1,123)	(688)	1,678	(111)	(248)	(638)
Net cash from operating activities (pre-tax)		(14,869)	(11,409)	(20,226)	(17,365)	(27,006)	(19,528)
Interest paid / received		59	238	156	53	(619)	201
Income taxes paid		(34)	(34)	(34)	(34)	(34)	(34)
Cash from operations (CFO)		(14,844)	(11,205)	(20,103)	(17,346)	(27,659)	(19,361)
Capex (includes acquisitions)		0	(961)	(210)	(247)	(293)	(374)
Other investing activities		(11,790)	3,743	13,389	(141)	0	0
Cash used in investing activities (CFIA)		(11,790)	2,782	13,178	(388)	(293)	(374)
Net proceeds from issue of shares		35,907	4,818	(16)	32,532	0	0
Movements in debt		0	0	0	0	(2,655)	0
Other financing activities		(7)	(7)	(7)	(159)	0	0
Cash from financing activities (CFF)		35,900	4,812	(23)	32,373	(2,655)	0
Currency translation differences and other		62	1,823	(402)	(1,738)	0	0
Increase/(decrease) in cash and equivalents		9,328	(1,788)	(7,351)	12,902	(30,607)	(19,735)
Cash and equivalents at end of period		46,851	45,063	37,712	50,613	20,006	272
Net (debt) cash		46,851	45,063	37,712	46,631	18,679	(1,056)
Movement in net (debt) cash over period		9,328	(1,788)	(7,351)	8,919	(27,952)	(19,735)

Source: Edison Investment Research and SymBio accounts.

Solely for the convenience of the reader the financial summary table has been converted at a rate of ¥113 to $1. SymBio reports statutory accounts in Japanese yen. These translations should not be considered representations that any such amounts have been or could be converted into US dollars at the assumed conversion rate.

Contact details	Revenue by geography
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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 Office, Executive VP and COO: Kazuo Asakawa	
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.	

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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