EDISON

SymBio Pharmaceuticals

Initiation of coverage

Transforming to a commercial-stage company

Pharma & biotech

SymBio is on the path to becoming a key specialty pharma partner for Asian markets following in-licensing deals for orphan blood cancer products Treakisym (Treanda) and rigosertib. The former was a pivotal deal, helping to establish SymBio, with rigosertib potentially propelling SymBio to the next phase with a commercial infrastructure. Treakisym sales could grow in coming years with expansion to additional indications, and this asset together with cash underpins the current share price.

Year end	Revenue (¥m)	PBT* (¥m)	EPS* (¥)	DPS (¥)	P/E (x)	Yield (%)
12/12	1,955	(1,732)	(90.76)	0.0	N/A	N/A
12/13	1,532	(1,605)	(69.42)	0.0	N/A	N/A
12/14e	1,806	(1,537)	(50.30)	0.0	N/A	N/A
12/15e	1,968	(1,796)	(58.75)	0.0	N/A	N/A

Note: *PBT and EPS are normalised, excluding intangible amortisation, exceptional items and share-based payments.

Treakisym provides downside protection

In-licensing Treakisym (bendamustine) from Astellas was a pivotal deal for SymBio, leading to its first approved product in key Asian markets. Sales are currently around $38m following rapid clinical development and successful commercial partnering. R&D investment in Treakisym has now peaked and future significant growth could come with approval in additional indications. Treakisym and net cash underpin the current valuation, with existing sales providing downside protection.

Rigosertib essentially a free option at current levels

The next key asset is rigosertib for a rare blood cancer, MDS, currently in Phase I trials in Japan. SymBio in-licensed rights to both the IV and the oral formulation from Onconova in 2011. A setback in the IV Phase III US development has not delayed progress in Japan and US pivotal development plans will help to refine the future strategy and clinical trial plans in Japan. SymBio plans to build its own sales force for rigosertib to maximise value.

Asia-Pacific specialty pharma

SymBio is focused on in-licensing niche opportunities in hard-to-treat indications often overlooked by big pharma. Building its own commercial infrastructure for rigosertib should help establish SymBio more firmly as a partner of choice in Asia-Pacific. An in-house screening process to select additional pipeline candidates for development and commercialisation will be key for driving operating leverage.

Valuation: Risk-adjusted NPV of ¥14.1bn ($141m)

We value SymBio at ¥14,135m ($141m) or ¥461/share, based on a risk-adjusted NPV, which includes ¥4,798m ($48m) net cash. Our forecasts suggest Treakisym and net cash underpin the current share price, with the market seemingly ascribing limited value to rigosertib. Cash should be sufficient to fund operations into 2017 prior to the potential launch of rigosertib, which SymBio is intending to market itself.

13 October 2014

Price	**¥259**
Market cap	**¥7,934m**
	¥100/$
Net cash (¥m) at end June 2014	4,798
Shares in issue	30.6m
Free float	67%
Code	4582
Primary exchange	Tokyo
Secondary exchange	N/A

Share price performance

%	1m	3m	12m
Abs	(14.2)	(4.8)	(47.6)
Rel (local)	(9.8)	(3.5)	(50.3)
52-week high/low		¥527	¥196

Business description

SymBio Pharmaceuticals is a Japanese specialty pharma company with a focus on oncology, haematology and autoimmune disorders. Treakisym was in-licensed from Astellas in 2005, with 2013 sales of c $38m in Asian markets. Rigosertib was in-licensed from Onconova and is in development for an orphan blood cancer.

Next events

Bendamustine EU approval in frontline iNHL	Q414/Q115
Treakisym sNDA filing for CLL and frontline iNHL in Japan	2015
Rigosertib US development plans	Q414
Rigosertib completion of Japan Phase I trials	2015

Analysts

Dr Philippa Gardner	+44 (0)20 3681 2521
Dr Mick Cooper	+44 (0)20 3077 5734
Jason Zhang PhD	+1 646 653 7027

healthcare@edisongroup.com

Edison profile page

Investment summary

Company description: Specialty sweet spot

SymBio was established in 2005 with the aim of becoming a specialty pharma company focused on addressing high unmet medical needs in Asia-Pacific within the oncology, haematology and autoimmune fields. SymBio in-licenses assets with proof-of-concept (Phase II) data for development and commercialisation in Asia-Pacific, removing the need for investment in early-stage R&D; to date three in-licensing deals have been executed. SymBio has successfully developed Treakisym (bendamustine) for the Asian market, with marketing rights out-licensed to select commercial partners. For rigosertib, the next product in the pipeline, SymBio plans to build a salesforce in Japan and is seeking complementary opportunities for future operating leverage; SymBio is also looking to expand globally. SymBio raised ¥2.6bn (net) at ¥560/share as part of the October 2011 IPO and most recently ¥2.8bn net in December 2013 at ¥400/share. It has around 85 employees and is based in Tokyo.

Exhibit 1: SymBio main product pipeline

Product	Indication	Stage	Comments
Treakisym (SyB L-0501)	r/r iNHL/MCL	Marketed	Main indication and major contributor to sales in Japan and key Asia-Pacific markets (Eisai reported ¥3,800m in 2013)
	CLL	Phase II pivotal	Phase II pivotal trial ongoing; could complete in H215
	Frontline iNHL	Preparing for filing	Planning to file sNDA in frontline iNHL/MCL once this indication is approved in Europe
	r/r aggressive NHL	Phase II pivotal	Phase II completed. Discussing route to approval with regulators
Rigosertib IV (SyB L-1101)	HR-MDS	Phase I	Phase I ongoing; could complete in H115; pivotal trial design will depend on US plans
Rigosertib oral (SyB C-1101)	LR-MDS	Phase I	Phase I ongoing; could complete in H115; pivotal trial design will depend on US plans

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

Valuation: Risk-adjusted NPV of ¥14.1bn ($141m) or ¥461/share

We value SymBio at ¥14,135m ($141m) or ¥461/share, based on a risk-adjusted NPV analysis. Our rNPV includes ¥4,798m ($48m) net cash, Treakisym and rigosertib. For Treakisym we include both current sales and upside from sales in frontline iNHL and CLL; we do not include any potential in r/r aggressive NHL. Our Treakisym forecasts and net cash underpin the share price, with rigosertib essentially a free option at current levels. For rigosertib, we include risk-adjusted contributions, assuming SymBio commercialises this asset alone. If rigosertib can be launched a year earlier than we expect, this could add c ¥50/share. If SymBio can expand Treakisym to additional indications, and can successfully develop and launch rigosertib, our valuation could be around ¥21bn ($210m).

Sensitivities: Treakisym expansion, rigosertib and deals

The main sensitivities for SymBio include (1) expansion of Treakisym to additional indications, including frontline iNHL to drive growth; (2) rigosertib success or failure, especially following the failure of the Phase III ONTIME trial in the US to meet the primary endpoint; however rigosertib did show a significant benefit in a subset of patients, which partner Onconova is now pursuing; and (3) the ability to execute future in-licensing deals, especially to leverage future commercial operations.

Financials: Cash runway to 2017

Net cash of ¥4,798m ($48m) should be sufficient to fund current operations into 2017, excluding any new in-licensed assets, prior to the potential launch of rigosertib. We assume additional funds will be needed at this point, both to start building out a sales and marketing infrastructure ahead of first potential rigosertib launch in 2019, and for milestones that could become due to partner Onconova if rigosertib is approved in both the US and Japan. Q214 financial results suggest SymBio is on track to meet its retained 2014 financial guidance, with which we are broadly in line.

Outlook: Specialty sweet spot

SymBio is aiming to become a specialty pharma company focused on hard-to-treat indications, via in-licensing in niche markets often overlooked by big pharma. Business development efforts resulted in a successful deal with Astellas for Treakisym, helping to establish a nascent SymBio in Japan and core Asia-Pacific markets. SymBio is now seeking to expand its offering and crystallise value by building out its first commercial infrastructure for rigosertib. In-licensing additional assets will be key for driving future operating leverage.

Targeting niche products and seeking operating leverage

SymBio actively targets US and European drug candidates with proof-of-concept data, with this strategy reducing early-stage drug discovery costs and risks. In Japan and Asia, pivotal Phase II "bridging" studies can be used to confirm overseas findings, building on existing efficacy data and to confirm safety in Asian patients without the need for costly Phase III trials. This allows SymBio to move swiftly through development, often with a moderate capital outlay. SymBio is focused on a number of disease areas, often orphan indications that may fall below the radar of larger specialty or Asian pharma companies. If SymBio is able to in-license a portfolio of complementary assets, it could leverage any commercial infrastructure, driving operational efficiencies.

Pivotal deal with Astellas for Treakisym and swift development

Treakisym was in-licensed from Astellas shortly after SymBio was established, despite SymBio being a nascent company with limited resources. However, the CEO and founder of SymBio had a significant network and experience in Asia as founding president and CEO of Amgen Japan, which enabled execution of this deal. The original agreement in Japan was later extended to include China/Hong Kong, South Korea, Taiwan and Singapore. Treakisym was approved in Japan only four years after the first trial started, with launch coming only two years after US approval and around the same time as approval in Europe. Treakisym is marketed by a select number of commercial partners (see Exhibit 4).

Three proof-of-concept candidates in-licensed to date

To date SymBio has evaluated over 390 products, whittling these down to 34 candidates on which due diligence was performed. This has led to three deals for assets with proof-of-concept clinical data, which are summarised in Exhibit 2. Rigosertib is the most recent addition, and this asset could propel SymBio towards establishing itself as a key speciality pharma in Asia-Pacific.

Exhibit 2: Business development deals to date

Product	Originator	Date	Current status
Treakisym (SyB L-0501)	Astellas	December 2005; expanded April 2007	Approved in key Asia-Pacific markets; label expansions being pursued.
Antiemetic transdermal patch (SyB D-0701)	Abeille Pharmaceuticals	March 2007	No further development following failure to show benefit in radiotherapy-induced nausea and vomiting (RINV) in Phase II.
Rigosertib (SyB L/C-1101)	Onconova	July 2011	Onconova planning to start a further Phase III with IV in 2015 and a pivotal Phase III with the oral in H115 in US/Europe. SymBio is conducting Phase I trials in Japan.

Source: Edison Investment Research, SymBio Pharmaceuticals

Commercial infrastructure leverage and diversification

SymBio plans to build a commercial operation to sell rigosertib in the future and complementary assets to leverage this infrastructure are being sought. In addition, SymBio is also seeking to diversify its focus outside of haematology. Although we have limited visibility on the timing of any future deals, in-licensing at least one asset in the next 12 months seems possible given SymBio's proven track record of successfully executing deals.

First tracks with Treakisym

In-licensing Treakisym from Astellas was a pivotal deal for SymBio, leading to its first approved product in Japan and key Asia-Pacific markets. SymBio quickly and successfully developed Treakisym in relapsed/refractory indolent NHL (r/r iNHL) and mantle cell lymphoma (MCL), allowing for launch only two years after US approval. Treakisym R&D investment has now peaked, and SymBio expects future sales growth with approval in other indications where development is already complete. Our valuation suggests that Treakisym, if sales grow to meet our forecasts, together with net cash underpin SymBio's current market capitalisation.

In-licensing Treakisym was a pivotal deal for SymBio

SymBio in-licensed Treakisym from Astellas in December 2005 for exclusive development and marketing rights in Japan; the deal was expanded in 2007 to China/Hong Kong, South Korea, Singapore and Taiwan. SymBio started Phase I development in 2006 and Treakisym was approved in Japan for r/r iNHL and MCL in October 2010. Treakisym approvals are summarised in Exhibit 3.

Exhibit 3: Treakisym approvals in Asia-Pacific

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

Source: Edison Investment Research, SymBio Pharmaceuticals. Note: iNHL: indolent non-Hodgkin's lymphoma; CLL: chronic lymphocytic leukaemia; r/r: relapsed/refractory; MCL: mantle cell lymphoma; MM: multiple myeloma.

In the absence of a salesforce, SymBio out-licensed commercial rights to select partners (Exhibit 4). Treakisym sales by Eisai in 2011, the first full year of launch in Japan, were ¥3,400m, growing to ¥3,800m ($38m) in 2013; these include sales in Japan, South Korea and Singapore, with Japan representing the majority. We believe current sales by other partners (InnoPharmax and Teva in Taiwan and Hong Kong, respectively) represent <5%. Precise deal terms have not been disclosed, but we believe these vary according to both partner and region. We estimate that SymBio earns an average net margin of around 10-12% on top-line reported Treakisym sales in Asia-Pacific.

Exhibit 4: 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; SymBio receives upfront and development milestones to ¥4bn (we estimate around ¥3bn have been received to date); Eisai and SymBio share development costs equally, with Eisai funding 100% of sales and marketing; deal included several additional indications
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 Pharmaceuticals

Sales from existing indications could reach ¥5,300m ($53m)

SymBio estimates that Treakisym in Japan in the two approved indications (r/r iNHL and MCL) commands a market share of >50%. Given this relatively high penetration, we forecast limited additional market share gains in coming years. However, a 3% price rise in April 2014 together with the recent approval in South Korea for r/r iNHL could boost existing sales (¥3,800 by Eisai in 2013) by around ¥400m ($4m). Beyond this near-term boost, we expect only limited growth in existing indications to 2020, when the orphan drug exclusivity expires, forecasting Treakisym sales of ¥5,300m ($53m) by 2020 with the majority from Eisai. Treakisym has not been subject to Japan's biennial round of price cuts (which average around 6% every two years) and we do not forecast future price cuts. Beyond 2020, we forecast a gradual decline in sales, as genericisation in Japan is generally not as abrupt as in other markets, with generics often only commanding around a 25-30%

share. A new Treanda liquid formulation was recently approved in the US and this could potentially extend Treakisym's market exclusivity beyond 2020, which could provide upside to our forecasts.

Expansion into further indications could more than double sales

Pivotal development in frontline iNHL is complete and SymBio is planning to file these data in Japan once bendamustine has been approved in Europe in this indication; if this occurs by YE14, then approval could come in H116 with launch in H216. This is a patient market of 7,100, which is c 50% larger than the currently approved r/r iNHL (4,700 patients). A pivotal Phase II CLL trial is ongoing and this indication could be filed in H116. With generally more treatment cycles per patient (six cycles in frontline iNHL versus four to five cycles in r/r iNHL), sales in both frontline iNHL and CLL could reach ¥8,151m ($82m) by 2020 if Treakisym can achieve a similar 50% market share as in r/r iNHL.

CLL is already approved in both the US and Europe, so we believe it has a high chance of also gaining approval in Japan. For frontline iNHL, bendamustine is under review in Europe with data from the StiL[1] study demonstrating a PFS (progression free survival) of 69.5 months for patients treated with BR (bendamustine + rituximab), significantly longer than 31.2 months for R-CHOP (rituximab/Rituxan in combination with CHOP chemotherapy: cyclophosphamide, doxorubicin, vincristine, and prednisone). The BRIGHT[2] study demonstrated that BR was non-inferior to R-CHOP in terms of complete response rate (31% versus 25%, respectively, p=0.0225).

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. It is possible that approval will only be granted subject to conducting an additional trial. However, we think it unlikely that SymBio will invest in further development in r/r aggressive NHL owing to expiry of market exclusivity in 2020. Hence we do not include a contribution from this indication in our valuation. If this indication can be approved, it could add ¥3,000-5,000m ($30-50m) in sales.

Overview of non-Hodgkin's lymphoma

Non-Hodgkin's lymphoma (NHL) is the most common type of lymphoma, a blood cancer that affects lymphocytes (white blood cells) and the lymphatic system. NHL is a broad group of more than 50 subtypes, which are generally classified according to the cell affected (various types of B-cell or T-cell lymphoma) and into either slow growing (indolent) or fast growing (aggressive). Treatment is largely dependent on the type and stage of disease, with frontline treatment often with R-CHOP.

Treanda was approved in the US in 2008 for the treatment of relapsed indolent B-cell NHL and chronic lymphocytic leukaemia (CLL). It is marketed by Cephalon (Teva) and is on a 2014 run rate of $740m, based on H114 US sales of $370m. In Europe, Levact/Ribomustin/Ribovact was approved in 2010 for CLL, relapsed iNHL and multiple myeloma; it is mainly sold by Mundipharma.

The main late-stage or newly approved products in NHL are either for use with or after bendamustine and are therefore unlikely to adversely affect its current use. Therefore, we see limited significant competitive threats to Treakisym in Asia ahead of orphan drug exclusivity expiry in 2020. Zydelig (idelalisib) was recently approved in the US and Europe for CLL and certain subtype(s) of NHL, although its use in NHL is for third-line treatment. Other late-stage development candidates include CD20 antibodies (similar to rituximab) such as ofatumumab (Arzerra) and obinutuzumab (Gazyva), both approved for CLL in the US and in Phase III development for NHL, including in Japan, for use with bendamustine.

---

1 Rummel MJ, Niederle N, Maschmeyer G et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. *Lancet*. 2013 Apr 6; 381 (9873): 1203-10.

2 Flinn IW, van der Jagt R, Kahl BS et al. Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study. *Blood.* 2014 May 8; 123 (19): 2944-52.

Right on track with rigosertib

SymBio in-licensed rigosertib (IV and oral formulations, Japan and Korean rights) from Onconova in 2011 for MDS (myelodysplastic syndromes), a rare blood cancer; it is partnered with Baxter in Europe. Failure to meet the primary endpoint in the IV Phase III trial has not delayed Japanese progress, where both the IV and oral formulations are in Phase I trials. Onconova is continuing to pursue US/European development and future clinical trial plans will help to refine the future strategy and development plans in Japan. SymBio plans to build its own sales force for rigosertib.

Rigosertib and MDS background

Rigosertib is a tumour-specific dual-specificity inhibitor, which inhibits both the PI3K (phosphoinositide 3-kinase) and the PLK (polo-like kinase 1) pathway. PI3K is often the driving force in cancer cell development, while PLK is abnormally expressed or mutated in cancer cells. It is primarily being developed as a treatment for MDS, a type of blood cancer. The IV formulation is being developed in higher-risk MDS (HR-MDS), with the oral formulation for both lower-risk MDS (LR-MDS) and potentially as first-line treatment in all MDS in combination with approved agents.

MDS is a group of blood disorders caused by improper blood formation in the bone marrow, leading to low blood counts. The most common symptom is anaemia (low red blood cell count), but also includes neutropenia (low neutrophil count) and thrombocytopenia (low platelet count). Around 30% of MDS patients go on to develop AML (acute myeloid leukaemia).

The commonly used International Prognostic Scoring System (IPSS) divides MDS into four groups, outlined in Exhibit 5, based on bone marrow blast percentage, chromosome abnormalities and blood counts. LR-MDS patients include IPSS low and Intermediate-1 (Int-1), with HR-MDS patients generally Int-2 and IPSS High. HR-MDS patients account for around 70-75% of all MDS and generally have a better prognosis with longer survival and lower risk of developing AML. LR-MDS patients are treated with supportive care to improve blood counts and quality of life; blood transfusions are a key component of treatment with patients often becoming transfusion-dependent. Revlimid (lenalidomide) is approved for HR-MDS patients having a specific chromosome abnormality (5q deletion, which accounts for around 10-15% of MDS patients).

For HR-MDS patients where survival can be months rather than years, treatment is to try and delay disease progression and prolong survival. Treatment is generally with a hypomethylating agent (HMA) such as Vidaza (azacitidine) and Dacogen (decitabine), both approved in the US. There are currently no approved treatments for HR-MDS patients who fail HMAs.

Exhibit 5: MDS classification and treatment

IPSS	% of MDS	Median survival (without treatment)	Treatment
Low	33%	5.7 years	Blood transfusions; Revlimid for del(5q); EPO (if <500 U serum EPO)
Int-1	38%	3.5 years	
Int-2	22%	1.1 years	SCT if eligible; Vidaza (preferred) or Dacogen; clinical trials or supportive care for poor performance status patients
High	7%	5 months	

Source: MDS IPSS Working Group; NCCN guidelines. Note: SCT: stem cell transplant.

Consistent survival in HR-MDS patients in US trials

Onconova has completed the Phase III ONTIME trial of rigosertib (IV) in HR-MDS patients who have failed prior HMA treatment. The trial in 299 patients compared rigosertib (IV) in combination with best supportive care (BSC) to BSC alone. HMA failures included patients who had progressed after HMA treatment, patients who failed to achieve a complete or partial response (CR, PR) or haematological improvement and patients who relapsed.

Rigosertib demonstrated a numerical, but not significant benefit compared to BSC in the trial. However, rigosertib was able to show a significant benefit in a predefined subset of primary HMA

failures (which includes patients who have either progressed, or failed to achieve a response following HMA treatment, representing 62% of the study population). Rigosertib's 8.2-8.5 month survival benefit was similar across both the subset and the full trial, and is consistent with earlier stage rigosertib data where survival was found to be 35 weeks (8.2 months) from a cross-trial analysis (data presented at ASH 2011) of four Phase I or II trials in 39 patients who were previously treated with Vidaza or Dacogen.

Exhibit 6: Median overall survival (OS) in the ONTIME trial

		Median OS	N	Hazard ratio	p value
ONTIME trial	Rigosertib	8.2 months	199	0.86	0.27
	BSC	5.8 months	100		
Primary HMA failures	Rigosertib	8.5 months	127	0.66	0.017
	BSC	4.6 months	57		

Source: Onconova

With consistency in rigosertib survival, the ONTIME trial appears to have failed owing to a higher than expected BSC survival. The trial was designed around an expected control arm survival of 17-22 weeks (4-5 months). However, in the ONTIME trial this was 5.8 months. Although median overall survival in Dacogen failures and Vidaza failures has been reported as 4.3 months (18 weeks)[3] and 5.6 months (24 weeks),[4] respectively, in the ONTIME trial this may have been lengthened by access to treatments including low-dose cytarabine (where survival in Vidaza failures has been reported as 7.3 months[2]) or to investigational treatments.

Partner Onconova plans to pursue rigosertib IV in primary HMA failures

Following failure of the ONTIME trial to meet its primary endpoint, Onconova has met with the FDA and several European regulatory agencies to discuss the data, in particular the significant 3.9-month benefit in primary HMA failures. Onconova is now intending to pursue rigosertib IV development in this patient group in order to try and secure regulatory approvals. Details around pivotal trial design are anticipated by YE14 and the trial could start in 2015.

US oral development is advancing towards Phase III in LR-MDS

The Phase II ONTARGET trial is ongoing and interim data were made available at ASH 2013 with full data to be presented at ASH 2014. The trial is investigating oral rigosertib as frontline treatment in 80 LR-MDS patients. The endpoint of the trial is achievement of transfusion independence (TI), a key quality of life parameter in these patients, and the endpoint upon which Revlimid received approval for a subset of patients in this indication. In the 33 patients on "intermittent" dosing (dosing for two out of three weeks) treated for at least eight weeks, 15 (45%) achieved TI lasting between eight and 53 weeks (median 17 weeks). These data also showed a correlation between a genomic methylation profile and response. Onconova is planning to start a pivotal trial for oral rigosertib in LR-MDS in H115 and plans to incorporate the biomarker work in the IV and oral Phase III studies.

Also looking at combinations and other tumours

Onconova is also investigating oral rigosertib in combination with Vidaza as frontline treatment for HR-MDS in a Phase I/II trial, in addition to rigosertib in head and neck cancer. A Phase II trial in head and neck cancer is ongoing, in addition to earlier-stage trials in other tumours.

[3] Jabbour, E., Garcia-Manero, G., Batty, N., Shan, J., O'Brien, S., Cortes, J., Ravandi, F., Issa, J.-P. and Kantarjian, H. (2010), Outcome of patients with myelodysplastic syndrome after failure of decitabine therapy. *Cancer*, 116: 3830–3834. doi: 10.1002/cncr.25247.

[4] Prébet T, Gore SD, Esterni B, Gardin C, Itzykson R, Thepot S, Dreyfus F, Rauzy OB, Recher C, Adès L, Quesnel B, Beach CL, Fenaux P, Vey N. Outcome of high-risk myelodysplastic syndrome after azacitidine treatment failure. *J Clin Oncol*. 2011 Aug 20; 29(24): 3322-7. doi: 10.1200/JCO.2011.35.8135.

Japan development will be driven by US/Europe progress

Rigosertib is in Phase I development in Japan for both the oral (started March 2013) and IV (started June 2012) formulations. Both trials being conducted by SymBio are expected to complete in H115. By the time these complete, the pivotal trials conducted by Onconova in the US should be underway. SymBio could either then start pivotal standalone bridging studies, or it could potentially expand the US/European Phase III trials to Japan and Asia-Pacific. Either route to market will likely involve a similar level of investment and scope of clinical trials (we assume around 20-25 patients for IV rigosertib in HR-MDS and potentially around 60-70 patients in LR-MDS with the oral formulation), but the latter could allow for approval around the same time as in the US (for Onconova, Edison forecasts IV launch in 2017 and oral in 2018). Until the precise path to market is defined, we more conservatively assume SymBio launches both the IV and oral in 2019.

Rigosertib peak sales in Japan and South Korea could be $100m

SymBio estimates that there are around 11,000 patients in Japan with MDS of which around 60-70% are HR-MDS patients and 30-40% are LR-MDS patients. In Japan the annual incidence (newly diagnosed cases) is 4,500-5,500 and we assume South Korea is around 40% of this (based on population size). This results in a newly diagnosed market of around 7,300 MDS patients a year in Japan and South Korea, of which around 5,000 are LR-MDS and the remainder are HR-MDS.

For HR-MDS, rigosertib IV is being developed as second-line treatment in primary HMA failures in the US, and we assume a similar indication will also be pursued by SymBio. HMA response rates are around 50-60%, therefore c 40% of patients are refractory; in addition, the majority of patients who do respond eventually relapse. Hence we assume there are around 1,800 new r/r HR-MDS patients each year in SymBio's target markets, of which around 60% are primary HMA failures (as per the patient population in the ONTIME trial). If we assume pricing is at parity to Vidaza in Japan (¥51,421 price per vial, which equates to an average ¥4,300k or $43k per patient), and that SymBio can achieve similar penetration as with Treakisym (>50%), this suggests IV rigosertib could have potential peak sales of ¥3,200m ($32m) in 2024 (conservatively factoring in 6% biennial price cuts).

For the c 5,000 LR-MDS patients, we assume 25% lower pricing than for the IV formulation (and factor in 6% biennial price cuts), which together with 50% penetration of this market suggests peak sales of ¥6,825m ($68m) in 2024. This suggests combined rigosertib MDS peak sales of ¥10,000m ($100m) in Japan and South Korea. This compares to Vidaza sales in Japan for HR-MDS of ¥9,692m in FY ending April 2013 ($97m), three years post launch (Dacogen is not currently approved in Japan).

Although we do not currently include any potential contribution for oral rigosertib in combination with Vidaza in frontline HR-MDS, this combination is being investigated by Onconova in a Phase I/II trial. With Vidaza sales on track to reach $100m in Japan this year, this could therefore be a fairly significant opportunity for rigosertib in Japan and South Korea. We estimate oral rigosertib sales in this indication could be around $75m, assuming broad uptake into the current Vidaza market and based on our lower price assumption for oral rigosertib. A more conservative 50% penetration could lead to additional oral rigosertib sales of $38m, which represent pure upside to our forecasts.

Aside from Dacogen, we believe rigosertib is the most advanced product in development for both LR- and HR-MDS in Japan. We would assume that products that are successfully developed for the US and/or Europe will also eventually be developed for the Japanese market. Products in Phase II development in HR-MDS include SGI-110 in Phase II from Otsuka/Astex, although this is more likely to replace Dacogen, and sapacitabine from Daiichi Sankyo/Cyclacel. For LR-MDS the closest competitors include ARRY-613 (Array Pharma) although this in only in Phase I.

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

Despite a setback with the failure of the Phase III rigosertib IV ONTIME trial in the US, partner Onconova is discussing a path forward with regulators; a development update is expected Q414 and a pivotal trial could start in 2015. Development of oral rigosertib continues and a pivotal Phase III trial is expected to start in H115. SymBio is conducting Phase I trials for the both the IV and the oral form in Japan, which could complete in H115. Hence, the US pivotal Phase III trials should be underway by the time these complete, which should then help to define the development strategy for Japan and South Korea. Onconova will likely require additional cash to pursue future trials, which could delay initiation of SymBio's future trials and could therefore affect launch timelines.

For Treakisym, a key outcome will be expansion to frontline iNHL. SymBio is planning to file a supplementary NDA in Japan once bendamustine has been approved in Europe in this indication, potentially allowing for first sales in frontline iNHL by H216. This could be a key future growth driver if approved. We do not currently include any contribution for r/r aggressive NHL, but if regulators agree to approve this indication based on the current data package, then this could be an additional contributor to future sales, which we do not currently include in our forecasts. Extending the 2020 market exclusivity in Japan could also provide upside to our forecasts.

SymBio is reliant on in-licensing assets to fill its pipeline and this will become even more important for leveraging future commercial operations. To date, SymBio has executed three deals for products with clinical proof-of-concept data, although development for one of these has been terminated following a lack of efficacy. 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 ¥14,135m ($141m) or ¥461/share (shown in Exhibit 7), based on a risk-adjusted NPV analysis, which includes ¥4,798m ($48m) net cash. We use a 10% discount rate for approved products and 12.5% elsewhere. Our valuation includes both Treakisym and rigosertib. For Treakisym we include current sales and upside from sales in frontline iNHL and CLL; we do not include any potential in r/r aggressive NHL. Our Treakisym valuation assumes that SymBio earns an average net margin of 10-12% on top-line reported Treakisym sales. Our rigosertib forecasts include future R&D spend in addition to the cost of building out a sales infrastructure; we do not include any potential in indications beyond those currently under development, which could include solid tumours, AML and broader use in MDS in combination with other agents.

Exhibit 7: SymBio rNPV valuation

Product	Indication	Launch	Peak sales ($m)	NPV (¥m)	Probability	rNPV (¥m)	NPV/share (¥/share)
Treakisym (existing sales)	r/r iNHL/MCL	2010	55	3,330	100%	3,330	108.7
Treakisym (label expansion sales)	Frontline iNHL; CLL	2016	80	2,954	90%	2,644	86.3
Rigosertib (IV); SyB L-1101	r/r higher-risk MDS	2019	30	3,165	50%	1,371	44.8
Rigosertib (oral); SyB C-1101	Lower-risk MDS	2019	70	7,179	35%	1,992	65.0
Net cash at end June 2014				4,798	100%	4,798	156.6
Valuation				**21,425**		**14,135**	**461.4**

Source: Edison Investment Research. Note: Peak sales are rounded to the nearest $5m.

For Treakisym we include existing sales in approved indications at 100% probability, assuming a 4.2% seven-year sales CAGR through to expiry of the current market exclusivity in 2020. Beyond this we assume a gradual sales decline. For label expansion sales, we only include contributions from both CLL and frontline iNHL; a CLL trial is ongoing, and with approval already in the US and Europe we believe this has a high likelihood of also gaining approval in Japan. In frontline iNHL the pivotal trial is complete and SymBio plans to file this once approval has been granted in Europe (it is under regulatory review). Frontline iNHL could be a significant market for Treakisym, with >50% more patients in Japan than in currently approved indications.

We do not include any contribution for Treakisym in r/r aggressive NHL, even though the Phase II trial has been completed. Discussions with regulators are ongoing. We do not include any spend on a further trial should one be required, with the only future Treakisym R&D spend for the ongoing CLL study (where costs are shared 50:50 with Eisai). In addition, we do not currently include a contribution from potential bendamustine sales in China where partner Teva could complete development by end 2014; China could also be a significant market for bendamustine if approved.

For rigosertib we include risk-adjusted valuations for both the IV and oral formulations in MDS. We assign a 50% probability to the IV and a 35% probability to the oral, in line with our rigosertib risk adjustments for Onconova. Our valuations include R&D spend for the ongoing Phase I trials in Japan in addition to future spend for the pivotal trials. We also include S&M spend where SymBio plans to build out a salesforce of 30-40 reps at launch. If rigosertib can launch in Japan around a year earlier than we currently assume, this could add around ¥1,500m ($15m) or ¥50/share to our valuation. If we include rigosertib at 100% probability, assuming it is successfully approved and launched, our valuation could increase by nearly ¥7,000m ($70m), or ¥230/share.

Financials

SymBio reported cash of ¥4,798m ($48m) at end June 2014, which includes current investments with more than three months' maturity; we do not exclude these longer-term investments from the cash in our valuation. With investment into Treakisym having peaked following completion of the frontline iNHL trial, we believe current cash should be sufficient to fund operations into 2017, prior to the potential launch of rigosertib. We assume additional funds will be needed at this point, to start building out a sales and marketing infrastructure ahead of first potential rigosertib launch in 2019, in addition to milestones that could become due to partner Onconova if rigosertib is approved in both the US and Japan (together totalling $10m for US approvals of the IV and oral, and $8m for Japan approvals). SymBio has access to an overdraft facility of ¥1,350m.

Our 2014 financial forecasts are broadly in line with SymBio guidance, summarised in Exhibit 8. Revenues consist of income from partners on Treakisym sales (income from Eisai is the bulk, representing 97% of revenue in 2013), in addition to any milestone income; within our financial forecasts we do not include revenues from unknown future milestone income, only including a small milestone in 2014 from Eisai on the recent Treakisym approval in r/r iNHL in South Korea. Recent Q214 results suggest the company is on track to meet its retained guidance.

Exhibit 8: SymBio 2014 financial guidance

	Outlook	Edison estimates	Difference
Revenue	¥1,785m	¥1,806m	+1.2%
R&D	¥940m	¥938m	-0.2%
SG&A (including R&D)	¥2,083m	¥2,055m	-1.3%
Operating loss (reported)	¥1,654m	¥1,604m	-3.0%
Ordinary loss (reported)	¥1,650m	¥1,534m	-7.0%
Net loss (reported)	¥1,654m	¥1,538m	-7.0%

Source: SymBio, Edison Investment Research

Exhibit 9: Financial summary

¥m	2010	2011	2012	2013	2014e	2015e	2016e
Year end December	JPN GAAP	JPN GAAP	JPN GAAP	JPN GAAP	JPN GAAP	JPN GAAP	JPN GAAP
PROFIT & LOSS							
Revenue	1,450	1,883	1,955	1,532	1,806	1,968	2,986
Cost of Sales	(238)	(1,224)	(1,362)	(1,214)	(1,354)	(1,385)	(2,102)
Gross Profit	1,212	658	593	318	451	582	884
Research and development	(1,118)	(1,945)	(1,438)	(1,053)	(938)	(1,193)	(1,321)
EBITDA	(640)	(2,106)	(1,743)	(1,620)	(1,617)	(1,864)	(1,827)
Operating Profit (before amort. and except.)	(636)	(2,100)	(1,737)	(1,615)	(1,607)	(1,842)	(1,790)
Intangible Amortisation	2	2	3	3	3	3	2
Exceptionals	(0)	(5)	(0)	0	0	0	0
Other	0	0	0	0	0	0	0
Operating Profit	(634)	(2,103)	(1,734)	(1,611)	(1,604)	(1,839)	(1,788)
Net Interest	(4)	3	5	10	69	46	24
Profit Before Tax (norm)	(640)	(2,098)	(1,732)	(1,605)	(1,537)	(1,796)	(1,766)
Profit Before Tax (FRS 3)	(639)	(2,101)	(1,730)	(1,601)	(1,534)	(1,793)	(1,764)
Tax	(4)	(4)	(4)	(4)	(4)	(4)	(4)
Profit After Tax (norm)	(644)	(2,101)	(1,736)	(1,608)	(1,541)	(1,800)	(1,770)
Profit After Tax (FRS 3)	(642)	(2,105)	(1,733)	(1,605)	(1,538)	(1,797)	(1,768)
Average Number of Shares Outstanding (m)	10.8	14.7	19.1	23.2	30.6	30.6	30.6
EPS - normalised (¥)	(59.49)	(143.38)	(90.76)	(69.42)	(50.30)	(58.75)	(57.76)
EPS - normalised and fully diluted (¥)	(59.49)	(143.38)	(90.76)	(69.42)	(50.30)	(58.75)	(57.76)
EPS - (IFRS) (¥)	(59.33)	(143.60)	(90.60)	(69.29)	(50.20)	(58.65)	(57.71)
Dividend per share (¥)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Gross Margin (%)	83.6	35.0	30.3	20.8	25.0	29.6	29.6
EBITDA Margin (%)	-44.2	-111.9	-89.1	-105.7	-89.6	-94.7	-61.2
Operating Margin (before GW and except.) (%)	-43.8	-111.6	-88.9	-105.4	-89.0	-93.6	-60.0
BALANCE SHEET							
Fixed Assets	50	78	82	53	130	203	313
Intangible Assets	1	13	11	8	5	2	0
Tangible Assets	22	17	14	9	88	165	277
Investments	27	48	57	37	37	37	37
Current Assets	4,213	7,178	5,421	7,634	6,086	4,282	2,470
Stocks	0	207	165	125	(140)	(143)	(217)
Debtors	6	162	148	0	49	81	164
Cash	3,916	6,311	4,240	5,294	3,961	2,129	308
Other	291	498	868	2,215	2,215	2,215	2,215
Current Liabilities	(178)	(646)	(599)	(251)	(251)	(251)	(250)
Creditors	(178)	(646)	(599)	(251)	(251)	(251)	(250)
Short term borrowings	0	0	0	0	0	0	0
Long Term Liabilities	(2)	(5)	(4)	(3)	(2)	(2)	(2)
Long term borrowings	0	0	0	0	0	0	0
Other long term liabilities	(2)	(5)	(4)	(3)	(2)	(2)	(2)
Net Assets	4,083	6,606	4,900	7,433	5,963	4,232	2,531
CASH FLOW							
Operating Cash Flow	(753)	(2,073)	(1,660)	(1,680)	(1,308)	(1,775)	(1,692)
Net Interest	5	(21)	3	12	70	45	24
Tax	(5)	(4)	(4)	(4)	(4)	(4)	(4)
Capex	(14)	(1)	(2)	0	(90)	(98)	(149)
Acquisitions/disposals	0	0	0	0	0	0	0
Financing	561	4,495	(409)	2,726	0	0	0
Dividends	0	0	0	0	0	0	0
Net Cash Flow	(206)	2,395	(2,071)	1,054	(1,333)	(1,832)	(1,821)
Opening net debt/(cash)	(4,121)	(3,916)	(6,311)	(4,240)	(5,294)	(3,961)	(2,129)
HP finance leases initiated	0	0	0	0	0	0	0
Other	0	0	0	0	0	0	0
Closing net debt/(cash)	(3,916)	(6,311)	(4,240)	(5,294)	(3,961)	(2,129)	(308)

Source: SymBio accounts; Edison Investment Research. Note: Other current assets at end December 2013 include ¥869m of "time deposits", effectively short-term investments in addition to €1,100m marketable securities, among others.

EDISON

Contact details	Revenue by geography
5-23-7 Shimbashi Minato-ku Tokyo 〒105-0004 Japan + 81 3 5472 1125 www.symbiopharma.com	N/A

CAGR metrics		Profitability metrics		Balance sheet metrics		Sensitivities evaluation	
EPS 2011-15e	N/A	ROCE 2014e	N/A	Gearing 2014e	N/A	Litigation/regulatory	●
EPS 2013-15e	N/A	Avg ROCE 2011-15e	N/A	Interest cover 2014e	N/A	Pensions	○
EBITDA 2011-15e	N/A	ROE 2014e	N/A	CA/CL 2014e	N/A	Currency	◖
EBITDA 2013-15e	N/A	Gross margin 2014e	25%	Stock days 2014e	N/A	Stock overhang	◖
Sales 2011-15e	1.1%	Operating margin 2014e	N/A	Debtor days 2014e	N/A	Interest rates	○
Sales 2013-15e	13.3%	Gr mgn / Op mgn 2014e	N/A	Creditor days 2014e	N/A	Oil/commodity prices	○

Management team

President and CEO: Fuminori Yoshida

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).

CMO: Masataka Ohta

Dr Ohta joined SymBio Pharmaceuticals in 2012 as chief medical officer with 16 years of experience in the pharmaceutical industry. Dr Ohta previously served as director of clinical development at Merck Serono Japan, and Novartis Oncology Japan. Dr Ohta graduated from Tokyo University, where he received his medical degree and PhD in virology. He also worked as an oncology research fellow at Thomas Jefferson University, and at the National Cancer Center Japan.

CSO: Albert Qin

Dr Qin joined SymBio in 2010 as medical director, bringing 16 years of experience in drug research and development. Prior to SymBio Dr Qin was medical director at Immunogen and associate director of clinical oncology at Pfizer, in addition to spending time at both Biogen and Bayer. Dr Qin has a medical degree from Shandong Medical University and a PhD in biochemistry and molecular pharmacology from Harvard University.

Principal shareholders	(%)
Fuminori Yoshida	9.89
Cephalon	8.45
JafCo	6.02
Weru Investment	3.86
Eisai	2.72
SBI Securities	1.79
GMO Click Securities	1.55

Companies named in this report

Astellas (4503 JP), Baxter (BAX US), Eisai (4523 JP), Onconova (ONTX US), Teva (TEVA US)

Frankfurt +49 (0)69 78 8076 960
Schumannstrasse 34b
60325 Frankfurt
Germany

London +44 (0)20 3077 5700
280 High Holborn
London, WC1V 7EE
United Kingdom

New York +1 646 653 7026
245 Park Avenue, 39th Floor
10167, New York
US

Sydney +61 (0)2 9258 1161
Level 25, Aurora Place
88 Phillip St, Sydney
NSW 2000, Australia

Wellington +64 (0)48 948 555
Level 15, 171 Featherston St
Wellington 6011
New Zealand