EDISON

SymBio Pharmaceuticals

Commercial outlook

At the turning point

Pharma & biotech

SymBio is approaching a major transition as it prepares to begin internal marketing of its lead product Treakisym (bendamustine), launch new liquid formulations of the drug and expand the market with new indications. At the same time, the company is moving past the recent clinical results from the Phase III study where rigosertib did not meet its primary endpoint and is determining the future direction of its pipeline product brincidofovir. We are taking this time to provide our clinical and commercial outlook.

Year end	Revenue (¥m)	PBT* (¥m)	EPS* (¥)	DPS (¥)	P/E (x)	Yield (%)
12/18	3,836	(2,626)	(158)	0	N/A	N/A
12/19	2,838	(4,250)	(184)	0	N/A	N/A
12/20e	2,608	(4,729)	(145)	0	N/A	N/A
12/21e	9,228	1,526	30	0	15	N/A

Note: *PBT and EPS are normalized, excluding amortization of acquired intangibles, exceptional items and share-based payments.

Tackling Treakisym marketing on all fronts

Treakisym is currently marketed in Japan by Eisai, but there is a planned transfer of the rights back to SymBio at the end of 2020. SymBio is preparing for this by both readying its internal salesforce as well as multiple pipeline management strategies. It has submitted a marketing application for the liquid ready to dilute (RTD) formulation and is advancing its rapid infusion (RI) formulation in the clinic. Additionally, the company has submitted a label expansion to the Pharmaceutical and Medical Device Agency (PMDA) for diffuse large B-cell lymphoma (DLBCL) based on robust data, which would double the addressable market.

Rigosertib misses the mark

The company's partner Onconova announced on 24 August 2020 that rigosertib had failed to meet its primary endpoints in its Phase III clinical study. The drug failed to show a survival benefit in the population of high-risk myelodysplastic syndrome patients. The drug continues to be dosed in an ongoing investigator-sponsored Phase I/IIa study in lung cancer, but we do not expect any further clinical investment in the program from Onconova.

Brincidofovir: Plan announced to target adenovirus

The company announced in August 2020 that it will develop brincidofovir for the treatment of adenovirus (AdV) secondary to hematopoietic stem cell transplant (HSCT) in pediatrics and adults. This is a shift from provisional plans to target hemorrhagic cystitis (vHC) and HHV-6 encephalitis (HHV-6). The company licensed worldwide rights to the drug in 2019 and is preparing for global Phase II studies.

Valuation: Decreased to ¥37.6bn or ¥1,068/share

We have lowered our valuation to ¥37.6bn or ¥1,068 per share from ¥39.0bn or ¥1,144 per share. This was driven by removing rigosertib from our models. Additionally, we have adjusted brincidofovir for the new AdV indication, which increased this program's valuation to ¥1,062m from ¥882m.

10 September 2020

Price	**¥406**
Market cap	**¥14,291m**
	¥110/US$
Net cash (¥m) at 30 June 2020	5,409
Shares in issue	35.2m
Free float	94%
Code	4582
Primary exchange	TYO
Secondary exchange	OTC US

Share price performance

%	1m	3m	12m
Abs	(1.0)	(21.0)	(28.0)
Rel (local)	(4.6)	(19.9)	(30.5)
52-week high/low		¥791	¥264

Business description

SymBio Pharmaceuticals is a Japanese specialty pharma company with a focus on oncology and hematology. The Treakisym powder formulation was in-licensed from Astellas in 2005; liquid Treakisym was in-licensed from Eagle Pharmaceuticals in 2017; and brincidofovir was licensed from Chimerix in 2019.

Next events

Treakisym RTD approval decision	September 2020

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Investment summary

Company description: A Japanese drug licensor

SymBio Pharmaceuticals is a Japanese specialty pharma company that has in licensed a series of assets for marketing in Japan, greater East Asia and worldwide markets. It owns the rights to bendamustine (under the brand Treakisym) and markets it (through partners) in China/Hong Kong, Korea, Taiwan, Singapore and Japan (its major market). The company additionally licensed two liquid formulations of the drug from Eagle Pharmaceuticals and is seeking approval to expand the label indication to include DLBCL. Additionally, the company has worldwide rights to brincidofovir (from Chimerix), which is preparing to re-enter the clinic.

Valuation: Decreased to ¥37.6bn or ¥1,068 per share

We have lowered our valuation to ¥37.6bn or ¥1,068 per share from ¥39.0bn or ¥1,144 per share. This valuation is based on a risk-adjusted NPV analysis. The reason for the adjustment is largely due to the removal of rigosertib from our model. The most valuable programs are the currently approved indications (low-grade NHL/MCL, r/r and first-line; CLL) for Treakisym at ¥19.0bn. This valuation is bolstered by the lifecycle management of introducing improved formulations of the drug to retain market share after generics enter the market in 2022. The next highest-value program is the DLBCL label expansion (¥12.2bn), which we expect approximately to double the addressable market for Treakisym.

Financials: Profitability forecasted for 2021

The company reported net cash of ¥5,409m at the end of H120. We do not expect the company to require additional capital as we model initial profitability in 2021 following the relaunch of Treakisym with the company's internal salesforce. We forecast revenue being down slightly in 2020 (¥2.6bn) compared to 2019 (¥2.8bn) because of ongoing supply issues with the lyophilized Treakisym product and a planned inventory rundown at Eisai before transferring rights back to SymBio.

Sensitivities: Transitions are not without risk

SymBio is undergoing a major transition as it prepares to market products internally for the first time, and this process carries a series of risks. The company will market Treakisym after Eisai returns the rights, and it will have to defend its market share. We expect generics to enter the market in 2022, and although the company has a pipeline management strategy to retain market share using the liquid formulations, these formulations have yet to be approved and the company will have to successfully market the differentiated features of these products. These products gained significant market share in the US, but success in SymBio's targeted markets cannot be ensured. The company has pending marketing applications for the ready to dilute formulation as well as the label expansion to DLBCL, and although we consider these low-risk applications, some uncertainty must be assumed with all regulatory hurdles. Brincidofovir is based on a well understood antiviral that has previously shown some indications of activity in AdV, but failed to reach statistical significance for the oral formulation, and has been associated with complications in the literature.

Licensing drugs for the Japanese market and beyond

SymBio's overarching strategy is to in-license approved or development-stage products approved in other territories for marketing in Japan and other parts of East Asia. The company's lead and currently its only marketed product is Treakisym (bendamustine), which is licensed from Astellas. The product is marketed across East Asia by the company's sublicensing partners, the biggest of which is Eisai in Japan. The product is approved for the treatment of chronic lymphocytic leukemia (CLL) and low-grade non-Hodgkin lymphoma (NHL) or mantle cell lymphoma (MCL).

The marketing agreement with Eisai expires in December 2020, and the company will be shifting marketing internally. Additionally, it has engaged in a series of lifecycle management activities to extend the life of the product. First, the company has in-licensed two improved formulations of the product from Eagle Pharmaceuticals: an RTD formulation that drastically reduces prep time for the drug; and a RI formulation that allows the drug to be infused in a much smaller volume. Additionally, the company is seeking approval to expand the label for the product to diffuse large B-cell lymphoma. The company completed registrational trials for the product in November 2019 and submitted a label expansion for approval in May 2020.

In addition to its Treakisym business, the company has a pipeline of in-licensed development-stage assets. It has licensed the Japanese rights to rigosertib (as both iv and oral formulations as SyB L-1101 and SyB C-1101 respectively) from Onconova. However, Onconova recently reported that the drug failed to meet its endpoints in a Phase III trial in high-risk myelodysplastic syndrome (MDS), so this program is unlikely to move forward. Additionally, the company licensed the worldwide rights to brincidofovir from Chimerix in 2019 (SyB V-1901 internally). The company has stated that it intends to develop the drug for AdV, a viral disease that typically only cause severe symptoms in immunocompromised individuals after hematopoietic stem cell transplant (HSCT) or solid organ transplant. The company is to start a multinational clinical program for the drug, which we assume will start with a Phase II study (although few details have been released).

Exhibit 1: SymBio pipeline

Drug	Program	Indication	Stage
Treakisym	SyB L-601	r/r low-grade NHL/MCL	Approved October 2010
		CLL	Approved August 2016
		1st line low-grade NHL/MCL	Approved December 2016
		r/r DLBCL	NDA partial change application submitted May 2020
	SyB L-1701 (RTD)	All	NDA filed September 2019
	SyB L-1702 (RI)	All	Phase I/II, completed patient enrolment
Rigosertib	SyB L-1101 (IV)	r/r high-risk MDS, monotherapy	Phase III recently failed, future uncertain
	SyB C-1101 (oral)	r/r high-risk MDS	Phase I Japan study complete, future uncertain
		1st line high-risk MDS, combination with azacytidine	Future uncertain
Brincidofovir	SyB V-1901 (IV)	AdV after HSCT (Global)	Multinational study in preparation
	SyB V-1901 (oral)	Formulation development	Beginning in 2020

Source: SymBio

The Treakisym franchise

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). Bendamustine is a nitrogen mustard chemotherapy agent used in the treatment of hematologic cancers. It is currently approved in Japan for the treatment of CLL, and low-grade NHL or MCL (first line and relapsed/refractory). The company has estimated that these indications represent a market of approximately 12,500 patients per year combined. It is currently seeking to expand the market for the drug by expanding the label to include DLBCL (submitted May 2020), which is currently being reviewed by the Pharmaceuticals and Medical Devices Agency (PMDA) (more below).

Moving towards internal marketing in Japan

In 2008, SymBio out-licensed the marketing of Treakisym to various commercial partners (an overview of the main agreements is shown in Exhibit 4). Although precise deal terms have not been disclosed, we estimate that SymBio earns an average net margin of around 10–12% on top-line reported Treakisym sales in Asia-Pacific. SymBio intends to establish its own sales organisation to market Treakisym in Japan after the current marketing arrangement with Eisai expires in December 2020. SymBio books revenue equal to about 50% of net in-market Treakisym sales under the agreement. Sales of the product are expected to slow down prior to the expiration of the agreement with Eisai as the latter runs down its inventory. However, this expected slowdown has been exacerbated by supply issues, where product obtained from Astellas (which manufactures the drug for SymBio) have repeatedly not met quality standards. We expect this issue to resolve as the company transitions out of its existing supply agreements at the end of 2020. SymBio recognised revenue of ¥2.8bn in 2019 compared to ¥3.8bn in 2018 from the drug.

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 Pharmaceuticals

Liquid formulations in development to extend product lifecycle

SymBio moved to extend the lifecycle of Treakisym when it in-licensed rights to patent-protected liquid formulations of Treakisym from Eagle in September 2017. The new liquid formulations of Treakisym that SymBio in-licensed from Eagle are more convenient for healthcare workers and for patients. The first in-licensed product is an RTD liquid formulation that will significantly reduce dose preparation time, making it easier and safer for health professionals. This compares to the freeze dried Treakisym, which has to be reconstituted before administration, a time-consuming process that carries the risk of exposing healthcare workers to cytotoxic powders and vapours. The second in-licensed product is an RI formulation that will cut drug infusion time to 10 minutes from 60 for the current Treakisym product (and the RTD formulation).

The RTD and RI formulations of bendamustine are marketed as Belrapzo and Bekenda respectively in the US. Belrapzo is marketed by directly by Eagle, which reported sales of $29.7m for the product in 2019. The more popular product is the RI formulation Bekenda, which is licensed to Teva Pharmaceuticals. Teva reported 2019 sales of its bendamustine products (which includes Bekenda and freeze-dried generics, but Teva notes that Bekenda is dominant) of $496m, down from $642m in 2018.

The liquid formulations are protected by patents that extend to 2031. Treakisym is likely to face competition from generic versions of the marketed freeze dried powder formulation from June 2022, but the company expects to switch the majority of patients to the more convenient liquid formulations following the intended launch of the RTD formulation in early 2021. The RTD product has been submitted for approval and a decision is expected by the autumn of 2020.

The RI product represents a greater change to the current treatment protocols, so approval of this product is expected to take longer. SymBio announced on 9 September 2020 that the final patient had been examined in the company's clinical study of the RI formulation. The trial was primarily aimed at confirming the safety of the RI formulation. The company states that, based on the current timeline, it expects the product to be approved in H222 and we expect the first significant sales in 2023.

SymBio aims to transition at least 90% of patients from currently marketed FD powder to liquid formulations by the end of 2021, and 100% by the end of 2022. We take a slightly more conservative view and model 95% of patients being switched to these products. We believe that this is achievable given the similar transition that Teva executed with Bekenda in the US.

Expanding the market to DLBCL

In addition to seeking approval for the new formulations, SymBio also hopes to expand the market for Treakisym to include the more severe blood cancer DLBCL. The company has completed clinical studies for this indication and applications for marketing approval have been submitted to the PMDA. The first application in May 2020 was for use in combination with rituximab and the second in July 2020 was for use with rituximab and polatuzumab vedotin.

DLBCL is an intermediate or high-risk form of NHL, but accounts for the largest fraction of NHL cases in Japan and elsewhere. Approximately 45% of NHL cases in Japan are DLBCL, corresponding to approximately 16,000 patients.[1] 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, which would approximately double the addressable market for the drug.

SymBio previously completed a Phase III study in Japan to support a label expansion of Treakisym (in combination with rituximab) to relapsed and refractory DLBCL in November 2019 and reported that it received positive results. The company presented the detailed results from this study at the European Hematology Association (EHA) virtual meeting in June 2020. The study enrolled 40 patients of whom 38 were evaluated for safety and efficacy.

The abstract for the presentation reported an objective response rate (ORR) in 29 of 38 (76%) patients, of which 18 of 38 (47%) showed a complete response (CR), with a median progression-free survival (PFS) of 11.9 months. These results are superior on a numerical basis to other reported studies of this combination. For instance, an Italian retrospective study reported 50% ORR, 28% CR, and a PFS of 8.8 months.[2] Other studies have reported lower response rates.[3] The safely profile presented in the abstract was also consistent with other results and predominantly showed hematologic adverse events (AEs). A majority of patients saw grade 3 or higher drops in lymphocyte counts (90%), neutropenia (74%) or reduction in CD4 lymphocytes (66%). This is to be expected for most drugs targeting hematologic malignancies and is indicative of the drug's activity.

This combination has been previously studied in a number of different trials across the globe and is among the arsenal of treatment regimens available to doctors despite not being formally approved. The BR treatment regimen (as it is typically called) has historically been used as a salvage treatment in patients following failure of first-line chemotherapy as an alternative to more aggressive chemotherapy salvage or autologous stem cell transplant. The BR regimen has a generally more tolerable profile than these other treatments. Because of this there have also been attempts to investigate it as an alternative treatment in the first line in frail patients.[4] However, a limitation to evaluating the data on the BR combination is that there is a lack of placebo controlled studies, although this has not limited other similar approvals. Bendamustine was approved in the

1 Chihara D, et al. (2013) Differences in incidence and trends of haematological malignancies in Japan and the United States. *Brit J Haem* 164, 536-545.

2 Arcari A. et al. (2016) Safety and efficacy of rituximab plus bendamustine in relapsed or refractory diffuse large B-cell lymphoma patients: an Italian retrospective multicenter study. *Leuk Lymph* 57, 1823-1830.

3 Vacirca JL, et al. (2014) Bendamustine combined with rituximab for patients with relapsed or refractory diffuse large B cell lymphoma *Ann Hematol* 93, 403-409.

4 Storti S, et al. (2018) Rituximab Plus Bendamustine As Front-Line Treatment In Frail Elderly (>70 Years) Patients With Diffuse Large B-Cell Non-Hodgkin Lymphoma: A Phase II Multicenter Study Of The Fondazione Italiana Linfomi. *Haematologica* 103, 1345-1350.

US for the treatment of indolent NHL in patients who have failed rituximab treatment, based on a single-arm study.

The company also provided a breakdown of response rates based on patient subgroups. Patients were segmented into those who had germinal center B-cell type (GCB) DLBCL or the generally more aggressive non-GCB subtype of the disease, as well response rates by age (Exhibit 3). These results showed strong activity across subgroups, including the more difficult to treat non-GCB patients and those over 75. These results are relevant because they continue to support the use of Treakisym in harder to treat populations.

Exhibit 3: Patient subgroup analysis

		ORR	CR
Cancer subtype	GCB	83%	67%
	Non-GCB	78%	39%
Patient age	Under 65	86%	71%
	65 to 74	75%	45%
	75 or older	73%	36%

Source: SymBio Pharmaceuticals

Rigosertib

SymBio in-licensed rigosertib (iv and oral formulations, Japan and Korean rights) from Onconova in 2011 for MDS, a rare blood cancer. The licensing agreement included a $7.5m upfront payment to Onconova and $22m in development and regulatory milestones, $30m in commercial milestones, and tiered royalties in the teens and up to 20%.

The drug was being studied in the Phase III INSPIRE trial of iv rigosertib for the treatment of second-line, higher-risk MDS (HR-MDS) following failure of hypomethylating agents (HMAs). On 24 August 2020, Onconova announced that the drug failed to meet its primary endpoint of improvement in overall survival: 6.4 months vs 6.3 months for placebo (p=0.33). Little other information was provided. The drug is still being tested in an investigator-sponsored trial for lung cancer (a Phase I/IIa study), but after the recent failure we do not expect the drug to be approved, and are removing it from our models and forecasts.

Onconova also developed an oral formulation of the drug and completed a Phase I/II dose escalation/expansion study in 2018. The oral formulation is being developed for the treatment of high-risk MDS in combination with azacitidine as a first-line treatment. The expansion trial for this study remains ongoing, and the company is also running a trial of the oral formulation in refractory MDS patients. SymBio has the Japanese rights to the oral formulation of the drug as well, and there is a possibility that some positive signs will be seen in the trials of the oral formulation. However, barring major surprises, we do not expect the data will be sufficient for these programmes to progress further.

Brincidofovir

At the end of September 2019 the company announced that it has licensed worldwide rights to the antiviral brincidofovir from Chimerix, excluding the prevention and treatment of smallpox. The deal includes a $5m upfront payment, double-digit royalties and $180m in downstream milestones payable to Chimerix. Chimerix will retain the rights to develop the drug for smallpox, but SymBio will be able to develop the drug worldwide for all other indications. On 5 August 2020 the company announced its plans to develop the drug for the treatment of AdV disease in pediatric patients following HSCT in a global clinical study. The drug has previous clinical experience in this indication, which will allow the company to progress immediately to later-stage trials (although the

precise clinical development plan has not been announced). This marks a shift from the previously announced intent to target viral hemorrhagic cystitis (vHC) and human herpesvirus 6 (HHV-6), two other diseases associated with HSCT.

Clinical history of brincidofovir

Brincidofovir is a derivative of the antiviral cidofovir, formed by conjugating a lipid tail to the drug. This improves the drug's properties by increasing cell permeability and, importantly, it reduces the dose-limiting renal toxicity that is characteristic of cidofovir. Both molecules are broad-spectrum inhibitors of DNA viruses that work by inhibiting DNA synthesis. The lipid tail also improves oral bioavailability and the oral formulation of the drug was the major development focus for Chimerix. However, the oral form of the drug has been implicated in some of the severe gastrointestinal (GI) side effects that have been reported in clinical studies. The iv formulation has been explored and Chimerix previously published data from a Phase I study showing improved tolerability of this form of the drug. Some GI toxicity was seen with 20mg given once a week, but the 10mg twice a week dose only had one patient with nausea (out of nine). Exposure at this dose was similar to the 100mg twice a week oral dosing used in the Phase III clinical study (more details below), which had 61% diarrhea, 34% abdominal plain, 31% nausea and 24% vomiting. Future studies will focus on the iv formulation.

Although there is little doubt that brincidofovir is an active molecule, its clinical development history has been complex. The lead indication of the drug for a long time under Chimerix was for the treatment of cytomegalovirus (CMV) following stem cell transplant, which it investigated in the oral formulation in a Phase III study that reported in 2015.[5] The study failed to reach its primary endpoint: no improvement in clinically significant CMV infection rates was seen at 24 weeks (51.2% for brincidofovir vs 52.3% for placebo), although the reasons behind this are complex. The drug showed antiviral activity during the 14 weeks that patients were on the drug, but this benefit deteriorated during the follow-up period. Moreover, patients on the drug arm had higher reported rates of graft-versus-host disease (GVHD) and other infections following the treatment period. There was a numerically higher rate of all-cause mortality on the brincidofovir arm (HR=1.6), although it failed to reach statistical significance (p=0.11). When investigating the cause of these surprising results, the study coordinators found that patients on the drug arm had over eight times the level of exposure to corticosteroids than the placebo arm. Moreover, the excess diagnoses of GVHD were attributable to acute GI GVHD. The rate of GI toxicity was very high in the drug arm (60.7% vs 36.2% for placebo), and one plausible explanation advanced by the study authors is that this toxicity was misdiagnosed as GVHD, leading to higher rates of steroid use in the drug arm and subsequently higher rates of infection. However, the authors were unable to differentiate GI GVHD from toxicity via histopathology.

The drug was also investigated for activity in against AdV by both Chimerix and independent investigators. One retrospective study (n=27) compared oral brincidofovir to cidofovir in pediatric HSCT patients with AdV viremia and found that 83% of patients who received brincidofovir had a 1-log or greater reduction in viral load (compared to 9% with cidofovir).[6] Chimerix performed a randomized, placebo controlled Phase II study (n=48) in HSCT patients with asymptomatic AdV, and although numerical improvement was seen in rates of treatment failure (as defined as

[5] Marty FM, et al. (2019) A Randomized, Double-Blind, Placebo-Controlled Phase 3 Trial of Oral Brincidofovir for Cytomegalovirus Prophylaxis in Allogeneic Hematopoietic Cell Transplantation. *Biol Blood Marrow Transpl* 25, 369-381.

[6] Hiwarkar P, et al. (2017) Brincidofovir is highly efficacious in controlling adenoviremia in pediatric recipients of hematopoietic cell transplant. *Blood* 129, 2033–2037.

increasing viral load) and all-cause mortality, these data failed to reach statistical significance.[7] A post hoc analysis found that in patients with baseline viral loads over 1,000 copies/mL, 86% on the BIW (twice a week) oral brincidofovir arm had a 2-log response compared to 25% on the placebo arm (p=0.04, although post hoc results should be interpreted with caution). This study similar to the CMV study reported increased rates of GVHD in the BIW brincidofovir arm (50% acute GVHD, 36% gut GVHD, compared to 17% and 11% in placebo) as well as increased rates of diarrhea (57% vs 28%, although other GI effects were lower).

Despite some indications of activity, Chimerix announced in May 2019 that it would be discontinuing all of its clinical programs for the drug due to enrolment difficulties across all of its trials. We suspect that fears over the risks of the drug negatively affected enrolment in these studies. Chimerix continues to develop the drug for smallpox under the animal rule. The company also transitioned to a new management team during this period, signaling a major shift in its strategy.

SymBio's plan

We view SymBio's decision to license brincidofovir as highly strategic. The limitations of the drug that have overshadowed its development appear to be in part due to the GI toxicity related with the oral formulation. SymBio hopes that the iv formulation can substantially reduce these risks, which appears to be the case with the 10mg dose (although some toxicity was seen at higher doses). This leaves the company with the worldwide rights to a molecule with well-understood antiviral activity across a range of indications. Moreover, the original drug cidofovir has never been approved in Japan, so brincidofovir approval could be the first of its kind in that country. The current plan for the drug is seek approval for the IV formulation of the drug following a large multinational development program (focused on the US, EU and Japan), which currently includes a Phase I clinical pharmacology study with healthy volunteers (to study drug-drug interactions) and a global Phase IIa study in pediatric AdV patients (to be run concurrently). The company has also communicated an intent to study the drug in adult AdV patients and to explore the use of the drug to other viral complications of HSCT and other transplant types (such as solid organ transplants) in the future.

The rates of AdV infection vary significantly between studies, but are generally lower for autologous transplants (2.5–14%) compared to allogeneic transplants (5–47%).[8] Patients with younger age are known to be at higher risk for the complication, although mortality is lower in this population. Rates of transplantation were 22,863 (9,237 allogeneic) in the US in 2017,[9] 41,100 (17,155 allogenic) in Europe in 2017,[10] and approximately 5,700 (3,700 allogeneic) in Japan in 2018.[11] Assuming that the company initially targets pediatric (approximately 13%) allogeneic transplant patients initially, this corresponds to an addressable global (US/Europe/Japan) population of approximately 1,000 transplant recipients per year (based on the mid-range, 26%, of reported infection rates above).

We agree with the company's rationale to pursue approval for AdV as opposed to the previously proposed indications of vHC and HHV-6. AdV is a more common complication for HSCT and the predicate drug cidofovir is already an established treatment. Although the market for the assumed initial indication of pediatric allogeneic transplants is small, there are expansion opportunities to the broader HSCT population and other varieties of transplant.

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7 Grimley MS, et al. (2017) Brincidofovir for Asymptomatic Adenovirus Viremia in Pediatric and Adult Allogeneic Hematopoietic Cell Transplant Recipients: A Randomized Placebo-Controlled Phase II Trial. *Biol Blood Marrow Transpl* 23, 512-521.

8 Sandkovsky U, et al. (2014) Adenovirus: Current Epidemiology and Emerging Approaches to Prevention and Treatment. *Curr Inf Dis Rep* 16, 416.

9 US Health Resources & Service Administration, Transplant activity Report.

10 Passweg JR, et al. (2019) The EBMT activity survey report 2017: a focus on allogeneic HCT for nonmalignant indications and on the use of non-HCT cell therapies. *Bone Mar Transpl* 54, 1575-1585.

11 The Japanese Data Center for Hematopoietic Cell Transplantation.

Sensitivities

SymBio faces a unique set of risks associated with its ongoing clinical and commercial plans. It is at a crossroads with Treakisym as it both prepares to internally market the product as well as launch new formulations and new indications. The company has not previously marketed any products and there is a risk it will not be able to retain market share once the reins have been passed from Eisai. Additionally, the commercial strategy for the product is contingent on its expanded approvals for the liquid formulations and/or DLBCL. Although we have little reason to expect that there will be issues with these marketing applications, there is unavoidable clinical and regulatory risk. Although there is evidence to support expansion of the market into DLBCL, the drug has not been approved for this indication elsewhere and it may face regulatory scrutiny. Moreover, even if the liquid formulations are approved, it is not certain that the company can convert existing patients on to these formulations to avoid generic competition, although these formulations have captured significant market share in the US.

The company's other development programs also face clinical and regulatory risk. Brincidofovir has not been previously approved and has faced previous clinical trial missteps. Brincidofovir although based on a drug commonly used for the treatment of AdV previously failed to show a statistical improvement in prior Phase II studies (albeit with the oral formulation).

Valuation

We have lowered our valuation to ¥37.6bn or ¥1,068 per share from ¥39.0bn or ¥1,144 per share. This reduction is driven by the removal of rigosertib from our model, which we previously valued at ¥1.8bn. Additionally, cash is lower as reported at the end of H120 (¥5.41bn compared to previous estimates of ¥5.58bn). These factors are offset by rolling forward our NPVs and an increase in the valuation of brincidofovir (see below).

Our valuation is based on a risk-adjusted NPV analysis of each of the company's products and development programs. We assume a 95% probability for success for the RTD and RI formulations of Treakisym as these products are already approved in other geographies. For the DLBCL label expansion, we assume a 90% probability of success on the basis of the positive results from the company's Phase III study and other strong support of efficacy in this indication in the literature. We assume the product will retail at approximately ¥80,000 per dose and expect a price cut of 5% following generic entrants in 2022. We expect to update these models when feedback is received from the PMDA on the company's outstanding applications for DLBCL and the RTD formulation.

We have changed some of our assumptions for brincidofovir to reflect the company's direction with the drug and intent to target pediatric AdV patients, which has increased this program's valuation to ¥1.06bn from ¥0.88bn. We assume that the company will seek initial approval for pediatric HSCT patients with AdV on a worldwide basis. The total number of addressable patients is slightly larger (approximately 1000 per year as outlined above, compared to 650 previously) to reflect the number of AdV patients in the US, EU, and Japan following allogeneic HSCT. We have also adjusted our pricing assumptions because of greater price durability in the US and Europe and assume 2% price growth annually (from ¥10m per patient at base). We assume that the company will run a 60 patient Phase II and a 150 patient Phase III study, similar to previous expectations. However, we have reduced the probability of success to 20% from 30%. This change is primarily to reflect that the drug will have a higher bar for acceptance in this indication because cidofovir is an established treatment already. There are also other risks, which include the increased burden of doing multi-national trials and the fact that the drug has already been unsuccessfully tested in this indication (albeit with a different and oral formulation), which may have an impact on enrolment.

Exhibit 4: Valuation of SymBio

Program	Indication	Prob. of success	Launch year	Peak revenue (¥m)	Valuation (¥m)
Treakisym	Low-grade NHL/MCL (r/r and 1st line); CLL	100–95%	2010	8,600	18,965.16
Treakisym (DLCBL)	r/r DLBCL	90%	2021	9,600	12,166.04
Brincidofovir	AdV following HSCT	20%	2025	9,100	1,062.05
Total					32,193.25
Net cash and equivalents (¥m, June 2020)					5,409.70
Total firm value (¥m)					37,602.94
Total basic shares (m)					35.18
Value per basic share (¥)					1,068.83

Source: SymBio Pharmaceuticals reports, Edison Investment Research

Financials

The company reported sales of ¥1.36bn for H120, down from ¥2.00bn for H119. The company reported a ¥1.8bn operating loss in H120. Sales continue to be depressed by issues with the supply of lyophilized Treakisym product. Given that the supply issues have persisted without abatement for a year now, we do not expect a resolution before rights are returned to SymBio at the end of 2020. In addition, there is a planned rundown in sales expected in 2020 as Eisai reduces its existing inventory in preparation for the transfer. We have removed the contribution from rigosertib in our forecasts, the main impact of which was an R&D investment of approximately ¥10bn over the next four years. We are not making any other major changes to our forecasts at this time.

We expect the company to become profitable in 2021 following the transfer of Treakisym rights back to the company from Eisai. Because of this we do not expect the company to require additional capital to advance its current operations, but it may need cash for additional in-licensing opportunities. We forecast ¥9.2bn in sales in 2021, driven purely by recognizing a larger portion of the Treakisym margin.

Exhibit 5: Financial summary

¥m	2018	2019	2020e	2021e	2022e
Year end 31 December	JPN GAAP	JPN GAAP	JPN GAAP	JPN GAAP	JPN GAAP
INCOME STATEMENT					
Revenue	3,835.5	2,837.8	2,608.1	9,227.8	11,483.8
Cost of Sales	(2,662.7)	(1,973.0)	(1,956.0)	(1,618.7)	(2,261.2)
Gross Profit	1,172.9	864.8	652.0	7,609.1	9,222.6
R&D	(1,832.7)	(2,441.6)	(2,203.0)	(465.0)	(820.0)
SG&A	(1,996.2)	(2,724.8)	(3,324.8)	(5,772.5)	(6,396.9)
EBITDA	(2,621.4)	(4,263.5)	(4,754.8)	1,465.0	2,103.4
Depreciation & amortisation	(34.7)	(38.1)	(121.0)	(93.4)	(97.7)
Normalised operating profit	(2,533.1)	(4,174.5)	(4,748.7)	1,498.7	2,132.9
Reported operating profit	(2,656.1)	(4,301.6)	(4,875.8)	1,371.6	2,005.7
Net interest	(92.7)	(75.0)	19.6	27.3	47.0
Joint ventures & associates (post tax)	0.0	0.0	0.0	0.0	0.0
Exceptionals	(0.0)	4.2	0.0	0.0	0.0
Profit Before Tax (norm)	(2,625.8)	(4,249.5)	(4,729.1)	1,526.1	2,179.8
Profit Before Tax (reported)	(2,748.7)	(4,372.5)	(4,856.2)	1,398.9	2,052.7
Reported tax	(3.8)	(3.8)	(3.8)	(467.7)	(591.2)
Profit After Tax (norm)	(2,625.8)	(4,249.5)	(4,729.1)	1,526.1	2,179.8
Profit After Tax (reported)	(2,752.5)	(4,376.3)	(4,860.0)	931.2	1,461.4
Minority interests	0.0	0.0	0.0	0.0	0.0
Discontinued operations	0.0	0.0	0.0	0.0	0.0
Net income (normalised)	(2,629.6)	(4,253.3)	(4,732.9)	1,058.4	1,588.6
Net income (reported)	(2,752.5)	(4,376.3)	(4,860.0)	931.2	1,461.4
Basic average number of shares outstanding (m)	17	23	33	35	36
EPS - basic normalised (¥)	(158.14)	(183.72)	(144.83)	30.09	44.64
EPS - diluted normalised (¥)	(104.91)	(180.46)	(143.00)	31.06	46.62
EPS - basic reported (¥)	(165.54)	(189.03)	(148.72)	26.48	41.07
Dividend (¥)	0.00	0.00	0.00	0.00	0.00
BALANCE SHEET					
Fixed Assets	200.9	386.5	395.1	394.5	409.7
Intangible Assets	71.4	240.5	228.8	202.3	184.6
Tangible Assets	57.0	75.5	95.9	121.8	154.6
Investments & other	72.6	70.4	70.4	70.4	70.4
Current Assets	6,038.5	4,887.5	3,657.8	4,743.0	6,360.2
Stocks	533.8	0.0	219.7	181.8	254.0
Debtors	411.7	549.3	285.8	1,011.3	1,258.5
Cash & cash equivalents	4,821.4	3,910.8	2,724.9	3,122.6	4,420.4
Other	271.6	427.4	427.4	427.4	427.4
Current Liabilities	(1,336.3)	(872.2)	(1,236.6)	(1,390.0)	(1,561.0)
Creditors	(654.9)	(33.2)	(424.0)	(486.9)	(566.7)
Tax and social security	(71.2)	(87.8)	0.0	0.0	0.0
Short term borrowings	0.0	0.0	0.0	0.0	0.0
Other	(610.2)	(751.3)	(812.6)	(903.1)	(994.3)
Long Term Liabilities	(1.3)	(1.6)	(1.6)	(1.6)	(1.6)
Long term borrowings	0.0	0.0	0.0	0.0	0.0
Other long term liabilities	(1.3)	(1.6)	(1.6)	(1.6)	(1.6)
Net Assets	4,901.8	4,400.1	2,814.7	3,745.9	5,207.3
Minority interests	0.0	0.0	0.0	0.0	0.0
Shareholders' equity	4,901.8	4,400.1	2,814.7	3,745.9	5,207.3
CASH FLOW					
Op Cash Flow before WC and tax	(2,714.0)	(4,334.4)	(4,735.2)	1,492.3	2,150.4
Working capital	184.5	(242.1)	346.8	(624.7)	(239.6)
Exceptional & other	208.8	229.5	127.1	127.1	127.1
Tax	(3.8)	(3.8)	(3.8)	(467.7)	(591.2)
Net operating cash flow	(2,324.5)	(4,350.7)	(4,265.0)	527.1	1,446.7
Capex	(26.2)	(216.5)	(102.3)	(129.4)	(148.8)
Acquisitions/disposals	0.0	0.0	0.0	0.0	0.0
Equity financing	4,272.1	3,740.0	3,201.7	0.0	0.0
Dividends	0.0	0.0	0.0	0.0	0.0
Other	0.0	0.0	0.0	0.0	0.0
Net Cash Flow	1,921.3	(827.2)	(1,165.7)	397.7	1,297.8
Opening net debt/(cash)	(2,947.1)	(4,821.4)	(3,910.8)	(2,724.9)	(3,122.6)
FX	(47.0)	(83.4)	(20.3)	0.0	0.0
Other non-cash movements	0.0	0.0	0.0	0.0	0.0
Closing net debt/(cash)	(4,821.4)	(3,910.8)	(2,724.9)	(3,122.6)	(4,420.4)

Source: SymBio Pharmaceuticals reports, Edison Investment Research

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Management team

President and CEO: Fuminori Yoshida	Corporate officer and CFO: Takaaki Fukushima
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 Fukushima was appointed to the role of CFO in January 2020. He has previously held CFO positions at Nidec Sankyo Corporation (2019) and was officer and deputy general manager of corporate management for Hitachi Metals.
Corporate officer, Head of Japan business unit, and COO: Shigeo Kimura	**Corporate officer and CDO: Nobuo Ishida**
Mr Kimura was appointed as managing executive officer, CCO, and general manager of Japan Business Division, and since March 2020, has been director, senior managing executive officer and general manager of the Japan Business Division. Prior to this he was the former Oncology Business Unit head at Bristol-Myers Squibb.	Mr Ishida is a SymBio corporate officer and chief development officer, as well as being head of R&D and director of R&D Support and Data Science. He was formerly oncology project head, Japan development, at AbbVie GK; also formerly global project leader, Oncology, R&D, at Bayer Healthcare.

Principal shareholders	(%)
Yoshida Fuminori	2.45
Cephalon Inc	1.84
Matsui Securities Co Ltd	0.88
Whiz Partners Inc	0.64
Eisai Co Ltd	0.59

Companies named in this report

Chimerix (CMRX), Eagle Pharmaceuticals (EGRX), Eisai (TYO.4523), Onconova (ONTX), Teva (TEVA)

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