EDISON

SymBio Pharmaceuticals

Regulatory update

Treakisym approved for DLBCL

Pharma & biotech

SymBio announced on 23 March 2021 that it has received marketing approval for Treakisym (bendamustine) for diffuse large B-cell lymphoma (DLBCL). The drug has been approved for relapsed and refractory disease in two combinations: with rituximab and polatuzumab vedotin or with rituximab alone. We expect this approval to approximately double the addressable market for the drug in Japan.

Year end	Revenue (¥m)	PBT* (¥m)	EPS* (¥)	DPS (¥)	P/E (x)	Yield (%)
12/19	2,838	(4,250)	(184)	0	N/A	N/A
12/20	2,987	(4,514)	(137)	0	N/A	N/A
12/21e	9,228	1,508	27	0	43.7	N/A
12/22e	11,484	2,017	37	0	31.9	N/A

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

Approval was expected after strong clinical results

Bendamustine is not approved for DLBCL in the US or Europe, despite being approved for other forms of non-Hodgkin lymphoma (NHL). This being said, the efficacy in this indication has been established in multiple clinical studies, including SymBio's pivotal clinical studies, which showed a 76% objective response rate (ORR) to treatment. This previously gave us significant confidence that the product would eventually be approved, as has now occurred.

DLBCL a significant market in Japan

We estimate that approximately 16,000 new patients will be diagnosed with DLBCL in Japan. We assume that approximately 70% of these patients will relapse, which corresponds to an addressable market for relapsed and refractory DLBCL of 11,200 per year. This would approximately double the market for the drug, which is currently also approved for low-grade NHL and chronic lymphocytic leukemia (CLL).

Part of bigger scheme to maximise Treakisym

The label expansion to DLBCL is part of the company's broader strategy to market and extend the lifecycle for Treakisym. The current DLBCL approval is for the freeze-dried Treakisym product, and the company has already submitted a marketing application to also expand the label for its ready-to-dilute (RTD) formulation to DLBCL as well. We assume that the rapid infusion (RI) formulation will include DLBCL in its label when it is submitted for approval later in 2021.

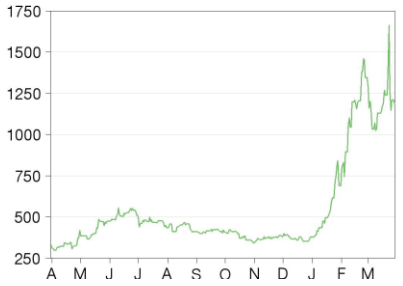
Valuation: Increased to ¥43.2bn on approval

We have increased our valuation to ¥43.2bn or ¥1,131 per basic share, from ¥39.7bn or ¥1,040 per basic share previously. We have removed some risk and lowered the discount rate for DLBCL. These factors have increased the valuation for this indication to ¥17.1bn from ¥13.7bn. Otherwise our models remain unchanged.

30 March 2021

Price	**¥1,180**
Market cap	**¥45,080m**
	¥110/US$
Net cash (¥m) at 30 December 2020	3.85
Shares in issue	38.2m
Free float	91%
Code	4582
Primary exchange	TYO
Secondary exchange	OTC US

Share price performance



%	1m	3m	12m
Abs	(12.6)	220.4	267.5
Rel (local)	(18.2)	192.4	169.1
52-week high/low		¥1,663	¥298

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 RI application	2021

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Edison profile page

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Treakisym label expansion to DLBCL

SymBio announced in a series of two press releases that it has received marketing approval in Japan for the use of Treakisym (bendamustine) for the treatment of DLBCL. The drug has been approved for this patient population in combination use with rituximab and polatuzumab vedotin or with rituximab alone. We are very pleased to see this approval, but are not surprised considering our high degree of confidence in the drug for this indication, based on the company's previously reported clinical results.

SymBio 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 study enrolled 40 patients of whom 38 were evaluated for safety and efficacy. The company reported an 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.[1] Other studies have reported lower response rates.[2] 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.[3] 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 US for the treatment of indolent NHL in patients who have failed rituximab treatment, based on a single-arm study.

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.[4] 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.

The expansion into this market is only part of the company's strategy to manage the long-term marketability of this product. Additionally the company is approving new formulations of the drug that will extend its lifecycle: the RTD formulation was approved in September 2020 and we expect

1 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.

2 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.

3 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.

4 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.

the company to submit an application for the RI formulation before the end of 2021. Both of these products would extend the patent runway to 2031, if the company can convert physicians onto the new formulations. Both of these formulations will need to be approved for the DLBCL indication, and the company has already submitted a supplemental application to the PMDA for expansion of the label for the RTD formulation to DLBCL.

Valuation

We have increased our valuation to ¥43.2bn or ¥1,131 per basic share, from ¥39.7bn or ¥1,040 per basic share. This increase is solely due to the approval for DLBCL. We have increased the probability of success to 100% for the freeze-dried product and the RTD product, and to 95% for the RI product, which matches the previously approved indication. As well, we have lowered the discount rate to 10% (from 12.5%), which is our standard for approved medical products. These factors have increased the valuation of the DLBCL indication to ¥17.1bn from ¥13.7bn previously. Otherwise our models remain unchanged.

Exhibit 1: 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	95–100%	2010	8,600	20,990.54
Treakisym (DLCBL)	r/r DLBCL	95–100%	2021	9,600	17,140.02
Brincidofovir	AdV following HSCT	20%	2025	9,100	1,242.42
Total					39,372.98
Net cash and equivalents (December 2020)					3,848.63
Total firm value (¥m)					43,221.61
Total basic shares (m)					38.20
Value per basic share (¥)					1,131.37

Source: SymBio reports, Edison Investment Research

Financials

The only changes to our model are minor accounting/bookkeeping adjustments with a negligible impact. We may adjust our forecasts in the future based on sales of Treakisym for the new indication. We currently forecast about ¥500m in DLBCL sales in 2021, because we expect some headwinds with a new marketing team targeting a new indication for the product.

Exhibit 2: Financial summary

JPN GAAP, year end: 31 December	¥m	2019	2020	2021e	2022e
INCOME STATEMENT					
Revenue		2,837.8	2,987.1	9,227.8	11,483.8
Cost of Sales		(1,973.0)	(2,120.2)	(1,618.7)	(2,261.2)
Gross Profit		864.8	866.9	7,609.1	9,222.6
R&D		(2,441.6)	(2,266.6)	(465.0)	(820.0)
SG&A		(2,724.8)	(3,106.5)	(5,647.7)	(6,398.5)
EBITDA		(4,263.5)	(4,441.4)	1,561.2	2,069.6
Depreciation & amortisation		(38.1)	(64.8)	(64.8)	(65.4)
Normalised operating profit		(4,174.5)	(4,403.8)	1,598.8	2,106.5
Reported operating profit		(4,301.6)	(4,506.2)	1,496.4	2,004.1
Net interest		(75.0)	(109.7)	(90.3)	(89.1)
Joint ventures & associates (post tax)		0.0	0.0	0.0	0.0
Exceptionals		4.2	529.5	0.0	0.0
Profit Before Tax (norm)		(4,249.5)	(4,513.5)	1,508.4	2,017.5
Profit Before Tax (reported)		(4,372.5)	(4,086.4)	1,406.1	1,915.1
Reported tax		(3.8)	(3.8)	(476.4)	(577.3)
Profit After Tax (norm)		(4,253.3)	(4,517.3)	1,032.1	1,440.1
Profit After Tax (reported)		(4,376.3)	(4,090.2)	929.7	1,337.7
Minority interests		0.0	0.0	0.0	0.0
Discontinued operations		0.0	0.0	0.0	0.0
Net income (normalised)		(4,253.3)	(4,517.3)	1,032.1	1,440.1
Net income (reported)		(4,376.3)	(4,090.2)	929.7	1,337.7
Basic average number of shares outstanding (m)		23.2	33.0	38.2	38.6
EPS - basic normalised (¥)		(183.72)	(137.10)	27.02	37.29
EPS - diluted normalised (¥)		(180.46)	(135.38)	26.72	36.89
EPS - basic reported (¥)		(189.03)	(124.13)	24.34	34.64
Dividend (¥)		0.00	0.00	0.00	0.00
BALANCE SHEET					
Fixed Assets		386.5	459.4	429.3	421.6
Intangible Assets		240.5	301.8	251.0	217.1
Tangible Assets		75.5	76.7	97.4	123.7
Investments & other		70.4	80.9	80.9	80.9
Current Assets		4,887.5	5,815.3	6,600.7	8,048.2
Stocks		0.0	944.4	181.8	254.0
Debtors		549.3	407.0	1,011.3	1,258.5
Cash & cash equivalents		3,910.8	3,848.6	4,792.4	5,920.4
Other		427.4	615.2	615.2	615.2
Current Liabilities		(872.2)	(1,615.3)	(1,423.3)	(1,525.4)
Creditors		(33.2)	(583.5)	(483.3)	(574.1)
Tax and social security		(87.8)	(81.9)	0.0	0.0
Short term borrowings		0.0	0.0	0.0	0.0
Other		(751.3)	(949.9)	(940.0)	(951.3)
Long Term Liabilities		(1.6)	(2.1)	(2.1)	(2.1)
Long term borrowings		0.0	0.0	0.0	0.0
Other long term liabilities		(1.6)	(2.1)	(2.1)	(2.1)
Net Assets		4,400.1	4,657.3	5,604.6	6,942.3
Minority interests		0.0	0.0	0.0	0.0
Shareholders' equity		4,400.1	4,657.3	5,604.6	6,942.3
CASH FLOW					
Op Cash Flow before WC and tax		(4,334.4)	(4,021.6)	1,470.9	1,980.5
Working capital		(242.1)	(229.0)	(23.8)	(228.6)
Exceptional & other		229.5	130.0	102.4	102.4
Tax		(3.8)	(3.8)	(476.4)	(577.3)
Net operating cash flow		(4,350.7)	(4,124.4)	1,073.1	1,276.9
Capex		(216.5)	(160.3)	(129.4)	(148.8)
Acquisitions/disposals		0.0	0.0	0.0	0.0
Equity financing		3,740.0	4,222.1	0.0	0.0
Dividends		0.0	0.0	0.0	0.0
Other		0.0	0.0	0.0	0.0
Net Cash Flow		(827.2)	(62.6)	943.7	1,128.1
Opening net debt/(cash)		(4,821.4)	(3,910.8)	(3,848.6)	(4,792.4)
FX		(83.4)	(1.5)	0.0	0.0
Other non-cash movements		0.0	1.9	0.0	0.0
Closing net debt/(cash)		(3,910.8)	(3,848.6)	(4,792.4)	(5,920.4)

Source: SymBio reports, Edison Investment Research

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