SymBio Pharmaceuticals Ltd.

(4582 JASDAQ) Issue date: April 16, 2019

We revise up the pipeline value to around JPY52 billion

Moving up from drugs venture firm to pharmaceuticals company

SymBio does not itself undertake drug discovery research but rather uses its judgement and its links with drug discovery companies around the world to introduce and develop promising new drug formulations. In particular, it focuses its development efforts on drugs for less common conditions in oncology and hematology in which, despite a felt medical need, the major pharmaceutical companies show little interest. In this niche area it seeks to maximize market share and revenues. In most cases, new drug candidates so selected have a proven track record of efficacy and safety, and therefore entail limited risk. Thus, the company's first successful product (Treakisym®) went from adoption by the company through to approval and launch in the market in a mere five years. More recently, this product has achieved standard therapy status. The company is now about to establish its own in-house sales structure to capitalize on additional indications and formulations, which will have the effect of lengthening the product's patent life cycle. The company will thereby become, in name and in fact, a full-fledged pharmaceuticals company.

Additional indications and life cycle management to generate earnings surplus

After being approved for the treatment of relapsed/refractory non-Hodgkin's lymphoma, a type of malignant lymphoma, and mantle cell lymphoma in 2010, Treakisym® was further approved in 2016 for chronic lymphocytic leukemia and untreated low-grade non-Hodgkin's lymphoma and mantle cell lymphoma. The company is now working on still further indications, notably relapsed/refractory medium/high grade non-Hodgkin's lymphoma (DLBCL) and has already completed registration of patients for Phase 3 clinical trials. It is also looking to extend the patent life-cycle of the product by changing formulations, since in 2020 ten years will have passed since Treakisym® was first approved and there is a risk from generics. This risk has been reduced by the introduction of an easy-to-use liquid formulation from the US company, Eagle Pharmaceuticals Inc., to replace the current freeze-dried formulation.

These measures could expand the Treakisym® market size at peak sales to around JPY20.4 billion. A lot of attention has recently been focused on the use of Treakisym® together with CAR-T, a leukemia therapy, and other new combination therapies, which could further expand the market of Treakisym®. The company has a lot of costs to confront, including those necessary for additional indications, and the introduction of a liquid formulation of Treakisym®. It also has to finance costs associated with the development of its second major product, rigosertib, for its ongoing search for new drugs and for the establishment of its own in-house sales structure. Despite this burden, however, it is likely that in the period ending December 2020 the company will achieve an operating profit surplus on the back of increased sales of Treakisym®.

Pipeline value after deducting new drug search costs: around JPY52 billion (pre-tax)

On the assumption that the company has its own in-house sales structure in place we revise upward to JPY40.4 billion our estimate of the pre-tax present value of Treakisym®. This reflects ①The rise in gross margin arising from the switch to a liquid formulation; ②A slightly earlier introduction of the liquid formulation; and ③Treakisym's status as the backbone of treatment for hematopoietic tumours. We put the 100% success probability expected in trials on relapsed/refractory medium-high grade non-Hodgkin's lymphoma (r/r DLBCL) at 100%.

We have revised up the present value of rigosertib to JPY18.7 billion, mainly because of the rise in its probability of success to 50% as a reflection of the favourable outcome of Phase 2 clinical trials of the oral formulation.

Deducting SymBio's ongoing new drug search costs and company-wide costs from the total value of both pipelines yields the company's corporate value, estimated at JPY52 billion (before tax). There is a significant difference between the company's market value and corporate value, even if we allow for the approximately JPY7 billion in new financing expected over the next two years.

Basic Report

Fair Research Inc.

Tsuyoshi Suzuki

Company Outline	
Location	Tokyo, Japan
President	Fuminori Yoshida
Established	March 2005
Capital	JPY12,972 million
Listed	October 2011
URL	www.symbiopharma.com
Industry	Pharmaceuticals
Employees	90 (parent basis)

Key Indicators (at April 15, 2019)	
Stock Price	190
Year High	272
Year Low	116
Shares Issued	82,398 thousand
Trading Unit	100 shares
Market Cap	15,656 mil. JPY
Dividend (est)	0
EPS (est)	-43.88JPY
PER (est)	na
BPS (actual)	53.06 JPY
PBR (actual)	3.58X

(Note: EPS,PER,BPS,PBR are on the basis of shares outstanding, excl. treasury shares)

Results	Revenues JPY mil	YOY %	OP Income JPY mil	YOY %	RP JPY mil	YOY %	Net Income JPY mil	YOY %	EPS JPY	Share Price High	Share Price Low
2014/12 Actual	1,955	27.6	-1,303	NA	-1,110	NA	-1,115	NA	-36.26	393	196
2015/12 Actual	1,933	-1.1	-2,551	NA	-2,630	NA	-2,632	NA	-81.30	383	177
2016/12 Actual	2,368	22.5	-2,127	NA	-2,316	NA	-2,313	NA	-58.82	509	173
2017/12 Actual	3,444	45.4	-3,947	NA	-3,976	NA	-3,977	NA	-79.78	311	200
2018/12 Actual	3,835	11.4	-2,656	NA	-2748	NA	-2,752	NA	-41.38	263	116
2019/12 Forecast	4,465	16.4	-3,587	NA	-3,612	NA	-3,616	NA	-43.88		

Company outline and philosophy

Business Model SymBio is evolving from drugs venture to pharmaceuticals company which, with neither labs nor factories, and thereby abjuring some of the risks of drug discovery, operates a niche strategy focusing on maximising profits	**SymBio Pharmaceuticals Ltd. has the following distinguishing characteristics:** ① Controls risk and maximises earnings with a "lableless" and "fabless" strategy. The company does not itself conduct research on new drug discovery. Rather, in its business model it seeks out and carefully investigates new drug candidates developed by drug discovery ventures and pharmaceutical companies around the world. A new drug candidate selected as a result of this process would typically be the subject of a licensing agreement and, following development in Japan, would either be licensed out to another company or commercialized by SymBio itself to maximise profits. (Since the company itself conducts drug development in Japan it is not simply a technology trader and can be classified as a bio-pharmaceuticals company.) ② Targets large market share and high earnings using a niche strategy. The company focuses its development efforts on drugs for relatively rare conditions in, for example, oncology and hematology which, despite strong medical needs, the major pharmaceutical companies have mostly avoided. It seeks to maximize market share and profits using this niche strategy. ③ Post-POC (proof of concept) strategy In most cases proof of concept has already been established. By insisting on prior evidence of efficacy and safety in human subjects, the company reduces the development risks of new drug candidates. The above characteristics of the company's business model allow it to avoid most of the risks confronting drug discovery companies, while at the same time maximising earnings potential.
The determinants of commercial success are interactions with a network of drug discovery companies and the ability to discern and evaluate The company is a bio-venture in the rare position of having a product which was approved and brought to market within five years of being adopted	The success or failure of this business model is, of course, dependent on having a network of drug discovery companies worldwide and a keenly discerning eye. Evidence of this is provided by the company's track record. Normally, it takes some 10-20 years to bring a drug from basic research to the market. In terms of the probability of success, some estimates suggest that, counting from the chemical compound stage, it is less than 1/30,000, and even from the POC stage, only around 7-8%. But SymBio managed to get its first product, Treakisym®, from adoption to manufacturing and commercial approval in only five years or so, and as early as July 2018 had established it as a recommended standard therapy. In the eleven or so years since founding, the company has screened 1,500 drug candidates, of which over 600 have been formally investigated in-house. And of these, five products have been adopted and two are currently under development.
Company structure and staff quality are key	We believe this track record has been made possible by the expertise of the company's staff and by the way the company is organized. SymBio has a staff of 90, of whom more than 40 are involved in research and development. The drug search function is supported by a Scientific Advisory Board (SAB) of specialists (including Nobel Prize candidates) who support drug search activities. Needless to say, the role played by the company's founder and CEO, Fuminori Yoshida, is of great value in terms of both the experience he brings and his extensive personal network (see CV below).

Fuminori Yoshida - Career

1949	Born in Tokyo
1971	Graduated from the Science Faculty (majored in Chemistry) of Gakushuin University
1973	Obtained master's degree from M.I.T (specialised in Life Sciences)
	Studied Management and Medical Policy Theory at Harvard University Graduate School
1975	Joined Mitsubishi Corporation
1977	Joined AHS Japan (currenty Baxter)
1980	Founded Japan Bio-Rad Laboratories
1991	Joined Japan Syntex (now Roche)
1993	CEO Amgen Japan, Vice-President Amgen Inc.
2005	Founded SymBio Pharmaceuticals Limited

Source: Fair Research Inc. using Securities Report filings and other information

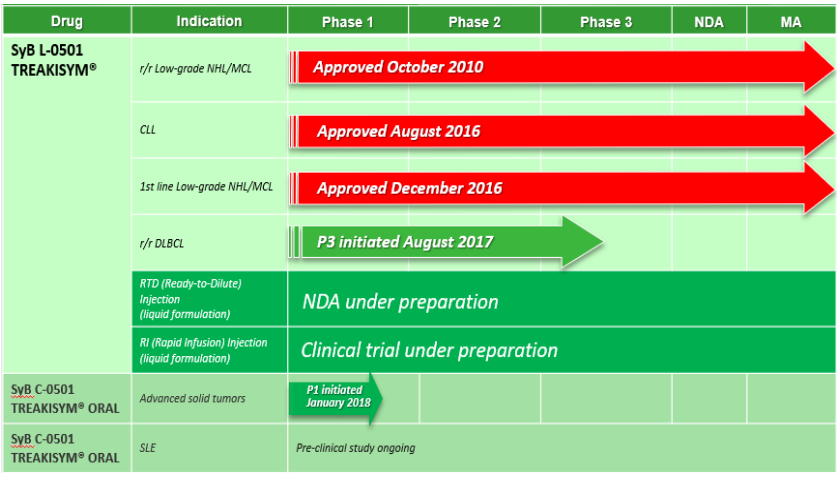
SymBio is on its way to becoming a full-fledged pharmaceuticals company. In 2018 its major product, Treakisym®, became a standard therapy, and the development of various drugs, including additional indications and formulation changes, is proceeding well. In addition, the company has decided to set up its own in-house sales structure.

Main pipeline products

As of March 2019 there were two main pipeline products under development: Treakisym® and rigosertib

(Supplementary information)
In October 2015 SymBio concluded an agreement with The Medicines Company in the United States under which it would license-in the self-administration pain control drug, IONSYS. The lump sum contract payment was JPY1 billion and Phase 3 clinical trials in Japan began in June 2016. In May 2017, however, the other party abruptly announced it was considering withdrawing from that business. Patient registration was therefore halted and in November 2017 the agreement was terminated. SymBio has requested the International Chamber of Commerce to arbitrate on its claim for compensation in the amount of JPY9 billion from The Medicines Company

(1) Treakisym®/SyB L-0501 (Freeze-dried agent)/SyB L-1701 (RTD preparation)/SyB L-1702 (RI preparation)/SyB C-0501 (oral preparation)



Source: SymBio company briefing

Treakisym® (generic name: bendamustine) is an anti-cancer agent which was first developed in Germany in 1971. It is used as a therapeutic drug for low-grade non-Hodgkin's lymphoma among malignant lymphoma and for chronic lymphocytic leukemia.

Malignant lymphoma

Lymphoma is a blood disease that is caused by lymphocytes (a type of white blood cell that activates immunity) becoming cancerous. There are two main types: Hodgkin's lymphoma (hereinafter HL) and non-Hodgkin's lymphoma (NHL). In the case of Japanese patients, malignant lymphomas are mostly (94%) of the NHL type. NHL is classified into one of the following three, depending on speed of disease progression. The Treakisym® treatment target is NHL, shown in red.

Types of malignant lymphoma

Degree of Maligancy (speed of progression)	Type
Low-grade (measured in years)	Small Lymphocytic MALT Follicular(Grade 1-3a) Marginal Zone B cell Lympa Plasma cell Nodal marginal B cell
Medium-grade (measured in months)	Plasma cell tumor Mantle cell Follicular (Grade 3b) Diffuse large cell type
High grade (measured in weeks)	Precusor B Lymphoblastic Burkitt Lymphoma

Source: Therapy Guide prepared by Eisai and SymBio

Treakisym® got approval only five years after introduction, and SymBio has since been adding new indications

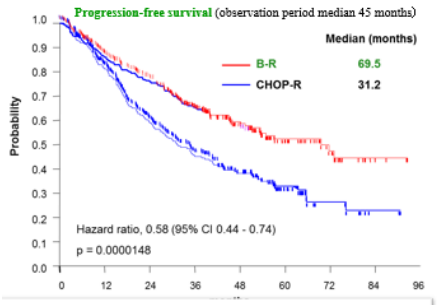
In December 2005, SymBio acquired from Astellas Pharma GmbH, the European subsidiary of Astellas Pharma Inc., the sole development and marketing rights in Japan. As a result of subsequent product development, in October 2010, just five years later, it had won approval for use on relapsed/refractory low-grade NHL and mantle cell lymphoma (MCL). Sales began in December of that year. Further, in August 2016 chronic lymphocytic leukemia and in December untreated low-grade NHL/MCL became additional approved indications. In the 2018 edition of Guidelines for Clinical Practice in Hematopoietic Tumors, published by the Japan Society of Hematology in July, Treakisym® was newly selected as a standard treatment option for all approved indications.

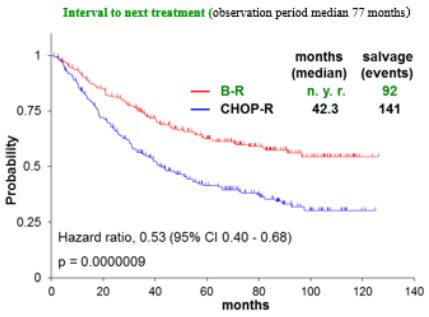
In 2010, the first approval was given, and two further indications were approved in 2016, thus providing further penetration of the market

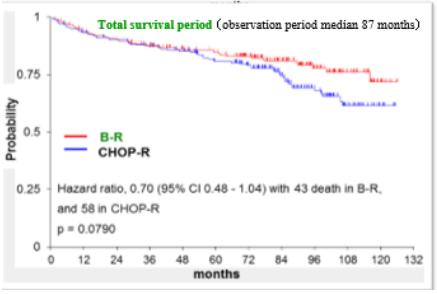
Behind this was the demonstration of superior performance of the B-R therapy, which combines Treakisym® (generic name: bendamustine) and rituximab, versus the conventional standard therapy, CHOP-R (see note below).

In July 2018 Treakisym® became a standard therapy

Comparative tests: CHOP-R therapy and B-R Therapy







Comparative safety	B-R (n=260) No. of patients	CHOP-R (n=253) No. of patients	P value
Alopecia	–	+++	< 0.0001
Sensory disorder	18	73	< 0.0001
Stomatitis	16	47	< 0.0001
Skin disorder (Erythema)	42	23	= 0.0122
Allergic reaction (skin)	40	15	= 0.0003
Infection	96	127	= 0.0025
Sepsis	1	8	= 0.0190

Ref.: Lancet 2013; 381: 1203-10

Source: Abstracted from company briefing materials. Shows superior results for B-R therapy

Note: CHOP-R therapy
A combination therapy of rituximab, a molecular target drug, cyclophosphamide, an anticancer drug, doxorubicin hydrochloride, vincristine sulfate, and prednisolone, a steroid drug.

The market penetration of Treakisym® consequently rose from an annual average of 35% in 2017 to 56% at the end of September 2018, completely outdoing the R-CHOP therapy, which had been the standard. In 2018, its eighth year on the Japanese market, sales (NHS price basis) rose to JPY8.5 billion.

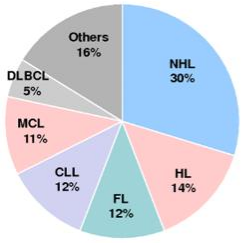
Market position of the B-R therapy

Source: Compiled by SymBio Pharmaceutical from M3 market surveys

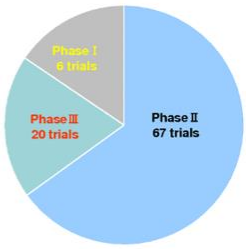
SymBio moves to set up its own sales sructure	In August 2008 SymBio licensed out to Eisai the joint development rights and sole sales rights of Treakisym® in Japan, buying in Treakisym® from Astellas Deutschland GmbH and wholesaling to Eisai, with Eisai having sole distribution rights in Japan and, we infer, bearing half the Treakisym® development costs. The licensing-out agreement with Eisai expires in 2020 and SymBio announced in October 2018 that it would have its own sales capability in place by 2021 (this in-house sales structure is described later in this report).
Patient registrations completed for Phase 3 targeting relapsed/refractory intermediate-high grade NHL	As of March 2019 development is going ahead with the aim of finding still further qualifying indications. In January 2018 the first patients were registered for Phase 3 clinical trials targeting the area of relapsed/refractory medium-high grade NHL (below, r/r DLBCL). Later, as a result of discussions with the PMDA, there was a change in the number of cases targeted and registrations completed in April 2019. Looking ahead, after completion of the period of follow-up on registered cases it will be necessary to statistically analyse efficacy and safety, and then to apply as scheduled in the first half of 2020 for authorisation for r/r DLBCL as an additional indication. In addition, Phase 1 clinical trials of the oral formulation to treat progressive solid cancers began in January 2018 and are presently ongoing. As of March 2019, 12 cases have been registered, with the main focus on confirming safety and seeking out cancer types against which the oral formulation is effective. In addition, in July 2018, pre-clinical studies were started in collaboration with the Keio University Medical School on systemic lupus erythematosus (SLE), a type of autoimmune disease. The plan is to move to Phase 1 some time in the second half of 2019. Note: In Japan the most commonly occurring intermediate-grade NHL is diffuse large B-cell lymphoma (DLBCL).
In addition to B-R, a variety of new combination therapies have been developed	In addition, there has recently been a lot of research and findings on various agents in combination with Treakisym®. Some actual examples are given below: ① A therapy combining anti-CD20 antibody obinutuzumab (brand name Gazaiba) and Treakisym® was approved for follicular lymphoma on July 2, 2018, thereby adding a new treatment option. Note: Follicular lymphomas account for approximately 80% of low-grade non- Hodgkin's lymphomas ② The CAR-T therapy (generic name: Kymriah) developed by Novartis is well known as a ground-breaking therapy for the treatment of hematopoietic tumors including leukemia, and in March 2019 was authorised in Japan as a therapy for relapsed/refractory acute lymphocytic leukemia (ALL) and DLBCL. Rather than competing with this CAR-T therapy, Treakisym® was approved as a drug to be combined with the pretreatment of the CAR-T therapy. ③ A SymBio survey has shown that in the United States and Europe there are now over a hundred studies underway testing new combinations of agents (BR+X) for therapies in the area of blood cancer. This fact suggests that the B-R therapy has now established itself as the main pillar in the area of hematopoietic tumours.

New combination therapies now being developed

By Disease



By Stage



Source: Compiled by SymBio from SyteLine Data

④Studies to test immunity checkpoint inhibitor combinations are being conducted worldwide and it is possible that their use will expand

Immunity checkpoint inhibitor combination therapies

Mechanism	Name	Stage	Indications	Combinations	Status
PD-1	Opdivo®(nivolumab)	Ph1/Ph2	r/r DLBCL	BR therapy +Opdivo +Gemcitabine	In progress
		Ph2	HL	B single agent +Opdivo +Adcetris	In progress
		Ph1/Ph2	r/r HL	B single agent +Opdivo +Gemcitabine	In progress
		Ph1/Ph2	r/r HL	BR therapy +Opdivo +Adcetris	Completed
PD-L1	Tecentriq® (atezolizumab)	Ph1/Ph2	NHL	B single agent +Tecentriq +Obinutuzumab	Completed
	Bavencio® (avelumab)	Phase 3	r/r DLBCL	BR therapy +Bavencio +Utomilumab	In progress
	Imfinzi® (durvalumab)	Ph1/Ph2	NHL-CLL	B +/- R+Imfinzi	In progress

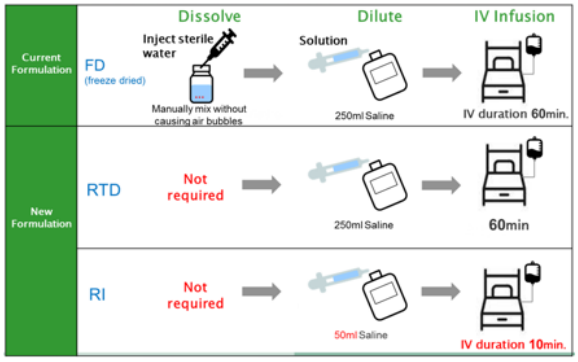
Note: Utomilumab is an immuno-conjugate stimulator now at the clinical stage of development
Source: Company briefing materials

In addition, the company is also proceeding steadily with life-cycle management via changes in formulation

A further important point is the issue of patent life-cycle management using changes in formulation. Treakisym® will be ten years from its initial approval in 2020 and from 2021 will face the risk posed by increasing competition from generics. To deal with this it plans to extend the life of the product (until 2031) by introducing new formulations. On September 21, 2017 SymBio announced that it was introducing two liquid formulations, a ready-to dilute (RTD) formulation and a rapid-infusion (RI) formulation from the US company, Eagle Pharmaceuticals Inc., to add to the existing freeze-dried (FD) version. While the current FD formulation can be stored at room temperature, it needs to be dissolved in a solvent first and diluted with physiological saline solution before administration, which takes time and effort. The liquid formulation, on the other hand, needs to be refrigerated but after that only requires dilution, making it less troublesome and less time-consuming for the medical facility. In the US, Teva Pharmaceutical Industries brought out an FD formulation in 2014, and in January 2016 brought to the market an RI formulation (generic name: Bendeka, licensed in from Eagle Industries) which can be ready for administration in an even shorter time. Within

the space of only two years Bendeka accounted for 97% of the Treakisym® market.

Comparison of FD, RTD and RI formulations



Source: SymBio company briefing

Life-cycle probably extended to 2031 by introdction of liquid formulations

The company has come to an agreement with the Pharmaceuticals and Medical Devices Agency (PMDA) that, since the RTD formulation has the same efficacy as the FD formulation, and is administered in the same way, no additional trials are necessary, and that pharmaceutical stability data alone will satisfy application requirements. This probably means that approval of the RTD formulation can be brought forward from 2021 to the October-December period of 2020. With respect to the RI formulation, it differs in terms of density and length of time required for administration, meaning that safety trials are required. Nevertheless, the PMDA has agreed that major tests are not necessary and that 36 cases confirming safety will be sufficient. The first patient registrations for clinical tests were completed in April 2019. An application for approval of the RI formulation will be submitted after completion of the main tests, with product launch scheduled for the first half of 2022. These formulations will have the effect of extending the product's life cycle to the end of 2031.

(2) Rigosertib (SyB L-1101 injection formulation, SyB C-1101 oral formulation)

Project	Indication		Phase 1	Phase 2	Phase 3	NDA Filing	Approval
Rigosertib IV	2nd line higher-risk MDS		Global Phase 3 study in progress				
Rigosertib Oral	2nd line higher-risk MDS	Mono	Japan	Patient enrollment in progress			
	1st line higher-risk MDS	Combo w AZA	Japan	Under preparation			
	1st line higher-risk MDS	Combo w AZA	Global Phase 3 study		Under preparation		

Rigosertib is being developed as both an oral and injection formulation mainly targeted at MDS

Rigosertib is an anti-cancer agent now being developed by the US company, Onconova Therapeutics, mainly as a therapy for myelodysplastic syndromes (MDS). In July 2011, after Onconova had completed Phase 2 trials, SymBio acquired sole development and distribution rights of the oral and injection formulations in Japan and South Korea (contract lump sum estimated at JPY800 million).

The current development status is as follows:

(a) Injection formulation
Joint international Phase 3 trials are now underway targeting patients with high-risk MDS who are unresponsive to the standard hypomethylating agent (HMA

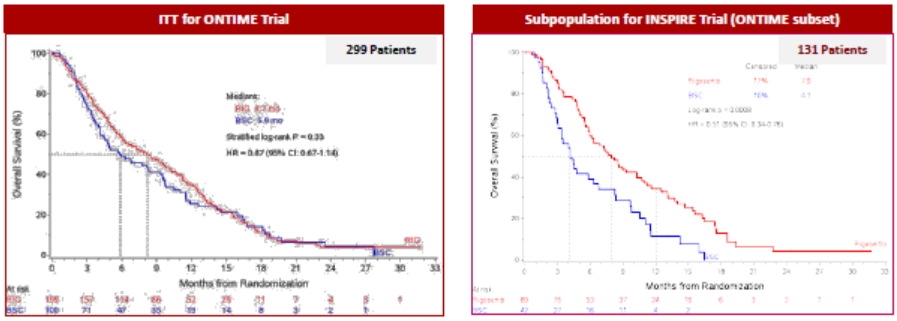
refractory) or have relapsed after treatment. SymBio is responsible for Phase 3 in Japan.

Under the IPSS (International Prognostic Scoring System), high risk MDS is classified as risk group 2, which is the higher of the two intermediate groups and suggests a high risk of transitioning to leukemia. The current standard treatments are azacitidine (trade name: Vidaza) and decitabine (Dacogen) but some high-risk MDS cases are resistant to the standard treatments or relapse after treatment. Rigosertib is indicated for such relapsed/refractory cases, ant there is at present no competing medicine authorized

Onconova completed Phase 3 (ONTIME) trials targeting relapsed/refractory high risk MDS in February 2014. The results of the trials showed no statistically significant difference between the cohort receiving rigosertib and the cohort receiving palliative care. However, if we look solely at HMA refractory cases or at cases in which there was deterioration during pre-treatment, a statistically significant difference was recognised in overall survival (OS) between the rigosertib cohort (7.9 months) and the control group (4.1 months). Onconova then changed the study design based on the results of subset analysis and from August 2015 initiated international joint Phase 3 (INSPIRE) tests for high-risk MDS patients who are HMA non-responsive or have-post treatment relapse.

Results of ONTIME trial (left) and subset analysis (INSPIRE tests with same cases, right)

Data from ONTIME paper* published in *Lancet Oncology*



ITT OS analysis of ONTIME – HR= 0.87; NS survival benefit
ITT OS of proposed INSPIRE population – HR = 0.51; P = 0.0008

*Guillermo Garcia-Manero, Pierre Fenaux, Aref Al-Kali, Maria R Baer, Mikkael A Sekeres, Gail J Roboz, et al. Rigosertib versus best supportive care for patients with higher-risk myelodysplastic syndromes after failure of hypomethylating drugs (ONTIME): a randomised, controlled, Phase 3 trial; *The Lancet Oncology* 2016 (17): 496–508

Source: Company briefing materials

Joint international Phase 3 trials now underway with design changes made by the main developer, Onconova. SymBio involved on the Japan side

From June 2012 SymBio began Phase 1 trials on relapsed/refractory high risk MDS, which were completed in October 2015. As a result of deliberations with Onconova and with the authorities, SymBio from December 2015 participated in joint international Phase 3 (INSPIRE) trials conducted by Onconova, taking charge of the clinical trials in Japan. In January 2018, on the basis of intermediate results from the INSPIRE trials, Onconova decided to continue with a larger number of cases (from 225 =>360) and SymBio did the same in Japan. As of March 19 2019, registrations have risen to 42 cases (50 cases targeted), so that it is thought an application can be made in in or around 2021 with approval following in or around 2022.

In January 2018 cases were increased on the back of intermediate results. Submission of application expected around 2021

(b) Oral formulation

Oral formulation - Onconova now planning to join currently proposed Phase 3 joint international

The safety and efficacy of the oral formulation (in combination with azacitidine) has already been demonstrated in Europe and the United States by Phase1/2 trials targeting high-risk MDS (14th International MDS Symposium, 2017). Further, the

trials

Phase 2 results of oral formulation rigosertib were presented at the 2018 symposium of the American Society of Hematology (ASH). In combination with azacitidine these showed good tolerance and an excellent overall response rate in HMA untreated and relapsed/refractory MDS patients.

Rigosertib Phase 2 clinical trials (ASH- 2018)

Response rate (2006 IWG basis)	HMA untreated (1st line, 29 cases)	HMA refractory (2nd line, 26 cases)
Overall response rate(ORR)	26 cases (90%)	14 cases (54%)
Complete remission (CR)	10 cases (34%)	1 case (4%)
Partial remission (PR)	0 cases	1 case (4%)

Source: Company briefing materials

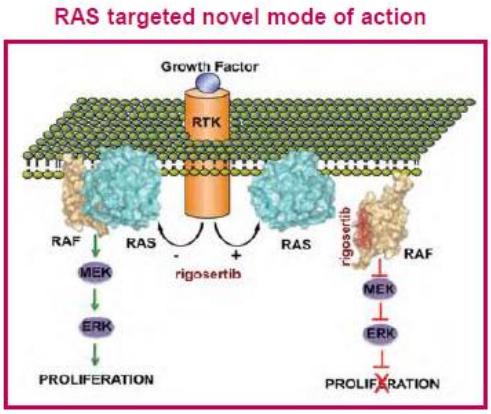
Given these circumstances, Onconova in December 2018 applied to the FDA for a Special Protocol Assessment (SPA) and is now planning to conduct Phase 3 trials, in combination with azacitidine, targeting untreated high-risk MDS.

Note on SPA: After the completion of Phase 2 trials a sponsor may seek the FDA's prior approval of the indications targeted at Phase 3, the purpose, study design, endpoints (notably the primary and secondary assessment criteria) and the statistical methodology. After completion of the trials these are accepted as they are as fulfilling the approval review requirements. This system increases the likelihood of approval if the endpoints are met and reduces the review process and the time required.

After consultations with the FDA scheduled for the first half of 2019, Onconova will commence Phase 3 trials in which the primary endpoint criteria is the overall response rate. Once the SPA is approved by the FDA, SymBio plans to join Phase 3 of the international joint trials scheduled by Onconova.

It is understood that the activity location of rigosertib is not downstream in the Ras pathway (e.g. MEK or ERK) but at a point where it can inhibit the Ras-RAF interaction. In recent years gene mutation analysis of hematologic malignancies has made rapid advances in line with the development of genome research, leading to a recognition of many types of illness. It seems in the future as the proper reaction to an illness with a particular gene mutation becomes clearer, we can hope for improvements in full response rates.

The rigosertib action mechanism



Source: Onconova presentation materials, October 2018

	A product now under development which could compete with rigosertib is Syros Pharmaceuticals' SY-1425 (oral formulation). It has completed Phase 2 clinical trials and preparations are now being made for Phase 3. It has been reported that in Phase 2 trials (10 cases) in combination with azacitidine and targeting acute myeloid leukemia (AML) and high risk MDS the full response rate was 50-60%. It should be borne in mind that among AML cases it targets only those with the gene variant RARα positive. Hence, there are few patients.

	Results for the 2018 business year and company's outlook for 2019 SymBio's sources of revenue consist of product sales and milestone income. It recorded a surplus in operating profit in the period ending December 2008 as a result of receiving a lump sum contract payment from Eisai to whom it had licensed out sole distribution rights of Treakisym® in Japan. Other than that, however, SymBio has consistently recorded operating losses.
The fall-off in sales growth in 2018 was due to one-off factors. In 2019, taking into account the temporary standstill in sales promotion activities prior to the switch to in-house marketing, we see sales rising at a rate of 16%	Sales in 2018 came to JPY3.83 billion, but most of that consisted of wholesaling Treakisym® to Eisai. The cost of sales (mainly the cost of acquisition from Astellas Deutschland GmbH) was JPY2.66 billion and the gross profit margin was JPY1.17 billion. We estimate that the wholesale price paid by SymBio to Eisai for Treakisym® was about 50% of the NHS price, and the wholesale cost to SymBio of buying in from Astellas Deutschland GmbH was around 66% of the wholesale price. Sales growth in 2018 was slower than that recorded in 2017. This was mainly because in October 2018, 87% of 25 ml. vials were visibly defective and shipments were temporarily stopped. Sales in 2019 are forecast at JPY4.46 billion, a 16% increase. The Treakisym® sales target (on the basis of NHS prices) is JPY10.1 billion, representing a downward revision from the previous forecast, but this takes account of an expected reduction in sales promotion activity on the part of Eisai as the transition to in-house marketing approaches.
R&D spending effectively rose in 2018, suggesting that product development is making progress	R&D expenditure in 2018 came to JPY1.83 billion, down on the previous year's JPY3.02 billion. However, JPY1.38 billion of the previous year figure was the estimated lump sum payment to Eagle Pharmaceuticals Inc. for the licensing-in of the liquid formulation, and JPY400-500 million was for costs associated with the self-administered IONYS pain control drug (development terminated in February 2018). If we deduct those items from the 2017 figure, we are left with JPY1.1-1.2 billion, against which the 2018 figure represents a YoY increase of JPY600-700 million. This shows that product development is, in reality, proceeding well. (In the 2018 R&D outlays, we estimate that around JPY1 billion was earmarked for Treakisym®, some JPY400 million for rigosertib, and JPY400 million for new drug search activities.) R&D in 2019 is forecast at JPY2.5 billion, up JPY670 million due to an increase in product development activity.
SG&A will continue to grow because of costs associated with the new sales structure	SG&A expenditures excluding R&D in 2018 came to JPY1.99 billion, roughly the same level as the previous year. Basic selling costs were around JPY1.4 billion, but we believe the 2017 figure was bloated by litigation costs related to IONSYS and by the initiation of various measures related to the company's transition to an in-house sales structure (e.g. 10 TM's taken on). For 2019, the company is planning for SG&A expenditures excluding R&D of JPY2.54 billion, reflecting more thorough preparations for the in-house sales group (20 TM structure described below).
End-2018 cash on the balance sheet stood at JPY4.8 billion. The company will continue to produce deficits in both 2019 and 2020, but multi-year fund raising will help it avoid a cash crunch	Looking at the company's balance sheet, the sale of warrants to EVO Fund and Whiz Fund and the exercise of those warrants represents funding of JPY3.5 billion, boosting end-2018 cash on the balance sheet to JPY4.82 billion. We see a continuation of losses in 2019 and 2020 as spending rises on pipeline development and provision of an in-house sales structure, but also the continuation of scheduled warrant issues and exercise of the warrants to bring in funding of approximately JPY3.5 billion in each year.

Evolution of SymBio's balance sheet and P&L

(JPYmil)

	Dec-13	Dec-14	Dec-15	Dec-16	Dec-17	Dec-18	Dec-19 (Forecast)
Sales	1,532	1,955	1,933	2,368	3,444	3,835	4465
Product revenues	1,432	1,940	1,933	2,137	3,444	3809	4,457
Milestone revenues	100	15	0	231	0	25	7
Cost of goods sold	1,214	1,428	1,483	1,737	2,413	2,662	2,998
SG&A	1,999	1,830	3,135	3,031	4,978	3,828	5,053
R&D costs	1,053	774	2,035	1,667	3,017	1,832	2,508
Operating income	-1,681	-1,303	-2,552	-2,127	-3,947	-2,656	-3,587
Recurring profit	-1,601	-1,110	-2,630	-2,317	-3,976	-2,748	-3,612
Profit before tax	-1,601	-1,112	-2,628	-2,309	-3,974	-2,748	
	4	4	4	4	4	4	
Net profit	**-1,605**	**-1,116**	**-2,632**	**-2,313**	**-3,978**	**-2,752**	**-3,616**
Liquid assets	7,634	7,290	4,827	6,685	4,037	6,038	
of which, cash	**6,163**	**5,692**	**4,261**	**5,719**	**2,947**	**4,821**	
Fixed assets	53	164	158	193	216	200	
Liquid liablities	251	488	551	942	1,011	1,336	
of which, payables	207	143	184	553	331	504	
Fixed liabilities	3	2	2	451	1	1	
of which, bonds	0	0	0	450	0	0	
Shareholders equity	7,336	6,763	4,132	5,054	2,702	4,372	
Warrants	97	200	300	431	537	530	
Net assets	7,433	6,964	4,432	5,485	3,239	4,901	

Source: Compiled by Fair Research Inc. using company filings

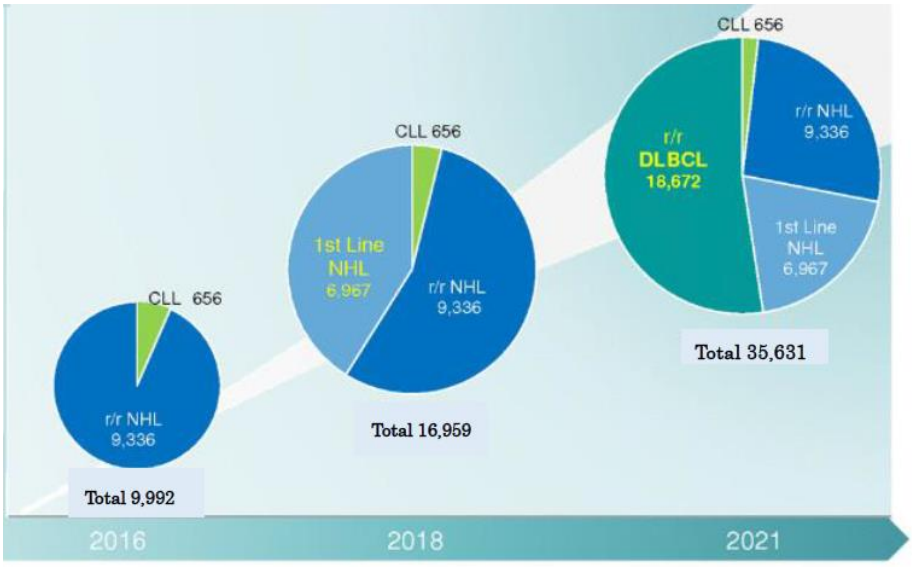
We estimate the value of Treakisym® for the three approved indications at JPY10.6 billion, and the value of the market for r/r medium-high grade NHL (now in Phase 3) at JPY9.8 billion

Market size for Treakisym® and rigosertib

We see the market for Treakisym® growing on the back of rising market penetration and an increase in qualifying indications. Looking first at areas in which approval has been received: ①Relapsed /refractory low grade NHL / MCL; ②Chronic lymphocytic leukemia (CLL); and ③untreated low grade NHL / MCL. In the case of ① sales have reached JPY4.72 billion but the number of patients requiring treatment is estimated at 9,336 and it is thought market penetration is now at 58%. It is expected that sales in this segment will be sustained by changes in formulation. For ②CLL and ③untreated low-grade NHL/MCL it is not long since approval was received and both together still bring in only JPY2.68 billion in terms of sales (FY2017). Patients indicated for this treatment total 656 for the first and 6,967 for the second, and market penetration stood at an estimated annual average of 65% in 2017, but there is an expectation this could change. Were we to assume that the market penetration of ② CLL rose to 55%, the size of the market would be JPY340 million. If we were to assume a maximum market penetration of 75% for ③ untreated low-grade NHL/MCL then the market size would be JPY5.57 billion. Again, in the area of Phase 3 relapsed /refractory medium-high risk NHL (r/r DLBCL) it is estimated there are somewhere in excess of 18,000 patients, and we model the market size, assuming a 60% penetration rate, at JPY9.77 billion.

As indicated above, total sales for the three indications for which approval has been secured come to JPY10.63 billion, and we estimate that adding in sales for the r/r DLBCL indication, now at Phase 3, will bring total sales to JPY20.4 billion. It should be noted that sales for new combination therapies, such as CAR-T, are not included in our current sales model.

The Treakisym® market



Source: SymBio company briefing materials

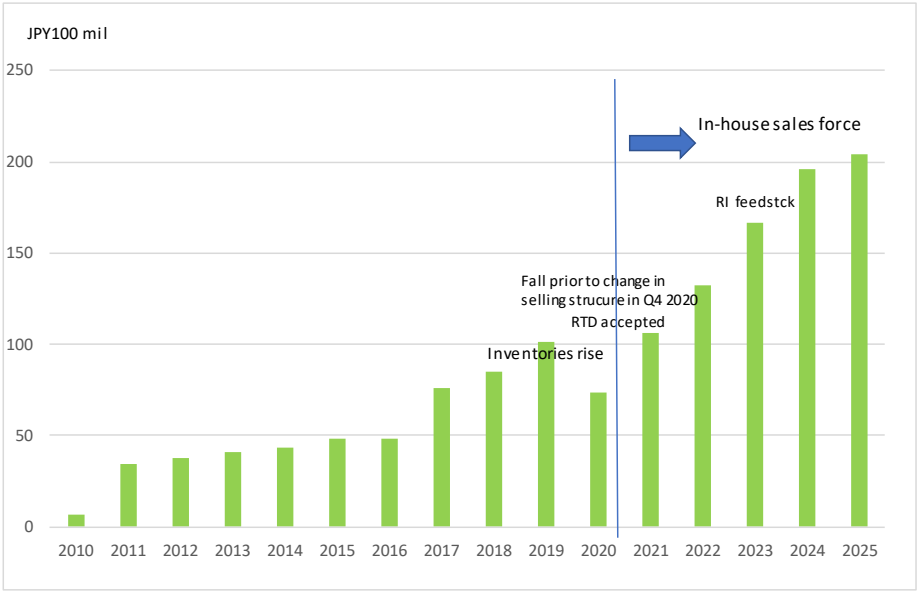
Considering the outlook for the next 3-4 years, as the company gets closer to the switch from delegating sales to Eisai to going it alone, there is a risk that Eisai will reduce its sales promotion activities and inventories will accumulate as a result. The subsequent possibility of a kickback in sales should therefore be taken into account.

Reflecting this possibility, SymBio has reduced its outlook for market penetration for 2020 in the untreated indication segment from 75% to 70% and is now looking

to achieving the 75% level in late 2021. Additionally, there is an expectation of an inventory adjustment (shrinkage in Eisai's inventories) before the switchover in the second half of 2020, leading to slow sales growth in 2020.

The company has also made a change to its outlook for the r/r DLBCL therapy, the launch of which should be on target in the first half of 2021. However, sales directed at r/r DLBCL will only really get going after 2022.

Treakisym® sales (NHS price basis)



Note: Actual sales figures until 2018. Company target figure for 2019. From 2020, estimates by Fair Research Inc.
Source: Company briefing materials and Fair Research Inc.

Reference: SymBio Pharmaceutical's medium-term management plan

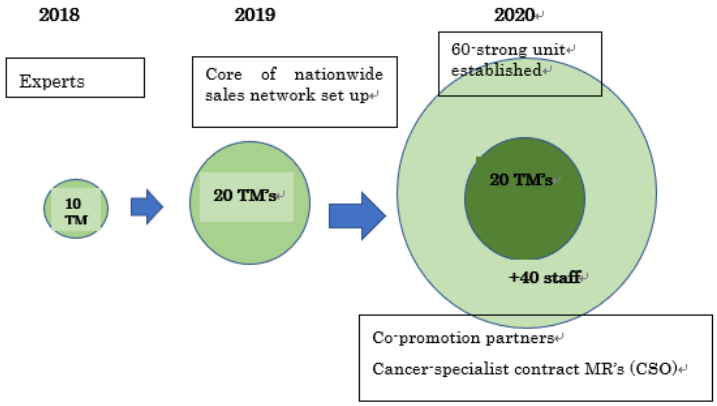
(JPY mil.)

	FY2019 Forecast	FY2020 Target	FY2021 Target	FY2022 Target
Net Sales	4,465	3,282	9,132	11,282 ～ 11,809
Operating Profit	-3,587	-5,180	1,225	2,084 ～ 2,464
Ordinary Profit	-3,612	-5,224	1,181	2,040 ～ 2,420
Net Profit	-3,616	-5,228	1,005	1,736 ～ 2,060

Note: Sales during the period of the medium-term management plan are related to Treakisym®. Rigosertib market launch not planned. Sales via Eisai until 2020, with company's own sales from 2021
Source: SymBio Medium-Term Management Plan, February 2019

Potential For rigosertib injection formulation JPY4.6 billion, and oral formulation JPY11.6 billion

The rigosertib injection formulation is indicated only for high-risk MDS patients who are HMA non-responsive. The number of such patients is estimated at 900 and using the price of Vidaza as reference we surmise the market has a value of around JPY4.6 billion. As for the oral formulation, we estimate the number of high risk MDS patients not indicated for the injection formulation at 2,300. We therefore surmise the size of the oral formulation market at JPY11.6 billion, bringing the total for both formulations to around JPY16 billion. However, the market size may fluctuate if, in the future, higher complete remission rates are sought by restricting indications to illnesses associated with a specific gene mutation.

Plans a staff of 60 for in-house sales unit	**Building own sales structure** As early as 2018 SymBio had taken on ten specialists to undertake Treakisym® sales activities as TM's (Treakisym Managers). Then, in 2019 the company increased this number to 20, and in 2020 plans to bring in 40 co-promotion partners (working partially on sales through other pharmaceuticals companies) or cancer-specific contract MR's (CSO's), bringing the total to 60. It is estimated there are 1,100-1,200 hospitals and clinics nationwide with hematology departments, of which 800-900 are hospitals. SymBio expects to cover the major institutions, that is about one-third or 400. It has divided the country into two areas and six blocs, to be covered by the 20 TM's (20 institutions for one TM), reinforced by the co-promotion managers and cancer-specific contract MR's. Because of the personnel expenses for TM's and MR's, together with the costs of promotion activities, Treakisym® sales expenses are expected to come to JPY1.7 billion annually, around JPY1 billion higher than in 2018.  Source: Company briefing materials

Modelling pipeline and corporate value

Modeling the present value of the SymBio pipeline

In the following we seek to model corporate value. To do this we take the value of Treakisym® (assuming indications are expanded to included r/r DBLCL, assuming also changes in formulation and a transition to in-house sales), and the value of rigosertib (both oral and injection formulations) using the discounted cash flow (DCF) method. From the sum of these two we deduct the total of company-wide costs (drug search activities and company-wide administrative costs) again using the DCF method. We assume a discount rate of 10% given that, while consistently running at a loss, SymBio is a pharmaceuticals venture which minimizes risk by operating without a research function or manufacturing function, and which actually has a product in the market.

＜Assumptions for Treakisym®＞

For market size we assume, as noted earlier, that peak sales are achieved in the fourth year following launch, that for the following three or four years peak sales are maintained, that subsequently the market shrinks at an annualised rate of 5%, and that from 2031 it contracts sharply at an annualised rate of 10%. Further, we infer a 100% probability of success to clinical trials targeting relapsed/refractory medium-high grade NHL, given that Treakisym® has established itself as a standard treatment in the area of hematopoietic tumours.

Eisai will continue to provide the sales channel until 2020, but from 2021 SymBio will itself take over. Also, from 2021 there will be an almost complete switch to liquid formulations (RTD and RI formulations). We assume these formulations will come with an improved cost compared to the current formulation. We assume the cost after the formulation changes will be about 30%, including royalties payable to Eagle Pharmaceuticals. Approval of the RTD formulations will generate milestone payments, which we assume will be approximately JPY700 million.

Development costs will be borne in full by the company, estimated at JPY1.6-1.7 billion per year from 2019 to 2020, and JPY500-600 million in 2021-2022.

Further, as noted earlier, sales costs will expand to an annual JPY1.7 billion assuming a 60-strong sales force headed by 20 TM's.

<Assumptions for rigosertib>

For market size we assume, as noted in the previous page, that peak sales are achieved in the fourth year following launch, that for the following three of four years peak sales are maintained, that subsequently the market shrinks at an annualised rate of 5%, and that from 2035 it contracts sharply at an annualised rate of 10%. The timing for market launch we infer is around 2023 for the injection formulation and 2024 for the oral formulation. Given the current clinical trial stages we posit the probability of success at 50% for the injection formulation (Phase 3) and 50% for the oral formulation (preparations now underway for Phase 3). We further posit formulation supply and royalty payments to Onconova at 25% of sales. Milestone payments will be payable on market launch for both formulations, and we are modelling JPY500 million for the injection formulation and JPY1.5 billion for the oral formulation. We have not included sales costs, since rigosertib will use the same sales channels and MR's as Treakisym®.

Quite apart from the two products dealt with above, R&D costs to cover the company's new drug candidate search and investigation activities, and company-wide administration costs, are generated on an annual basis. We have modelled recurrent new drug R&D costs of JPY200-300 million and company-wide

administration costs of JPY1.4 billion, for a total of JPY1.7 billion.

Using the assumptions noted above, we have calculated the discounted present value of the company's pipeline and present our conclusions in the table below. Treakisym® has a value (before tax) of JPY40.4 billion and rigosertib a value (before tax) of JPY18.7 billion, for a total of JPY59.1 billion.

Our modelling suggests that SymBio's product pipeline value (before tax), taking into account both products, together with the present value of company-wide costs and current cash and deposits on the balance sheet, comes to around JPY51.8 billion. Using a discount rate of 8% yields a value of around JPY61.8 billion.

Taking into account the cost of recurring drug discovery activities, company-wide management costs, and current cash and deposits, the value of SymBio's pipeline (pre-tax) is estimated at JPY51.8 billion (10% discount rate).

Modelling SymBio's pipeline value

(JPY100 mil)

	Discount Rate	
	10%	8%
Total (pre-tax)	**518.5**	**618.5**
Treakisym	404.7	469.7
Rigosertib	187.1	232.1
Company-wide costs	-121.5	-131.5
Cash, etc.	48.2	48.2

(Ref) Asssuming eff. tax rate of 31%

	Discount rate 10%	Discount rate 8%
Total (after tax)	357.8	426.8
2019/4/12		
Market value		154.9

Source: Calculated by Fair Research Inc.

Addendum

On February 28, 2019, SymBio announced a stock consolidation to combine four shares into one at the end of June. As a result of consolidation: ① Administration costs are lower due to the smaller number of shares; and ② While low-priced stocks are more easily a target of speculation, appreciation of the stock price can correct that. On the other hand, it has been pointed out that even if the stock price apparently rises due to the consolidation, this will only make it more susceptible to a subsequent fall. This opinion reflects the fact, observable from multiple occurrences, that the stocks of a company with poor long-term results becomes a low-priced stock and is then subjected to consolidation. It is necessary to focus on fundamentals, which are the key to stock price formation, and to bear in mind that stock consolidation does not, of itself, bring about a change in corporate value.

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