Delta-Fly Pharma

Aims to develop gentle anti-cancer agents with module technology

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Business

Drug discovery startup working on anticancer agents

Business model: Using its proprietary module technology, pharmaceutical company Delta-Fly conducts R&D into new anticancer agents. Module technology is a unique drug discovery method that takes the active ingredients (modules) of anticancer agents from existing drugs whose patents have expired or whose development was halted due to side effects and combines them to create new drugs with an improved balance of clinical efficacy and safety. Anticancer agents usually take over 10 years to develop. However, very little basic research is necessary in module technology, which lowers development risks and enables potential approval after R&D of six to eight years. The new agents are patentable as new drugs.

DFP-10917 most advanced drug in pipeline: This is an anticancer drug for treating relapsed or refractory acute myeloid leukemia (AML). A Phase III clinical trial began in the US in April 2019. Delta-Fly aims to obtain FDA approval in the US in 2021 and launch the drug in 2022. It expects to receive a milestone payment from partner Nippon Shinyaku, which plans to initiate a Phase I clinical trial in Japan in FY03/20.

Performance trends

Sales and profit decline due to clinical trial delay

FY03/19 results: Operating revenue, JPY0mn (JPY150mn in FY03/18), operating loss JPY593mn (operating loss of JPY244mn). R&D expenses JPY377mn (+JPY178mn YoY). Sales and profit declined as Delta-Fly did not receive an expected milestone payment following delayed launch of the Phase I clinical trial in Japan due to amended protocols for the US-based Phase III clinical trial for DFP-10917.

FY03/20 forecasts: Operating revenue, JPY0mn (JPY0mn in FY03/19), operating loss JPY1.1bn (operating loss of JPY593mn). Launch of clinical trials for two pipeline drugs in addition to DFP-10917 likely to widen losses as R&D expenses rise to JPY822mn.

Medium-term strategy

Launch one drug yearly from 2022

Drug pipeline progress: Delta-Fly currently has six drugs in its pipeline, four of which are undergoing clinical trials in Japan and the US. The company is preparing to start clinical trials for the remaining two.

Launch one drug p.a.: Delta-Fly plans to launch drugs in succession. It expects FDA approval of DFP-10917 in 2021 and launch in 2022; DFP-14323 (indication: non-small-cell lung cancer) in 2023; DFP-11207 (pancreatic cancer) in 2024; and DFP-14927 (solid tumors and blood cancer) in 2025.

Sights set on supplying drugs after launch: In general, sales royalties are 10–15% of sales under license agreements, but outsourcing manufacture to major overseas contract manufacturers and supplying drugs to licensees could yield higher margins.

Strengths and weaknesses

Strengths

Quick development with low R&D costs: Development risks reduced due to nearly no need for basic research. Enables patent acquisition with small investment in short time.

Track record of tie-ups with major companies: Delta-Fly has collaboration agreements covering two of its six pipeline drugs, and another is undergoing joint development. Also in partnership talks with pharmaceutical companies in Japan, the US, and Europe.

Weaknesses

Unique business model not well understood: The company's viability is misunderstood as it is lumped in with other biotech startups.

No commercialization track record: Although Delta-Fly has six drugs in its pipeline, none has been approved or launched yet.

Profit growth drivers

To date: Licensing revenue from pipeline

Medium-term: Commercialization of drug candidates and progress in pipeline development

Indices	
Market capitalization	JPY8.0 bn
Share price (June 21, 2019)	JPY1,821
Shares issued (incl. treasury shares)	4,369,600 shares
Foreign stockholding ratio (March 31, 2019)	0.00 %
BPS (FY03/19)	JPY801.93
PBR (FY03/19)	2.27 x
PER (FY03/20 Est.)	-7.4 x
Dividend (FY03/20 Est.)	JPY0.00
Dividend yield (FY03/20 Est.)	0.00 %
ROE (FY03/20 Est.)	-30.5 %
Net debt / Equity ratio (FY03/19)	-1.0 %

(JPYmn)		Operating revenue	YoY	Operating profit	YoY	Recurring profit	YoY	Net income	YoY	EPS (JPY)	BPS (JPY)	ROA (RP-based)	ROE
FY03/14	Parent	211	-	-	-	-302	-	-303	-	-137.82	54.55	-	-
FY03/15	Parent	409	93.4%	-	-	-288	-	-290	-	-127.65	208.66	-45.9%	-
FY03/16	Parent	145	-64.5%	-	-	-596	-	-598	-	-185.53	134.20	-76.6%	-
FY03/17	Parent	902	521.3%	329	-	323	-	305	-	88.31	222.51	38.5%	49.5%
FY03/18	Parent	150	-83.4%	-244	-	-245	-	-246	-	-71.20	228.15	-26.7%	-31.0%
FY03/19	Parent	0	-100.0%	-593	-	-671	-	-674	-	-170.16	801.93	-30.3%	-31.0%
FY03/20 Est.	Parent	0	-	-1,066	-	-1,066	-	-1,066	-	-244.85	-	-	-

Source: Shared Research based on company data
Notes: Figures may differ from company materials due to differences in rounding methods.
The company conducted a 500-for-1 stock split effective June 25, 2018. Figures are adjusted for the split.

Business

Company overview

Delta-Fly is a drug discovery startup that specializes in anticancer agents using module technology (discussed later). It aims to develop anticancer treatments gentle on the body and the wallet. Current president Kiyoshi Eshima established the company in December 2010 in Tokushima, gathering a team of colleagues with over 20 years' experience in anticancer agent development. The company listed on TSE Mothers in October 2018.

Anticancer agents gentle on the patient

- Can be used with peace of mind
- Few side effects
- Small financial burden (low price)

Business model

R&D into new drugs using module technology

Module technology

Module technology is a unique drug discovery technique that combines components (modules) that comprise active ingredients in drugs to create new anticancer agents with an improved balance of clinical efficacy and safety.

Module technology: Drug discovery technique that combines components of active ingredients in drugs, and/or adjusts dosage and administration, to create novel drugs

Delta-Fly manufactures new drugs that have equivalent efficacy and fewer side effects compared with off-patent drugs or anticancer agents whose development was halted due to side effects by combining their active ingredients. All base medicines being used require almost no basic investigation because either they are already in use as drugs, or the reasons as to why their development was halted are evident (i.e., data is available for failed clinical trials). Delta-Fly also resolves problems with existing anticancer agents by adjusting their dosage and methods of administration to enable indications for other forms of cancer or reduce side effects.

The company takes compounds that were not fully utilized due to strong side effects despite efficacy or did not reach the regulatory approval stage, and if they appear to have potential for improved safety without losing efficacy, it attempts to alter their chemical structures. The work up to this point is handled in-house, but all subsequent processes leading to drug manufacture are outsourced to contractors.

Example of module technology (DFP-11207)

Issues	New clinical effects
Insufficient continuation of treatment due to hematotoxicity including platelet count decrease	Maintaining 5-FU blood concentration at low levels; no platelet decrease; reduction in blood toxicity
Modules targeted for improvements	**Module improvements**
5-FU prodrug (FT), inhibition of gastrointestinal tract disorders (OXO), effector compound	Replacing FT with EMFU, and OXO with CTA; making it one compound

Source: Shared Research based on company data

Delta-Fly also applies many and varied approaches aside from modifying the chemical structures of modules. These include reviewing indications, adopting drug delivery systems (DDS*), and tweaking administration methods and dosages.

*DDS (Drug Delivery System): Drug administration technology to maximize therapeutic effects by managing distribution of a drug within the body, through targeted delivery (to a specific organ or tissue) of the minimum necessary amount at an appropriate time over a specified period of time. It enables a reduction in the number of times a drug is administered as well as side effects.

The company president Kiyoshi Eshima and other anticancer drug experts exchange ideas regarding module technology during weekly meetings that connect the offices in Tokushima, Tokyo, Canada, and China. The company does not merely concentrate on finding the means to shrink tumors but rather develops drugs from the perspective of what is good for the patient.

Modules to create ideal drugs

Modules in the original sense of the word are interchangeable, highly functional components that make up hardware or software. In module technology, Delta-Fly chooses suitable drug components—proprietary or otherwise—that can bring the idea of "anticancer agents gentle to the patient" (the company's ideal) to reality, combines them, and makes solid improvements applying clever techniques. Its aim is to develop affordable anticancer drugs with few side effects that can be used with peace of mind.

Shorter development period and lower R&D expenses

With module technology, it is possible to shorten the development period by up to nine years versus typical drug development processes. Because Delta-Fly focuses on resolving issues in existing anticancer agents, there is a high likelihood that it will obtain favorable results in clinical trials. According to the company, success rates of anticancer drug discovery are typically in single digits, but success rates from basic investigations using module technology have been higher, at roughly 50–70%.

Unlike generic drugs, Delta-Fly's pipeline products developed under module methodology are new compounds, and are patented as new drugs. Even if the patents covering substance rights for existing compounds have expired, it is possible to apply for a new-use patent, which the company can hold for 20 years. It can also apply for international patents under the Patent Cooperation Treaty covering about 30 countries worldwide.

Key patents held by Delta-Fly Pharma

Pipeline	Name of patent	Term (valid through)	Granted countries and regions
DFP-10917	Method for administration of anticancer drug containing deoxycytidine derivative	April 27, 2029	Granted in the US. PCT transfer procedure in progress in Japan, China, South Korea, Russia, major EC countries, and Australia
	Stable crystal of 1-(2'-cyano-2'-deoxy-β-D-arabinofuranosyl) cytosine monohydrochloride	May 13, 2039	Transfer procedure in progress in Japan, the US, China, South Korea, Russia, and major EC countries
	Pyrimidine nucleoside derivative	Expired	Term of the patent expired except for the US
DFP-10825	RNAi molecule targeting thymidylate synthase and application thereof	March 28, 2030	Transfer procedure in progress in Japan, the US, China, South Korea, Russia, and major EC countries
	Liposome containing shRNA molecule targeting a thymidylate synthase and use thereof	May 22, 2031	Section 30 applied
DFP-11207	Novel 5-fluorouracil derivative	October 05, 2030	Planning to apply for transfer procedure in Japan, the US, China, South Korea, Russia, and major EC countries
DFP-14323	Pharmaceutical composition for treatment of or remission in elderly or terminal cancer patient	November 24, 2035	Granted in Japan and Taiwan
DFP-14927	Novel PEG derivative	December 03, 2034	Granted in Japan and the US

Source: Shared Research based on company data.
Note: "Section 30 applied" means that under patent law, exceptions to loss of novelty apply

Clinical trials overseas

Delta-Fly is conducting clinical trials in the US as well as in Japan. Clinical trials of new drugs cost less in the US than in Japan, and it is relatively easy to enroll patients with rare diseases in the US. Clinical trials in Japan are shorter for new drugs already approved in the US, so the company hopes to commercialize these drugs sooner.

Out-licensing sales rights only

According to Delta-Fly, if it retains the manufacturing rights, despite having a sales agreement with a partner, it will continue to manufacture drugs after commercialization. By contracting R&D and manufacturing to several major Southeast Asian and US companies

that are familiar with approval standards of the US FDA (Food and Drug Administration), it should be able to maintain high margins after market launch.

Background to promoting module technology

In general, it takes nine to 17 years from basic research for the compounds that act on cancer until regulatory approval. It normally takes two or three years to conduct basic research including searching for drug discovery seeds and testing the toxicity of drug candidates. Module technology involves chemical compounds that have already been used in humans, so it requires almost no basic research. While toxicity testing is absolutely essential for any new drugs, according to Delta-Fly it is possible to enter the stage of preclinical studies in roughly one year of starting development. Results of preclinical studies conducted to confirm the efficacy and safety of drug candidates can be extrapolated from prior studies. Further, since the development starts with a focus on resolving known issues with the drug, side effects are well known, and hence there is a reduced development risk such as failure during clinical trials. This shortens the time spent on R&D, and it appears likely that the process from drug discovery through approval will take six to eight years using module technology.

Drug development process: Comparison of conventional process and Delta-Fly's

Process	Period (years)		Description	
	Normal	Delta-Fly Pharma		
Basic research	2–3	1	Search for new drug candidate compound (through synthesis, screening, and other)	
Preclinical study	3–5	1	Study to test efficacy and safety with animals	
Clinical studies	3–7	3–5	Phase I	Study to test safety with a small number of healthy individuals (patients for anticancer drugs)
			Phase II	Exploratory study to test efficacy and safety with small number of patients
			Phase III	Confirmatory study to test efficacy and safety with a large number of patients
Application and approval	1–2	1	Reviews by regulatory authority in each country or region	
Total	9–17	6–8		

Source: Shared Research based on company data. Examples are typical drug R&D processes.

Unique business model

The Ministry of Economy, Trade and Industry classifies biotech startups into three broad business model categories. Delta-Fly does not look for drug discovery seeds or obtain licenses from other companies; it has its own development pipeline of several drugs, and outsources development and manufacture to major contract research organizations (CROs). This is a unique business model not seen in other Japanese companies.

Biotech startup business models

		Example of a Japanese company
Platform	Has the technology to conduct research for drug discovery seeds and out-licenses them	PeptiDream
Pipeline acquisition	Acquires prospective pipelines outside the company through M&A or in-licensing	Sosei Heptares
Fully integrated	Covers the full spectrum of operation, from seeds search and development to sales and marketing	NanoCarrier

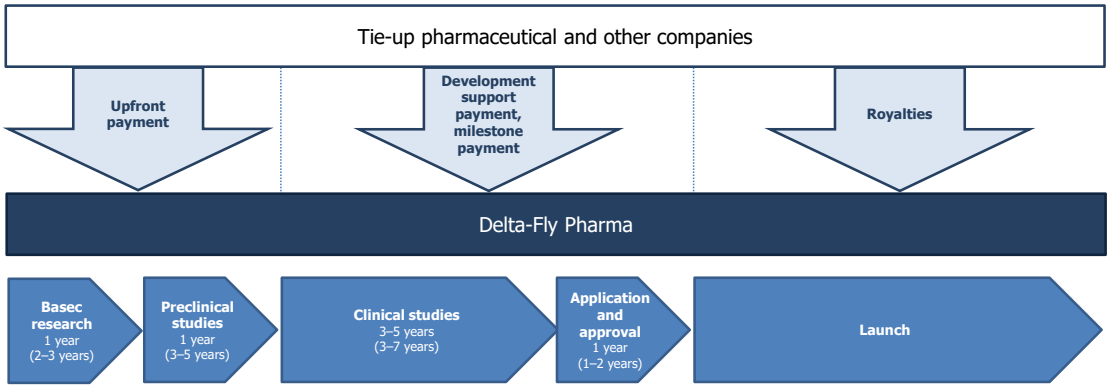
Source: Shared Research based on Ministry of Economy, Trade and Industry material ("Business models and financing activities of biotech startups" released in 2017).

Four forms of revenue in near term

Delta-Fly has six pipeline drugs, but none has been commercialized yet. In the near term the only source of revenue is payments from tie-up pharmaceutical companies. In general, revenues move progressively from upfront payments, milestone payments, and development support payments to royalties.

Types of revenue
- Upfront payments
- Milestone payments
- Development support payments
- Royalties

Overview of business model



Source: Shared Research based on company data.
Note: Years in parentheses () show typical duration of each process.

Revenue to date

In FY03/15 and FY03/16, Delta-Fly received development support payments from Kyowa Chemical Industry (not listed). Of the company's six pipeline products, it has an agreement for DFP-10917 with Nippon Shinyaku (TSE1: 4516) and for DFP-14323 with Kyowa Chemical Industry, receiving a total of JPY700mn in upfront payments and roughly JPY200mn in development support payments from Yakult Honsha (TSE1: 2267) in FY03/17. It received JPY150mn in milestone payments for DFP-14323 from Kyowa Chemical Industry in FY03/18.

Delta-Fly had expected to receive a milestone payment of JPY200mn from Nippon Shinyaku in FY03/19 for the initiation of a Phase I clinical trial of DFP-10917 in Japan, but the delayed launch of the US-based Phase III clinical trial postponed the start of the Japanese trial. As a result, the company booked no operating revenue in FY03/19. Delta-Fly said it basically does not enter partnerships before Phase II clinical trials. The company is looking for partners in markets outside Japan among several European and US pharmaceutical companies in conjunction with the launch of the US-based Phase III clinical trial for DFP-10917. It is also negotiating partnerships with Japanese pharmaceutical companies regarding DFP-17729, and expects to receive an upfront payment when it reaches an agreement sometime during FY03/20.

Development progress of DFP-10917

Clinical trials are underway in Japan and the US for four of the company's six pipeline drugs. Preparations are underway to start clinical trials for another two. DFP-10917 is at the most advanced development stage.

DFP-10917: Cancer cell cycle regulator

Phase III clinical trial for DFP-10917 launched in the US

DFP-10917 is an anticancer drug administered by continuous infusion with indications for relapsed or refractory acute myeloid leukemia (AML). Through continuous intravenous infusions in low doses over an extended period of time, this new deoxycytidine derivative is taken up by the DNA in cancer cells and induces apoptosis (cell death) by causing DNA strand breaks.

The base for DFP-10917 is a drug originally developed for colorectal cancer by Taiho Pharmaceutical (not listed), a consolidated subsidiary of Otsuka Holdings (TSE1: 4578). It was not approved as it was ineffective on solid tumors and caused strong side effects in large doses. Delta-Fly thought that it might be applicable to leukemia because there were some responses in blood samples of animal models.

DFP-10917 has been shown to be effective in treating patients with relapsed or refractory acute myeloid leukemia who do not respond to standard treatments. The company made changes to the conventional route of administration and tried low-dose, continuous IV infusions over extended periods (14 days, 24 hours a day). Phase I and Phase II clinical trials

were conducted in the US, and in the Phase II trial, 14 of 29 patients showed complete response (CR), with the disappearance of all signs of cancer. The high 48.3% overall response rate demonstrated efficacy of the drug.

Overview of DFP-10917

	Base drug (CNDAC)	DFP-10917
Indication	Colorectal cancer	Relapsed/refractory acute myelogenous leukemia
Method of administration	High-dose, short-time IV drip or oral	Low-dose, long-time prolonged infusion (14 days, 24 hours)
Mechanism of action	DNA synthesis inhibition (S phase action)	Cell cycle (G2/M phase stop)
Status	Side effects: strong Response rate: low Non-approved	Side effects: weak Response rate: Phase-II 48.3% Phase-III on-going

Existing drug: CNDAC **New drug: DFP-10917**

Source: Shared Research based on company materials and interviews
Note: Chemical structure is not altered as the company has adjusted dosage and administration. New-use patent filed.

Delay to the Phase III clinical trial

While preparations were being made for a Phase III clinical trial, a new drug for AML was developed in the US for the first time in 20 years. As a result, the company had to delay the start of the Phase III trial as it had to partially amend the trial protocol based on the new treatment system. Delta-Fly resubmitted the protocol to the FDA, and in April 2019 began preparations to enroll patients for the Phase III study. The trial is already registered at the clinical trial registration site of a US public institution. Patient enrollment is scheduled to start in June 2019. Delta-Fly said it is in partnership negotiations with a number of overseas pharmaceutical companies regarding licensing agreements for markets outside Japan.

Only 29 patients were enrolled in the Phase II trial, but the company aims to enroll 450 patients for the Phase III trial, and is budgeting R&D spending of about JPY800mn in FY03/20.

In Japan, Delta-Fly has a partnership agreement with Nippon Shinyaku (TSE1: 4516). However, the delay in the US-based Phase III trial also delayed the start of a Phase I trial in Japan, so the company did not receive the JPY200mn milestone payment it expected in FY03/19, and had no operating revenue in FY03/19. The Phase I trial looks likely to begin in Japan during FY03/20, and the company should receive the milestone payment it expected in FY03/19, although this is not yet incorporated in its forecasts.

Endpoint of the Phase III clinical trial

For the US-based Phase III clinical trial, the company plans to increase the number of patients enrolled in stages to 150, 300, and 450. Currently it appears that the response rate for drugs used in standard treatment in the US is about 10% for relapsed or refractory AML. The FDA may grant fast-track approval if the complete response rate for DFP-10917 can be sustained over a certain time frame, and there is a high likelihood that complete responses in 150 patients will be the endpoint. If that is the case, Delta-Fly thinks that R&D expenses for the Phase III trial will be about JPY1.5bn.

Earnings impact

Around 30% of new-onset AML patients are cured with standard treatments, but 70% of these patients have recurrence. In Japan, the US, and Europe, there are several tens of

thousands of relapsed or refractory AML patients yearly. Annual sales for DFP-10917 are estimated to reach a maximum of about JPY50bn for Japan, the US, and Europe combined, generating operating revenue of around JPY10bn for the company. In addition, sales could be several multiples of this if the drug is also used in conjunction with therapies for new-onset cases.

The company plans to launch DFP-10917 on the market in 2022 after obtaining approval for the New Drug Application (NDA) from the FDA during 2021. It expects upfront payments from overseas pharmaceutical companies it is in negotiations with and a milestone payment from Nippon Shinyaku which is scheduled to launch a Phase I clinical trial in Japan in FY03/20.

Other drugs in the development pipeline

DFP-14323: Immuno-modulator

DFP-14323 is an oral anticancer agent indicated for non-small-cell lung cancer (NSCLC). The company is developing the drug in collaboration with its partner Kyowa Chemical Industry (unlisted). The base is Ubenimex, a drug already approved as a therapeutic agent for treating acute non-lymphocytic leukemia, so Delta-Fly was able to start development from a Phase II clinical trial without preliminary investigations of any kind.

The company aims to speed up the Phase II clinical trial that is currently underway in Japan by expanding the number of facilities involved from 1 to 10. It submitted a partially amended clinical trial protocol to the Pharmaceutical and Medical Devices Agency (PMDA). The company thinks it will be able to start a Phase III clinical trial sometime before spring of 2020.

It expects to launch DFP-14323 in Japan after obtaining approval for the indication of lung cancer by fiscal 2023.

DFP-11207: Cancer cell metabolism regulator

DFP-11207 is an oral anticancer agent used on solid tumors such as pancreatic cancer. It has a very low incidence of the side effects seen in the 5-FU* anticancer formulations wherein blood platelet numbers decline. Phase I clinical trials in Europe and the US are complete, and soon reports regarding the food effect study conducted thereafter will be presented at a US academic conference. Currently preparations are underway for a Phase II trial, and the company plans to commercialize the drug in 2025.

*5-FU: Cytotoxic agent containing fluoride pyrimidine chemical substances. It is effective in inhibiting the growth of or killing cancer cells by using enzymes that are abundant in cancer cells to inhibit DNA synthesis. Side effects include reduced numbers of white blood cells, red blood cells, and platelets due to myelosuppression.

DFP-14927: Polymeric delivery of DFP-10197

DFP-14927 is an intravenous anticancer drug with indications for solid tumors and blood cancers. It is a compound made by functionalizing DFP-10917 through binding the substance with polyethylene glycol.

The company's joint development partner, Sanyo Chemical Industries (TSE1: 4471), has been a shareholder since before Delta-Fly's listing. The polyethylene glycol that Sanyo Chemical Industries produces under the trade name Macrogol has low toxicity, and is listed in the Japanese Pharmaceutical Excipients drug addendum as a tablet coating, among other uses.

In January 2019, the US FDA completed a safety review, and the substance obtained IND approval. The company will start enrolling patients in Q2 FY03/20 for a Phase I clinical trial which includes an expanded trial corresponding to an early Phase II study targeting pancreatic and other gastrointestinal cancers. It plans on obtaining approval and launching the product in the US by fiscal 2025.

DFP-10825: Oligonucleotide therapeutics delivery

DFP-10825 is an anticancer drug administered intraperitoneally, with indications for peritoneal dissemination of metastatic cancer including gastric and ovarian cancer. Peritoneal dissemination refers to cancer cells being scattered in the peritoneal cavity due to the progress and metastasis of primary cancer originating from abdominal organs such as the stomach, liver, pancreas, intestine, kidney, or ovaries. It is classified as stage IV.

Oligonucleotide therapeutics target ribonucleic acid (RNA), preventing the generation of proteins that cause cancer, thereby suppressing the function of abnormal genes as well as cancer aggravation and metastasis. It has few side effects and appears to be a promising treatment to eradicate cancer, but an issue is the difficulty of delivering it to the interior of cancer cells because it decomposes readily and rapidly in the body.

Delta-Fly noticed this and looked for a way to improve effectiveness by changing the route of administration, and it conjectured that direct administration inside the abdominal cavity might be the answer. It started preparing to manufacture new active pharmaceutical ingredients and formulations with a view to launching clinical trials. It aims to start clinical trials in the US and Japan by fiscal 2020.

DFP-17729: Tumor microenvironment regulator

DFP-17729 is an oral anticancer agent developed under an entirely new concept applicable to solid tumors. This agent stops the proliferation of cancer cells by neutralizing the acidic microenvironment in which they grow with an alkaline formulation. The company started development focusing on already approved and marketed urine alkalinizing agents, after noting that 65% out of 30 terminally ill pancreatic cancer patients survived for at least two years in a prior clinical trial.

In FY03/21, Delta-Fly plans to start clinical trials in Japan targeting pancreatic cancer, and is negotiating partnerships with Japanese pharmaceutical companies ahead of this. Details of collaboration such as joint development or out-licensing have not been determined yet, but Delta-Fly would like to speed up development in any case.

Company development pipeline (as of May 2019)

Development code	Administration	Indication	Region	Preclinical study	Clinical study: Phase I	Clinical study: Phase II	Clinical study: Phase III	Application	Approval	Launch
DFP-10917 (Cell cycle regulator)	Prolonged infusion	Relapsed/refractory acute myeloid leukemia (AML)	US				Phase III clinical study on-going		2021 (E)	2022 (E)
			Japan	Preparing for Phase I clinical study						
DFP-14323 (Cancer immuno modulator)	Oral	Non-small cell lung cancer (NSCLC)	Japan			Phase II clinical study on-going				2023 (E)
DFP-11207 (Cancer cell metabolism regulator)	Oral	Solid tumor (pancreatic cancer, other)	Europe and US	Preparing for Phase II clinical study						2024 (E)
DFP-14927 (Polymeric agent of DFP-10917)	Infusion	Solid tumor, blood cancer	US		Phase I clinical study on-going					2025 (E)
DFP-10825 (Oligonucleotide therapeutics delivery)	Intraperitoneal	Peritoneal disseminated metastatic cancer (gastric and ovarian cancer)	—	Preclinical study on-going						2026 (E)
DFP-17729 (tumor microenvironment regulator)	Oral	Solid tumor, other	Japan		Preparing for clinical studies					2026 (E)

Source: Shared Research based on company data.

Medium-term outlook

Drug development pipeline progress

Of the six drugs currently in the pipeline, four are undergoing clinical trials in Japan and the US. Preparations are underway to start clinical trials for another two.

Launch of DFP-10917

The company first plans to obtain approval for and commercialize DFP-10917

Delta-Fly's immediate focus is to get FDA approval for and launch its first pipeline drug, DFP-10917. DFP-10917 is an anticancer agent for treating relapsed or refractory acute myeloid leukemia, and its launch is much anticipated as it will be the first drug with indications for relapsed acute myeloid leukemia. However, the Phase I clinical trial to be conducted by the company's partner Nippon Shinyaku in Japan has been postponed due to amended protocols for the US-based Phase III clinical trial. This is because additional comparison tests became necessary following the development of a new drug for new-onset leukemia in the US for the first time in 20 years, and not because there is an issue with DFP-10917 itself. The company thinks that the Phase III clinical trial in the US may be completed as early as mid-2020, followed by analysis and application filing, and expects to obtain approval from the FDA in 2021 and launch the drug in 2022.

Plans to launch one drug yearly

Delta-Fly has five pipeline drugs in addition to DFP-10917. It expects a series of launches: DFP-10917 in 2022, DFP-14323 (indication: NSCLC) in 2023, DFP-11207 (pancreatic cancer) in 2024, and DFP-14927 (solid tumors and blood cancer) in 2025.

The company says it may be able to use the revenues generated from these launches to fund subsequent pipeline drug development on its own, and thereby avoid fundraising risk.

Sights set on supplying products following market launch

Potential profit boost from supplying products

Typical drug sales royalties are 10–15% of sales, but outsourcing manufacture to major manufacturing contract companies (keeping costs low and maintaining quality) and then supplying drugs to licensees on its own can boost margins to 30–35%.

On the flip side, Delta-Fly relies on contractors not just for manufacturing facilities but for everything from basic research to production technology, stable product supply, and quality control. As such, all of the manufacturing responsibilities fall on Delta-Fly.

Competition

There are many listed biotech startups involved in drug discovery. While some use specific technology to manufacture drugs, e.g., NanoCarrier Co., Ltd. (TSE Mothers: 4571) and its polymeric micelles, no company in Japan or overseas has the same business model as Delta-Fly, which uses a variety of methods.

The ratio of R&D expenses to sales for biotech startups varies at each stage of clinical trials, so a simple comparison is not possible. However, we understand that the company figure is well above those of others in the industry: an average of 18.6% for the 10 major Japanese pharmaceutical companies (Shared Research estimate), 11.1% for the drug manufacturing sector, and 3.3% all-industry average (Ministry of Internal Affairs and Communications, 2017 Survey of Research and Development).

Typical R&D expenses in drug discovery comprise JPY200mn in basic investigations and preclinical studies, JPY300mn for Phase I trials, JPY300–500mn for Phase II, and JPY1.5bn to as much as JPY5.0bn for Phase III. However, Delta-Fly says it is able to achieve significant reductions in R&D expenses with its unique business model. The company was able to raise more than JPY3.0bn from its recent TSE Mothers listing, and if DFP-10917 is approved and launched as expected, the company said it might be able to self-fund subsequent pipeline developments.

Latest full-year results for drug discovery startups

Ticker	Company	FY end	Revenue (JPYmn)	ROE	R&D expenses (JPYmn)	R&D expenses % of sales	Description [% of total revenue]
4565	Sosei Heptares	Dec	2,872	-13.2%	5,384	187.5%	Drug discovery startup, having business bases in Japan and UK; bolstered technological capabilities through acquisitions [Pharmaceuticals 100]
4582	SymBio Pharmaceuticals	Dec	3,835	-77.8%	1,833	47.8%	Focuses on the three areas of cancer, blood, and pain management. In-licenses new drug candidate substance for development and commercialization [Pharmaceuticals sales 100]
4587	PeptiDream	Jun	6,426	17.4%	921	14.3%	Discovered candidate for cyclized peptides using the base technology PDPS, together with a large pharmaceuticals company, and out-licensed it to the partner; also engages in its own drug discovery [Alliance 100]
4571	NanoCarrier	Mar	496	-35.3%	1,793	361.5%	Drug discovery startup focusing on cancer; aims for new drugs with limited side effects by using micellar nanoparticles [Development support payment, other 100]
4591	Ribomic	Mar	64	-32.3%	612	956.3%	Drug discovery startup from University of Tokyo. Develops molecularly-targeted drug (aptamer drug) using RNA (ribonucleic acid) [Drug discovery 100]
4592	SanBio	Jan	741	-60.2%	3,721	502.2%	Develops regenerative cell medicines for central nervous system deficits; founded in the US, reorganized in Japan [Regenerative cell medicine using allogeneic stem cells 100]
4593	Healios	Dec	0	-38.0%	4,269	-	Biotech startup for development of therapeutic drugs using iPS cells and mesenchymal stem cell; also engages in joint development with Sumitomo Dainippon Pharma [Pharmaceuticals 100]
4597	Solasia Pharma	Dec	318	-36.4%	1,463	460.1%	Drug discovery startup focusing on cancer; operates without manufacturing facility, focusing on clinical development through inlicensing development rights for candidate substance [Pharmaceuticals and medical devices 100]
4598	Delta-Fly Pharma	Mar	0	-31.0%	376	-	Drug discovery startup; researches and develops anticancer drugs with high safety and efficacy through Module Drug Discovery combining exising anticancer substance [Pharmaceuticals 100]

Source: Shared Research based on company materials

Note: Sosei Heptares results for nine months due to changed fiscal year-end.

Why other companies do not emulate the company's business model

In module technology (drug discovery), the company begins by focusing on issues surrounding the base anticancer agents such as side effects and excessively high prices, and seeks to find out how to resolve them. Major pharma companies that have already begun manufacturing and selling anticancer agents must of course be intimately familiar with drugs they have developed themselves. However, highlighting problems, e.g., side effects, of such approved medicines would negate the products they are selling after having invested huge amounts in R&D. Meanwhile, in general researchers are keen to engage in the entire drug development process from looking for the initial seed to launching a product on the market themselves; they rarely think of using other companies' discoveries. Further, the market size for drugs created using the module technology is believed to be somewhere between that for blockbuster drugs and generics, so it would be difficult to get returns from large investments.

Also, drug discovery using module technology requires a team with many years of experience and network with physicians involved in clinical trials. Delta-Fly is working on development using drug data supplied by the company's scientific counselors and advisers. These include professor emeritus at Kyoto University Hiromi Wada, who has treated more than 3,000 cancer patients to date. The company uses these data to support its module drug development and patent applications. In light of the foregoing, it appears that new entrants would find it difficult to emulate the Delta-Fly's business model.

Strengths and Weaknesses

Strengths

- **Development is quick with low R&D expenses:** The pharmaceutical industry is characterized by lengthy R&D periods of over ten years and low success rates, with huge sums spent on R&D in a quest for efficacy and safety with a focus on substances that can be used as medicines. However, drug discovery applying the company's module technology focuses on resolving problems with drugs that are off-patent. Because it uses existing anticancer agents and drugs, almost no basic discovery research is necessary. Also, the company can readily forecast clinical efficacy and safety, which shortens the development period and reduces development risks such as failure of clinical trials. As less time is spent on R&D, the process from drug discovery through approval is estimated at six to eight years.

  The company leverages its knowledge and expertise on anticancer agents to come up with the appropriate combinations, adjusts administration methods and dosages, and applies other technologies (including polymeric and DDS technologies) to find a quick, effective, and low-cost path to patenting a new drug.

- **Track record of tie-ups with major companies:** Of the six drugs in its pipeline, Delta-Fly receives licensing revenue for DFP-10917 (from Nippon Shinyaku) and DFP-14323 (Kyowa Chemical Industry) through collaboration agreements. In conjunction with the launch of the Phase III clinical trial in the US for DFP-10917, it is in negotiations with several pharmaceutical companies in Europe and the US regarding collaboration in markets outside Japan. When Nippon Shinyaku begins a Phase I clinical trial, Delta-Fly stands to receive a milestone payment. The company is also negotiating partnerships with Japanese pharmaceutical companies regarding DFP-17729, and expects to receive an upfront payment upon contract signing in FY03/20. Among its partners, Sanyo Chemical Industries (TSE1: 4471) holds 3.43% of outstanding shares.

Strengths

- Development is quick, with low R&D expenses
- Track record of tie-ups with major companies

Weaknesses

- **Unique business model not well understood:** Delta-Fly is commonly seen as a biotech startup due to its involvement in developing anticancer agents, but in fact it has its own unique business model that differs from those of typical biotech startups. Under its module technology, there is virtually no need for basic investigation and hence, development is quicker, so the company's budget can be thinner than those of overseas biotech startups. R&D expenses rise sharply once clinical trials begin, but if fundraising becomes unfeasible, the company can manage its funding requirements by postponing the start of a clinical trial. Even if the company were not able to raise additional funding, if it puts other pipeline drugs on hold until the launch of DFP-10917 in 2022, it could self-fund and there would be no significant shortfall. Despite having a business model that differs from those of typical biotech startups, the company tends to be lumped in with them, causing even a deliberate postponement of clinical trials to have a significant impact on its share price and raise concerns about its viability.

- **No commercialization track record:** Although Delta-Fly has six drugs in its pipeline, none of them has been approved or commercialized yet. In the drug development process, decisions on whether to go ahead with a clinical trial are made by current management on a rule of thumb basis, in light of over 20 years' experience in developing anticancer agents and familiarity with clinical trials. Although there has been an element of trial and error in initial development stages, the company has had no major missteps yet. However, a potential concern is the loss of expertise based on experience over many years in the event of management changes.

Weaknesses

- Unique business model not well understood
- No commercialization track record

Earnings

Losses continue on upfront spending ahead of new drug approval and commercialization

FY03/18 results

The company posted operating revenue of JPY150mn (-83.4% YoY), operating loss of JPY244mn (operating profit of JPY329mn in FY03/17), pre-tax loss of JPY245mn (pre-tax profit of JPY323mn), and net loss of JPY246mn (net income of JPY305mn).

FY03/18 results:
- Operating revenue: JPY150mn (-83.4% YoY)
- Operating loss: JPY244mn (operating profit of JPY329mn in FY03/17)
- R&D spending: JPY199mn (-37.2% YoY)

Operating revenue and profit

The company received a milestone payment of JPY150mn under an exclusive licensing agreement for DFP-14323 in Japan signed in March 2017 with Kyowa Chemical Industry. R&D and SG&A expenses declined following the review of the timing of launch of clinical trials for the company's development pipeline, but profit fell due to a significant decline in revenue.

FY03/19 results

Operating revenue, JPY0mn (JPY150mn in FY03/18), operating loss JPY593mn (operating loss of JPY244mn). R&D expenses JPY377mn (+JPY178mn YoY). Sales and profit declined as the company did not receive an expected milestone payment on delayed launch of the Phase I clinical trial in Japan due to amended protocols for the US-based Phase III clinical trial for DFP-10917.

FY03/19 results: Lower revenue and profit
- Operating revenue: JPY0mn (JPY150mn in FY03/18)
- Operating loss: JPY593mn (operating loss of JPY244mn)
- R&D spending: JPY377mn (+89.1% YoY)

Operating revenue and profit

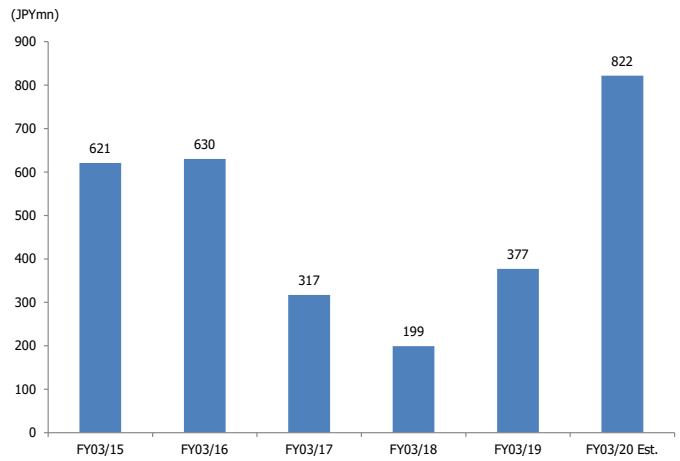
The start of the US-based Phase III clinical trial for DFP-10917 (a cell cycle regulator) was delayed due to a partial amendment to the protocol. In turn this delayed the start of scheduled Phase I trial in Japan, so the company did not receive an expected milestone payment from Nippon Shinyaku. Meanwhile losses widened as it incurred higher R&D expenses of JPY377mn (+JPY178mn YoY) to prepare for the start of clinical trials.

FY12/20 company forecast

FY03/20 forecasts: Operating revenue of JPY0mn (JPY0mn in FY03/19), operating loss JPY1.1bn (operating loss of JPY593mn). In addition to the launch of a Phase III clinical trial for DFP-10917 in the US, a Phase II trial for DFP-14323 and a Phase I trial for DFP-14927 are underway. Progress on clinical trials for multiple pipeline drugs will cause R&D expenses to rise to JPY822mn (roughly 2.2x YoY) and widen losses.

FY03/20 forecasts:
- Operating revenue: JPY0mn (flat YoY)
- Operating loss: JPY1.1bn (operating loss of JPY593mn)
- R&D spending JPY822mn (+118.1% YoY)

R&D expenses



Source: Shared Research based on company data
Note: Figures may differ from company materials due to differences in rounding methods.

In FY03/20, the Phase III clinical trial for DFP-10917 will account for the bulk of investment. Going forward, as the remaining pipeline drugs move through development stages, R&D expenses will be on an uptrend.

Income statement

(JPYmn)	FY03/15 Parent	FY03/16 Parent	FY03/17 Parent	FY03/18 Parent	FY03/19 Parent	FY03/20 Par. Est.
Operating revenue	109	145	902	150	0	0
YoY	-48.5%	33.4%	521.3%	-83.4%	-100.0%	-
R&D expenses	621	630	317	199	377	822
YoY	-	1.4%	-49.6%	-37.2%	89.1%	-
R&D ratio	570.7%	434.0%	35.2%	132.9%	-	-
SG&A expenses	69	99	256	194	216	244
YoY	-	43.5%	158.8%	-24.1%	10.9%	-
SG&A ratio	63.4%	68.2%	28.4%	129.6%	-	-
Operating profit	-	-	329	-244	-593	-1,066
YoY	-	-	-	-	-	-
OPM	-	-	36.4%	-162.5%	-	-
Non-operating income	0	0	0	0.805	0.806	0
Non-operating expenses	0	0	6	1.492	79.495	0
Rcurring profit	-288	-596	323	-245	-671	-1,066
YoY	-	-	-	-	-	-
RPM	-264.7%	-410.2%	35.8%	-163.0%	-	-
Extraordinary gains	0	0	0	0	0	0
Extraordinary losses	0	0	0	0	0	0
Net income	-290	-598	305	-246	-674	-1,066
YoY	-	-	-	-	-	-
Net margin	-266.6%	-411.6%	33.8%	-164.2%	-	-
Operating revenue details	Development support payment	Development support payment	DFP-10917 tie-up DFP-14323 tie-up	DFP-14324 milestone		

Source: Shared Research based on company data
Note: Figures may differ from company materials due to differences in rounding methods.

Delta-Fly received development support payments in FY03/15 and FY03/16, upfront payments for DFP-10917 and DFP-14323 in FY03/17, and a milestone payment for DFP-14323 in FY03/18. In FY03/19, the company did not book any operating revenue. The start of the Phase III clinical trial for DFP-10917 in the US was postponed, and this in turn delayed the start of scheduled Phase I trial in Japan, so the company did not receive an expected milestone payment.

Balance sheet

(JPYmn)	FY03/18 Parent	FY03/19 Parent
Current assets	832	3,532
Cash and deposits	781	3,508
Inventories	0	0
Other	50	24
Fixed assets	32	35
Tangible fixed assets	31	32
Intangible fixed assets	0	0
Investments and other assets	1	4
Total assets	864	3,567
Current liabilities	29	57
Interest-bearing debt	7	7
Other	22	50
Fixed liabilities	13	6
Interest-bearing debt	13	6
Other	0	0
Total liabilities	42	63
Total net assets	822	3,504
Total liabilities and net assets	864	3,567

Source: Shared Research based on company data
Note: Figures may differ from company materials due to differences in rounding methods.

Cash and deposits increased following the issue of shares accompanying the company's listing on the TSE Mothers market, so current assets increased by JPY2.7bn from FY03/18. Net assets also increased by JPY2.7bn YoY due to increased capital and capital surplus following the listing.

Cash flow statement

(JPYmn)	FY03/17 Parent	FY03/18 Parent	FY03/19 Parent
Cash flows from operating activities	-252	100	-585
Cash flows from investing activities	-1	0	-4
Cash flows from financing activities	-7	293	3,317

Source: Shared Research based on company data
Note: Figures may differ from company materials due to differences in rounding methods.

Operating cash flow is volatile as licensing revenue is a component of operating revenue, and tends to be negative due to upfront investment in areas such as R&D. However, fixed expenses on their own are about JPY1.0bn per annum, so as of end-FY03/19 Delta-Fly would be able to operate for three years given its cash balance of JPY3.5bn.

There are no noteworthy investing cash flow activities, partly because the company outsources manufacture.

In FY03/19, financing inflows were significant due to gains of JPY3.3bn from issuing shares accompanying the TSE Mothers listing in October 2018.

Per-share data (JPY)

(JPY)	FY03/14 Parent	FY03/15 Parent	FY03/16 Parent	FY03/17 Parent	FY03/18 Parent	FY03/19 Parent
Shares issued (year-end; '000)	3	4	5	5	6	4,370
EPS	-302.4	-127.7	-185.5	88.3	-71.2	-170.2
Dividend per share	0.0	0.0	0.0	0.0	0.0	0.0
Book value per share	54.6	208.7	134.2	222.5	228.2	801.9

Source: Shared Research based on company data
Note: The company conducted a 500-for-1 stock split effective June 25, 2018. Figures are adjusted for the split. In October 2018 it issued shares accompanying stock market listing.

History

Date	Description
December 2010	Delta-Fly Pharma established with the aim to provide therapies that can be recommended to cancer patients in the family
October 2012	Initiated Phase-I clinical study of DFP-10917 in the US (for relapsed/refractory acute myeloid leukemia)
April 2013	Singed an agreement with Yakult Honsha Co., Ltd. granting (with options) rights for development and commercialization in Japan of anticancer drug candidate compound held by Delta-Fly Pharma
July 2014	Initiated Phase I clinical study of anticancer drug candidate compound DFP-11207 in the US (for treatment of solid tumor)
February 2015	Initiated Phase-II clinical study of DFP-10917 in the US (for relapsed/refractory acute myeloid leukemia)
April 2016	Signed an exclusive licensing agreement with Kyowa Chemical Industry Co., Ltd. on anticancer drug candidate compound DFP-14323 in Japan
March 2017	Signed an exclusive licensing agreement with Nippon Shinyaku Co., Ltd. on anticancer drug candidate DFP-10917 in Japan
March 2018	Signed an agreement with Sanyo Chemical Industries, Ltd. on co-development of new anticancer drug using drug delivery system
October	Listed on the Mothers market of the Tokyo Stock Exchange

Source: Shared Research based on company data.

Delta-Fly aims to provide cancer treatments that its employees can recommend to their own families. It was founded by the current president and representative director Kiyoshi Eshima in Tokushima in December 2010. Doctor Eshima was involved in R&D for roughly 30 years at Taiho Pharmaceutical, a consolidated subsidiary of Otsuka Holdings engaged in research into anticancer agents.
The company name, Delta-Fly, has its origins in “dragonfly.” It expresses the company’s attitude to move forward and overcome difficulties, as dragonflies only move forward and can easily traverse mountains.

Top management

President and representative director: Kiyoshi Eshima (born in 1949)

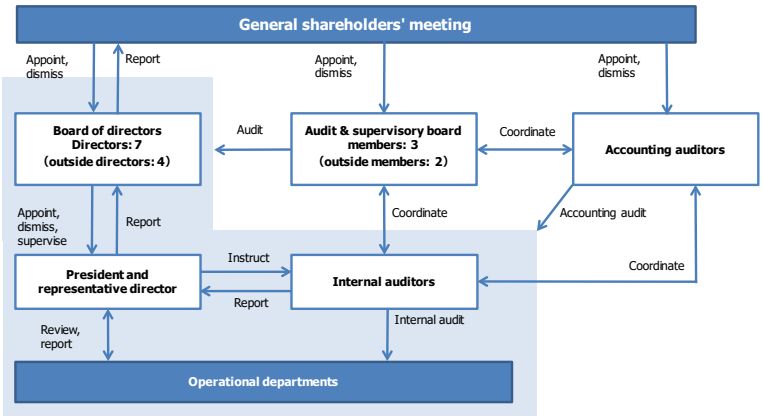
1976 Master's degree, Tokyo Institute of Technology Graduate School of Engineering
1976 Joins Taiho Pharmaceutical
2005 Director and head of development center
2007 Director and head of Tokushima research center
2010 Visiting professor, Tokushima University, Center for research administration and collaboration (current post)
2010 Representative director and president of Delta-Fly Pharma

Shareholders

Top shareholders	Shares held	Shareholding ratio
Kiyoshi Eshima	775,000	17.7%
Kyodai Venture NVCC Number One Investment Limited Partnership	574,300	13.1%
Mitsubishi UFJ Capital Number Three Investment Limited Partnership	225,000	5.1%
Yakult Honsha Co., Ltd.	217,500	5.0%
Innovation Engine Number Three Investment Limited Partnership	172,800	4.0%
BBH/SUMITOMO MITSUI TRUST (UK) LIMITED FOR SMT TRUSTEES (IRELAND) LIMITED FOR JAPAN SMALL CAP FUND CLT AC	168,200	3.8%
The Master Trust Bank of Japan, Ltd. (Trust account)	158,400	3.6%
Sanyo Chemical Industries, Ltd.	150,000	3.4%
Nissay Capital Number Six Investment Limited Partnership	146,100	3.3%
DITPartners Co., Ltd.	125,000	2.9%
SUM	2,712,300	62.1%

Source: Shared Research based on company data
Note: As of March 31, 2019

Corporate governance



Form of organization and capital structure	
Controlling shareholder	None
Parent company ticker	n.a.
Directors	
Number of directors under Articles of Incorporation	8
Directors' terms under Articles of Incorporation (years)	1
Chairman of the board of directors	President
Number of directors	7
Number of outside directors	4
Number of independent outside directors	4
Audit & supervisory board	
Number of audit & supervisory board members under Articles of Incorporation	4
Number of members of audit & supervisory board	3
Number of outside members of audit & supervisory board	3
Number of independent outside members of audit & supervisory board	2
Other	
Number of independent officers (outside directors and outside members of audit & supervisory board)	6
Implementation of measures regarding director incentives	In place
Eligibility for stock options	Inside and outside directors and members of audit & supervisory board, employees
Disclosure of directors' compensation	None
Policy on determining amount of compensation and calculation methodology	In place
Takeover defenses	None

Source: Shared Research based on company data

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