COMPANY RESEARCH AND ANALYSIS REPORT

Carna Biosciences, Inc.

4572

TSE JASDAQ Growth

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Summary

Aiming for IND applications (notification of clinical trials) for two BTK inhibitors in the first half of 2019

Carna Biosciences, Inc. <4572> (hereafter, also “the Company”) is a bio-venture company that conducts drug discovery and drug discovery support businesses focused on the functions of kinase, which are intracellular signaling substances. In its Drug Discovery and Development business, it is developing kinase inhibitors for cancers and for diseases with high unmet medical needs. In May 2016, it licensed-out the CDC7 kinase inhibitor, a cancer drug candidate, to ProNAi Therapeutics, Inc. (currently, Sierra Oncology, Inc.; hereafter, Sierra) and concluded a global licensing agreement with it.

1. Advancing the stages of the two BTK inhibitors to preclinical trials

As a topic for FY12/17, within its pipeline the Company has advanced the stages of 2 non-covalent BTK inhibitors to the preclinical trials stage. For the first, AS-871, which it is developing for autoimmune-inflammatory disorders such as rheumatism, it has started preclinical trials in Europe in preparation for the submission of an Investigational New Drug (IND) application (notification of the start of clinical trials). Its features include high kinase selectivity and a low risk of side effects. Rheumatism therapeutic agents on the market include the antibody pharmaceutical Adalimumab, and also the small molecule compound Tofacitinib (JAK inhibitor), and the market scale is large, at ¥2tn. However, as there are disadvantages with existing drugs, such as drug prices and sides effects, there is a need for the development of a safer and more highly effective therapeutic agent, so it is expected that AS-871 will be licensed-out if its development progresses smoothly. The second compound is CB-1763, which is being developed for blood cancer. The Company has also started preclinical trials for it in Europe and is progressing preparations toward an IND application in the first half of 2019. In terms of its features, in addition to having high kinase selectivity and a low risk of side effects, it is expected to be effective even for patients who have developed resistance to its forerunner drug, the BTK inhibitor Ibrutinib, and it will attract attention in the future as a next generation BTK inhibitor. Worldwide sales of Ibrutinib in FY16 exceeded ¥240 billion. Both development compounds can be seen as candidates to become blockbuster drugs, so we will be paying attention to development trends in the future.

2. Overview of the FY12/17 results

In the FY12/17 consolidated results, net sales decreased 19.0% year-on-year (YoY) to ¥657mn and the operating loss was ¥699mn (a loss of ¥423mn in the previous fiscal year). In the Drug Discovery and Development business, the upfront licensing agreement payment of ¥98mn that was recorded in the previous fiscal year was not recorded, while in the Drug Discovery Support business also, net sales fell 7.7% due to the decline in Japan sales. In costs, R&D expenses increased ¥157mn, mainly following the start of the AS-871 preclinical trials, which was a factor behind the higher operating loss.

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3. Outlook for the FY12/18 results

The outlook for FY12/18 is for net sales to increase 81.1% YoY to ¥1,190mn and an operating loss of ¥679mn. In the Drug Discovery Support business, the forecast is for sales to increase 14.2% from the higher sales to North America. For FY12/18, milestone income of ¥440mn is expected on the start of clinical trials of CDC7 kinase inhibitor, which is licensed-out to Sierra. The reason why the operating loss will remain at the same level as the previous fiscal year, despite the higher sales, is that for the two BTK inhibitors that have entered preclinical trials, the Company will conduct upfront investment in R&D, including for preclinical trials based on Good Laboratory Practice (GLP) standards toward IND applications in the first half of 2019. R&D expenses are expected to increase ¥343mn to ¥1,014mn.

4. Procuring funds for clinical trials costs through the exercising subscription rights to shares and borrowing

For its development pipeline, the Company has shown that its policy is to conduct development in-house up to the Phase IIa clinical trials and then license-out the compound to pharmaceutical companies after increasing its market value. Of course, it is possible that the value of a development compound is evaluated and it is licensed-out at a prior stage. But at the current time, it is forecasting that it will continue to invest in R&D on a scale of ¥1bn a year, including on development costs toward clinical trials. The Drug Discovery Support business is expected to earn profits in a range of ¥100mn to ¥200mn a year, but if the Company does not receive upfront licensing agreement payments and milestone income alongside the licensing-out, it is highly possible that it will continue to record an operating loss. Therefore, in July 2017, the Company issued subscription rights from a third party allocation, and announced its policy to procure funds through the exercising of these rights. If all the rights are exercised, it can procure about ¥2.3bn (share dilution ratio, 15.0%. It had procured ¥287mn by January 2018). The Company also borrowed ¥300mn from a bank in January 2018. As of the end of December 2017, cash and deposits were ¥1,856mn, which it will allocate to the financing of its current business activities.

Key Points

- Conducts the Drug Discovery and Development business and the Drug Discovery Support business focused on the functions of kinase
- Advancing the development of BTK inhibitors for rheumatism and blood cancer
- Conducting upfront investment in FY12/18 to accelerate preclinical trials and to build a structure to implement clinical trials in-house

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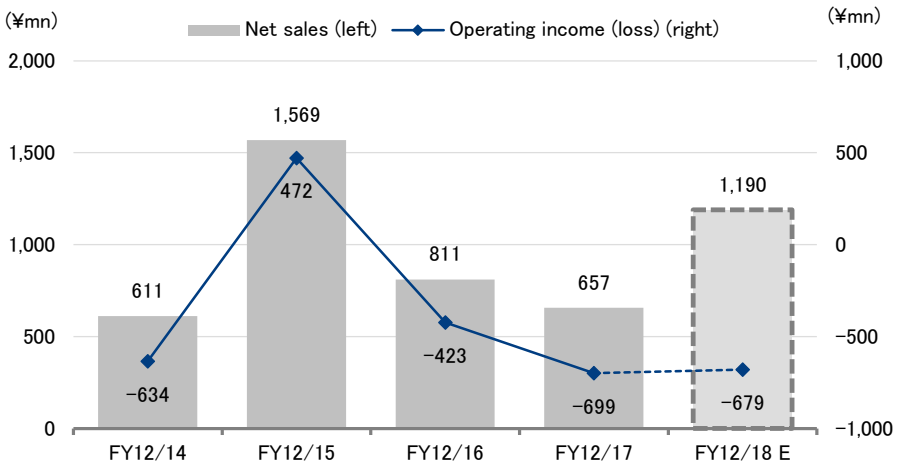
Summary

Results trend



Source: Prepared by FISCO from the Company's financial results

Company profile

Conducts the Drug Discovery and Development business and the Drug Discovery Support business focused on the function of kinase

1. Company history

The Company was established in Kobe, Hyogo Prefecture, in April 2003, by way of spin-off of the pharmaceutical research facility of Dutch pharmaceutical major Organon's Japanese entity Nippon Organon K.K., and it aimed to develop a drug discovery support business and a drug discovery and development business specializing in kinase.

It established its corporate headquarters and laboratory in April 2003 in the Kobe International Business Center (KIBC) in Kobe City. In 2004, it set up a laboratory for animal testing in the Kobe Business Support Center for Biomedical Research Activities and commenced animal testing. In March 2008, it listed its shares on the JASDAQ NEO (currently JASDAQ Growth) exchange, and the following month, it established a sales subsidiary, CarnaBio USA, Inc., as its first overseas base. Since 2010, it has focused in earnest on drug-discovery research, and in June 2015, in a first for the Company, it concluded a licensing agreement for a pipeline compound with Janssen Biotech, one of US-based Johnson & Johnson's pharmaceutical divisions, but in August 2016, this agreement was ended for strategic reasons at Janssen Biotech. Also, in February 2016, within the incubation laboratory of J&J Innovation in south San Francisco, the United States, it opened the research facility CarnaBio C-Lab. This facility is located within a cluster of biotech research facilities and therefore offers several advantages, including for constructing a network of many bio-venture researchers and obtaining the latest technologies and information. The joint research with EpiBiome, Inc., which was begun in January 2017, was one of the achievements. Furthermore, in May 2016, it concluded a worldwide exclusive licensing agreement with Sierra for the CDC7 kinase inhibitor.

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History

Date	Major event
April 2003	Established in Kobe, Hyogo Prefecture, with the spin-off of Nippon Organon K.K., aimed at developing a drug discovery support business and a drug discovery and development business specializing in kinase
October 2003	Commenced operations in the Kobe International Business Center
August 2004	Established a new facility at the Kobe Business Support Center for Biomedical Research Activities and commenced animal testing
October 2007	Established a new chemical testing facility at the Kobe Healthcare Industry Development Center
March 2008	Listed on the JASDAQ NEO exchange (currently JASDAQ Growth)
April 2008	Established CarnaBio USA, Inc., in the US
December 2008	Integrated its headquarters and research facility, shifting to the Kobe Business Support Center for Biomedical Research Activities
October 2013	Made ProbeX K.K. a fully-owned subsidiary by way of simplified share swap
June 2015	Concluded an exclusive global licensing agreement with Janssen Biotech of the US for BTK inhibitors created by the Company (Agreement ended in August 2016)
February 2016	Opened CarnaBio C-Lab as its U.S. research facility
May 2016	Concluded a global, exclusive licensing agreement with U.S. ProNAi Therapeutics, Inc. for its CDC7 kinase inhibitor

Source: Prepared by FISCO from Company materials

Kinase inhibitors is an oral medicine that can be developed as therapeutic agents with few side effects

2. The characteristics of kinase inhibitors

While on the one hand anti-cancer and other medications in use up to the present time are effective treatments, on the other hand they have serious side effects that place a considerable mental and physical burden on the patient. In contrast, molecular targeted drugs*, of which kinase inhibitors are a leading example, selectively inhibit the functions of the specific molecules that are functioning abnormally within the body, so they have the advantage that compared to conventional treatments, their therapeutic effects are high but they have few side effects. The first time a kinase inhibitor was approved for manufacturing and marketing was in 2001, when the FDA in the United States approved Imatinib (trade name: Glivecm, manufacturer and distributor: Novartis International AG <NVS>)as a treatment for chronic myelogenous leukemia. Subsequently also, more than 30 types of kinase inhibitor have been approved as therapeutic agents for various cancers, while in 2012, Tofacitinib (trade name: Xeljanz, manufacturer and distributor: Pfizer Inc. <PFE>) was approved as a rheumatoid arthritis therapeutic agent. In such ways, the conditions they are indicated for are spreading, and as one of the representative molecular targeted therapeutic agents, currently R&D is being actively conducted into them around the world, including in major pharmaceutical companies and research facilities.

* Drugs with therapeutic effects from inhibiting the functions of specific molecules that cause a disease.

Among them, Ibrutinib (trade name: Imbruvica, manufacture and distributor: Janssen Pharmaceuticals Inc.), which was approved for the first time in 2013 as a BTK inhibitor, has a high therapeutic effect for blood cancer, and it has achieved considerable success, such as an estimated sales scale of ¥800bn at its peak. So BTK inhibitors are also an extremely attractive target in the licensing market. For these BTK inhibitors, the Company is current progressing two compounds to preclinical trials.

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In the field of molecular targeted drugs, other than into kinase inhibitors (small molecule compounds) R&D is also being actively conducted into antibody drugs (high molecule compounds). But on examining the differences between kinase inhibitors and antibody drugs, we find that antibody drugs are biopharmaceuticals and require large-scale cell culturing facilities for their production, so their medication costs are extremely high and moreover they must be administered at a hospital by injection, so arguably they place a considerable burden on the patient. In contrast, kinase inhibitor drugs are small molecule compounds, and apart from being able to keep medication costs low by allowing mass production through chemosynthesis, their characteristics include that because they are oral medicines, they may be prescribed for home use, so the patient does not have to visit the hospital and the physical burden placed on them is light.

Its strengths are its expertise in screening and profiling, and its high quality kinase production technologies

3. The drug discovery research process

In the drug discovery research process for kinase inhibitors, first, the specific target kinase for the disease in question on which drug discovery research will be undertaken is determined. Then there is selection from a screening process for hit compounds that function to inhibit this specific kinase function. Then several types of compounds that are likely drug candidates are selected from amongst the hit compounds and, based on this, similar compounds are further synthesized to optimize the molecular structure to realize enhanced selectivity and reduced side effects. For example, if the target kinase A is functioning abnormally, a compound that inhibits only A is important to develop a drug with few side effects. This is because if a different kind of kinase is inhibited, other normal functions will not work and these changes in the body will be manifested as side effects. The testing to determine which kinase functions that a developed compound inhibits and which it does not is called “profiling.” After this sort of research process is completed, drug candidate compounds to proceed to the preclinical trials are identified from the compounds that have been optimized.

In the research process for a series of kinase inhibitor drugs, what is important is the evaluation system for drugs used in screening and profiling (called “assays”). This is because if the quality of the kinase used in the assays, the precision of the measuring system, or the ability to duplicate results are not high, it will be difficult to select a drug candidate compound, and also the research efficiency will be lowered. The Company’s strengths are its expertise in screening, profiling, and also its production technologies for high quality kinase.

As of the end of December 2017, the Company possessed 367 varieties of kinase and 446 products, making it a world leader in terms of number of kinases produced. By way of reference, it is said that 518 varieties of kinase exist in human cells and thus the Company covers approximately 70% of them. The functions that most of the remaining 30% perform in the body are not clear, so the product lineup of kinase that has drug candidates is already substantial. Competitors that undertake kinase production and screening services include Thermo Fisher Scientific Inc. of the United States and Merck Millipore of Germany.

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Its business model is to earn drug discovery development costs from Drug Discovery Support business and to achieve major results from licensing-out

4. Business description

As well as the parent company, the Group is comprised of two consolidated subsidiaries (CarnaBio USA, Inc. and ProbeX K.K.) and has two business segments, the Drug Discovery Support business and the Drug Discovery and Development business. The Company's fundamental technologies consist of its assays kinase expertise, including on kinase production technologies, profiling, screening and other technologies required in kinase inhibitor research, and its ability to construct a library of original compounds with kinase inhibitory activity. The Company obtains stable income from the Drug Discovery Support business utilizing its fundamental drug discovery technologies, while conducts the Drug Discovery and Development business with the funds gained. Its business model aims to achieve high growth and returns by licensing out the drugs which are discovered in the Drug Discovery and Development business.

(1) Drug Discovery and Development business

This business is based on the Company's fundamental drug discovery technologies relating to kinase inhibitors. It can search efficiently for drug candidate compounds by utilizing its technologies for manufacturing high quality kinase and its advanced profiling and screening technologies. In addition, it has a fully-fledged chemical synthesis laboratory in-house and can optimize compounds at any time, which is a factor differentiating it from its competitors. All the drugs in the Company's drug discovery pipeline have been created either independently by the Company or through joint-research with academia or other organizations, and they are highly original. It not only possesses a library of unique compounds with kinase inhibitory activity that it has created up to the present time, it also has the human resources and facilities in place to evaluate in-vitro and in-vivo and has completed the main investment to construct the research system. Following its business expansion, the Company is planning to change its laboratory layout in FY12/18. Going forward, it will invest in building a structure to implement clinical trials in-house.

In terms of the business model, the Company conducts R&D in-house up to clinical trials Phase IIa, licenses-out drug candidate compounds that are considered promising, receives upfront licensing agreement payments and milestone income in return for the licensing out, and obtains royalty income after the market launch. Up to the present time, it has licensed-out compounds in the preclinical trial stage to pharmaceutical companies and other organizations, but going forward it is aiming to maximize the value of licensing-out in the development pipeline by conducting development in-house up to the clinical trials stage to confirm the compound's efficacy and safety in humans, and then licensing it out.

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The Company selects unmet medical needs (where innovative treatment methods haven't been established) as the core of its drug discovery research themes, undertaking research into cancer and inflammatory immunological diseases as key disorder areas and building pipelines in both the first-in-class*1 and best-in-class programs*2. Drugs with sales on a scale of over ¥100bn are referred to as blockbusters, and the Company's R&Ds are conducted in its drug discovery pipeline towards the goal of producing drugs that can become blockbusters for the Company.

*1 Within the therapeutic agents for a certain condition, it refers to an original pharmaceutical that has new targets and mechanisms of action, and which significantly changes the conventional system of treatment (an innovative new pharmaceutical).
*2 Within the therapeutic agents for a certain condition, it refers to a pharmaceutical, which although it does not have a novel mechanism of action, has a clear advantage over other existing drugs by giving new value to the existing targets and mechanisms of action.

(2) Drug Discovery Support business

This business involves the sale and provision of products and services to pharmaceutical companies, universities and other research facilities to support the drug discovery research they are engaged in. The products it sells are kinase proteins used in kinase inhibitor drug discovery research and assay kits*1, while its services include carrying out screening and profiling of the compounds that form the foundation of drugs produced by pharmaceutical companies and other organizations, developing assay kits from specific requests by customers, and cell-based assay services developed by the Company or the companies it collaborates with. Amidst the advances in kinase inhibitor research, cell-based assay services meet customer needs for lower costs and faster evaluation of compounds at a cellular level. Further, its subsidiary ProbeX, undertakes R&D and provides stable cell lines based on complementary split luciferase assay technology*2. Most of the sales in this business segment are from kinase proteins and screening and profiling services. The main customers for these services are ONO PHARMACEUTICAL CO., LTD. <4528> in Japan and Gilead Sciences, Inc. in the United States.

*1 Assay is the generic term for measurement testing and refers to checking how much a test compound inhibits or doesn't inhibit a target kinase function (measurement of kinase activity), with the kinase required for testing, the buffering solution, and the other necessary elements being sold as a kit.
*2 Complementary split luciferase assay technology refers to a technique of utilizing a phenomenon whereby the luciferase (an enzyme present in the body of light-emitting organisms, such as fireflies) DNA sequence is divided into two at an appropriate juncture, and each of these pieces is introduced into a cell to produce luciferase protein fragments within the cell that do not exist in the natural world. When these protein fragments become physically close within the cell, even though they are divided, light emission is restored.

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Advancing the BTK inhibitors to preclinical trials

Advancing the development of BTK inhibitors for rheumatism and blood cancer

Within its development pipeline, in 2017 the Company advanced the stages of two non-covalent BTK inhibitors (AS-871 and CB-1763) to preclinical trials. In 2018, it is progressing preparations for each toward their clinical trials, and it seems that it wants to submit the IND applications in the first half of 2019. As both are candidates to become blockbusters, we will be paying attention to the development trends in the future. Non-covalent refers to a type in which after the molecules of the drug bind to a molecule, such as to BTK, the bonded molecules of the drug separate from each other over time. In addition to Ibrutinib, currently most of the other BTK inhibitors being developed are covalent drugs that do not separate once bonded, and if the Company succeeds in developing non-covalent BTK inhibitors, it will be able to differentiate its products from its competitors in terms of functions, which can be expected to raise their market values.

1. AS-871

The Company is developing AS-871 for immune-inflammatory disorders (including rheumatism). Its characteristics include that it is non-covalent, has high kinase selectivity, and a low risk of side effects. It has demonstrated excellent therapeutic effects for arthritis in a mouse model, and it has been confirmed that it is also effective in a model for systemic lupus erythematosus*, which has been designated as an intractable disease.

* It is a disease that produces various autoantibodies due to some cause, and as a result, causes systemic inflammatory organ damage. It is considered to be the most intractable disease among the autoimmune diseases.

Looking at the kinase selectivity profile published by the Company, we see that while Ibrutinib inhibits many kinase, AS-871 inhibits only two types of kinase other than BTK, so its risk of side effects is overwhelmingly lower. Ibrutinib, which has strong side effects, is not used as a rheumatism therapeutic agent.

Also, in the test using the arthritic mouse model, the arthritis score remained high even after the administration to the vehicle group, but the score decreased in the group administered AS-871, and a result was obtained in which the score was reduced to less than half that of the vehicle group. Although there is no data comparing it to existing drugs, according to CRO that conducted the test, it was evaluated as having extremely high medical efficacy. There are several types of therapeutic agent for rheumatism on the market, such as HUMRIA, which is an antibody pharmaceutical, and Tofacitinib (JAK inhibitor, manufacturer and distributor: Pfizer) which is a small molecule therapeutic agent. As the drug prices of antibody pharmaceuticals are high and it is necessary for the patient to go to the hospital once or twice a month to be administered it by injection, a problem is they place a significant economic and physical burden on the patient. Conversely, because Tofacitinib has high medical efficacy but also strong side effects, it is currently only used for patients for which antibody pharmaceuticals, such as HUMIRA, are not effective. Therefore, there is the need for the development of a safe, small molecule therapeutic agent. As the global market for therapeutic agents for rheumatism and other immune-inflammatory disorders is on a scale of around ¥2tn, if the development of AS-871 is a success, it may grow to be a blockbuster.

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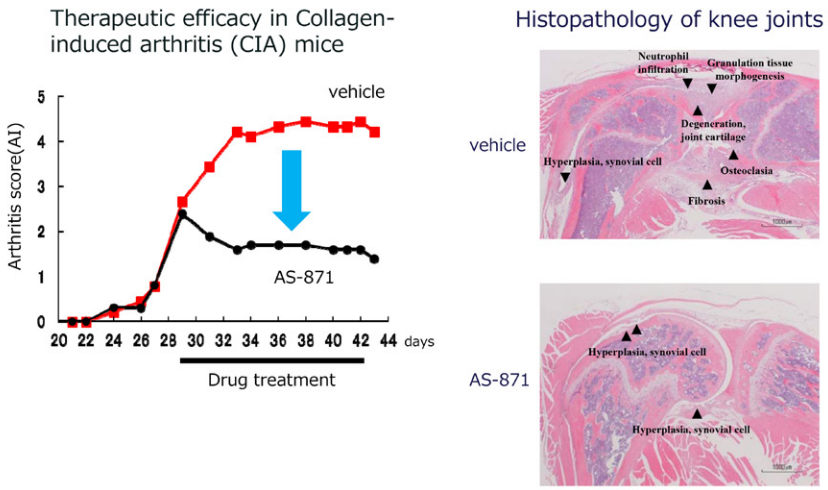
Advancing the BTK inhibitors to preclinical trials

AS-871, a non-covalent BTK inhibitor



Source: Company's results briefing materials

The Company started preclinical trials in Europe from FY12/17 Q2, and it plans to implement GLP toxicity tests and other tests toward clinical trials in FY12/18, and to submit the IND application in the first half of 2019. Also, it is considered highly possible that it will conduct the Phase 1 clinical trials in the United States. This is because there are many licensing out candidates in the United States, and moreover its market is huge.

2. CB-1763

CB-1763 is being developed for blood cancer. Its characteristics include that it is non-covalent, that it has high kinase selectivity so a low risk of side effects, that it has shown strong inhibitory activity against Ibrutinib-resistant BTK (C481S-mutant BTK), and that its strong anti-tumor effects have been confirmed in a lymphoma model.

BTK inhibitor portfolio

CB-1763

Development undergoing targeting cancer

- Small molecule BTK inhibitor
- Non-covalent/reversible
- High kinase selectivity
- Inhibits both BTK wild type and ibrutinib resistant BTK C481 mutants
- Displayed strong anti-tumor effects in lymphoma model
- Preclinical development undergoing with IND submission targeted in the first half of 2019
- Potential applications for autoimmune diseases

Source: Company's results briefing materials

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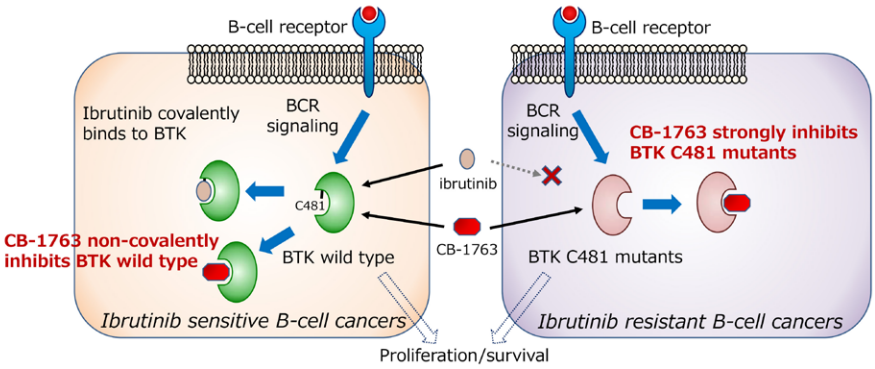
Advancing the BTK inhibitors to preclinical trials

As a blood cancer therapeutic agent, Ibrutinib is already on the market as a BTK inhibitor, but recent clinical studies have reported that in some patients to who Ibrutinib is continuously administered, BTK mutates and becomes resistance to Ibrutinib, reducing its therapeutic effect. Ibrutinib covalently binds to the wild-type BTK and inhibits its functions, but due to some cause, BTK mutates (C481-mutant BTK) and becomes resistant to Ibrutinib, weakening its inhibitory effects and resulting in the proliferation of blood cancer cells. CB-1763, which is being developed by the Company, is non-covalent and it has been confirmed that it has strong inhibitory effects against both the wild-type and the C481-mutant BTK. In terms of kinase selectivity also, it affects much fewer types of kinase than Ibrutinib, so the risk of side effects is assumed to be low. In these ways, CB-1763 has several advantages over existing drugs, which is why it is attracting attention as a next generation BTK inhibitor.

CB-1763: Next Generation BTK Inhibitor

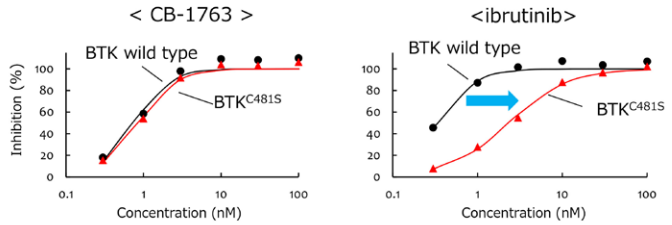
CB-1763 is a next generation non-covalent BTK inhibitor, designed to inhibit both BTK wild type and BTK C481 mutants in a highly selective and reversible manner.



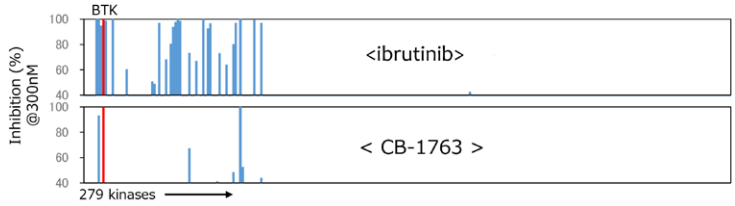
Source: Company's results briefing materials

CB-1763 retains potency for BTK mutant

- CB1763 inhibits both WT and C481S mutant BTK enzymes



- CB-1763 is a highly selective inhibitor



Source: Company's results briefing materials

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Advancing the BTK inhibitors to preclinical trials

Blood cancer therapeutic agents include Rituximab (trade name: Rituxan, developer: Biogen Inc.), which is an antibody pharmaceutical that in 2016 had sales on the scale of approximately ¥800bn, and the BTK inhibitor Ibrutinib, which had sales of around ¥240bn. As CB-1763 has strong inhibitory effects even against Ibrutinib-resistant BTK, if its development is successful, it may become a blockbuster.

Furthermore, it has been confirmed that CB-1763 is also effective against rheumatism, and it is a compound for which the diseases it is indicated for are expected to expand in the future. The Company began preclinical trials in Europe in January 2018, and in 2018 it will decide on the drug substance (the final version of the compound) and establish the manufacturing process and implement the synthesizing on the scale of Kg toward submitting the IND application in the first half of 2019. The same as for AS-871, it is highly possible that the clinical trials will be conducted in the United States.

The Company's policy for both compounds is to advance their development in-house up to the Phase IIa clinical trial, with the aim of licensing them out after increasing their market values. But it is also possible that it will not wait to license them out, if it finds a partner with suitable conditions.

Results trend

The operating loss increased slightly in FY12/17, including due to higher R&D expenses

1. Overview of the FY12/17 results

In the FY12/17 consolidated results, net sales decreased 19.0% YoY to ¥657mn, operating loss was ¥699mn (compared to operating loss of ¥423mn in the previous fiscal year), ordinary loss was ¥711mn (ordinary loss of ¥440mn), and loss attributable to owners of parent was ¥737mn (loss of ¥289mn).

FY12/17 consolidated results

(¥mn)

	FY12/16 results	FY12/17		
		Company target	Results	YoY change
Net sales	811	701	657	-154
Gross profit	557	-	435	-122
SG&A expenses	981	-	1,134	+152
(R&D expenses)	513	-	670	+157
Operating income (loss)	-423	-727	-699	-275
Ordinary income (loss)	-440	-738	-711	-270
Extraordinary income	151	-	-21	-173
Profit (loss) attributable to owners of parent	-289	-766	-737	-447

Note: Company targets are the values announced in November 2017
Source: Prepared by FISCO from the Company's financial results

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Net sales declined ¥154mn YoY. This was mainly because an upfront licensing agreement payment of ¥98mn, which was recorded for the CDC7 kinase inhibitor in the Drug Discovery and Development business in the previous fiscal year, was not recorded, and also due to the effects of the lower sales to Japan in the Drug Discovery Support business. In costs, R&D expenses increased ¥157mn, mainly for the costs toward the start of the preclinical trials for the two BTK inhibitors. As a result of these factors, the operating loss increased ¥275mn. The Company also recorded extraordinary income in the previous fiscal year of ¥177mn as a gain on the sale on investment securities, so loss attributable to owners of parent increased ¥447mn.

2. Trends by business segment

(1) Drug Discovery and Development business

In the Drug Discovery and Development business, the Company initially forecast milestone income (US$4mn) on the start of the clinical trials of the CDC7 kinase inhibitor* (Sierra development number: SRA141), which it licensed-out to Sierra in 2016. But it did not record this amount as the start of the clinical trials was pushed-back until 2018. On the other hand, the operating loss increased from ¥616mn in the previous fiscal year to ¥841mn due to the rise in R&D expenses.

> * The mechanism of the CDC7 kinase inhibitor is that in the chromosome cycle, such as DNA replication, which is important in cell division, by inhibiting the CDC7 kinase that is deeply involved in its regulation, it destabilizes the genome in cancer cells and kills these cells. Since normally functioning cells are not affected, the risk of side effects is thought to be low. Sierra is focusing on developing a drug that will inhibit the kinase involved in DDR.

The CDC7 kinase inhibitor seems to have therapeutic effects for many cancers, but according to the results of the tests of SRA141's anti-tumor activity published by Sierra on February 27 of this year, SRA141 strongly inhibited tumor growth in rats in the tumor-bearing models of blood cancer (MV4-11) and colorectal cancer (colo-205). Some of the rats were even completely cured in the blood cancer model, while in the colorectal cancer model also, it was reported that tumor regression was observed in more than half of the cases. Based on these results, Sierra plans to submit the IND application in the second half of 2018 and proceed to the Phase 1/2 trials for colorectal cancer patients. Against the backdrop of its indication for colorectal cancer in Phase 1/2, it seems that the Company analyzed the development situation for the forerunner drugs from Sierra (Takeda Pharmaceutical Company Limited <4502>: currently in Phase II clinical trials, Eli Lilly: currently in Phase I clinical trials) and strategically decided on a development policy. Sierra has temporarily slowed down the development of SRA141, and the strategy is considered to be in accordance with this decision. In the agreement with Sierra, it seems that the total amount of milestone income that the Company will receive alongside the progress made in the CDC7 kinase inhibitor program is US$270mn, while after its market launch, it will receive a percentage of net sales with a royalty rate of somewhere from 5% to 9%.

In terms of the topics for FY12/17, in Q1 the Company concluded a joint research agreement with EpiBiome.

In Q2, the Company concluded a joint research agreement with Professor Yutaka Kawakami of the Keio University School of Medicine, who is a leading figure in Japan in the field of immunotherapy research, with the aim of establishing a new cancer immunotherapy. Within the situation of the attention being focused on cancer immunotherapy, the aim is to develop a new immunity checkpoint modulator drug.

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(2) Drug Discovery Support business

In the Drug Discovery Support business, net sales decreased 7.7% YoY to ¥657mn and operating income declined 25.6% to ¥142mn. Breaking down net sales, sales to Japan decreased 15.8% to ¥352mn, to North America increased 5.4% to ¥210mn, to Europe declined 9.2% to ¥65mn, and to other regions rose 31.7% to ¥29mn. The reasons for the decline in sales to Japan were that sales to its main customer of ONO PHARMACEUTICAL fell from ¥194mn in the previous fiscal period to ¥144mn, including from the effects of it keeping down R&D expenses, although sales to other companies trended strongly. Sales to North America increased YoY mainly due to the rise in sales of the cell-based assay services. Sales to Europe declined, as although kinase proteins and profiling services performed well, orders that were scheduled to be recorded in December were pushed back. When excluding the effects of this, sales to Europe would have been basically unchanged YoY. Sales to other regions mainly grew for China and South Korea. While the scale is still small, it would seem that the drug discovery and development of kinase inhibitors has become active in China also.

In FY12/17, the Company aimed to acquire orders for large assay kits (about ¥100mn / kit) for the lipid kinase DGK (Diacylglycerol kinase; only the Company in the world sells all 10 activated types), but it was unable to acquire orders during the period. A factor seems to be that in the last one or two years, the management strategies of the mega-pharmas and the leading biotech ventures has been changing. Specifically, as development costs for drug discovery have been constantly increasing, it has become difficult to improve results, and therefore they are changing to a strategy of incorporating biotech ventures with promising pipelines into their groups through M&A, rather than starting from the basic research. Due to this change of management strategy, companies have become cautious in their decisions on research investment, and it would seem that this has had a considerable effect.

However, there has been no change to the high level of attention being paid to DGK in the field of small molecule cancer immunotherapy. This is because DGK's involvement has been clarified in the functions of the killer T cells that attack cancer cells. Specifically, it is understood that two types of kinase, called DGKα and DGKζ, play the role of transmitting a signal that puts the killer T cells to sleep. Therefore, if a drug inhibits the actions of DGKα and DGKζ, the killer T cells would be activated and their ability to attack the cancer cells restored. In therapies using checkpoint inhibitors, such as Opdivo, therapeutic effects are only seen in around 30% of melanoma and other cancer patients, but it is estimated that this is because these are patients whose whole body immune system has declined or even if their immune system is functioning, their killer T cells are not fully active. It is known that killer T cells do not function sufficiently because of the actions of DGKα and DGKζ, so it is expected that the therapeutic effects of cancer immunity checkpoint inhibitors will be further increased if a candidate compound that targets DGKα and DGKζ is developed.

Since DGK's substrate is lipid, it is not soluble in water, so it is extremely difficult to construct and handle an assay system. Even if you simply purchase the DGK protein, it is highly likely that it will take considerable time to construct the assay system. Therefore currently, the Company is promoting the sales of the assay kits that it has already developed. Presently, evaluation on a small scale is underway at customers, and it is aiming to acquire orders for large contracts during 2018.

In terms of the other topics for FY12/17, from Q3 the Company started a profiling service for a microbiome (bacterial flora) held by EpiBiome of the United States, which is its joint research partner. In addition, from Q4 it started sales in Japan of an assay kit for the kinase of AssayQuant Technologies, Inc., which is a venture company that has received an exclusive technology license from MIT of the United States. Further, to protect its intellectual property, the Company registered patents for the CDC7 kinase inhibitor in Japan, Australia, and Mexico, and also for the TNIK inhibitor in Japan, the United States and China, and for the BTK inhibitors in Japan, the United States, South Korea, and Australia.

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Its policy is to procure funds for the upfront investment for R&D, including clinical trials costs, through the exercising subscription rights to shares from third party allocations.

3. Financial position and management indicators

Looking at the financial condition at the end of FY12/17, total assets were ¥2,190mn, a decrease of ¥375mn from the end of the previous fiscal year. This was mainly due to the declines in cash and deposits of ¥304mn, accounts receivable-trade of ¥30mn, and property, plant and equipment of ¥14mn.

Total liabilities were ¥812mn, a decreased of ¥14mn from the end of the previous fiscal year. While interest-bearing debt decreased ¥73mn, accounts payable-other and income taxes payable increased ¥47mn and ¥14mn, respectively. Also, net assets were ¥1,377mn, a decrease of ¥361mn from the end of the previous fiscal year. Capital stock and capital surplus increased ¥367mn following the issue of shares from the exercising subscription rights to shares, but retained earnings declined ¥737mn due to the recording of loss attributable to owners of parent.

Looking at the financial indicators, in the indicators of stability, the shareholders' equity ratio fell from 67.6% in the previous fiscal year to 62.2%, while the interest-bearing debt ratio rose from 27.2% to 28.5%. The main factor was the reduction in cash and deposits following the increase in business costs, including R&D expenses. The Company expects that in the future, the development costs for clinical trials for its development compounds will increase, and therefore in July 2017, it issued subscription rights to shares by a third party allocation to procure the funds for these clinical trials. If all the rights are exercised, it will be able to procure funds of around ¥2.3bn. In terms of the specific uses of the funds, it anticipates that ¥1,000mn will be used for the preclinical trials of the development compounds and ¥500mn for the Phase 1 clinical trials, while it plans to use the remaining amount to advance the production and licensing-in of new pipeline compounds. As of the end of January 2018, it had procured funds of ¥287mn. In addition, in January 2018, it borrowed ¥300mn from a bank, and for the time being it will finance its development costs through these funds.

Consolidated balance sheet

(¥mn)

	FY12/14	FY12/15	FY12/16	FY12/17	Change
Current assets	907	1,995	2,492	2,134	-358
(cash and deposits)	626	1,624	2,161	1,856	-304
Non-current assets	313	341	73	56	-17
Total assets	1,221	2,337	2,566	2,190	-375
Total liabilities	391	467	826	812	-14
(interest-bearing debt)	160	213	697	624	-73
Total net assets	830	1,870	1,739	1,377	-361
(stability)					
Shareholders' equity ratio	67.2%	79.7%	67.6%	62.2%	-5.4pt
Interest-bearing debt ratio	13.2%	9.1%	27.2%	28.5%	+1.3pt

Source: Prepared by FISCO from the Company's financial results

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The status of 16th and 17th series subscription rights to shares and the specific uses of the funds procured

Issue no.	Exercise status
16th series	Number of dilutive shares, 930,000; number of shares exercised, 226000 (exercise rate, 24.3%); funds procured, ¥287mn Cumulative number of shares exercised, 226,000 (exercise rate 24.3%); funds procured, ¥287mn
17th series	Number of dilutive shares: 465,000; none exercised
Exercise period	July 11, 2017, to July 10, 2019
Lower limit exercise price	¥1,022
Estimated amount to be procured	¥2,373mn

Source: Prepared by FISCO from the Company materials

Specific uses	Amount	Scheduled expenditure period
Preclinical trials for development compounds	¥1,000mn	January 2018 to December 2019
Clinical trials for development compounds (Phase 1)	¥500mn	January 2019 to December 2020
Production and licensing-in of new pipeline compounds	¥873mn	January 2018 to December 2020

Source: Prepared by FISCO from the Company materials

Business outlook

Conducting upfront investment in FY12/18 to accelerate the preclinical and clinical trials

1. Outlook for the FY12/18 results

The forecasts are for net sales to increase 81.1% YoY to ¥1,190mn, operating loss of ¥679mn (compared to a loss of ¥699mn in FY12/17), ordinary loss of ¥694mn (a loss of ¥711mn), and loss attributable to owners of parent of ¥758mn (a loss of ¥737mn).

Looking at the breakdown of net sales, they are set to recover in the Drug Discovery Support business, increasing 14.2% YoY to ¥750mn, while in the Drug Discovery and Development business, milestone income of ¥440mn from Sierra is expected. The reason why the operating loss will be about the same as FY12/17, despite the major increase in net sales, is that the Company plans to increase ¥343mn in R&D expenses to ¥1,014mn, mainly for the costs of the AS-871 and CB-1763 preclinical trials. In addition, it plans to recruit more employees in order strengthen the R&D structure and is also forecasting around ¥50mn as the costs of changing the laboratory layout. The outlook for R&D expenses is that they will continue to be around ¥1bn in FY12/19 also.

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Business outlook

Outlook for FY12/18 consolidated results

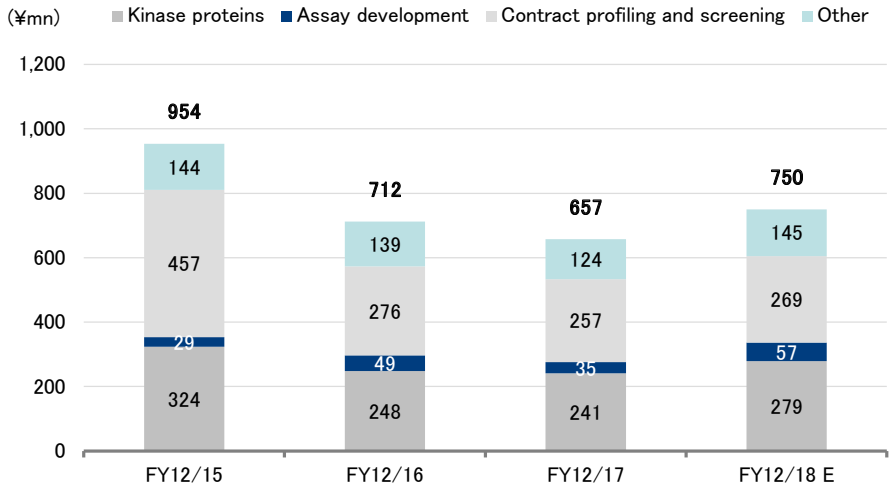
(¥mn)

	FY12/17 results	FY12/18		Factors
		Company target	YoY change	
Net sales	657	1,190	+532	
Drug Discovery Support business	657	750	+92	Increase in sales to the United States
Drug Discovery and Development business	-	440	+440	Milestone income from Sierra
Operating income (loss)	-699	-679	+20	
Drug Discovery Support business	142	150	+7	
Drug Discovery and Development business	-841	-829	+12	Increase in R&D expenses
Ordinary income (loss)	-711	-694	+17	
Profit (loss) attributable to owners of parent	-737	-758	-20	Impairment loss due to capital investment
R&D expenses	670	1,014	+343	Upfront investment for the preclinical development of AS-871 and CB-1763
Capital investment	18	63	+45	R&D equipment etc.
Exchange rate (¥ / US dollar)	112.17	110.00		

Source: Prepared by FISCO from the Company materials

In the Drug Discovery Support business, the outlook for net sales by region is that sales to Japan will increase ¥14mn YoY to ¥366mn, to North America will rise ¥50mn to ¥260mn, to Europe will grow ¥15mn to ¥80mn, and to other regions will increase ¥14mn to ¥43mn. In particular, sales are expected to grow to North America due to strategic customer visits. By main product, the forecasts are for sales of kinase proteins to increase ¥38mn to ¥279mn, of profiling and screening to rise ¥12mn to ¥269mn, and of assay development services to grow ¥22mn to ¥57mn. The results forecasts would seem to be highly achievable, as they do not incorporate the acquisition of large orders of DGK assay kits.

Drug Discovery Support business net sales



Source: Prepared by FISCO from the Company materials

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2. Status of the other compounds in the development pipeline

As previously described, within the Company's development pipeline, AS-871 and CB-1763 have entered preclinical trials, and the aim is for them to enter clinical trials from 2019 and onwards. It is also advancing the development of several other pipeline compounds targeting kinase.

Pipeline Status

Compound	Target Kinase	Indication	Lead generation	Lead optimization	Candidate selection	Preclinical trials	Clinical trials	New drug application –launch
SRA-141 (AS-141)	CDC7	Cancer					Licensed-out to Sierra Oncology, Inc.	
NCB-0846	Wnt-signal (TNIK)	Cancer						
AS-871	BTK	Autoimmune Diseases				advanced		
CB-1763	BTK	Blood Cancer Immuno-Oncology				advanced		
NCB-0594	Wnt-signal (TNIK)	Cancer Immuno-Oncology						
Small Molecule	TGFβ signaling	Blood Cancer Immuno-Oncology						
	Kinase	Autoimmune Diseases		advanced				
	N/A	Malaria						
	Kinase	Neurodegenerative disease						
	DGK	Immuno-Oncology	new					

Source: Prepared by FISCO from the Company's results briefing material

(1) Wnt-signal (TNIK) inhibitor

For the Wnt-signal inhibitor that targets cancer stem cells, the Company is conducting R&D into two types of compounds, NCB-0846 and NCB-0594, in collaboration with the National Research and Development Agency's National Cancer Center Japan.

It is expected to be indicated for colorectal cancer. This is because mutations in the Wnt-signal gene have been found in over 90% of cases of colorectal cancer, and it is considered that the cancer stem cells are activated by the constant activation of the Wnt-signal transmission pathway, which causes the cancer to recur. It has been clarified that the TNIK kinase is a substance that is deeply involved in this activation of the Wnt-signal pathway and that suppressing the activity of this kinase also suppresses the expression of colorectal cancer stem cells. Therefore, it is expected to be a therapeutic agent that will lead to a cure for colorectal cancer in the future, but a problem has emerged during its development.

This is the point that even if the cancer stems cells die, the cancer cells surrounding them will continue to grow larger, so it is difficult to verify if killing the stem cells has a life-prolonging effect. At the present time, it is difficult to confirm the life-prolonging effect in animal models, since human cancer stem cells do not die if they are inserted into mice. In such ways, there are many problems that must be addressed for the Wnt-signal inhibitor, as it is a first-in -class program and completely new. But the Company intends to steadily conduct R&D for it, including establishing an evaluation method that can confirm the above-described drug efficacy in humans.

The difference between NCB-0846 and NCB-0594 is that because NCB-0846 simultaneously inhibits multiple kinases, it has the effect of killing both cancer cells and cancer stem cells, but NCB-0594 selectively inhibits the Wnt-signal, so it has the effect of killing only cancer stem cells.

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(2) TGFβ signaling inhibitor

The Company has been conducting joint research with Hiroshima University since 2015 on the TGFβ signing inhibitor targeting chronic myelogenous leukemia cancer stem cells. They are currently optimizing the compounds and it seems it may still take some time to progress to preclinical trials. Methods of treating leukemia include chemotherapy using anti-cancer drugs and hematopoietic stem cell transplants, but a problem with both is their severe side effects that place a considerable burden on the patient, which contrasts with molecular targeted drugs, including the kinase inhibitor Imatinib and Ibrutinib that each have sales on a scale of hundreds of billions of yen. However, both are drugs for suppressing the proliferation of leukemia cells, and do not kill the leukemia stem cells. In contrast, the TGFβ signaling inhibitor being developed by the Company is intended to be a curative therapy that will kill the leukemic stem cells, and if its development is successful, it may become a blockbuster. Therefore, the Company's policy is to advance the development in-house up to the Phase IIa clinical trial, and then to license-out the compound after confirming its efficacy and safety in humans.

(3) Neurodegenerative disease therapeutic agents

For kinase inhibitors targeting neurodegenerative diseases, the Company is currently optimizing compounds as therapeutic agents for Alzheimer's disease and Parkinson's disease, and going forward, it plans to select the preclinical candidate compounds. It seems that the Company can form compounds that have strong inhibitory effects on the targeted kinase at the cellular level, so in the future, it will progress the selection of the compounds while confirming the compound has the same effects in-vivo (in the brain). However, as it takes time and costs to breed animals suitable for Alzheimer's research and to confirm effects, for the future it is considering schemes that will start with joint research with pharmaceutical companies and that will lead to licensing agreements.

It is considered that many of the biochemical causes of Alzheimer's disease and Parkinson's disease remain unknown, but the current common treatment methods are to use multiple therapeutic agents to supplement dopamine, a neurotransmitter in the brain responsible for body movement, and to inhibit dopamine degradation. The kinase inhibitor for which the Company is progressing R&D is a drug which, based on the tau hypothesis, inhibits the accumulation of phosphorylated tau proteins and suppresses nerve necrosis.

(4) Others

In terms of the other themes, as well as the new addition of the small molecule compound with DGK as the target kinase, attention is also focusing on the additions of the blood cancer BTK inhibitor (CB-1763), the Wnt-signal inhibitor (NCB-0594), and the TGFβ signaling inhibitor program indicated for "cancer immunity." Cancer immunity is a field in which many pharmaceutical companies are currently working, based on the clinical effects of PD-1 antibodies, such as Nivolumab. In 2017, the Company started joint research with Professor Yutaka Kawakami of the Keio University School of Medicine, who is a leading researcher in the field of cancer immunotherapy, and progress in the R&D in this field is expected in the future.

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Shareholder returns policy

For the time being is allocating funds to R&D investment

The Company is a drug discovery venture currently in the R&D stage and it continues to have negative retained earnings carried forward, so it does not currently pay a dividend. Going forward, for the time being its policy is to allocate funds as a priority to drug discovery and to investment in R&D into fundamental drug discovery technologies, and thereby to work to strengthen its management foundations and enhance corporate value. In terms of returning profits to shareholders, it will consider paying a dividend at the stage when it becomes possible to do so in the future upon considering its business results and financial condition.

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