Carna Biosciences, Inc.

4572
TSE JASDAQ Growth

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FISCO Ltd. Analyst
Yuzuru Sato
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Summary

Aiming to start clinical trials for two blockbuster candidates from the second half of 2019 to 2020

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, mainly for diseases with high unmet medical needs such as cancers and autoimmune diseases. 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. Trends in the development pipeline

Preclinical trials are being progressed for the Company’s two BTK inhibitor drugs, which are the main candidates in the development pipeline, aiming to start the phase I clinical trials sometime in 2019 and 2020. For AS-0871, which is being developed for autoimmune diseases such as rheumatism, it is aiming to apply for Clinical Trial Authorization (CTA; a clinical trial protocol notification) in Europe in 2019 and also to start the phase I clinical trial within the year. 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 ¥6tn* in 2017. Therefore, the competition to develop them is also intense. But AS-0871 had advantages, including high kinase selectivity and a low risk of side effects, and if the results of the clinical trials are good, it is highly likely to be licensed-out.

* Source: Evaluate Ltd., EvaluatePharma @ World Preview 2018, Outlook to 2024

Also, for AS-1763, which is being developed for blood cancer, the Company is aiming to submit the Investigational New Drug (IND) application for clinical trial plan notifications in the United States during 2019 and to start the clinical trials in 2020. The strengths of AS-1763 are high kinase selectivity and a low risk of side effects, and it can also be expected to be effective even for patients who have developed resistance to its forerunner drug, the BTK inhibitor Ibrutinib. If it demonstrates superior safety and efficacy, it may be designated a breakthrough therapy* and the possibility that it will be licensed-out can be expected to further increase. Ibrutinib is a large-scale therapeutic drug that is forecast to achieve sales of ¥800bn at its peak, and if the development of AS-1763 is a success, the Company can expect similar growth potential.

* Breakthrough therapies is a system of the FDA in the United States aimed at promoting the development and review of drugs indicated for life-threatening diseases. Upon receiving the designation from the FDA, it is possible to shorten the time until approval by a priority review, and in some cases, the application for marketing approval can be made even at the stage of completion of the phase II clinical trial. To be designated a breakthrough therapy, preliminary clinical evidence is needed that shows significant improvements in clinically important evaluation items compared to existing therapies.
2. Overview of the FY12/18 results

In the FY12/18 consolidated results, net sales increased 14.8% year-on-year (YoY) to ¥754mn and the operating loss was ¥1,144mn (a loss of ¥699mn in the previous fiscal year). In the Drug Discovery and Development business, the Company concluded an agreement with Sumitomo Dainippon Pharma Co., Ltd. <4506> for the joint research, development, and commercialization of a kinase inhibitor for psychiatry and neurology disease, and it recorded ¥50mn as an upfront licensing agreement payment. The Drug Discovery Support business also performed well, including achieving record high sales for overseas. Conversely, in expenses, R&D expenses increased ¥469mn YoY, which was the main reason for the higher operating loss.

3. Outlook for the FY12/19 results

The outlook for FY12/19 is for net sales to increase 64.3% YoY to ¥1,240mn, as milestone income of US$4mn is expected from Sierra and the Drug Discovery Support business will continue to expand. However, the operating loss is forecast to be ¥1,658mn, further increasing on the previous fiscal year, due to the rise in R&D expenses, mainly for the clinical development of the BTK inhibitor drugs. At the end of FY12/18, cash and deposits were ¥1,355mn, and although there remains one part of the unexercised portion of the subscription rights to shares, it is thought that going forward also, new financing will be needed as the development stages continue.

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 inhibitor drugs for rheumatism and blood cancer
- In FY12/19, expects milestone income from Sierra, while in the US, will progress system construction toward the start of the clinical trials

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 functions 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. Furthermore, in May 2016, it concluded a worldwide exclusive licensing agreement with US-based Sierra for the CDC7 kinase inhibitor developed by the Company.

As an overseas business development, the Company opened the research facility CarnaBio C-Lab within the incubation laboratory of J&J Innovation in South San Francisco in the United States in February 2016. It conducted fundamental research aiming to develop new drug discovery technologies, while incorporating cutting-edge technologies and information. As it had achieved a certain level of results, this facility was closed at the end of January 2019. But in February of the same year, an office was opened in South San Francisco City toward advancing clinical development.

* It succeeded in developing a screening system able to discover BRAF inhibitors with few side effects, and the research results were published in the international scientific journal Scientific Reports (January 24, 2019).

<table>
<thead>
<tr>
<th>Date</th>
<th>Major event</th>
</tr>
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<tbody>
<tr>
<td>April 2003</td>
<td>Established in Kobe, Hyogo Prefecture, with the spin-off of Nippon Organon K.K., aimed at developing a drug discovery support businesses and a drug discovery and development business specializing in kinase</td>
</tr>
<tr>
<td>October 2003</td>
<td>Commenced operations in the Kobe International Business Center</td>
</tr>
<tr>
<td>August 2004</td>
<td>Established a new facility at the Kobe Business Support Center for Biomedical Research Activities and commenced animal testing</td>
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<tr>
<td>October 2007</td>
<td>Established a new chemical testing facility at the Kobe Healthcare Industry Development Center</td>
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<tr>
<td>March 2008</td>
<td>Listed on the JASDAQ NEO exchange (currently JASDAQ Growth)</td>
</tr>
<tr>
<td>April 2008</td>
<td>Established CarnaBio USA, Inc., in the US</td>
</tr>
<tr>
<td>December 2008</td>
<td>Integrated its headquarters and research facility, shifting to the Kobe Business Support Center for Biomedical Research Activities</td>
</tr>
<tr>
<td>October 2013</td>
<td>Made ProbeX K.K., a fully-owned subsidiary by way of simplified share swap</td>
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<tr>
<td>June 2015</td>
<td>Concluded an exclusive global licensing agreement with Janssen Biotech of the US for BTK inhibitors created by the Company (Agreement ended in August 2016)</td>
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<tr>
<td>February 2016</td>
<td>Opened CarnaBio C-Lab as its U.S. research facility</td>
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<tr>
<td>May 2016</td>
<td>Concluded a global, exclusive licensing agreement with U.S. Sierra Oncology, Inc. for its CDC7 kinase inhibitor</td>
</tr>
<tr>
<td>March 2018</td>
<td>Concluded an agreement with Sunットomo Dainippon Pharma for joint research to discover new kinase inhibitors for psychiatry and neurology disease, and for their subsequent development and commercialization.</td>
</tr>
<tr>
<td>February 2019</td>
<td>Opened an office in South San Francisco, the United States, for clinical development</td>
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Source: Prepared by FISCO from the Company materials

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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: Gleevec, 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 currently progressing two compounds to preclinical trials.

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 2018, the Company possessed 369 varieties of kinase and 450 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 practically comprehensive. Competitors that undertake kinase production and screening services include Thermo Fisher Scientific Inc. of the United States and Reaction Biology Corporation of the United States.

In the Drug Discovery Support business, its business model is to conduct drug discovery and development using the income gained and then to achieve major results from licensing-out these drugs.

4. Business description

As well as the parent company, the Group is comprised of one consolidated subsidiary (CarnaBio USA, Inc.) 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. Also, in FY12/18, it established the Clinical Development Department in the R&D Headquarters, and started building a system to conduct in-house clinical trials. Currently, the system consists of two people in each of the head office and newly opened office in the United States, but it intends to increase a little more its human resources with expertise in clinical development.

As the management policy for the Drug Discovery and Development business, the Company is building pipelines for both first-in-class*1 and best-in-class*2 through selection, mainly for diseases with strong unmet medical needs for which a revolutionary treatment method has not yet been established, and a research system with a small number of highly skilled researchers, particularly focusing on cancer and autoimmune diseases as the priority areas. In addition, except for one part of the pipeline, 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. It also strategically licenses-out one part of the pipeline at an earlier stage, of the preclinical trials stage.

*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 evaluation of compounds at a cellular level. The Company conducted an absorption merger of ProbeX in the spring of 2018 in order to improve management efficiency. ProbeX was a subsidiary that conducted R&D and provided stable cell lines based on complementary split luciferase assay technology*2.

*1 Assay is the generic term for measurement testing and refers to checking how much a test compound inhibits or does not 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.
Company profile

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 for overseas, Gilead Sciences, Inc., in the United States.

Trends in the development pipeline

Advancing the development of BTK inhibitor drugs for rheumatism and blood cancer

1. The BTK inhibitor drug development schedule

Within the Company’s development pipeline, two non-covalent* BTK inhibitor drugs (AS-0871 and AS-1763) that are attracting attention are expected to enter into clinical trials sometime from the second half of 2019 to the first half of 2020. The plan for AS-0871, which is being developed indicated for autoimmune diseases (rheumatism, etc.), is to complete the preclinical trials being implemented in Europe in FY12/19, submit the CTA application, and start the phase I clinical trial in Europe within the year. Conversely, the aim for AS-1763, which is being developed indicated for blood cancer, is to finish the preclinical trials being implemented in Europe in 2019, submit the IND application in the United States, and start the clinical trials from 2020 onwards.

* Non-covalent refers to a type in which after the molecules of the drug bind to the targeted molecule, such as to BTK, the bonded drug molecules separate 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.

The reason that the Company is implementing all of the preclinical trials in Europe is that it is the Japanese corporation of Organon N.V., which is a major Dutch pharmaceutical company from which the Company originates that has a network of human resources to which the preclinical trials can be outsourced. However, the location of the AS-1763 clinical trials will be in the United States, because the Company itself has in place a structure to progress clinical development in the United States. Conversely, for AS-0871 in Europe, it will outsource it to a CRO (contract research organization).

The Company does not seem to have any particular targets for the licensing-out periods, and if the economic conditions are meet, it may conclude agreements at any time.

2. Pipeline Status

(1) AS-0871: BTK Inhibitor (Indication: Autoimmune diseases)

The Company is developing AS-0871 for autoimmune diseases (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.
Trends in the development pipeline

Looking at the kinase selectivity profile published by the Company, AS-0871 has only two types of kinase that it inhibits other than BTK, and therefore the risk of side effects is overwhelmingly low. Also, in the results of 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-0871 to less than half that of the vehicle group.

AS-0871, a non-covalent BTK inhibitor

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 autoimmune diseases is on a scale of around ¥6tn and development competition is fierce, but if the development of AS-0871 is a success, it may grow to be a blockbuster.

(2) AS-1763: BTK Inhibitor (Code changed from CB-1763) (Indication: Blood cancer)

AS-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, and the indication can be extended to autoimmune diseases.
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 resistant 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. AS-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. Moreover, in animal experiments, it was clarified that it has a tumor proliferation inhibitory effect. Lymphoma cells (OCI-Ly10 cells), which is one type of human blood cancer, were transplanted into mice, and the sizes of the tumors in the group to which AS-1763 was not administered were about 5 times bigger after 23 days, whereas they were only around twice as big in the group to which AS-1763 was administered. Currently, several BTK inhibitors are undergoing clinical trials, but on looking only at the experiment data, the Company evaluates AS-1763 to be the best-in-class. From the above, attention is focusing on it as the leading candidate to be a next generation BTK inhibitor.

**AS-1763: Next Generation BTK Inhibitor**

- **AS-1763 inhibits both WT and C481S mutant BTK enzymes**

  ![Graph showing inhibition of BTK wild type and C481S mutant](image)

- **AS-1763 is a highly selective inhibitor**

  ![Graph showing inhibition of 279 kinases](image)

Blood cancer therapeutic agents include Rituximab (trade name: Rituxan, developer: Biogen Inc.), which is an antibody pharmaceutical that in 2017 had sales on the scale of approximately ¥800bn, and the BTK inhibitor Ibrutinib, which had sales of around ¥350bn. As AS-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 AS-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.
(3) Wnt-signal (TNIK) inhibitor (Indication: Colorectal cancer)

For the Wnt-signal inhibitor that targets cancer stem cells, the Company is conducting R&D 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 stem 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 conduct R&D for it, including establishing an evaluation method that can confirm the above-described drug efficacy in humans.

Since previously the Company has been developing two types of compounds, NCB-0846 and NCB-0594. But the problem for both compounds, of the difficulty of dissolving them in water, has not been solved, and the situation is that it they have once again been redone to proceed from the optimization of the compounds.

(4) Kinase Inhibitor (Indication: Psychiatry & neurology disease)

In March 2018, the Company concluded a joint research, development, and commercialization agreement with Sumitomo Dainippon Pharma for a kinase inhibitor for psychiatry and neurology diseases, and currently the joint research is being progressed. They are aiming to develop groundbreaking new kinase inhibitors in the psychiatry and neurology field through combining the Company's expertise in discovering and producing kinase inhibitors and Sumitomo Dainippon Pharma drug discovery research expertise in the psychiatry and neurology field. Based on this agreement, in FY12/18 the Company recorded an upfront licensing agreement payment of ¥50mn, and it will also record research milestone income of ¥30mn at the stage of deciding on the candidate compound to use in the preclinical trials.

For the kinase inhibitors to be developed, Sumitomo Dainippon Pharma will conduct the clinical development and be granted the worldwide exclusive sales rights for all indications except in the cancer field. In the future, in the event of deciding to shift to clinical development and sales, the Company will receive a maximum, total amount of ¥10.6bn as development and sales milestone income in accordance with the development stage and the extent to which the sales targets were achieved. After the market launch also, it will receive a certain percentage of royalty income according to the sales amount.

(5) TGFβ signaling inhibitor (Indication: Blood cancer)

The Company has been conducting joint research with Hiroshima University since 2015 on the TGFβ signaling inhibitor targeting chronic myelogenous leukemia cancer stem cells. They are currently at the stage of optimizing the compounds, but if they make steady progress in narrowing down the compounds, it is possible they will proceed to preclinical trials during 2019.
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. Imatinib and Ibrutinib, which are molecular targeted drugs, have been launched and each has 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 TGF$\beta$ 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 drug. Therefore, the Company intends to advance to the preclinical trial stage as soon as possible, progress the clinical development in-house, and then license it out after confirming its safety and efficacy in humans.

**Trends in the development pipeline**

In terms of other candidates in the pipeline, the newly added small molecule compound with DGK as the target kinase will attract attention going forward. This is because DGK kinase’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 DGK$\alpha$ and DGK$\zeta$, play the role of transmitting a signal that puts the killer T cells to sleep. Therefore, if a drug inhibits the actions of DGK$\alpha$ and DGK$\zeta$, the killer T cells would be activated and their ability to attack the cancer cells restored. In therapies using checkpoint inhibitors, 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 DGK$\alpha$ and DGK$\zeta$, so it is expected that the therapeutic effects of cancer immunity checkpoint inhibitors will be further increased if a candidate compound that targets DGK$\alpha$ and DGK$\zeta$ is developed.

In addition, the fact that AS-1763 for blood cancer and the Wnt-signal inhibitor and TGF$\beta$ signaling inhibitor have been newly added to the indication of “cancer immunotherapy” will attract attention. Recently in the cancer treatment fields, the use of checkpoint inhibitors has started to spread, and because the companies developing checkpoint inhibitors are also conducting joint development of promising drugs for combination therapy, there have been cases where major agreements have been concluded. In March 2018, Eisai <4523> concluded a joint development agreement with Merck of the United States for combination therapy using the Eisai anti-cancer drug Lenvima (lenvatinib), and the Merck Keytruda (pembrolizumab), and it could receive approximately ¥611bn from Merck in upfront licensing agreement payments and development and sales milestone payments. Going forward, the Company is also expected to progress development with an eye on opportunities such as combination therapy with checkpoint inhibitors.

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<th>Compound</th>
<th>Target Kinase</th>
<th>Indication</th>
<th>Discovery</th>
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<td>DGK/ASK</td>
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<td></td>
<td>Immunotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small Molecule</td>
<td>Wnt-signal</td>
<td>Cancer</td>
<td>Immunology-Onco</td>
<td>Joint research with the National Cancer Center-Japan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Frizzled</td>
<td>Psychiatry &amp; neurology</td>
<td>Concluded a joint research and development agreement with Symbio, Ophthome Pharma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGF$\beta$ signaling</td>
<td>Frizzled</td>
<td>Autoimmune Diseases</td>
<td>Joint research with Hosein University</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frizzled</td>
<td>Autoimmune Diseases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N/A</td>
<td>Malaria</td>
<td></td>
<td>Joint research with the Kitasato Institute for Life Sciences, Kitasato University</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DGK</td>
<td>Immunology-Onco</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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Results trends

The operating loss increased in FY12/18 due to upfront investment in R&D

1. Overview of the FY12/18 results

In the FY12/18 consolidated results, net sales increased 14.8% YoY to ¥754mn, the operating loss was ¥1,144mn (compared to a loss of ¥699mn in the previous fiscal year), the ordinary loss was ¥1,159mn (a loss of ¥711mn), and the loss attributable to owners of parent was ¥1,210mn (a loss of ¥737mn). Net sales increased by double digits, as in the Drug Discovery and Development business, ¥50mn was recorded as an upfront licensing agreement payment from Sumitomo Dainippon Pharma, and also as results in the Drug Discovery Support business trended favorably, particularly for overseas. The main reason for the higher operating loss was that R&D expenses increased ¥469mn, mainly for the preclinical trial expenses for the two BTK inhibitors.

<table>
<thead>
<tr>
<th>FY12/18 consolidated results</th>
<th>FY12/18</th>
<th>FY12/17</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Revised target</td>
<td>Results</td>
</tr>
<tr>
<td>Net sales</td>
<td>657</td>
<td>754</td>
</tr>
<tr>
<td>Gross profit</td>
<td>435</td>
<td>503</td>
</tr>
<tr>
<td>SG&amp;A expenses</td>
<td>1,134</td>
<td>1,648</td>
</tr>
<tr>
<td>(R&amp;D expenses)</td>
<td>1,136</td>
<td>1,140</td>
</tr>
<tr>
<td>Operating income (loss)</td>
<td>-1,136</td>
<td>-1,144</td>
</tr>
<tr>
<td>Ordinary income (loss)</td>
<td>-711</td>
<td>-1,152</td>
</tr>
<tr>
<td>Profit (loss) attributable to owners of parent</td>
<td>-737</td>
<td>-1,204</td>
</tr>
</tbody>
</table>

Note: Revised targets are the value announced in December 2018
Source: Prepared by FISCO from the Company’s financial results and results briefing materials

(1) Drug Discovery and Development business
At the beginning of FY12/18, the Company expected US$4mn milestone income in the Drug Discovery and Development business, alongside the start of the clinical trials of the CDC7 kinase inhibitor* licensed-out to Sierra (Sierra’s development code: SRA141). As the completion of the IND application was in 3Q, and the timing of the dosing of the first patient, which is a milestone condition, has been shifted to 2019, so in the same way the milestone income has been shifted to FY12/19. Therefore, the only sales recorded in FY12/18 was the upfront licensing agreement payment from Sumitomo Dainippon Pharma of ¥50mn (no sales were recorded in the previous fiscal year). Conversely, the operating loss rose from ¥841mn in the previous fiscal year to ¥1,261mn due to the increase 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.
Sierra will be advancing Phase I/II clinical trials of SRA141, which is indicated for colorectal cancer. Sierra presented the results of the preclinical trials at an international cancer research and therapies conference held in November 2018, and reported that SRA141 selectively and strongly inhibits CDC7. Currently, two companies are ahead in terms of conducting CDC7 kinase inhibitor clinical trials (Takeda Pharmaceutical Company Limited <4502> is conducting a phase II clinical trial and Eli Lilly and Company <LLY> is conducting a phase I clinical trial). But according to Sierra’s analysis, SRA141 has superior efficacy to Eli Lilly’s development compound, and while it has a similar laboratory level of efficacy as Takeda Pharmaceutical’s development compound, it is evaluated as having superior kinase selectivity (meaning a lower risk of side effects). In the agreement with Sierra, the Company will receive total milestone income of US$270mn alongside the progress made in the CDC7 kinase inhibitor program, and after it is market launched, it will receive a high single-digit percentage of sales as the royalty rate of the sales total.

As the other topics for FY12/18, in May 2018 the Company newly concluded an agreement to conduct joint research into new drug discovery targets discovered by the National Cancer Center Japan’s research group in the cancer stem cell field. It is also steadily progressing its intellectual property strategy for the development compounds. It has registered patents for the CDC7 kinase inhibitor in Japan, Europe, and the United States, for the BTK inhibitor drug in Europe, Canada, and Singapore, and for the Wnt signal inhibitor in Europe.

(2) Drug Discovery Support business
In the Drug Discovery Support business, net sales increased 7.2% YoY to ¥704mn, for the first sales increase in three fiscal periods. But operating income declined 17.7% to ¥117mn, for the third consecutive period of decline. However, this was mainly due to the increase in R&D expenses alongside the development of new products and services.

Looking at the breakdown of net sales, sales to Japan decreased 18.1% to ¥288mn, to North America increased 18.5% to ¥249mn, to Europe rose 44.9% to ¥94mn, and to other regions grew 146.5% to ¥71mn. Sales were a new record high if looking only at for overseas. The fall in sales for Japan was from the impact of net sales to the main customer, Ono Pharmaceutical, declining from ¥144mn in the previous fiscal year to ¥90mn, and they have continuously declined since peaking in FY12/15. On the other hand, for North America, sales of profiling services grew significantly, while sales of other products and service, including kinase proteins and cell-based assay services, also performed strongly. The factors in the background to this strong performance were the expansion of the customer groups, mainly newly formed bio-ventures, and also that the development of kinase inhibitors is being actively conducted.

For Europe, sales of kinase proteins were favorable, while projects postponed from the previous fiscal period to this fiscal period also contributed to the higher sales. In addition, the switch from the previous passive sales policy to active sales proved successful. In the other regions, in China, sales of kinase proteins increased significantly, and it seems that in China also, the development of kinase inhibitors has become more active.

As the topics for FY12/18, the Company started a new cell-based assay service from December 2018. This service uses the NanoBRET™ technology of Promega Corporation, which is a leading company for research reagents using light-emission technologies. NanoBRET™ technology can easily measure various indicators, such as how the compound acts on the targeted kinase, or the kinase’s selectively and affinity, and it is able to effectively evaluate compounds. The number of measurable kinase started from 47 types, and the plan is to increase this number in the future. Inquiries are already rising and higher sales are expected from FY12/19 onwards.
Investigating new financing to allocate to upfront investment in R&D

2. Financial position and management indicators

Looking at the financial position at the end of FY12/18, total assets were down ¥420mn on the end of the previous fiscal year to ¥1,770mn. This was mainly because in current assets, cash and deposits decreased ¥500mn. In non-current assets, investment and other assets increased ¥44mn.

Total liabilities were up ¥70mn on the end of the previous fiscal year to ¥882mn, primarily as interest-bearing debt increased ¥62mn. Total net assets were down ¥490mn to ¥887mn. This was mainly because although capital stock and capital surplus rose ¥730mn in total due to the issue of shares from the exercise of subscription rights to shares, retained earnings declined following the recording of a loss attributable to owners of parent of ¥1,210mn.

Looking at the financial indicators, in the indicators of stability, the shareholders’ equity ratio fell from 62.2% in the previous fiscal year in 49.7%, while the net debt total assets rose from 28.5% to 38.8%. This was mainly due to the decrease in cash and deposits alongside the increase in R&D expenses and other business expenses. The Company expects development expenses to rise in the future also toward the clinical trials of the BTK inhibitors, and therefore to raise the funds for this, it is issuing subscription rights to shares through a third-party allocation. At the end of January 2019, 590,000 shares remained as the unexercised portions of the 16th and 17th series. If that they were all exercised at the minimum exercise price of ¥1,022, the Company could raise funds of more than ¥600mn, which combined with the cash and deposits at the end of FY12/18, would become around ¥2bn. Conversely, in FY12/19, a loss attributable to owners of parent of ¥1,693mn is expected, so it is necessary to be aware of the point that it may conduct new financing in the future.
Results trends

Consolidated balance sheet

<table>
<thead>
<tr>
<th></th>
<th>FY12/14</th>
<th>FY12/15</th>
<th>FY12/16</th>
<th>FY12/17</th>
<th>FY12/18</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current assets</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(cash and deposits)</td>
<td>907</td>
<td>1,995</td>
<td>2,492</td>
<td>2,134</td>
<td>1,671</td>
<td>-462</td>
</tr>
<tr>
<td>Non-current assets</td>
<td>313</td>
<td>341</td>
<td>73</td>
<td>56</td>
<td>98</td>
<td>42</td>
</tr>
<tr>
<td>Total assets</td>
<td>1,221</td>
<td>2,337</td>
<td>2,566</td>
<td>2,190</td>
<td>1,770</td>
<td>-420</td>
</tr>
<tr>
<td>Total liabilities</td>
<td>391</td>
<td>467</td>
<td>826</td>
<td>812</td>
<td>882</td>
<td>70</td>
</tr>
<tr>
<td>(interest-bearing debt)</td>
<td>160</td>
<td>213</td>
<td>697</td>
<td>624</td>
<td>686</td>
<td>62</td>
</tr>
<tr>
<td>Total net assets</td>
<td>830</td>
<td>1,870</td>
<td>1,739</td>
<td>1,377</td>
<td>887</td>
<td>-490</td>
</tr>
</tbody>
</table>

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

The status of 16th and 17th series subscription rights to shares
(as of January 31, 2019) and the specific uses of the funds procured

<table>
<thead>
<tr>
<th>Issue no.</th>
<th>Exercise status (as of January 31, 2019)</th>
</tr>
</thead>
<tbody>
<tr>
<td>16th series</td>
<td>Number of dilutive shares, 930,000; number of shares exercised, 804,000 (exercise rate, 86.5%)</td>
</tr>
<tr>
<td>17th series</td>
<td>Number of dilutive shares: 465,000; none exercised</td>
</tr>
<tr>
<td>Exercise period</td>
<td>July 11, 2017, to July 10, 2019</td>
</tr>
<tr>
<td>Lower limit exercise price</td>
<td>¥1,022</td>
</tr>
</tbody>
</table>

Source: Prepared by FISCO from the Company materials

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

Source: Prepared by FISCO from the Company materials

In FY12/19, expects milestone income from Sierra, while in the US, will progress system construction toward the start of the clinical trials

3. The FY12/19 Company results forecasts

For the consolidated results for FY 12/19, the forecasts are for net sales to increase 64.3% YoY to ¥1,240mn, operating loss of ¥1,658mn (compared to a loss of ¥1,144mn in FY12/18), ordinary loss of ¥1,671mn (a loss of ¥1,159mn), and loss attributable to owners of parent of ¥1,693mn (a loss of ¥1,210mn).

Looking at the breakdown of net sales, in the Drug Discovery and Development business, milestone income of ¥440mn will be recorded from Sierra on the start of the phase I clinical trial, while in the Drug Discovery Support business, net sales are expected to increase 13.5% to ¥800mn from the continuing strong sales for overseas. It is anticipated that the milestone income from Sierra will be received during 2019, and the assumption for the exchange rate is ¥110 to US$1. For operating income, in the Drug Discovery and Development business, a loss of ¥1,802mn is expected (compared to a loss of ¥1,261mn in the previous fiscal year). This will mainly be due to the increase in expenses for the BTK inhibitor drugs’ preclinical trials and clinical trials. Conversely, in the Drug Discovery Support business, the outlook is for operating income to increase for the first time in four fiscal periods from the effect of the higher sales, rising 22.9% to ¥144mn. For the Company as a whole, R&D expenses are forecast to increase 76.3% to ¥2,011mn.

We encourage readers to review our complete legal statement on “Disclaimer” page.
Results trends

### Outlook for FY12/19 consolidated results

<table>
<thead>
<tr>
<th></th>
<th>FY12/18 results</th>
<th>FY12/19 Target</th>
<th>YoY change</th>
<th>Change %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Net sales</strong></td>
<td>754</td>
<td>1,240</td>
<td>485</td>
<td>64.3%</td>
</tr>
<tr>
<td>Drug Discovery Support business</td>
<td>704</td>
<td>800</td>
<td>95</td>
<td>13.5%</td>
</tr>
<tr>
<td>Drug Discovery and Development business</td>
<td>50</td>
<td>440</td>
<td>390</td>
<td>790.0%</td>
</tr>
<tr>
<td><strong>Operating income (loss)</strong></td>
<td>-1,144</td>
<td>-1,658</td>
<td>-513</td>
<td>-</td>
</tr>
<tr>
<td>Drug Discovery Support business</td>
<td>117</td>
<td>144</td>
<td>26</td>
<td>22.9%</td>
</tr>
<tr>
<td>Drug Discovery and Development business</td>
<td>-1,261</td>
<td>-1,802</td>
<td>-540</td>
<td>-</td>
</tr>
<tr>
<td><strong>Ordinary income (loss)</strong></td>
<td>-1,159</td>
<td>-1,671</td>
<td>-511</td>
<td>-</td>
</tr>
<tr>
<td><strong>Profit (loss) attributable to owners of parent</strong></td>
<td>-1,210</td>
<td>-1,693</td>
<td>-483</td>
<td>-</td>
</tr>
<tr>
<td><strong>R&amp;D expenses</strong></td>
<td>1,140</td>
<td>2,011</td>
<td>870</td>
<td>76.3%</td>
</tr>
<tr>
<td><strong>Capital investment</strong></td>
<td>58</td>
<td>43</td>
<td>-15</td>
<td>-25.9%</td>
</tr>
<tr>
<td><strong>Exchange rate (¥/US dollar)</strong></td>
<td>110.45</td>
<td>110</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

(1) Measures in the Drug Discovery and Development business

In the Drug Discovery and Development business, in February 2019 the Company opened an office for clinical development in South San Francisco, the United States, and allocated two full-time employees to it, who are advancing the preparations toward the start of clinical trials from 2020 onwards. One of the people recruited was previously the head of the clinical development department in a pharmaceutical manufacturing company, while the other had been engaged in research in the C-Lab. In the future, the CarnaBio USA will be the center of the clinical development bases, and a system is being constructed to progress new drug development.

(2) Measures in the Drug Discovery Support business

As the measures in the Drug Discovery Support business, the Company aims to achieve the further growth in sales in North America and to get the new cell-based assay service (NanoBRET™) on track. Also, an agency is to be set up in southern Europe toward expanding European sales. The overall sales target for this business is ¥800mn. The sales outlook by region is sales for Japan to increase ¥32mn YoY to ¥320mn, for North America to rise ¥51mn to ¥300mn, for Europe to grow ¥6mn to ¥100mn, and for other regions to increase ¥9mn to ¥80mn. Within Japan, in order to cover for the decline in sales to Ono Pharmaceutical, the Company intends to increase sales to other customers. For other regions, sales for China are growing quickly, doubling compared to in the previous fiscal year, and they may reach ¥100mn. As a measure to expand sales, it has started Web seminars for end customers while providing detailed explanations of products and services in Chinese, which is leading to the acquisitions of orders.

Also, in the sales forecasts by main product, sales are forecast to increase for all of them; specifically, by ¥36mn YoY to ¥351mn for kinase proteins, by ¥21mn to ¥248mn for profiling and screening, by ¥5mn to ¥32mn for assay development, and by ¥33mn to ¥169mn for cell-based assay-related and others.
### 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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