COMPANY RESEARCH AND ANALYSIS REPORT

Gene Techno Science Co.,Ltd.

4584

TSE Mothers

19-Aug.-2019

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http://www.fisco.co.jp

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https://www.g-gts.com/en/features/

Summary

Increasing medium- to long-term growth potential by strengthening in the cell therapy field using stem cells from human exfoliated deciduous teeth

Gene Techno Science Co., Ltd. <4584> (hereafter, also “the Company”) is a drug discovery bioventure spun out from Hokkaido University. As a specialist in biologics, in the field of biosimilars, it was the first company in Japan to be approved by the Ministry of Health, Labour and Welfare under its biosimilar guidelines to manufacture and sell a Filgrastim* biosimilars. In 2016, it became a group company of Noritsu Koki Co., Ltd. <7744>, but through a subsequent share exchange, it became an equity method affiliate. Following on from the biosimilars business and the new biologics business, it concluded a capital and business partnership agreement with Japan Regenerative Medicine Co., Ltd., to launch a new biotech business and entered-into the cell therapy field. In April 2019, it made a subsidiary of Advanced Cell Technology and Engineering Ltd. (ACTE), a company developing cell therapy products using stem cells from human exfoliated deciduous teeth.

* A granulocyte growth factor drug product (G-CSF). Following chemotherapy (dosages of anti-cancer agents), white blood cells decrease and immunity is weakened (called neutropenia), causing various symptoms, and filgrastim is used to treat this. The innovator drug is Gran by Kyowa Kirin Co., Ltd. <4151>.

1. Strengthening in the cell therapy field using stem cells from human exfoliated deciduous teeth

The Company is developing the new biotech business as its third business, following on from the biosimilars business and the new biologics business. In the biotech business’s core business field of cell therapy, the Company will develop stem cells from human exfoliated deciduous teeth together with its subsidiary ACTE going forward, in addition to promoting the development of cell therapy using cardiac stem cells that have been innovated together with Japan Regenerative Medicine for some time now. Compared to other mesenchymal stem cells, stem cells from human exfoliated deciduous teeth are highly able to differentiate into bone, cartilage, and nerve cells, and they have an extremely high proliferation capability, and these cells can be collected from deciduous teeth. Therefore, one of their features is that they place little burden on the donor. They are expected to be indicated for fields including for alveolar bone regeneration and conditions of the central nervous system, such as for spinal cord injuries and cerebral palsy. As the first stage, in May 2019 the Company announced that it had concluded a joint research and development agreement with ORTHOREBIRTH Co., Ltd., which develops and sells an artificial bone filling material, and the two companies will develop the therapeutic treatment for cleft lip and cleft palate*1. ACTE is also progressing joint research with several major pharmaceutical companies toward commercializing cell therapy products. Currently, it is at the stage where its business partner, Nikon CeLL innovation Co., Ltd. is constructing the clinical-use Master Cell Bank (MCB)*2, and the completion of the MCB will put in place an environment for providing clinical-grade cells. From FY3/21 to FY3/22, it is expected that multiple pipeline products will be developed, including at its partners.

*1 Cleft lip and cleft palate: a condition caused by a birth abnormality of the oral cavity. It is a congenital condition in which a tear remains when one side of the palate does not close at the time of development.
*2 The seed cells from which all cell therapy medicine products are produced are grown via the minimum number of passages under constant culture conditions, and distributed into multiple ampoules.

2. State of progress for the development pipeline

Looking at the progress made in the development pipeline, for Ranibizumab*3 biosimilars (an age-related macular degeneration therapeutic agent), which is a biosimilar in the ophthalmology field that the Company is jointly developing with Senju Pharmaceutical Co., Ltd., the final patient registration for the phase 3 clinical trial was completed in February 2019 (one-year observation period). If the results are good, it is expected that they will be able to apply for manufacturing and sales approval during 2020. The Company will also work on licensing-out overseas. For darbepoetin alfa*4 biosimilars (renal anemia therapeutic agent), the joint development partner Sanwa Kagaku Kenkyusho Co., Ltd., submitted New Drug Application in September 2018, and it is expected that sales approval will be acquired during FY3/20. The Company will earn royalty income according to sales after it is market launched. In addition, in the new biologics business, it is progressing the development of GND-004 as a pharmaceutical candidate for the ophthalmic and cancer fields. It will collect data from animal experiments during FY3/20 with the aim of licensing it out from FY3/21 onwards.

*3 A vascular endothelial growth factor inhibitor for ophthalmologic conditions. With age-related macular degeneration, neovascularization occurs in the macular region, which is the center of the retina, and the purpose of using this drug is to improve the symptoms that develop with neovascularization, such as a decrease in vision (age-related macular degeneration) due to hemorrhaging and swelling. Its forerunner drug is Novartis Pharma's Lucentis.

*4 A sustainable-type erythropoiesis stimulating factor pharmaceutical preparation. It is used to ameliorate symptoms in renal-anemia patients, from maintenance-period chronic kidney disease through to the dialysis period. Its forerunner drug is Kyowa Kirin's Nesp.

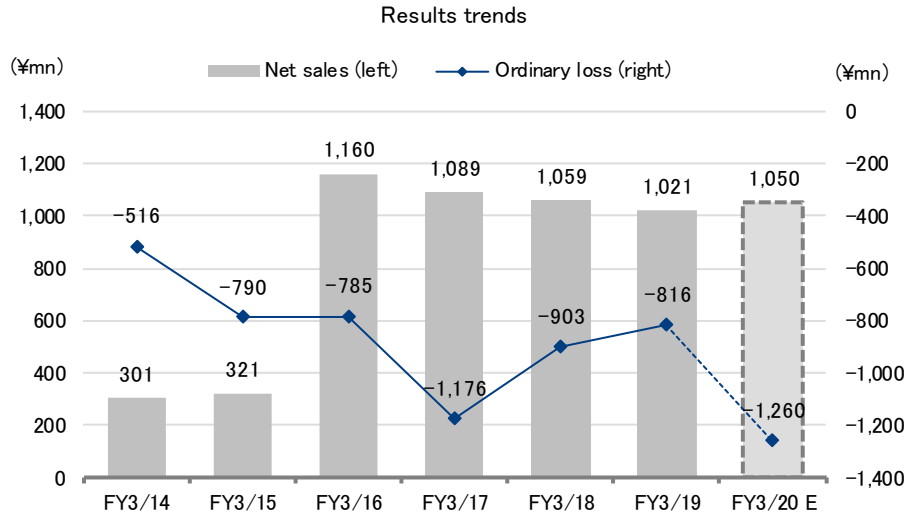
3. Results outlook

The Company is disclosing consolidated results from FY3/20 because it made ACTE a subsidiary. Compared to the previous fiscal period's stand-alone results, the forecasts are for net sales to increase 2.8% YoY to ¥1,050mn, an operating loss of ¥1,220mn (compared to a loss of ¥805mn in FY3/19), and a loss attributable to owners of parent of ¥7,260mn. In the existing businesses, sales are projected to remain at around the same level as in the previous fiscal year, so the reason for the higher net sales will be the sales from ACTE. The operating loss will rise mainly due to an increase in R&D costs, and in addition, as the Company plans for a one-time write off of ACTE's goodwill of approximately ¥6bn. Therefore, the final loss will increase significantly, but as it will be a loss without cash out, it will have no financial impact. From FY3/21 onwards, the operating loss is forecast to contract as biosimilar R&D costs will have peaked-out, and the outlook is for the Company to enter a sales-growth phase from FY3/22 onwards following the expected market launch of GBS-007 Ranibizumab biosimilars. In addition to this, through generating earnings from licensing out and other methods in the cell therapy business and the new biologics business, it is considered that the Company will become profitable from FY3/22 onwards. It will still be several more years before the cell therapy business starts generating earnings, but it can be said that its medium- to long-term growth potential has increased through it entering-into this field.

Key Points

- As its third business pillar, the Company intends to develop the cell therapy business using stem cells from human exfoliated deciduous teeth
- Has in sight market launching two biosimilars from FY3/20 onwards
- The loss will contract from FY3/21 as R&D costs will have peaked-out, and is aiming to become profitable from FY3/22 onwards

Summary



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

Company profile

A bioventure spun out from Hokkaido University that is a pioneer in biosimilar development in Japan

1. History

The Company is a bioventure that was established within Hokkaido University in 2001 with the objective of developing diagnostic and therapeutic agents based on the research of the University's Division of Molecular Interaction in the Institute for Genetic Medicine. In terms of research and development of new biologics, it licensed out the anti-integrin alpha 9 antibody to Kaken Pharmaceutical Co., Ltd. <4521> in June 2007. The Company also began developing biosimilars in order to build a stable earnings foundation. In 2007, it entered into a joint-development agreement with Fuji Pharma Co., Ltd. <4554> for a filgrastim biosimilar, and in November 2012 it became the first biosimilar product approved for manufacturing and sales under Japan's biosimilar guidelines. This product has been marketed by Fuji Pharma and Mochida Pharmaceutical Co., Ltd. <4534> since May 2013. The Company was listed on the Tokyo Stock Exchange (TSE) Mothers market in November 2012.

Whilst strengthening its biosimilar development pipeline, the Company has been actively forming partnerships with other companies for joint developments. It entered into an agreement with Sanwa Kagaku Kenkyusho for the joint development of darbepoetin alfa biosimilars in January 2014, then it concluded basic agreements for joint development and sales with Mochida Pharmaceutical in the oncology field in August 2015 and with Senju Pharmaceutical in the ophthalmology field in November of the same year, and they are progressing the joint development of each.

Also, in 2016 the Company concluded a capital and business partnership agreement with Noritsu Koki Group's Japan Regenerative Medicine, which conducts development in the cell therapy field. Then in April 2019, it made a wholly-owned subsidiary of ACTE, which is developing cell therapy products, including by using stem cells from human exfoliated deciduous teeth, and this clarified that it intends to develop the cell therapy business to be its third business pillar.

History

Date	Major event
March 2001	Established in Sapporo with the objective of developing diagnostic and therapeutic agents based on the research of the Division of Molecular Interaction, Institute for Genetic Medicine, Hokkaido University
June 2002	As a bioventure certified by the National Institute of Advanced Industrial Science and Technology (AIST), it newly established research facilities within the Hokkaido Center of AIST and reinforced its research and development into new biologics
June 2007	Licensed-out the anti-integrin alpha 9 antibody to Kaken Pharmaceutical Co., Ltd.
October 2007	Entered into a joint-development agreement with Fuji Pharma Co., Ltd. for a filgrastim (G-CSF) biosimilar
January 2008	Licensed-in a filgrastim biosimilar cell line and basic production technology from Dong-A Pharmaceutical Co., Ltd.
November 2012	Fuji Pharma Co., Ltd. and Mochida Pharmaceutical Co., Ltd. domestically acquired manufacturing and sales approval for the filgrastim biosimilar (launch in May 2013)
November 2012	Listed on the Tokyo Stock Exchange (TSE) Mothers (market of the high-growth and emerging stocks)
August 2013	In the biosimilar business, entered into a capital and business partnership with ITOCHU CHEMICAL FRONTIER Corporation
January 2014	Entered into a joint-development agreement with Sanwa Kagaku Kenkyusho Co., Ltd., for a darbepoetin alfa biosimilar
June 2014	Entered into a nucleic-acids joint business agreement with Gene Design Inc. with the objective of commercializing a nucleic-acid pharmaceuticals platform
November 2014	Entered into a capital and business partnership with ORTHOREBIRTH Co., Ltd., which is conducting research and development on synthetic bones
August 2015	Entered into a basic agreement for a business partnership with Mochida Pharmaceutical Co., Ltd. toward the joint development and sales of a biosimilar in the anti-cancer field (concluded an agreement to launch a joint business in December 2016)
November 2015	Entered into a basic agreement for a capital and business partnership with Senju Pharmaceutical Co., Ltd. toward the joint development and sales of a biosimilar in the ophthalmology field (concluded an agreement to launch a joint business in May 2016)
March 2016	Entered into a capital and business partnership agreement with NK Relations, a group company of Noritsu Koki (became a Group subsidiary in June 2016)
October 2016	Entered into a capital and business partnership agreement with Japan Regenerative Medicine, a group company of Noritsu Koki
December 2016	Entered into a capital and business partnership agreement with JSR Corporation
February 2017	Entered into a joint R&D agreement with Juntendo University for immunological tolerance induction
March 2017	Entered into a capital and business partnership agreement with ITOCHU CHEMICAL FRONTIER Corporation for the joint development of a second biosimilar
May 2017	Together with AIN HOLDINGS Inc., and others, the Company established Minerva Medica with the aim of starting a stem cell therapy business (investment ratio, 25%)
April 2018	Entered into a capital and business partnership agreement with NanoCarrier
July 2018	Entered into a joint research agreement with chromocenter Inc., to establish a platform to develop high-yield protein producing cell lines
August 2018	Entered into a joint research agreement with SOLA Biosciences, LLC. of the United States to establish a platform to develop high-yield protein cell lines
September 2018	Started commissioned research with GPC Laboratory Co., Ltd., to establish a platform to develop high-yield protein cell lines
April 2019	Made Advanced Cell Technology and Engineering Co., Ltd., a wholly-owned subsidiary through a share exchange
May 2019	Entered into a joint R&D agreement with ORTHOREBIRTH Co., Ltd., toward creating treatments for cleft lip and cleft palate

Source: Prepared by FISCO from the securities report and press releases

As its third business pillar, the Company intends to develop the cell therapy business using stem cells from human exfoliated deciduous teeth

2. Business description

The Company announced "GTS 3.0 –Biotech Engineering Company, striving for value creation" as the target for its next stage from FY3/19. For this, it will utilize to the greatest possible extent the expertise and findings in biotechnologies that it has accumulated in its business activities up to the present time, and the stem cells from human exfoliated deciduous teeth treatment platform possessed by its new subsidiary, ACTE. In addition to the rare and intractable diseases it has dealt with in the past, it has set pediatric diseases as a priority target and it is working to develop and provide advanced treatments not only using biosimilars and new biologics, but also using cell therapy technologies.

(1) About ACTE

The Company made ACTE a wholly owned subsidiary through a share exchange in April 2019 in order to make the cell therapy business its third business pillar. ACTE is developing cell therapy products that use stem cells from human exfoliated deciduous teeth, and following its establishment in 2008, it became known as the first company in Japan to launch a dental pulp stem cells bank business. It currently has a network in Japan of approximately 2,200 dental clinics, and it provides bank services for autologous dental pulp cells and allogenic stem cells from human exfoliated deciduous teeth. It conducts a business of selling the culture supernatant that is generated when cultivating stem cells from human exfoliated deciduous teeth to customers including medical clinics and cosmetics manufacturers. In its FY5/18 results, it recorded net sales of ¥178mn and an operating loss of ¥46mn, and it has around 10 employees.

The autologous dental pulp cells bank service is a service to store teeth, such as deciduous teeth and wisdom teeth, for treatments for oneself and for one's children and family in the future, and since the launch of this service in 2009, ACTE has stored hundreds of teeth. On the other hand, in order to develop treatments that can be applied to people other than oneself, in the allogenic dental pulp cells bank service, it cultivates stem cells from human exfoliated deciduous teeth that are provided free of charge by donors, and it provides these cells to its partner companies, universities, and others for research purposes. These companies and universities are developing treatments that use stem cells from human exfoliated deciduous teeth.

Stem cells from human exfoliated deciduous teeth are stem cells produced and processed using cells called dental pulp that are present inside teeth. The features of these cells include that, compared to other mesenchymal stem cells, they are easily differentiated into bone, cartilage, and nerve cells, and that the regenerative capability of the cells collected from deciduous teeth is extremely high. According to a research paper published in the past, in an experiment using mice, they were found to have nearly three times the bone regenerative capability of mesenchymal stem cells derived from bone marrow, and there was also a difference between them of several times in terms of the amount of secretion of nerve growth factor and brain-derived neuropathic factor. Therefore, in terms of the indications of stem cells from human exfoliated deciduous teeth for cell therapy treatments, these cells are considered to be optimal for treatments in the bone regeneration and nervous system conditions fields. With regards to the cells' regenerative capability also, in the same comparison, experimental results have been reported that there is a difference of about two times for the speed of cell division and approximately three times for the cell division limit number. This means that when they are put into practical use, they will outperform other mesenchymal stem cells in terms of cost competitiveness. Furthermore, they have the advantages that the burden placed on the donor is extremely small and that they can be collected from many donors, because the cells are collected from deciduous teeth.

Utilizing these characteristics, the Company plans to progress research and development while focusing on five targets diseases and conditions; cleft lip and cleft palate, hygpoganglionosis, cerebral palsy, spinal cord injuries, and congenital albinism. There are also many pharmaceutical companies that are focusing on the potential of stem cells from human exfoliated deciduous teeth, and even before it became a subsidiary of the Company, ACTE had been conducting joint research with its partners, of DAIICHI SANKYO COMPANY, LIMITED <4568> in the central nervous system conditions field, Eisai Co., Ltd. <4523> in the neurodegenerative diseases field, and SEKISUI CHEMICAL CO.,LTD. <4204> in the periodontal diseases field.

Overview of the targeted diseases and conditions

Disease/condition name	Cleft lip and cleft palate (infant)	Intestinal aganglionosis (infant)	Cerebral palsy (infant)	Congenital albinism (infant)	Spinal cord injuries
Symptoms	Eating and speech disorders	Intestinal obstruction (22% mortality)	Quadriplegia	Visual impairment, photophobia	Loss of motor functions and sensory perception functions
Existing treatments	Lip arthroplasty + iliac bone graft	Enterectomy, colostomy	Not established	Not established	Not established
Number of patients	2,000 newborn babies/ year	100 (designated incurable disease 101)	2,000 newborn babies/ year	8,000 (designated incurable disease 164)	5,000 /year , 100,000
Treatment goal	Maxilla regeneration	Ganglion regeneration	Nerve and vascular regeneration	Pigment-cell regeneration	Nerve regeneration

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

In January 2018, the Company entered into a business partnership agreement with NIKON CORPORATION <7731> with the aim of constructing a clinical-use MCB to use for cell therapy products made from stem cells from human exfoliated deciduous teeth. Currently, Nikon's subsidiary, Nikon ceLL innovation is developing a manufacturing method for clinical-use MCB. In the future, both companies are planning to stably supply stem cells from human exfoliated deciduous teeth to research facilities, pharmaceutical companies, and others using clinical-use MCB derived from stem cells from human exfoliated deciduous teeth in compliance with GCTP/GMP*. When conducting clinical trials for cell therapy products, stem cells from human exfoliated deciduous teeth must be manufactured with a clinical-use MCB that is compliant with GCTP/GMP, so it expected that the respective projects will be progressed after the MCB is constructed. The construction of the MCB is scheduled to be completed during FY3/20.

* GCTP (Good Gene Cell & Tissue Practice; compliance criteria based on a Ministerial Ordinance on the manufacturing control and quality control standards for cell therapy products) / GMP (Good Manufacturing Practice; compliance criteria based on a Ministerial Ordinance on the standards for manufacturing control and quality control of drugs and quasi-drugs).

Other than the Company, cell therapy products using dental pulp stem cells are being developed by JCR Pharmaceuticals Co., Ltd. <4552> and TEIJIN LIMITED <3401> jointly, and by a subsidiary of AIR WATER INC. <4088>. However, ACTE is the only company that manages a dental pulp cell bank, and at the stages of promoting clinical development and commercialization in the future, for aspects such as cost competitiveness and a high patient matching rate, it can be said that a strength of the Company's Group is that it is already building a system that will enable it to procure many stem cells from human exfoliated deciduous teeth.

(2) Biosimilars

Biologics refer to pharmaceuticals that are manufactured utilizing the ability of microorganisms or cells to create specific proteins (such as hormones, enzymes, and antibodies) that are useful for pharmaceuticals. As it involves creating pharmaceuticals using the proteins that are originally present in the human body, a strength of biologics is that they are kind to the human body, and antibody pharmaceuticals, which are one type of biologics, have a lower risk of side effects as they act directly on the diseased or affected area.

General pharmaceuticals (small molecule drugs) are mass-produced by chemosynthesis on a molecular level. But in contrast, biologics utilize gene recombination technologies and cell culture techniques to synthesize microorganisms and cells in large volume, and therefore major costs must be undertaken for their development and the manufacturing facilities for their mass production. They also tend to have shorter expiry periods than small molecule drugs, leading to higher product prices.

In the same way that general pharmaceuticals have innovator drugs, which are the drugs that were developed first and then followed by generic pharmaceuticals that use the same molecules as these innovator drugs, biosimilars are the follow-on products of biologics. In the case of biosimilars, the drug efficacy and safety do not change compared to the innovator drug because the type of protein is the same as that in the innovator drug. However, the sugar chain attached to the protein is slightly different, so biosimilars are not identical to their innovator drugs. Therefore, in order to demonstrate the similarity between the innovator drug and the biosimilar, it is necessary to establish an independent manufacturing process and to accumulate physicochemical data to prove their similarity. It is also necessary to conduct clinical trials to prove the biosimilar's safety and efficacy. Approvals are given based on meeting these requirements, and therefore the R&D costs of biosimilars are much higher than those of generic pharmaceuticals.

As the drug price of biosimilars are set at around 70% of the prices of the innovator drugs, high productivity in the manufacturing process is important for the commercialization of biosimilars. In particular, there are not many companies in Japan that possess the expertise necessary to establish the required manufacturing process or to analyze the characteristics and the quality levels of the developed biosimilars. The Company specializes in biologics and biosimilars and has accumulated a track record in this field from conducting research and development for more than 10 years, establishing its position as the leading expert for the development of biologics and biosimilars in Japan.

When comparing new biologics and biosimilars, the period of time from the start of research to market launch is 16 to 17 years for a new biologic, but only 6 to 8 years for a biosimilar. In the case of a new biologic, it takes 2 to 3 years to investigate a target for new drug development (functional analysis) and 2 to 4 years to screen the drug candidate compounds. It also takes a long time from the start of the non-clinical trials to the end of the clinical trials. Therefore, the scale of the R&D costs is ¥50bn to ¥100bn for a new biologic, but only ¥5bn to ¥10bn for a biosimilar. Moreover, the probability of success, from development through to market launch, is considerably higher for a biosimilar compared to a new biologic. So for a bioventure like the Company, it can be said that the biosimilar business is a field with high development efficiency.

However, the follow-on biologics that are absolutely the same as their innovator, forerunner biologics, such as for the active ingredient, drug substance, additives, and manufacturing method (hereafter, biosames), acquired manufacturing and sales approval in Japan for the first time in 2018, and there are concerns about the impact that sales of biosames will have on biosimilars. In August 2018, Kyowa Kirin Frontier Co., Ltd., acquired manufacturing and sales approval for the darbepoetin alfa injection syringe KKF, which is a biosame of Nesp developed and sold by Kyowa Kirin <4151>, the parent company. The sale of a biosame by a subsidiary of a company that sells its forerunner product could detract from the motivation of companies to develop biosimilars, depending on the price level, and the pros and cons of this have been discussed. But for the time being, its price in June 2019 was listed as the same price level as the biosimilars (70% of the price of the forerunner product), and discussions will continue in the Central Social Insurance Medical Council, while observing conditions in the future. If the price level is the same, the Company views that it will be an environment in which it can be competitive, with few differences in terms of aspects such as effectiveness and equivalence.

Characteristics of biologics

- Biologics refers to the application of gene recombination, cell culture and other technologies and techniques, and the utilization of the ability of microorganisms or cells to create proteins for the mass production and commercialization of specific proteins (including hormones, enzymes, and antibodies) as pharmaceuticals.
- The main biologics include insulin (a diabetes therapeutic agent), interferon (a hepatitis C therapeutic agent), and adalimumab (a rheumatism and psoriasis therapeutic agent).

	Biologics	General pharmaceuticals
Size (molecular weight)	Approx. 10,000~	100~
Manufacturing method	Synthesized within microorganisms and cells	Chemosynthesis
Production	Unstable (the product can change depending on the conditions of the microorganisms and cells)	Stable

Explanation of biosimilars

- Biosimilars are pharmaceutical products that have demonstrated the equivalent efficacy and safety compared to previously approved biologics through clinical trials.

Differences between biosimilars and other generic pharmaceuticals

	Biosimilars	Other generic pharmaceuticals
Molecular structure	Large and complex	Small and simple
Efficacy and safety	Substantially the same as innovator drug (Amino acid sequence is the same, but aspects such as the molecular structure and manufacture process differ)	Same as the forerunner product (the molecular sequence and structure are the same)
Development cost and manufacturing equipment cost	High (¥20–30 billion) Innovator drug: ¥100 billion	Low (around ¥0.1 billion) Innovator drug: ¥30-¥100 billion
Price difference against innovator drug	70% of innovator drug price 60% for oral drugs when more than 10 biosimilars of a specific innovator drug are launched	60% of innovator drug price 50% for oral drugs when more than 10 generic products of a specific innovator drug are launched

Source: extracted from “Current conditions of biosimilars” by the Ministry of Health, Labour and Welfare (July, 2014)

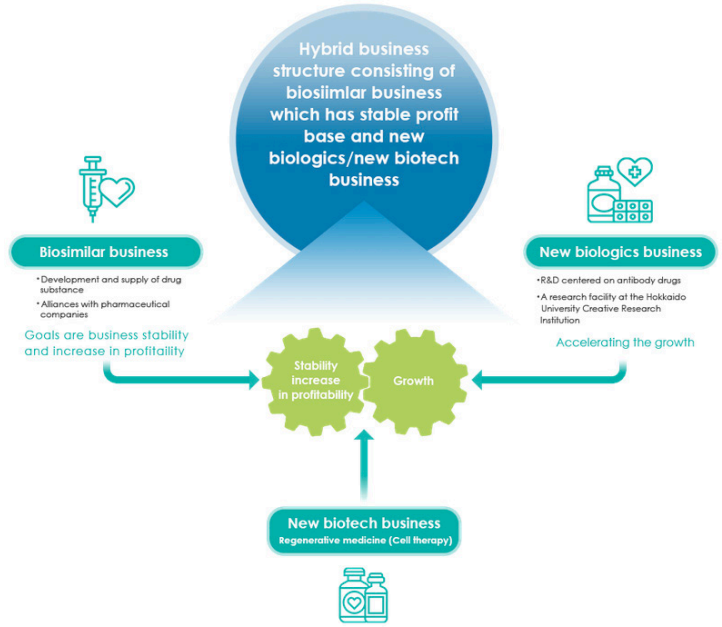
The basic policy is to aim to efficiently generate earnings through joint developments and licensing-out

(3) Business structure

The Company’s business model is characterized by the development of a virtual business structure for the biosimilars business that is expected to have high stability and generate earnings at an early stage, and for the new biologics business that aims for high growth. In addition to these two businesses, it will work on the new biotech business, which includes regenerative medicine and cell therapy, to become the third business pillar.

Company profile

Business structure



Source: The Company's website

a) Biosimilars business

The earnings model for the biosimilar business is comprised of sales from earnings at the R&D stage and the post-market-launch stage from supplying the drug substance that will be the main raw material for the drug product developed by the pharmaceutical company that is collaborating with the Company. Earnings are also comprised of agreement upfront payments and development milestone payments that depend on the progress made in the non-clinical and clinical trials. The Company outsources all of the tasks that are the sources of earnings in the biosimilar business, of the manufacturing, analysis, and evaluation and other testing of the drug substance.

As an example, for the market-launched filgrastim biosimilar, the Company paid royalties to license-in the cell line from Dong-A Socio Holdings (formerly, Dong-A Pharmaceutical Co. Ltd.) of South Korea, it developed the drug substance and the manufacturing process for its commercial production, and it sells the developed drug substance to its partner, Fuji Pharma. Fuji Pharma manufactures and sells the drug product, and it also supplies the drug product to Mochida Pharmaceutical. The filgrastim biosimilar developed by the Company accounts for approximately 30% of the filgrastim sales in Japan since sales started in 2013, and this ratio is expected to rise even further in the future. Filgrastim biosimilars are sold by a number of pharmaceutical manufacturers other than Fuji Pharma and Mochida Pharmaceutical, including Nippon Kayaku Co., Ltd. <4272>, Takeda Teva Pharma Co., Ltd., Sawai Pharmaceutical Co., Ltd. <4555>, and Sandoz Co., Ltd. However, it seems that in Japan, the products of Fuji Pharma and Mochida Pharmaceutical, which hold the phase 3 clinical trial data, have the highest shares of the market.

b) New biologics business

The Company implements its new biologics business from the basic research for drug discovery. It conducts research not only in-house, but also jointly with universities and other research institutes. Manufacturing, quality testing, and non-clinical trials for the discovery of drug candidates are outsourced to CROs both domestically and overseas. As enormous costs will be subsequently incurred at the clinical trials stage, in principle its basic policy is to license-out the candidate to a pharmaceutical company at this stage.

Therefore, as its earnings model, the Company mainly enters into joint research and development agreements or license agreements and obtains earnings from agreement upfront payments, development milestone payments depending on the progress made in the development, and then from royalties after the product is launched. In its track record of licensing-out, Kaken Pharmaceutical was granted the exclusive development, manufacturing, and sales rights for the anti-integrin alpha 9 antibody (indicated for immune diseases and cancers) in 2007.

c) New biologics business

In the cell therapy business using cardiac stem cells, it concluded a capital and business partnership agreement with Japan Regenerative Medicine in 2016, and they are jointly progressing the commercialization of cell therapy products aiming at improving infant heart functions using the cardiac stem cells researched and developed by the Company.

In the cell therapy products business using stem cells from human exfoliated deciduous teeth, the sequence is that the stem cells from human exfoliated deciduous teeth procured by ACTE are manufactured and processed at Nikon as the clinical-use MCB, which are then sold to the research institutes and pharmaceutical companies that are its joint-development partners as cell therapy products. Also, its business model is that through conducting the joint development of cell therapy products using stem cells from human exfoliated deciduous teeth with pharmaceutical companies, it receives earnings from agreement upfront payments, development milestone payments, and royalties depending on sales. There is also the possibility of the Company to develop products in-house and expand its sales channels on its own to increase earnings from indications for rare diseases, intractable diseases and infant diseases.

Status of the development pipeline

Has in sight market launching two biosimilars from FY3/20 onwards

1. Biosimilars business

In the biosimilars business, it is expected that GBS-011 (darbepoetin alfa biosimilars) will be market launched in FY3/20 and GBS-007 (Ranibizumab biosimilars) in FY3/22. For the other products in the pipeline also, it is possible that clinical trials will start during FY3/20. Filgrastim biosimilars, which has already been market launched in Japan, is achieving annual sales of ¥900mn, from drug-substance sales and other, mainly to its partner Fuji Pharma. While it will depend on the drug price, in the future sales are expected to trend at around the same level.

Status of the development pipeline

Biosimilars

Project	Therapeutic Area	Development Research	Clinical Trial		Application/ Marketing/ Approval/ Launch	Partner
			Phase 1	Phase 3		
GBS-001 Filgrastim	Oncology					Fuji Pharma Co., Ltd. Mochida Pharmaceutical Co., Ltd.
GBS-004 Bevacizumab	Oncology					
GBS-005 Adalimumab	Immunological disease					Terminating an agreement with Changchun Changsheng Life Sciences Limited (China) and searching new partners
GBS-007	Ophthalmic disease			UPDATE!!		Senju Pharmaceutical Co., Ltd. License out to Ocumension Therapeutics (China and Taiwan)
GBS-008 Palivizumab	Infectious disease					
GBS-010 PEG-filgrastim	Oncology					
GBS-011 Darbepoetin alfa	Renal disease			UPDATE!!		Sanwa Kagaku Kenkyusho Co., Ltd.

Source: The Company's results briefing materials

(1) GBS-011

GBS-011 is a biosimilar of darbepoetin alfa (product name: Nesp), which is a renal anemia therapeutic agent, and Sanwa Kagaku Kenkyusho, the Company's joint-development partner, submitted New Drug Application for it in September 2018. As it takes more than a year on average from the time of application until the approval, if the approval review goes smoothly, it is expected to acquire manufacturing and sales approval during FY3/20. After it is market launched, the Company will receive royalties depending on sales. This product is manufactured by Dong-A ST of South Korea, while the Company is conducting joint development in the form of supporting the development by Sanwa Kagaku Kenkyusho, so it is considered that its impact on earnings will not be that great. In FY18, sales in Japan of Nesp were ¥53.7bn, and the scale of the biosimilars potential market* is estimated to be approximately ¥22.5bn. During the same period as Sanwa Kagaku Kenkyusho, JCR Pharmaceuticals also applied for marketing approval, and the previously mentioned Kyowa Kirin Frontier is expected to start selling the biosame in the latter half of 2019, which will serve as a test case on the extent to which biosames will impact biosimilars.

* Note: the potential market scale is calculated as approximately 40% of that of the innovator drugs (innovator drugs net sales × biosimilar penetration volume rate 60% × 70% of the innovator drug price)

(2) GBS-007

GBS-007 is a biosimilar of the anti-VEGF antibody drug Ranibizumab (trade name: Lucentis), which is an age-related macular degeneration therapeutic agent, and the joint development partner Senju Pharmaceutical announced that it had completed the final patient registration for the phase 3 clinical trial in February 2019. The observation period is one year, so all of the clinical trials will be completed by February 2020. After that, it will collect and analyze the clinical data and prepare the application documents over a period of several months, and once these are prepared, it will apply for manufacturing and sales approval. If the application goes smoothly, it will receive sales approval in FY3/22. As age-related macular degeneration therapeutic agents in Japan, two anti-VEGT antibody drugs, Ranibizumab and Aflibercept (product name: Eylea) are already on the market, and Lucentis has net sales of approximately ¥23bn and Eylea of around ¥60bn. The potential, total demand in Japan for biosimilars of age-related macular degeneration therapeutic agents is estimated to be around ¥35bn, of which, the replacement demand for Lucentis is around ¥9bn. The differences between the two drugs include that while the administration period is about one and a half months with Lucentis, Eylea's is slightly longer, at about two months, and also that the effects of the two drugs differ depending on the patient. They are administered by an eye injection, which places a heavy burden on the patient, so the preference tends to be for Eylea, which has a longer administration period.

In addition, since sales in the world market are about ¥200bn for Lucentis and about ¥700bn for Eylea, if biosimilars are sold overseas, this could have a significant impact on the Company's business results. The patents in Japan will expire for Lucentis in 2020 and for Eylea in 2022, when it will become possible to sell biosimilars. A new anti-VEGF drug is scheduled to be launched in 2020 with a more effective administration period of approximately three months, but it seems there is still a demand for low-cost biosimilars. Overseas, only Samsung Bioepis and another company are conducting phase 3 clinical trials for the biosimilars, and there remains plenty of room for other companies to enter into this area.

In this environment, in January 2019 the Company announced that it had entered into an exclusive license agreement with China's Ocumension Therapeutics (hereinafter Ocumension) in China and Taiwan. Going forward, in accordance with the roles allocated to the three companies, of Senju Pharmaceutical, Ocumension, and the Company, they will supply the drug substance and manufactured drug, conduct the clinical trials, and perform other tasks, toward market launches in China and Taiwan. In the current agreement, the Company and Senju Pharmaceutical will receive agreement upfront payments from Ocumension, and they are also scheduled to receive development milestone payments according to the development stage and royalties depending on sales after the market launch. In addition, they plan to continue working on licensing-out activities for the European and US markets.

(3) GBS-010

GBS-010 is a biosimilar of PEG-filgrastim (product name: G-Lasta / Neulasta) that reduces the frequency of drug administration and increases the sustainability of the drug's effects by modifying PEG (polyethylene glycol) with filgrastim. The non-clinical trials have already been completed, while the clinical trials may start in the early 2020s. The PEG-filgrastim biosimilars is based on the substance used for filgrastim biosimilars, which has already been market launched, which gives the Company an advantage in terms of progressing its development. It is thought that it is being developed so that it can be launched without delay in the fall of 2022, which is when the reexamination period of the forerunner drug ends. Sales of G-Lasta in Japan in FY18 were ¥20.7bn, and the potential demand for biosimilars is estimated to be around ¥8bn.

(4) Others

In addition, the Company has one or two product seeds in its biosimilars pipeline, and it plans to launch projects for them once it finds partners.

Overview of joint research projects to develop biosimilars

Partner	Chromocenter Inc.	SOLA Biosciences, LLC	GPC Laboratory Co. Ltd.
Announcement date	July 2018	August 2018	September 2018
Joint research objective	Establish a platform to develop high-yield protein producing cell lines that are directly linked to the production of large amounts (cost competitive) of biologic drug substances		
Specific measures	Using the artificial chromosome vector technologies owned by chromocenter, the aim is to optimize the gene construct that encodes the amino acid sequence of the recombinant protein and thereby construct highly productive cell lines for biosimilars.	The Company concluded an agreement to introduce the Tapboost® technology owned by SOLA to align the structural arrangement of the target recombinant proteins in the cells, increase the efficiency of the functions exhibited, and construct highly productive cell lines to produce biosimilars.	The aim is to construct even more highly productive cell lines by introducing multiple, high-function factors into existing biosimilar production cell lines. High-function factors are factors that reduce intracellular stress and that efficiently secrete proteins produced intracellularly. Introducing these factors into cells in a well-balanced manner improves the protein secretion functions of existing cell lines, which can be expected to increase the efficiency of drug substance production and to reduce costs.

Ultimately the aim is to integrate the research results of the various companies and to maximize the resulting value. Specifically, with the cell line regarded as a factory, through optimizing the gene composition rate, the aims are to improve the protein production efficiency (chromocenter) and to reduce the rate of defective products in the manufacturing progress (SOLA), and to realize extracellular secretion of the produced protein, or in other words, to improve distribution efficiency (GPC Laboratory), by controlling the expression of multiple genes,. This is the technological background to the project.

Source: Prepared by FISCO from the Company's materials

2. New biologics business

For new biologics, the Company licensed-out the anti-integrin alpha 9 antibody to Kaken Pharmaceutical, but in terms of its development status, hardly any progress has been made. In this situation, the Company is focusing on GND-004 as a novel antibody drug candidate for indications in the ophthalmology and cancer fields. GND-004 is a neovascularization inhibitor with a mechanism of action (anti-RAMP2 antibody) different from Lucentis and Eylea, so demand is expected from patients with ophthalmology-related diseases for which both these drugs are not effective, or from cancer patients for which Bevacizumab (brand name: Avastin) is not effective. The Company filed a patent application for the antibody in September 2017, and it is currently at the stage of conducting animal experiments to accumulate the data necessary for licensing out. While creating the data, it is aiming to license it out to pharmaceutical companies at an early stage.

New biologics

Project	Therapeutic Area	Basic Research	Development Research	Clinical Trial			Application/ Marketing/ Approval/ Launch	Partner
				Phase 1	Phase 2	Phase 3		
GND-001 Anti alpha-9 integrin antibody	Immunological disease, Oncology							Kaken Pharmaceutical Co., Ltd.
GND-004 Anti RAMP2 antibody	Ophthalmic disease, Oncology							Looking for partners
GND-007	Immunological disease							

Source: The Company's results briefing materials

3. New biotech business

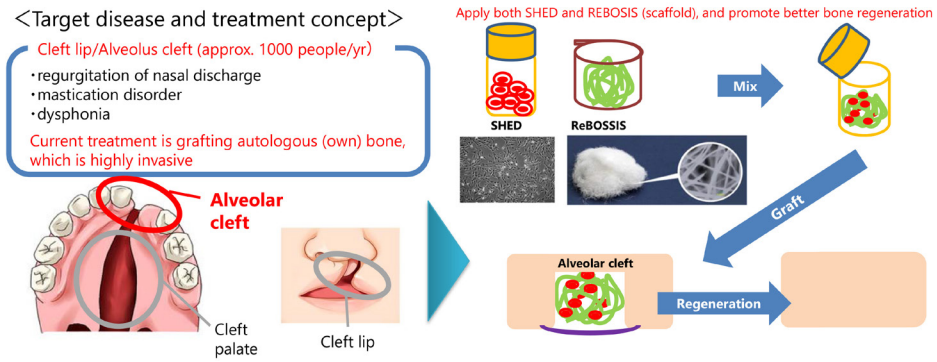
In the regenerative medicine and cell therapy field, in May 2019 the Company concluded a joint research and development agreement with ORTHOREBIRTH, which developed and sells ReBOSSIS*1, an artificial bone filling material, and they will start research into creating treatments for cleft lip and cleft palate that combine stem cells from human exfoliated deciduous teeth with ReBOSSIS. The cleft lip and cleft palate condition is caused by the abnormality of neural crest cells*2, and stem cells from human exfoliated deciduous teeth, which are also neural crest cells, are the optimal cell source. The cotton-like, artificial bone filling material ReBOSSIS is compatible with stem cells from human exfoliated deciduous teeth in terms of characteristics and high bone regeneration capability is expected, so is considered highly likely that this development will be successful.

*1 ReBOSSIS is a product that has been approved by the US FDA for the treatment of fractures and has demonstrated safety and high ability to induce bone regeneration. It is made of biodegradable material, so it disappears after bone regeneration and there is no risk of artificial components remaining in the body.

*2 Neural crest cells are cells that form at the boundary between the part that becomes the epidermis and the part that becomes the nerve in the ectoderm (the cells that form the future skin and nerves), and they are originally cells derived from ectoderm. They are pluripotent cells that can move to various regions in the body during development and differentiate not only into tissue and organs derived from ectoderm, but also into tissue derived from mesoderm and endoderm, at the destination site.

There are two points here; it can be a non-invasive, preschool treatment, and a low-cost treatment. In the past, surgery was required for an autologous transplant of the patient's own ilium, and it was necessary to wait until the patient was of an age when a sufficient amount of ilia could be removed. The problem is this treatment is highly invasive, but if a treatment method by cell therapy using stem cells from human exfoliated deciduous teeth can be established, this problem would be solved. First, they will study optimizing the stem cells from human exfoliated deciduous teeth and artificial filling material at the test tube level, and the plan is to verify the effects of the bone regenerative capability in animal experiments. The issues for the clinical development include how to determine the contents of the clinical trials, because it will be indicated for infants, and how to proceed with the recruitment of subjects.

Image of indicated diseases/conditions and treatments



Source: The Company's results briefing materials

Status of the development pipeline

For the other candidates in the pipeline, in October 2016, Japan Regenerative Medicine, a member of the Noritsu Koki Group with which the Company has a capital and business partnership, began clinical trials for the treatment for improving cardiac functions using cardiac stem cells, the first such treatment in the world, and the trial is advancing under Japan's SAKIGAKE Designation System*. If it makes smooth progress in the clinical trials and the results are good, it will be able to receive manufacturing and sales approval in the first half of the 2020s. The Company is providing Japan Regenerative Medicine with support, including for the non-clinical trial and manufacturing development. Also, although the current clinical trial is based on autologous transplants, going forward the two companies will jointly examine the possibility of non-autologous transplants and an expansion of indications, and in the future they plan to expand into the European and US markets.

* For innovative new drugs that meet certain requirements, such as the severity of the disease they are indicated for, the aim is to shorten the approval review period by designating these drugs as pioneering products from an early stage of their development, and treating them as a priority for the consultations and review relating to the regulatory approval. Through utilizing this system, it is possible to reduce the standard review period to 6 months, which is around half of the length of the usual time.

New biotech business

Project	Basic Research	Clinical Trial	Conditional and Time-limited Authorization※	Marketing (Further confirmation on safety and efficacy)	Marketing Authorization	Marketing Continues	Partner
GCT-101 Cell therapy using SHED for alveolar cleft							Orthorebirth Co., Ltd.
JRM-001 Cell therapy using cardiac stem cell for hypoplastic left heart syndrome							Japan Regenerative Medicine Co., Ltd.
Induction of immune tolerance for organ transplant							Juntendo University Junten Bio Co., Ltd.
Cell therapy using mesenchymal stem cell derived from bone marrow for diabetic nephropathy							Sapporo Medical University Minerva Medica Co., Ltd.

※Expedited approval system for regenerative medicine
Post-marketing safety measures must be taken, including prior informed consent of risk to patients.

Source: The Company's results briefing materials

Results trends

Operating loss decrease in FY3/19 due to a delay in the R&D period

1. Overview of FY3/19 results

In the FY3/19 results, net sales decreased 3.6% YoY to ¥1,021mn, the operating loss was ¥805mn (compared to a loss of ¥913mn), the ordinary loss was ¥816mn (a loss of ¥903mn), and the net loss was ¥856mn (a loss of ¥904mn).

Sales achieved the Company target, with net sales declining only 0.1% YoY to ¥906mn, mainly from sales of filgrastim biosimilars. However, revenue from services declined ¥27mn to ¥2mn, and revenue from intellectual property rights, etc., decreased ¥9mn to ¥112mn, and these declines were the main earnings-decrease factors. In costs, R&D costs, mainly in the biosimilars business, declined ¥162mn to ¥945mn, including due to a delay in the R&D period, and this was the primary reason why the operating loss contracted YoY and compared to the Company forecast. The Company also recorded an extraordinary loss of ¥45mn as a reward for services for retiring directors.

Results trends

FY3/19 results

(¥mn)

	FY3/18 Results	FY3/19			
		Company target	Result	YoY change	vs. target change
Net sales	1,059	1,060	1,021	-38	-38
(net sales of products)	908	-	906	-1	-
(other revenue)	151	-	114	-36	-
Gross profit	637	-	609	-27	-
SG&A expenses	1,550	-	1,414	-135	-
(R&D expenses)	1,107	1,300	945	-162	-354
Operating loss	-913	-1,180	-805	107	374
Ordinary loss	-903	-1,180	-816	86	363
Net loss	-904	-1,182	-856	48	325

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

Will shift to consolidated results from FY3/20, and the final loss is forecast to temporarily increase due to the one-time write off of ACTE's goodwill

2. FY3/20 outlook

The Company will start disclosing consolidated results from FY3/20 as it has made ACTE a subsidiary. Compared to the non-consolidated results in FY3/19, the forecasts are for net sales to increase 2.8% to ¥1,050mn, an operating loss of ¥1,220mn (compared to a loss of ¥805mn in FY3/19), an ordinary loss of ¥1,260mn (a loss of ¥816mn), and a loss attributable to owners of parent of ¥7,260mn (a net loss of ¥856mn).

The main reasons for the higher sales will be that, although it is anticipated that sales of Filgrastim biosimilars will be basically unchanged YoY and revenue from intellectual property rights, etc., will be small, the contribution of ACTE will increase sales by approximately ¥100mn. Costs will increase, primarily because R&D costs, centered on biosimilars, will rise ¥255mn YoY to ¥1,200mn, and also for the costs to relocate the headquarters. In addition, the effects of making ACTE a subsidiary is expected to have a negative impact of around ¥20mn at the operating profit stage, so the operating loss is forecast to increase YoY to ¥1,220mn.

Goodwill of approximately ¥6bn was generated from ACTE being made a subsidiary, and the Company plans to record it all together as an extraordinary loss. Non-consolidated results as of the end of FY3/19 recorded net assets of ¥2,731mn, and it seems that that it might have excess debt. But there was no cash out due to ACTE being made a subsidiary through a share exchange, so net assets on the consolidated balance sheets were not affected by the approximately ¥6bn amount. As ACTE's net assets are thought to have been worth around ¥100mn in the most recent fiscal year, at the end of FY3/20 it is estimated that consolidated net assets will be in the range of ¥1.5bn to ¥1.6bn, if there is no exercising of share subscription rights and new financing.

FY3/20 outlook

(¥mn)

	FY3/19 Result	FY3/20 (consolidated)	
		Company target	YoY change
Net sales	1,021	1,050	29
(R&D expenses)	945	1,200	255
Operating loss	-805	-1,220	-415
Ordinary loss	-816	-1,260	-444
Loss attributable to owners of parent	-856	-7,260	-6,404

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

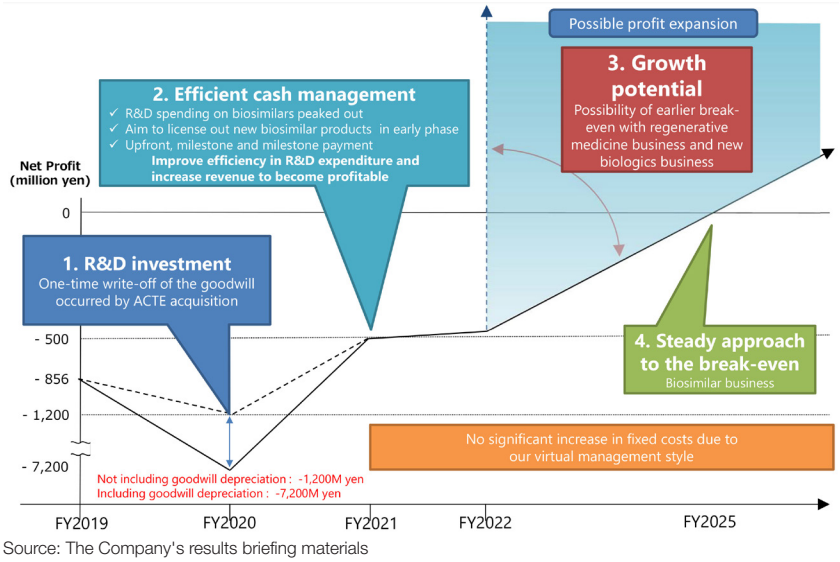
The loss will contract from FY3/21 as R&D costs will have peaked-out, and is aiming to become profitable from FY3/22 onwards

3. Roadmap to profitability

The Company recently clarified its roadmap to profitability. In FY3/21, biosimilar R&D costs will have peaked out and it will work on the early licensing out of GND-004, a new biologic indicated for the ophthalmologic and cancer fields. It will also acquire agreement upfront payments and other income from licensing out projects, so the net loss attributable to owners of parent is expected to be around ¥500mn. In the biosimilars business, it is forecast that filgrastim biosimilars will keep its current sales level in the future, and in addition, from FY3/22 sales are expected to enter an expansion phase from the launch of the Lucentis biosimilars. So it is forecast that at the latest, the Company will steadily achieve profitability by FY3/25.

Also, from FY3/22, in the cell therapy field using stem cells from human exfoliated deciduous teeth, other than the five fields being targeted by the Company for its own developments, it is expected that development projects with its multiple partner companies, including DAIICHI SANKYO, Eisai and SEKISUI CHEMICAL, will make concrete progress. So it is possible that it will obtain additional earnings, such as agreement upfront payments and development milestone payments, including in the new biologics business. If these businesses make steady progress, the Company may become profitable at an even early stage.

Roadmap to profitability for GTS 3.0



Source: The Company's results briefing materials

If no progress is made with the exercise of share subscription rights, it may be necessary to raise new funds in the first half of 2020

4. Financial position and fund raising

Looking at the financial condition at the end of FY3/19, total assets were up ¥126mn from the end of the previous fiscal year to ¥3,151mn. The main change factors include increases in cash and deposits of ¥118mn due to the exercising of share subscription rights, accounts receivable of ¥154mn, and decrease in advanced payments of ¥171mn.

Total liabilities were down ¥1mn from the end of the previous fiscal year to ¥420mn. Looking at the main change factors, there were decrease in arrears of ¥23mn, increases in income taxes payable of ¥20mn, and retirement benefits allowance of ¥4mn. Net assets were up ¥127mn from the end of the previous fiscal year to ¥2,731mn. This was because although a net loss of ¥856mn was recorded, capital and the capital surplus both increased ¥491mn due to the exercising of share subscription rights.

In July 2018, the Company issued the 6th share subscription rights to procure funds to develop biosimilars and new biologics. At the end of March 2019, it had raised ¥978mn, while it newly procured of ¥40mn in April and May. The number of shares corresponding to the unexercised portion of shares is 1,743,000 shares, and if all are exercised at the exercise price lower limit of ¥714.5, the Company will be able to procure the remaining amount of around ¥1.2bn. The share price is currently below the exercise price lower limit, and no progress will be made in exercising the share subscription rights as long as the share price does not go above ¥714.5 at the very least. At the end of March 2019, cash and deposits were approximately ¥2bn, and if results trend in line with the Company's forecast in FY3/20 and the share subscription rights are not exercised, the balance of cash and deposits at the end of FY3/20 is expected to be around ¥1bn. Given that it will continue to record a loss in FY3/21, it seems that it will need to look for new funding.

When the Company made ACTE a wholly owned subsidiary through a share exchange, it issued 7,250,000 of its own shares to ACTE's existing shareholders. The number of outstanding shares at the end of FY3/19 was 20,342,000, for a dilution rate of 35.6%. The conditions for selling the issued shares are 1) they cannot be sold before the end of September 2019; 2) during the six months from October 2019 to the end of March 2020, each shareholder can sell up to 50% of the shares allocated to them, and also within the same period, if the share price exceeds 150% of the share price on the effective date (share price of ¥832 on April 1, 2019), the shares can be sold without restriction; and 3) they can be sold without restriction from April 1, 2020, onwards.

Balance sheet (summary)

(¥mn)

	FYE3/15	FYE3/16	FYE3/17	FYE3/18	FYE3/19	Change
Current assets	1,092	1,520	3,421	2,692	2,821	129
(Cash and deposits)	599	817	2,379	1,891	2,009	118
Non-current assets	54	173	284	332	329	-3
Total assets	1,146	1,694	3,706	3,025	3,151	126
Current liabilities	92	1,279	189	404	400	-4
Non-current liabilities	783	11	16	16	19	3
Total liabilities	876	1,290	205	421	420	-1
(Interest bearing debt)	775	810	-	-	-	-
Net assets	270	403	3,500	2,604	2,731	127
Management indicators						
Shareholders' equity ratio	21.7%	22.6%	93.8%	85.0%	85.6%	0.6pt
Interest-bearing debt ratio	310.8%	212.0%	-	-	-	

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

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