Contributing to People's Health through the Creation of Products and Services with Unique Characteristics

Pharmaceuticals Business: R&D

Material issues and related SDGs

Realizing a healthy future by creating innovation

Strengthening efforts to protect the global environment

Resolving social issues and coexisting with the community

Three foundations we value

- Pursuit of originality
- Continuously tackling the challenges of new modalities
- Giving our all in thinking about patients

Quickly delivering new world-class therapeutic agents to the patients who need them

Kazuchika Takagaki
Director, Research & Development

By actively engaging in R&D of drugs for intractable and rare diseases for which there have been no effective treatments, Nippon Shinyaku succeeded in developing Uptravi, a pulmonary arterial hypertension (PAH) treatment that has grown into a blockbuster, and Viltepso, a Duchenne muscular dystrophy (DMD) treatment, the first nucleic acid drug in Japan. Behind these successes are three principles that have been important to the R&D Division: 1) pursuit of originality in R&D, 2) Continuously tackling the challenges of new modalities, and 3) Giving our all in thinking about patients. As a result of continuing our R&D based on these three foundations, we believe that we have overcome the high and difficult barrier of developing new therapeutic agents for intractable and rare diseases, which have been considered difficult in the past.

We will continue to pursue originality, continuously take on the challenge of new modalities, and give our all in thinking about patients as the foundation of our R&D, but it is essential that we speed up R&D in order to deliver innovative new drugs to patients suffering from diseases as soon as possible. With regard to the R&D system and its mechanisms, we will work to optimize resource allocation, rationally prioritize projects, and improve the efficiency of R&D using AI and IT. In this way, we will increase the speed of development and the probability of success, and by actively introducing new and superior technologies from the outside through open innovation, we will realize the early launch of products unique to Nippon Shinyaku.

Review of the 6th Five-Year Medium-Term Management Plan and Remaining Issues

Under the 6th Five-Year Medium-Term Management Plan, we aim to increase our global significance as a company with a meaningful existence in the healthcare field, and as the R&D Division, we have taken on the challenge of creating new value through R&D.

In FY2023, the final year of the 6th Medium-Term Management Plan, we obtained manufacturing and marketing approval for two drugs. The first is high-risk acute myeloid leukemia treatment Vyxeos (code no.: NS-87), in-licensed from Jazz Pharmaceuticals, underwent Phase I/II study in Japan and we applied for approval in June 2023 and received approval in March 2024. The other is Fintepla (code no.: ZX008), for which we entered into an exclusive distribution agreement with UCB S.A. (formerly Zogenix, Inc.) in Japan. Fintepla received approval for the additional indication of Lennox-Gastaut syndrome by UCB Japan in March 2024. Progress has been made in the development phase of Fintepla, and in July 2023, we started a Phase III study in patients with CDKL5 deficiency. NS-863, which is currently under development for circulatory and metabolic diseases, began Phase I study in August 2023. In October 2023, Gazyva, a humanized anti-CD20 monoclonal antibody (code no.: GA101), began Phase III study in systemic lupus erythematosus without nephropathy.

Over the course of five years, we have launched four products: Viltepso (code no.: NS-065/NCNP-01) for the treatment of DMD, Defitelio (code no.: NS-73) for the treatment of sinusoidal obstruction syndrome, MonoVer (code no.: NS-32) for the treatment of iron deficiency anemia, and Fintepla. In addition, we added the indication for chronic thromboembolic pulmonary hypertension to the PAH treatment Uptravi (code no.: NS-304) and expanded the indication of myelodysplastic syndrome treatment Vidaza to the treatment of acute myeloid leukemia. As a result, we launched a total of six new products, achieving the target of launching more than one new product on average per year. On the other hand, there were termination of development for NS-18, and delays of development concerning NS-089/NCNP-02 for DMD treatment and NS-304's additional indication for ASO. These were intended to be launched during the period of the Medium-Term Management Plan, meaning our speed of clinical development is an issue yet to be addressed. Additionally, efforts to develop new modalities such as next-generation nucleic acids and gene therapies took longer than expected to develop candidates.

Strategies and Focus Initiatives to Achieve the 7th Five-Year Medium-Term Management Plan

In the 7th Five-Year Medium-Term Management Plan, we have set "fostering growth drivers to replace Uptravi" and "continuous pipeline expansion" as key themes. As growth drivers during the 7th Medium-Term Management Plan, we will launch four DMD drugs, three hematological malignancy drugs, and an average of two or more new products per year through the expansion of indications for Uptravi, Fintepla, and Gazyva. In addition, we will focus on newly acquired products to further expand the number of our products on the market.

In addition, we will continue to expand our pipeline based on the three pillars of in-house drug discovery, in-licensing, and PLCM. With regard to in-house drug discovery, we will utilize open innovation and AI drug discovery to combine and bolster our strengths with the technologies of other companies. In nucleic acid drugs, we will work on drug discovery in the central nervous system area in addition to DMD, and promote the use of new nucleic acid drug discovery modalities through open innovation. With regard to in-licensing, we will prioritize items that lead to global sales and work to acquire at least one in-licensed product per year. With regard to PLCM, we will start working on secondary indication diseases earlier than in the past, and make efforts to maximize the value of our pharmaceuticals.

In the 7th Medium-Term Management Plan, we set out to "speeding up R&D" as one of the ways to strengthen our management foundation. In clinical development, multiple clinical studies were delayed during the 6th Medium-Term Management Plan, and in order to solve these issues, we will improve the probability of success and speed up the process by rigorously checking the progress of the entire Company, strengthening compliance with regulatory authorities in each country, bolstering project management, formulating robust trial plans, and pursuing the possibility of accelerated approval. In drug discovery research, we aim to shorten the time from the drafting of a theme to the entry into clinical study, and to

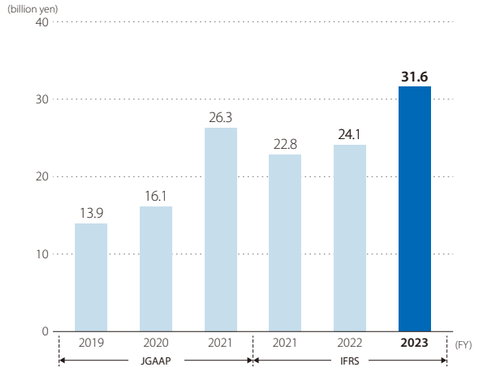
Contributing to People's Health through the Creation of Products and Services with Unique Characteristics

Pharmaceuticals Business: R&D

build a system that enables us to launch one product a year. In addition, as part of our financial strategy for sustainable growth set among the management foundations we plan to strengthen, we plan to invest 190 billion yen in R&D over five years and 38 billion yen in capital investment, including the construction of a new research building at the Discovery Research Laboratories to respond to new technologies and create innovation.

With the aim of realizing a healthy future by creating innovation, which we identified as one form of our materiality, the R&D Division will work together in accordance with the 7th Medium-Term Management Plan.

Research and development expenses



Accessing seeds of world-leading drug discovery

The area around Cambridge, Massachusetts on the East Coast of the U.S. is home to many world-leading academia and affiliated hospitals such as Harvard University and the Massachusetts Institute of Technology. Many startups and biotech companies are also concentrated, making it a hotspot for innovation. Our establishment of Innovation Research Partnering (IRP) here will increase early access to the world's most advanced drug discovery technology seeds and opportunities for co-creation with world-class scientists. This will enable Nippon Shinyaku to efficiently conduct information gathering and exploration activities that will lead to the introduction of innovative technologies and early products.

Promotion of patient centricity-based drug discovery research

We have set a long-term goal for 2035 to use drug discovery research themes based on patient centricity to promote R&D activities aimed at bringing drugs to market, and we are now working toward this goal. In FY2023, we aimed to increase opportunities for drug discovery researchers to interact with patients or with people who are close to patients. We would like to introduce two specific initiatives. As the first initiative, we asked patients and their families to create video messages for our Company, which were viewed by all employees of the R&D Division. Employees who watched the videos commented, "It gave me an opportunity to rethink what I can do as an employee of a pharmaceutical company," and "I realized that our work has an impact on the lives and livelihoods of patients and their future." As a second initiative, in October 2023, Mr. Takeshi Shukunobe, President and CEO of PPeCC, gave a talk to employees entitled "The Significance of Listening to the 'Voices' of People with Illness," which was attended by approximately 330 employees. Employees who attended the talk commented, "I thought it would be difficult to hear directly from people with illnesses, but I was able to recognize that it is possible," "I felt that it is important to think together about how to live with hope in the future," and "It is important to incorporate this into the work of each department. I think it would be good if drug discovery researchers had more opportunities to hear directly from people with illness." At Nippon Shinyaku, there have not been many opportunities to hear directly from patients and their families. Through this initiative, we were able to reaffirm the importance of increasing opportunities to talk directly to and getting to know patients.

In order to achieve our vision for 2035, we believe that it is important not only to provide opportunities to interact with patients and those close to patients, but also to aim for drug discovery together, and we will continue working on the development of this system going forward.

Building where IRP is located

Increasing partnering opportunities and diversifying in-house drug discovery

For technologies and compounds under development that are in the preclinical stage or earlier, IRP and the Modality Strategy Team at the head office are responsible for partnering functions, and for developed compounds that are in the clinical stage and have confirmed proof of concept (POC), NS Pharma based in New Jersey, U.S., and the Licensing Department at the head office are responsible for partnering functions. In this manner, dividing work by stage of development and region enables efficient scouting activities and leads to an increase in partnering opportunities.

By partnering with academia and venture companies with distinctive technology seeds, we aim to create new therapeutic technologies not only by layering the pipeline of developed products, but also by combining Nippon Shinyaku's strengths with cutting-edge technologies. Since the development of new therapeutic technologies is one of the important factors in the development of drugs for intractable and rare diseases for which there are no effective treatments yet, and for drug discovery in new disease areas, we believe that the increase in partnering opportunities will bring diversity to our own drug discovery.

Consideration of animal welfare

Research using animals is indispensable to verifying the safety and efficacy of pharmaceuticals. Nippon Shinyaku has established internal rules regarding animal research in accordance with relevant laws, regulations and guidelines, and has established the Animal Research Committee. The committee screens all animal research to ensure that they are conducted with appropriate consideration based on the principles of the 3Rs (Replacement, Reduction, Refinement). Our implementation system for animal testing confirms compliance with relevant laws and regulations through periodic self-inspections, and is certified by the Japan Pharmaceutical Information Center (JAPIC), a third-party organization. In addition to optimizing the environment for raising animals and reducing stress, we provide education on animal welfare as part of regular training for those involved in animal testing.

NIPPON SHINYAKU PEOPLE

Bringing drugs to more patients as a team

I had been a project manager for hematological malignancy drugs such as NS-87 (Vyxeos: a treatment for high-risk AML) since April 2021. The main task of a project manager is to promote development and maximize product value with a view to post-launch. In that role, I was always thinking about what we could do to bring drugs to market as soon as possible and to as many patients as possible. I was impressed by the fact that the project team worked together to obtain approval for the manufacture and sale of NS-87 in March 2024, expanded the range of patients the drug could be administered to through consultation with the authorities, and was able to deliver the drug to a broader number of patients, and shortened the development period for another hematological malignancy treatment by more than one year.

Michiyo Akagi
Planning and Coordination Section 1, R&D Planning and Administration Department
(currently, Planning Section 2, Licensing Department)

Contributing to People's Health through the Creation of Products and Services with Unique Characteristics

Pharmaceuticals Business: R&D

Pipeline (As of August 7, 2024)

Japan

Code no. (generic name)	Domain classification	Indications	Origin	Development	Phase: I	Phase: I/II In preparation	Phase: I/II	Phase: II In preparation	Phase: II	Phase: III	NDA filing	Launch
NS-065/NCNP-01 (Viltolarsen)	Intractable and rare diseases	Duchenne muscular dystrophy	Co-development: National Center of Neurology and Psychiatry	Nippon Shinyaku								
LY3527727 (Pirtobrutinib)	Hematological malignancies	Mantle cell lymphoma*	Alliance: Eli Lilly Japan K.K.	Eli Lilly Japan K.K.								In preparation
NS-304 (Selexipag)	Intractable and rare diseases	Pediatric pulmonary arterial hypertension	Nippon Shinyaku	Co-development: Janssen Pharmaceutical K.K.								
ZX008 (Fenfluramine hydrochloride)	Intractable and rare diseases	CDKL5 deficiency disorder	Distribution partnership UCB S.A. (formerly Zogenix, Inc.)	UCB S.A (formerly Zogenix, Inc.)								
GA101 (Obinutuzumab)	Intractable and rare diseases	Lupus nephritis	Licensed-in from: Chugai Pharmaceutical Co., Ltd.	Co-development: Chugai Pharmaceutical Co., Ltd.								
GA101 (Obinutuzumab)	Intractable and rare diseases	Pediatric nephrotic syndrome	Licensed-in from: Chugai Pharmaceutical Co., Ltd.	Co-development: Chugai Pharmaceutical Co., Ltd.								
GA101 (Obinutuzumab)	Intractable and rare diseases	Systemic lupus erythematosus without nephropathy	Licensed-in from: Chugai Pharmaceutical Co., Ltd.	Co-development: Chugai Pharmaceutical Co., Ltd.								
LY3527727 (Pirtobrutinib)	Hematological malignancies	Mantle cell lymphoma	Alliance: Eli Lilly Japan K.K.	Eli Lilly Japan K.K.								
LY3527727 (Pirtobrutinib)	Hematological malignancies	Chronic lymphocytic leukemia	Alliance: Eli Lilly Japan K.K.	Eli Lilly Japan K.K.								
NS-304 (Selexipag)	Circulatory and metabolic system	Arteriosclerosis obliterans	Nippon Shinyaku	Nippon Shinyaku								
NS-580	Gynecological diseases	Endometriosis	Nippon Shinyaku	Nippon Shinyaku								
NS-580	Urological diseases	Chronic prostatitis / Chronic pelvic pain syndrome	Nippon Shinyaku	Nippon Shinyaku								
NS-089/NCNP-02 (Brogidirsen)	Intractable and rare diseases	Duchenne muscular dystrophy	Co-development: National Center of Neurology and Psychiatry	Nippon Shinyaku								
NS-229	Intractable and rare diseases	Eosinophilic granulomatosis with polyangiitis	Nippon Shinyaku	Nippon Shinyaku								
NS-401 (Tagraxofusp)	Hematological malignancies	Blastic plasmacytoid dendritic cell neoplasm	Licensed-in from: The Menarini Group	Nippon Shinyaku								
NS-050/NCNP-03	Intractable and rare diseases	Duchenne muscular dystrophy	Co-development: National Center of Neurology and Psychiatry	Nippon Shinyaku								
NS-917 (Radgocitabine)	Hematological malignancies	Relapsed/refractory acute myeloid leukemia	Licensed-in from: Delta-Fly Pharma, Inc.	Nippon Shinyaku								
NS-025	Urological diseases	Urological diseases	Nippon Shinyaku	Nippon Shinyaku								
NS-863	Circulatory and metabolic system	Circulatory and metabolic system diseases	Nippon Shinyaku	Nippon Shinyaku								

* Relapsed or refractory mantle cell lymphoma due to resistance or intolerance to other BTK inhibitors

Overseas

Code no. (generic name)	Domain classification	Indications	Origin	Development	Phase: I	Phase: I/II In preparation	Phase: I/II	Phase: II In preparation	Phase: II	Phase: III	NDA filing	Launch
NS-065/NCNP-01 (U.S.) (Viltolarsen)	Intractable and rare diseases	Duchenne muscular dystrophy	Co-development: National Center of Neurology and Psychiatry	Nippon Shinyaku								
NS-065/NCNP-01 (Global) (Viltolarsen)	Intractable and rare diseases	Duchenne muscular dystrophy	Co-development: National Center of Neurology and Psychiatry	Nippon Shinyaku								
CAP-1002 (deramiocel)	Intractable and rare diseases	Duchenne muscular dystrophy	Partnership: Capricor Therapeutics Inc.	Capricor Therapeutics Inc.								
NS-089/NCNP-02 (Brogidirsen)	Intractable and rare diseases	Duchenne muscular dystrophy	Co-development: National Center of Neurology and Psychiatry	Nippon Shinyaku								
NS-229	Intractable and rare diseases	Eosinophilic granulomatosis with polyangiitis	Nippon Shinyaku	Nippon Shinyaku								
NS-050/NCNP-03	Intractable and rare diseases	Duchenne muscular dystrophy	Co-development: National Center of Neurology and Psychiatry	Nippon Shinyaku								

Intellectual Property

The Nippon Shinyaku Group is committed to tackling the challenge of new modalities in drug discovery and globalization in order to realize our Business Philosophy of "Helping People Lead Healthier, Happier Lives." We recognize that intellectual property (IP) plays an important role in promoting these purposes, and through the protection and utilization of IP, we will strengthen the superiority of our business and continuously improve corporate value. We also adopt the basic attitude of respecting third-party IP rights, practicing thorough IP-related risk management including ownership investigations.

R&D activities and intellectual property

The Intellectual Property Department collaborates with the R&D Division from the early stages of research. By doing this, we can protect pharmaceuticals and functional foods produced in-house in a long-term, multifaceted and strategic way, using not only substance patents, but also use patents, process patents, formulation patents, dosage and administration patents and so on. In addition, we are considering building and utilizing a patent portfolio to strengthen our global R&D strategy and business strategies in an internal committee consisting of multiple department managers. This includes determining patent application and maintenance policies based on our own R&D and business strategies and those of other companies.

Understanding and analyzing intellectual properties

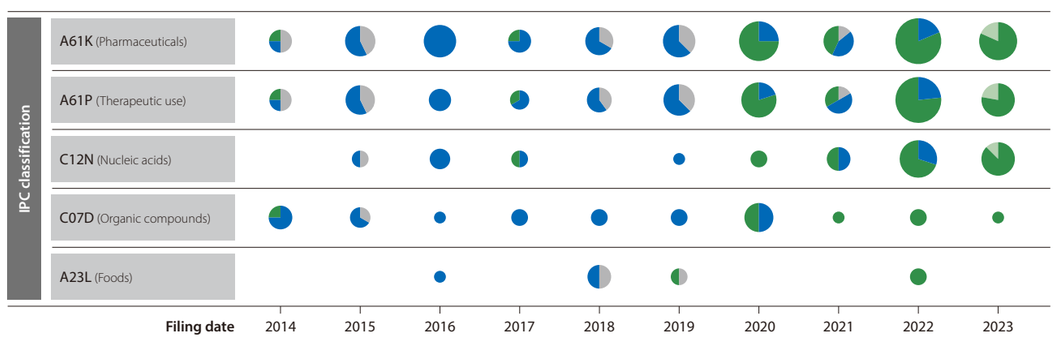
With the basic attitude of respecting third-party IP rights, the Nippon Shinyaku Group regularly conducts ownership investigations regarding its products. We conduct patent trend analysis and IP analysis of competitors in specific technical fields believed to be important for us over the medium to long term. As a result, we manage IP risk at an early stage and utilize the obtained analysis results in our R&D strategy and business strategy.

Furthermore, the Group analyzes IP protecting its products and their surroundings and utilizes these rights, including strategic licensing, to create opportunities for in-house R&D and business expansion.

Building our reputation and brand based on trademarks

We determine the appropriate product names according to the medicines and functional foods produced in-house. By protecting them with trademark rights, we build the reputation and brand of our products.

Application trends by International Patent Classification (IPC) (Top 5 classifications)



Invalid: A patent that has already expired or has been abandoned, or an application that has not been granted (e.g., rejected during review, abandoned by the applicant, etc.)
Valid: A patent that has been registered and the rights have been validly accrued
Pending review: A patent application that is under review in the patent office of the respective country
In the PCT international phase: A patent application that has been filed under the Patent Cooperation Treaty (PCT) but has not yet been reviewed by the national patent offices.

* Data analysis and compilation was conducted independently by Nippon Shinyaku using PatSnap Analytics.