Global Expansion

Viltepso, a treatment for Duchenne muscular dystrophy (DMD) which received accelerated approval from the U.S. Food and Drug Administration (FDA) in August 2020, is the first product we marketed ourselves in the United States. In order to further expand the global business, Nippon Shinyaku has worked in collaboration with NS Pharma, Inc. (NSP), a Group company located in New Jersey in the United States, to strengthen research and development, supply chain, medical affairs, and marketing structures. In building the research and development structure at NSP, we actively employed human resources with experience in development related to rare diseases, as well as those with experience in handling regulatory affairs with the FDA. Moreover, in terms of the marketing structure, in addition to the sales and marketing department familiar in Japan, we established the departments needed for promoting sales in the United States, including the Market Access Department for direct negotiations with insurance companies and the Patient Support Department that helps patients and their families with drug delivery.

➡P. 34 Pharmaceutical Business R&D
➡P. 42 Pharmaceutical Business Resource Procurement, Production & Assurance

R&D and Business Development Activities in the United States

Nippon Shinyaku is developing multiple products in global trials, including Viltepso and subsequent exon skipping drugs. NSP serves the role of a global base for Nippon Shinyaku's clinical development and business development activities, and collaborates closely with Nippon Shinyaku on a daily basis in managing clinical trials as well as licensing and alliance activities. In addition to these roles, in January 2023, NSP opened the new Innovation Research Partnering (IRP) office in Cambridge Innovation Center (CIC) located in Cambridge in the United States, said to be one of the biggest innovation transmission centers. The Boston area of the United States lies at the heart of an ecosystem in which diverse players, including government, universities, research organizations, private-sector companies, and financial institutions, collaborate with each other to create constant innovation. By locating our own drug discovery seeds and technology search base here, we aim to accelerate our in-house drug discovery research and build a richly diverse research and development portfolio by increasing our access to world-leading drug discovery technologies and seeds and our opportunities for co-creation with world-class scientists leveraging open innovation.

Marketing Activities in the United States

Drug cost reimbursement in the United States

Since Japan has a national health insurance system, patients can receive medical services for a certain co-payment whichever medical institution they attend. However, in the United States, individual patients are enrolled in private and public insurance, and co-payment amounts also vary. There are also a certain number of patients with no insurance.

Against this background, in the United States, pharmaceuticals are not always prescribed in accordance with a physician's treatment plan. If the insurer does not approve drug reimbursement, the patient covers the full cost of the drug out-of-pocket, which makes the process leading up to actual prescribing difficult. Therefore, pharmaceutical companies negotiate drug reimbursement with individual insurers, and the Market Access Department plays this role at NSP. The Market Access Department worked to establish favorable reimbursement policies (criteria for allowing insurance reimbursement) for the reimbursement of Viltepso drug costs by negotiating mainly with the major private- and public-sector insurers.

NS Support, a comprehensive patient support service

In order to receive insurance reimbursement for Viltepso, patients must attend a specialist medical institution for genetic testing and motor function evaluations. Due to the vast size of the United States, many patients find it difficult to attend such medical institutions regularly in addition to frequent visits for the administration of the drug. Consequently, many of these patients receive in-home administration of Viltepso. In these cases, making practical arrangements for drugs and coordination with hospitals is essential, but maintaining these arrangements for weekly administration is a major burden. As the actual insurance reimbursement procedures are all different depending on the insurer, it is necessary to look into the procedure first, and the work involved in making an application is a major burden for both medical professionals and patients and their families. To alleviate these burdens, NSP offers a comprehensive patient support service called NS Support led by the Patient Support Department. Through this service NSP provides medical professionals, patients, and their families with guidance and support on insurance reimbursement procedures and help with practical arrangements related to drugs and nurses for in-home infusion treatments.

NS Support
NS PHARMA ACCESS SOLUTIONS

Overview of Marketing Activities

NSP engages in detailing activities for health professionals to provide information on Viltepso. Detailing activities using online interviews have become more widespread, partly due to the impact of COVID-19, and face-to-face interviews are also conducted alongside detailing activities at the moment. We published the four-year, long-term administration data on

Voice

Jonathan Cabral
NS Pharma, Inc.
Head of Patient Service

Helping patients and their families navigate many challenges

I have three main responsibilities. First, to manage NS Support; second, to manage the Patient Engagement Leads (PELs*); and third, to collaborate and support the patient advocacy group.

The most challenging part of the job is to help patients and their families navigate the many challenges of getting on and staying on Viltepso. These families have complex lives with many difficulties beyond Viltepso that take their time and attention. PELs speak directly with patients and their families, and they provide appropriate information. Many stakeholders including parents of patients and patient advocacy groups have a strong desire to cure their child's disease. NSP is committed to communicating the safety and efficacy of Viltepso based on solid evidence.

* PEL (Patient Engagement Lead): Responsible for providing total information and support to patients, including daily lives.

Global Expansion

Viltepso as an academic paper in May 2023, and, in addition to the academic activities conducted by the Medical Affairs Division so far, the Sales and Marketing Division has also started detailing activities utilizing this data. The Market Access Division and the Patient Support Division are also actively making use of the data to explain Viltepso's long-term effects and safety data to insurers, patients and their families.

The Supply Chain Department maintains close communication with 3PL providers*, medical facilities, specialty pharmacies, and companies that provide in-home drug administration services to ensure patients receive Viltepso at the required time and place, with a commitment to timely delivery and stable supply. The department is also seeking to establish a function as a supply center for other countries and regions besides the United States, in the future, such as Europe.

* 3PL provider (third party logistics provider): A company that is contracted to execute comprehensive logistics services, including the storage and delivery of products

Development of DMD Therapeutic Agents to Follow Viltepso

In DMD, dystrophin proteins are not produced due to dystrophin gene mutations. This causes progressive muscle strength deterioration leading to motor dysfunction and finally decline in respiratory and cardiac functions.

Nippon Shinyaku has been engaged in research and development of nucleic acid drugs for many years. An exon skipping drug binds to a specific exon in a precursor of messenger RNA (pre-mRNA), removing the specific exon during the splicing process (exon skipping). This allows production of a shortened, but still functional, dystrophin protein. A variety of different genetic mutations are found in DMD. Viltepso is an exon 53 skipping drug, and approximately 8% of all DMD patients have a genetic mutation amenable to exon 53 skipping. Nippon Shinyaku is promoting research and development of other exon skipping drugs so that treatment opportunities can be offered to DMD patients with different genetic mutations.

At present, we are conducting clinical development in Japan and the United States for exon 44 and exon 50 skipping drugs as nucleic acid drugs to follow Viltepso. Besides these, we are also promoting research into exon 51, exon 45, and exon 55 skipping drugs with the aim of clinical development. If all these treatments are released in the future, it will be possible to offer therapeutic agents, including Viltepso, to around 40% of DMD patients.

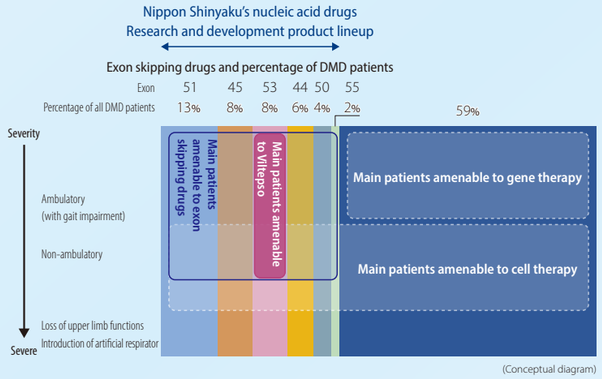
Furthermore, to offer treatment opportunities to the remaining 60% of patients using modalities other than nucleic acid drugs, we are promoting research into gene therapy, and we have entered into a partnership with Capricor Therapeutics for the commercialization and distribution of CAP-1002, a cell therapy, in the United States and Japan.

Gene therapy for DMD is a method of treatment that involves administering a viral vector containing the microdystrophin (miniaturized dystrophin) gene into the human body. At present, we believe that the main patients eligible for gene therapy will be DMD patients who are ambulatory and cannot be treated with exon skipping drugs.

CAP-1002 is a therapeutic drug that involves administering cells that secrete exosomes (extracellular vesicles), which act to reduce oxidative stress, inflammation, and fibrosis and promote increase in myocyte generation. Capricor Therapeutics is currently conducting a Phase III trial of CAP-1002 for non-ambulatory DMD patients in the United States. Unlike exon skipping agents such as Viltepso, CAP-1002 can be administered regardless of the type of genetic mutation, and is expected to be widely used among DMD patients, primarily non-ambulatory patients.

Going forward, we will continue working to expand our treatment lineup to ensure that more DMD patients can receive the best treatment in accordance with their different genetic backgrounds and degrees of disease progression. Making maximum use of our experience in global clinical development and our own marketing structure in the United States in addition to Japan cultivated through the launch of Viltepso, we will continue to deliver treatments to as many DMD patients as possible, as quickly as possible.

Patients amenable to skipping



(Conceptual diagram)

Research and development products for DMD

Development products	Targets	Non-clinical	PI	PII	PIII	Launch
NS-065/NCNP-01 (viltolarsen)	Exon 53				PIII Underway	
NS-089/NCNP-02	Exon 44			PII In preparation		
NS-050/NCNP-03	Exon 50			PI/PII In preparation		
NS-051/NCNP-04	Exon 51					
Exon 45 skipping	Exon 45					
Exon 55 skipping	Exon 55					
CAP-1002	-					
Gene therapy	-					

Further Accelerating Global Expansion

Efforts to obtain approval in more countries

Viltepso received conditional accelerated approval in the United States based on the results of Phase I/II trials in Japan and the Phase II trial in North America. Going forward, in order to expedite approval in countries around the world, we will submit applications for approval in countries where it is possible utilizing data from the Phase II trials conducted by Nippon Shinyaku and NSP to date and the Phase III global trial currently underway.

In terms of obtaining approvals in Europe and China, as a result of discussions with the relevant regulatory authorities, it was decided to submit applications for approval based on the results of ongoing global Phase III trial. In September and November of 2021, we established Beijing Nippon Shinyaku Co., Ltd. and Tianjin Nippon Shinyaku Co., Ltd., respectively, to promote the expansion of our China business, including the application for approval. Going forward, through these two group companies in China, we will put in place a system to provide Viltepso to patients and medical institutions that need it in China. In Europe, we are considering a range of options, including building our own marketing structure or a strategic alliance with a partner company. With regard to submitting applications for approval in other regions, we are engaging in consultation and verification with the relevant authorities in individual countries on approval requirements and other matters.

Supply program in countries where Viltepso is not yet approved

Currently, Viltepso is marketed in Japan and the United States only. When patients in other regions wish to receive Viltepso, one way to do so is by participating in clinical trials conducted by us and NSP. There are clinical trial sites around the world, but patients who can participate in clinical trials are limited by age restrictions and other enrollment requirements. In addition, even if patients are able to participate in clinical trials, there are concerns about no longer having the opportunity to receive Viltepso during the period from the completion of drug administration as part of the trial until approval is received in their respective countries. Therefore, we launched the "Viltepso Managed Access Program" in 2021 in order to provide the drug on an ongoing basis for patients who have participated in and completed clinical trials, as well as to those who are unable to participate.

By developing and delivering treatments in areas and fields with unmet treatment needs, Nippon Shinyaku aims to realize a society in which patients and their families around the world can live with smiles on their faces.

Uptravi, a product discovered and developed in-house and launched in the United States in 2016, is now sold in over 70 countries through partner companies and has become a blockbuster product with sales in excess of $1.0 billion a year. For Viltepso, which we launched in the United States in 2020, we developed our own marketing structure based on NSP, and sales surpassed ¥10.0 billion in FY2022. As this shows, we consider collaboration with partner companies or marketing products ourselves for each product and country to deliver the drugs required by patients around the world in the optimum way.