

Getting Viltepso to the Patients Who Need It

A core R&D challenge faced by Nippon Shinyaku is the development of therapies for intractable and rare diseases with no established treatment. Approved in Japan in March 2020 for Duchenne muscular dystrophy (DMD), Viltepso is the result of many years of research into nucleic acid medicines at our Discovery Research Laboratories in Tsukuba. Having gained approval from the U.S. Food and Drug Administration (FDA) in August 2020, we are now undertaking a range of activities in Japan and the U.S. to provide information to raise understanding of the disease among patients and people around them.



Japan

DMD is an inherited condition affecting boys at a frequency of about one case per 3,500 births. The estimated DMD patient population in Japan is about 5,000. There has been no established treatment except the use of steroids for symptomatic relief. We started researching oligonucleotide drugs to target the gene that causes DMD in 2009. The nucleic acid drugs work by targeting specific gene sequences to help regulate the production of proteins. They offer the possibility of treating diseases where conventional small molecule drugs have proven ineffective.

Viltepso: from development to gaining to manufacturing and marketing approval

Developed in a joint research program with the National Center of Neurology and Psychiatry (NCNP), Viltepso was the first antisense oligonucleotide discovered in Japan. It is made up of a chain of 21 morpholinos, or modified nucleic acids. DMD patients have gaps in the gene that codes for the protein dystrophin, with the DMD subtype related to the site of the missing exons (43–52, 45–52, 47–52, 48–52, 49–52, 50–52 and 52). By binding to the exon 53 site, Viltepso enables cellular machinery for gene transcription to skip over exon 53, resulting in dystrophin that is shorter than usual but still functional.

We received Sakigake designation from the MHLW for Viltepso in October 2015, followed by its orphan drug designation in August 2019. It was designated as a drug applicable for conditional early approval in October 2019. Based on the results of the clinical trials in the U.S. and Japan, it was granted an approval by the MHLW in March 2020 for patients with forms of DMD amenable to exon 53 skipping.

Provision of information

To support better therapeutic outcomes after the drug's approval, we have been conducting a range of activities aimed at providing patients and people around them with information to increase understanding of the disease so the value of Viltepso can be properly realized by medical institutions and patients.

If DMD patients are to live a longer and fuller life in the future, family members and other adults need to recognize signs of the disease at an early stage to enable opportunities for appropriate treatment. This calls for activities to support greater education. On March 20, 2021, we hosted an online seminar on Nippon Shinyaku's YouTube channel entitled, "Creating Better Futures for Children: Muscle-related Pediatric Diseases" (the event was also sponsored by the Ministry of Education, Culture, Sports, Science and Technology, and the Japan Muscular Dystrophy



Generic name: viltolarsen

This treatment for DMD is an antisense oligonucleotide consisting of modified nucleic acids called morpholinos. DMD is an intractable and progressive disease that has lacked any fundamental therapy until now. Viltepso was developed to help address the cause of this disease.

Association). The live event featured presentations by three specialists in the field to support enhanced understanding of DMD. We are also using this YouTube channel to host DMD-related content in cooperation with patients and their families affected by muscular dystrophy, including accounts of their experiences with confronting the disease firsthand and related thoughts.

Our hope is that events such as these can provide the opportunity to take the first optimistic steps towards a better life for patients by helping parents and others to understand how the therapeutic landscape has changed for DMD.

By continuing activities to help educate DMD patients and their families about the disease, we hope this will translate to opportunities for patients to live better.

Overseas

In a bid to deliver supplies of the drug to medical institutions and patients as early as possible, sales of the DMD treatment Viltepso in the U.S. started on August 19, 2020, just one week after we received accelerated approval for the product from the U.S. FDA.

Viltepso is the first product that we are marketing in the U.S. using our in-house resources. Medical representatives and medical affairs personnel from the Group subsidiary NS Pharma, Inc. (NSP), which is based in New Jersey, are involved in detailing the product and gathering data to help us gauge how to satisfy clinical demand. Following the launches in Japan and the U.S., we have filed a submission for regulatory approval in China, and are in discussions with regulators in Europe to secure approval at the earliest juncture. We are also looking at how to help DMD patients in other parts of the world gain access to Viltepso.

Status of DMD therapy in America

As in Japan, DMD affects approximately one in every 3,500 male newborns in the U.S. Of these, we estimate Viltepso could be administered to roughly 400 patients from an ambulatory stage. However, it is not an easy road for potentially eligible patients to gain access to Viltepso.

The universal health insurance system in Japan means patients cannot be refused treatment if they are covered under the system, irrespective of the treatment or medical institution involved. Financial costs for the patient's family consist of a co-payment of 10–30%.

The health insurance system in the U.S. is significantly different. Whether the cost of a drug such as Viltepso is reimbursed depends largely on the type of insurance policy covering the patient's family. As well as the public schemes Medicare and Medicaid, many Americans have private health insurance. Around 10% of patients in the U.S. are uninsured. This means it is necessary to provide support to ensure all the patients who need Viltepso can access the drug. NSP has established a support hub called NS Support to assist those families coping with DMD.

Role of NS Support

Variations in the insurance coverage of patients mean that eligibility for drug cost reimbursement by the insurer must be determined prior to medical treatment on an outpatient basis. Physicians in the U.S. often carry the administrative burden of determining these questions with the patient's insurer.

Another major challenge in the U.S. due to its geographical size (approximately 26 times larger than Japan) is the difficulty that many patients face to attend regular appointments at the specialist facilities that provide DMD therapy. In such cases, the drug is administered at home, implying a need for secure deliveries and good communications with the hospital.

NS Support provides a comprehensive care coordination and support service to assist DMD patients and their families and to help reduce the burden for treating physicians. NS Support offers guidance to families and physicians navigating the administrative procedures involved in the insurance reimbursement of Viltepso, and helps families administering the drug at home with supplies and related issues.

Development of in-house sales/ marketing system for the U.S. market

Unlike in Japan, where Viltepso can be prescribed once a physician has decided the best treatment option based on patient consent, negotiations with the individual insurance companies are required in the U.S. to gain approval for reimbursement of Viltepso. Managing this process is NSP's market access team, a function unique to the U.S. market. Locally recruited staff are tasked with following up each individual case. With many working from home due to the COVID-19 pandemic, the operations demand excellent communication skills to help build the necessary mutual trust. In this way, securing the patient's access to Viltepso is reliant on sustained efforts by dedicated teams to negotiate with insurers and resolve other related issues.

Future global development

In the U.S., NSP began selling Viltepso in August 2020 through our in-house sales set-up. Elsewhere, efforts are continuing to gain regulatory approval in China, Europe, and other markets as early as possible. An NDA was filed in June 2021 in China, where discussions with regulatory authorities are ongoing. We are considering which approach is optimal in each market based on our in-house resources in that market and our strategic partnerships with other companies.

NSP is also coordinating the global Phase III clinical study and other clinical trials of Viltepso. We continue to gather clinical data and plan to effectively use the data to enable provision of more detailed therapeutic information.

To support the provision of our distinctive and high-quality products to patients and medical institutions worldwide, our focus going forward remains on the accelerated global development of our operations by expanding on the existing business to build an organization that is well-suited to developing a global business, covering every stage from R&D to manufacturing, distribution and sales. We are focusing on the development of the Group's global product pipeline under the 6th Five-Year Medium-term Management Plan through prioritized investment in Viltepso, other successor exon-skipping therapies, and other drugs with global sales potential.

NS Pharma, Inc. (NSP)

NSP was established in July 1999 to enable the collection of information in the U.S. to support the early development of investigational compounds with global potential. Based in Paramus, New Jersey, NSP oversees the clinical development in North America of our in-house portfolio, as well as acting as the global coordinator for licensing and promotional activities in the U.S. and Europe.



Nippon Shinyaku's Initiatives in Response to the COVID-19 Pandemic

We would like to express our sincere gratitude to the healthcare professionals working on the frontlines of the fight against the COVID pandemic.

As a company concerned with human life and health, Nippon Shinyaku strives to maintain flexibility in order to continue fulfilling our goals as a pharmaceutical company, not only supplying pharmaceutical products in a stable manner by ensuring the safety of employees amid the risk of infection, but also pursuing R&D into potential treatments.

Stable product supply

To ensure a stable supply of pharmaceutical drugs, we practice effective and efficient risk management, adopting business continuity plans (BCP) at manufacturing sites and establishing our own checklists, thus maintaining the safety stock. Against risks involved in the procurement of active pharmaceutical ingredients (APIs), we have enlisted multiple suppliers and reinforced our ties with suppliers and other business partners. As a result, we are proud to say that our systems of pharmaceutical manufacturing and product supply to healthcare institutions are free of problems at the moment.



Research and development of therapeutics

Drawing on Nippon Shinyaku's strengths and capabilities in the area of nucleic acid drugs, we are pursuing research and development of anti-viral medicines using long-chain RNA, and the reprofiling of low-molecular-weight drugs.

Coronaviruses are single-stranded RNA viruses and therefore have high mutation rates. Nippon Shinyaku is looking into how nucleic acid drugs can be made into long-lived antiviral medicines suitable for treating not just COVID-19 but indeed any mutant coronavirus, in addition to the SARS and MERS viruses of the past and any new coronavirus infections that may emerge in the future.

Some 20 years ago, Nippon Shinyaku succeeded in the synthesis of long-chain RNA linking over 100

nucleotide bases, and we are now leveraging that proven platform technology in developing not only COVID-19 medications but also guide RNA for genome editing, for example.

The company also is investigating the potential of reprofiling, using existing drugs and drugs now in development. Sudden worsening of COVID-19 symptoms is closely associated with the hyperreactivity of the immune system (cytokine storm). If this can be controlled, it should be possible to prevent severe respiratory failure. Research has shown that cytokine storms can be curtailed by inhibiting intracellular signaling pathways such as Janus kinase (JAK) or interleukin-6 (IL-6), and Nippon Shinyaku is pursuing this angle further.



Telework system

From January 2018, we initiated a telework system to enable people to work from home for any teleconferences with areas in different time zones.

From April 2019, we extended the system to allow flextime workers to work from home or a rented conference facility under circumstances where it is difficult to commute to the designated workplace due to illness or injury, childcare or nursing care commitment or suspension of public transport due to bad weather.

Since April 2020, "all employees" have been eligible to work from home, and can do so simply to avoid infection with COVID-19, without needing to comply with the aforementioned conditions. Many

employees have taken up this offer. Nippon Shinyaku believes that telework contributes to a flexible and efficient working environment that in turn improves operational efficiency, reduces commuting time and effort, and helps employees to balance childcare and nursing care with work. In November 2020, we overhauled our telework system to enable all employees to fulfill their duties outside the workplace depending on their job and work-life balance (other than individuals unable to do so for security or job-specific reasons).

We are working to improve communication and ensure the psychological well-being of teleworkers through greater availability of digital devices, with a view to encouraging further uptake of telework and enhancing productivity.

Initiatives to prevent the spread of infection

Working modes	<ul style="list-style-type: none"> In principle, employees work from home to the extent that teleworking is possible. Employees who need to come to company workplaces make active use of the flextime system and/or staggered commuting hours to reduce potential viral exposure in crowded public transportation systems. Special leave is provided in daily or hourly units to employees receiving COVID-19 vaccinations.
In-house meetings and external assignments	<ul style="list-style-type: none"> In principle, all in-house meetings are held online. When an in-house meeting is held in person, a maximum duration of 30 minutes is recommended. In principle, all business trips, including inter-prefectural travel, have been suspended. The company's conference rooms, offices and cafeterias are equipped with acrylic partitions to prevent the spread of droplets, and hand disinfectants are provided at the entrances/exits of the buildings and the rooms.
Non-work employee events, gatherings, club activities, etc.	<ul style="list-style-type: none"> All non-work events, gatherings, club activities and the like that are usually held among employees on the company premises outside the regular working hours have been suspended.
Sales activities	<ul style="list-style-type: none"> Employees are advised to accurately inform themselves of the situations at the places they intend to visit for sales activities and act in compliance with the prescribed rules.
Thorough implementation of preventive measures	<ul style="list-style-type: none"> All employees coming to the company workplaces are strictly ordered to take their temperature beforehand and effectuate other health checkups and keep records. Employees are ordered to thoroughly implement basic measures to prevent infection, such as wearing masks, washing their hands and adopting protective gestures when coughing.
Responses in regions under state of emergency	<ul style="list-style-type: none"> In principle, teleworking (working from home) is the standard working mode. Necessary measures are devised in consideration of the respective office spaces and operational characteristics of different departments of the company to maintain the percentage of personnel coming to the company workplaces at around 30%. For sales activities, priority is given to web- or telephone-based meetings, and personnel effectuating in-person sales visits are advised to go directly to their destinations and go straight home afterwards.
Workplace vaccinations	<ul style="list-style-type: none"> In the headquarters area in Kyoto, the Company administered first and second doses of the new coronavirus vaccine to about 1,000 applicants, including employees, temporary staff, and suppliers, in early July and early August, respectively.

Initiatives to Promote Digital Transformation (DX)

At Nippon Shinyaku, we are promoting digital transformation (DX) based on the idea that effective utilization of digital technology constitutes a key element in management geared toward sustainable growth. In fiscal 2020, we created a division dedicated to DX and related affairs (the Digital Planning and Promotion Section) within the Information System Department. At the same time, we launched an inter-departmental DX promotion project to accelerate the promotion of DX on a company-wide scale.

Nippon Shinyaku's initiatives for promoting DX

Actively utilizing AI, IoT and RPA* in the respective departments, we are aware that it is essential to accelerate company-wide DX in a well-organized manner to achieve overall optimization and augment the company's competitiveness. As a milestone on the path to these objectives, we are working toward obtaining "DX Certification" and having the company's stocks selected to be on the list of "DX Stocks." To this end, we are formulating a DX vision and DX strategies, and assembling the infrastructure necessary for DX promotion and governance.

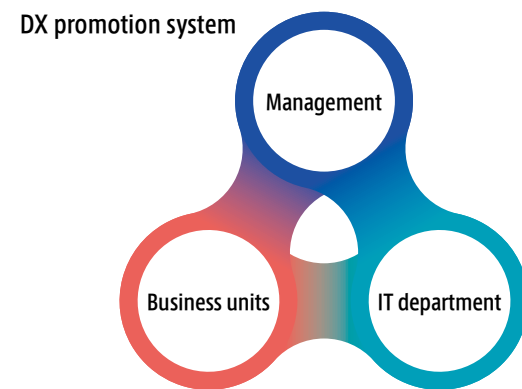
Moreover, we are planning a flexible review of our corporate organization and HR placement to advance measures including a company-wide productivity boost, work style reform, cost optimization, and new business creation, all supported by digitization. For DX-oriented HR development, we have launched several initiatives, including participation in training programs at universities and support for employees in obtaining learning opportunities and acquiring formal related qualifications. We are continuing the policy of training in-house specialists and improving the overall IT literacy of all employees.

* RPA: Robotic Process Automation, also known as "digital labor," refers to a software-based robotic technology that automates processes conventionally operated on a PC.

DX promotion system and DX-oriented HR development strategy

At present, the Digital Planning and Promotion Section is mainly in charge of gathering information on and adopting the latest digital technologies, identifying the needs of respective departments, and pursuing DX-oriented HR development. At the same time, we are aware that accelerating company-wide DX requires an organization and system with reinforced capabilities and authority. Accordingly, in the DX promotion project, we are discussing what shape our DX promotion system should take.

Nippon Shinyaku's DX-oriented HR development centers around two pillars: DX specialist training for candidates selected from among all employees and initiatives for IT literacy enhancement for all employees.

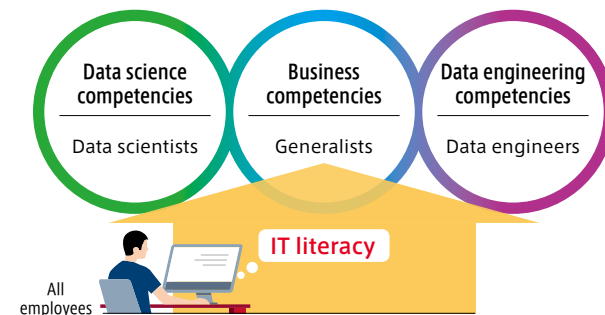


DX-oriented HR development

DX specialist training and education

- Data scientist training and education
- Generalist training and education
- Data engineer training and education

* Online group training for five selected trainees in each category



IT literacy enhancement initiatives for all employees

- In-house digital webinars (10 events, about 1,500 participants in total)
- Web-related skill improvement seminars (two events)
- Publication of in-house digital information magazines (in-house portal; published three or four times each month; a total of 42 issues)
- Programs encouraging the acquisition of an "IT Passport" and other formal qualifications (129 participants)
- Reverse mentoring (one event)
- Anything-about-IT consultations (about 20 cases)

* The figures in () are information on the events held in FY2020.



Case 01 Introduction and utilization of digital solutions

In this age characterized by drastic change and uncertainties, it is essential to be able to capture needs more accurately and rapidly than ever before, and to be flexible in adopting and utilizing digital solutions. In this process, digital solutions, adopted and utilized flexibly, can serve as powerful tools. For this reason, at Nippon Shinyaku, we examine and adopt digital solutions, with the departments concerned with the identification of needs assumed as principal actors and the Information System Department providing technical support. In this way, we can ensure the maximization of digital solutions thus adopted. The concrete digital solutions introduced thus far include AI-enabled voice-to-text conversion for our pharmaceutical consultation service, and an AI chatbot for an in-house product information.

As for RPA of routine tasks, it has been spreading on a company-wide basis, regardless of departments and operations. In FY2020, a total of some 100 tasks have been automated by RPA throughout the company, equivalent to about 10,000 workhours. Since RPA liberates employees from repetitive tasks, enabling them to shift their focus to more creative ones, their level of motivation has improved. For broader and more active RPA application, we are continuing events and activities that involve all employees, including in-house information meetings, development support meetings, and competitions between robots developed by different departments.

As a digital solution that benefits all personnel, an information sharing platform utilizing Microsoft365 and Teams was constructed in FY2020, under the theme of "Connection at any time, from anywhere and with anyone." This has nearly eliminated the difference between working from home and in the office, contributing to the prevention of the spread of COVID-19 at the same time.



We held an "RPA Robot Competition" with entries from the 13 departments utilizing RPA, with the President's Award going to the Odawara Central Factory's Production Planning Department.

Case 02 Enjoyable DX-oriented HR training programs

In FY 2020, Nippon Shinyaku inaugurated in-house DX webinars at the frequency of once to twice per month. The objective of this event is to improve the company-wide level of IT literacy through lectures and presentations on the latest digital technologies and DX-related in-house activities. The web-based sessions are easily accessible via smartphones, tablets, and other smart devices from the company's offices and sites across Japan by rearranging the schedule during the regular working hours. The webinars will continuously be held at least once each month in the future. By providing all employees with equal opportunity to regularly access digital information, the company aims to create an environment wherein personnel can proactively engage in DX while having fun.

In FY2020, we also inaugurated reverse mentoring on the theme of DX: younger employees well versed in digital technologies mentor management team members, with whom they otherwise rarely work together directly, instructing them in digital skills and informing them of the latest trends. We intend to continue organizing this event in the future.



Young employee offering reverse mentoring to director Takashi Takaya

DX is a means and not an end in itself.

DX is a means to change the way we work, to improve productivity, to create new businesses, and so on, and it is not an end in itself. Therefore, I think that involving all employees in promoting DX is a great opportunity for us in terms of corporate culture reform and HR development. The introduction of digital solutions and the training of DX-oriented personnel can prompt employees to review what they do at work and how they do it in their respective areas of responsibility. This can further prompt them to develop and improve their skills more proactively, adding assets to the company and leading to sustainable development in the future.

To that end, we will continue to pursue various initiatives supporting DX promotion, maintaining a focus on fun and positivity to put a smile on the faces of all employees.

Comment from DX promotion coordinator



Kenji Matsunaga
Digital Planning and Promotion Section Manager
Information System Department