Message from the President

Shigenobu Maekawa
President

By supplying distinctive products of high quality, Nippon Shinyaku contributes to people leading healthier and happier lives

6th Five-Year Medium-term Management Plan Numerical targets for FY2023

(Consolidated)	FY2018 results	**FY2019 results**	FY 2023 target	CAGR*1
Net sales	¥114,716 million	**¥116,637 million**	¥150,000 million	5.5%
Pharmaceuticals	¥100,223 million	**¥101,643 million**	¥133,000 million	5.8%
Functional Food	¥14,492 million	**¥14,994 million**	¥17,000 million	3.4%
Operating income	¥20,644 million	**¥21,668 million**	¥40,000 million	14.2%
Net income attributable to owners of the parent	¥16,302 million	**¥16,866 million**	¥30,000 million	13.0%
EPS*2	¥242	**¥250**	¥445	13.0%
ROE*3	12.5%	**12.0%**	10% or more during term of 6th Plan	

*1 CAGR: Compound Annual Growth Rate *2 EPS: Earnings Per Share *3 ROE: Return On Equity

6th Five-Year Medium-term Management Plan: Progress Status

In fiscal 2019, the management plan's first year, we made steady progress towards achieving our fiscal 2023 performance goals.

The Japanese economy slowed considerably due to the impact of the consumption tax hike and the COVID-19 outbreak, amid a persistently uncertain outlook. Conditions for Nippon Shinyaku and the broader pharmaceutical industry were harsh due to various initiatives to restrict healthcare spending in Japan, including stronger measures to promote greater use of generics. The coronavirus outbreak also had the effect of restricting numbers of patient visits to doctors. In the food industry, conditions remained challenging due to the low growth in spending by thrifty households, rising logistics and labor costs, and more intense competition.

Amid these business conditions, we recorded net sales of ¥116,637 million in fiscal 2019, a rise of 1.7% year on year despite the negative impact of the NHI price revision and lower revenues from the licensing of industrial property rights compared to fiscal 2018, when milestone payments were received for the pulmonary arterial hypertension (PAH) treatment Uptravi. Co-promotion sales revenues increased in fiscal 2019, and new products reporting higher sales included Gazyva (CD20-positive follicular lymphoma), Vidaza (myelodysplastic syndromes), Uptravi (PAH), and Zalutia (urinary disorders caused by benign prostatic hypertrophy). There was also a fresh contribution from Defitelio, which we introduced in September 2019 for the indication of sinusoidal obstruction syndrome. Net sales of pharmaceuticals rose 1.4% to ¥101,643 million. In the Functional Food business, higher sales of protein preparations, preservatives and other products contributed to a 3.5% year-on-year increase in net sales to ¥14,994 million.

In terms of profits, operating income increased 5.0% to ¥21,668 million due to the growth in sales offsetting the increase in the cost-of-sales ratio caused by factors such as the NHI price revision. Ordinary income rose 4.2% to ¥22,442 million, and net income attributable to owners of the parent increased 3.5% to ¥16,866 million.

Fiscal 2019 was the first year of our medium-term management plan. Overall, as in fiscal 2018, we recorded growth in sales and profits, representing steady progress towards achieving the fiscal 2023 performance goals.

Products to be launched during the 6th Five-Year Medium-term Management Plan

Already launched (as of August 20, 2020)

In-house	**Viltepso** (generic name: viltolarsen) Duchenne muscular dystrophy (DMD) — Japan/overseas	In-licensed: **Defitelio** (generic name: defibrotide sodium) Sinusoidal obstruction syndrome (treatment) — Japan

Regulatory approval targeted by FY2023

In-house	Exon 44 skipping drug DMD — Japan/overseas	**NS-018** (ilginatinib) Myelofibrosis — Overseas
In-licensed	**NS-32** (ferric derisomaltose) Iron deficiency anemia — Japan	**ZX008** Intractable epilepsy — Japan
PLCM	**NS-304** (selexipag) Chronic thromboembolic pulmonary hypertension — Japan	**NS-304** (selexipag) Arteriosclerosis obliterans — Japan
PLCM	**Macitentan** Chronic thromboembolic pulmonary hypertension — Japan	**NS-17** (azacitidine) Acute myeloid leukemia — Japan

Early regulatory approval targeted from FY2024

NS-580 Endometriosis	**NS-304** Lumbar spinal stenosis	**NS-87** Secondary acute myeloid leukemia	**NS-917** Relapsed/refractory acute myeloid leukemia

DMD treatments other than Viltepso and exon 44 skipping drug

Progress with "Six Actions" from 6th Five-Year Medium-term Management Plan

We are taking "six actions" to realize our vision, with the aim of strengthening our platform for sustainable growth.

1. Creation of new value through R&D

In the Pharmaceuticals business, we are working to enhance our development pipeline by focusing on four therapeutic areas (urology, hematology, intractable and rare diseases, and gynecology) and utilizing external and internal resources to pursue in-house drug discovery, in-licensing, and product life cycle management (PLCM), while seeking to add new drug-discovery modalities such as nucleic acid drugs and gene therapy. In the urology field, we began co-promotional activities with Janssen Japan for the launch in Japan of two new prostate cancer treatments, Erleada in May 2019 and Zytiga in February 2020. In the hematology field, besides launching Defitelio for the treatment of sinusoidal obstruction syndrome in September 2019, we also began Phase I/II clinical trials with NS-87, a treatment for secondary acute myeloid leukemia in-licensed from Jazz Pharmaceuticals plc. In addition, we received manufacturing and marketing approval in Japan for the Duchenne muscular dystrophy (DMD) treatment Viltepso in March 2020, and we began selling it in May 2020. We also began development of an oligonucleotide therapy for treating novel coronavirus infections within a broader review of the positioning of our existing sales and clinical development portfolio.

In the Functional Food business, we use external and internal resources to supply ingredients for functional foods with the excellent quality and originality expected of a pharmaceutical maker. In fiscal 2019, we launched a series of new products, in line with our policy of introducing high-value-added products that satisfy market needs.

2. Development of global business

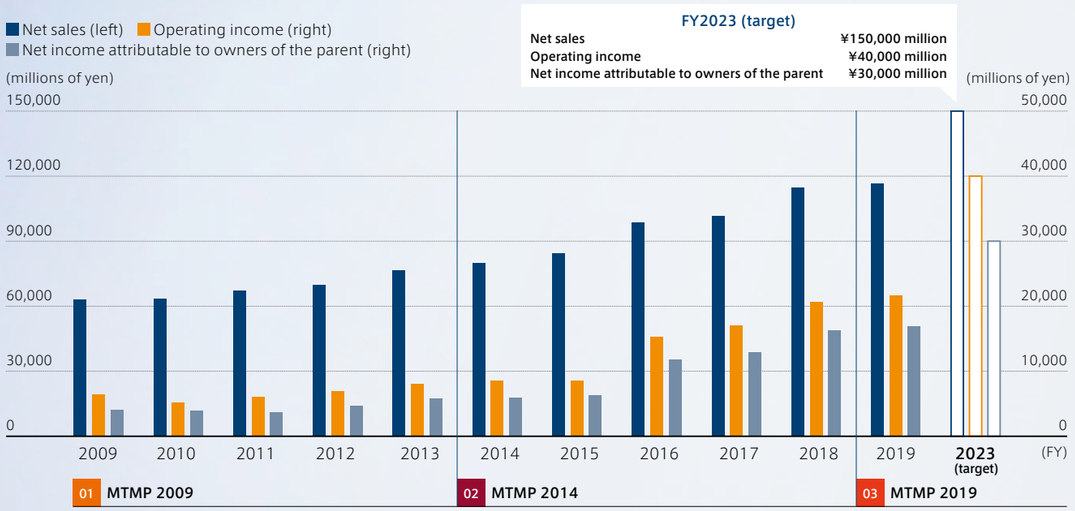
In collaboration with our global licensee Actelion Pharmaceuticals Ltd, a Janssen Pharmaceuticals company of Johnson & Johnson, we are steadily expanding sales of our in-house product Uptravi in Japan and overseas markets. Efforts to broaden its indications are also underway.

We commenced a rolling submission of an NDA to the US FDA for Viltepso in February 2019 based on the outcome of the Phase II clinical trials in the US. This process ended in September 2019, and we received official notification of acceptance in February 2020. Joint international Phase III clinical trials are currently underway. Our local US subsidiary NS Pharma is hiring sales personnel and building a local sales network. We expect to create a base for sustained growth in the US from the launch of Viltepso and successor oligonucleotide drugs and the myelofibrosis treatment NS-018, among other products. In Europe and China, we are targeting early NDA submissions for Viltepso, and we are also considering developing local sales networks utilizing in-house resources or our alliances with strategic partners.

Please refer to the Feature section (pp. 18–23) for more detailed information about "1. Creation of new value through R&D" and "2. Development of global business."

Evolution using Medium-term Management Plans

Prior to the 6th five-year plan, we have achieved steady growth by formulating and implementing medium-term management plans to cope with changing business conditions and related issues.



FY2023 (target)	
Net sales	¥150,000 million
Operating income	¥40,000 million
Net income attributable to owners of the parent	¥30,000 million

FY2009-2013

01 2009: 4th Five-Year Medium-term Management Plan Innovation and Growth

Overview

		Plans	Results
1.	Pipeline enhancement	·In-house drug discovery, in-licensing, product life cycle management (PLCM)	·In-house drugs: NS-018, NS-065/NCNP-01 ·In-licensed: ACT-064992, NS-24, GA101, tadalafil, Lunabell ULD
2.	Scientific product management	·Well-balanced growth between existing products and new products	·Investment in detailing based on clear allocation of resources in response to promotion of generics; steady progress with new products
3.	Functional Food	·Expand business and generate stable profits	·Business expanding, but transformation to stable profit structure still underway
4.	Low cost management	·Improved profitability	·Target of about ¥2 billion in cost reductions achieved
5.	Supporting employee growth	·HR development support ·Revise HR systems	·Creation of CASA (CAreer Support Academy) for development support/training; initiatives include Terakoya Academy, training for executives, next-generation leader training, level-specific training, support for MBA/PhD qualifications
6.	CSR activities	·Earning public trust	·New CSR initiatives: Children's Literary Awards, Nippon Shinyaku Kira-Kira Mirai Kodomo Bokin children's fund, Smiles Art Project, Public Service Award for Kyoto Kiwanis

FY2014-2018

02 2014: 5th Five-Year Medium-term Management Plan Aiming for New Growth –Pursuit of Originality–

Overview

		Plans	Results
1.	R&D strategy	·Develop pipeline to support regular product launches in areas of focus ·Reduce costs and speed up R&D by building manufacturing facility for clinical trial APIs	·Launched seven products, including Zalutia and Uptravi ·Enhanced pipeline via in-licensing agreements for six compounds, including NS-73 and NS-32 ·Completed clinical trial API manufacturing facility in March 2016; R&D sped up due to faster production of oligonucleotides and other APIs
2.	Marketing strategy	·Develop product groups in three areas (PAH, urology, hematology) into growth drivers	·New growth drivers created in Vidaza and Zalutia, each with sales of more than ¥10 billion ·Increased awareness of our presence in field of PAH due to detailing activities linked to launches of Uptravi and Opsumit
3.	Supply chain strategy	·Invest in production facility for high-bioactivity drugs to enable manufacture of in-house products	·Manufacturing plant for highly active solid formulations completed in July 2017 ·Manufacturing of Uptravi shifted in-house
4.	Overseas business strategy	·Expand operations using approaches tailored to conditions in each national market	·Uptravi: substantial contribution to growth from launch in many overseas markets ·NS-065/NCNP-01: preparations made to file US NDA and establish local sales organization
5.	Functional Food business	·Transform Functional Food business into highly profitable entity	·Operating margin significantly improved ·Supplement business started, creating foundation for transformation
6.	Human resource strategy	·Upgrade recruitment and training, recognizing that human capital is the source of originality	·Flextime system introduced for MRs (industry first in Japan) ·Outside specialist personnel recruited ·Recognized as "White 500" firm in Certified Health and Productivity Management Organization Program

FY2019-2023

03 2019: 6th Five-Year Medium-term Management Plan Aiming for Sustainable Growth –Pursuit of Further Originality–

Overview

		Plans
1.	Creation of new value through R&D	·Pharmaceutical R&D Strategy: Create original value by widening scope of drug discovery through addition of new modalities and technologies to the drug-discovery platform that produced selexipag (small molecule) and viltolarsen (oligonucleotide) ·Functional Food R&D Strategy: Bring to market continuous stream of highly original products by upgrading R&D capabilities
2.	Development of global business	·To supply distinctive products worldwide, build organization completely geared to development of global business from R&D to production, logistics and sales; accelerate pace of development in global operations built up in 5th Five-Year Medium-term Management Plan
3.	Increase in corporate value by strengthening ESG management	·Boost enterprise value and achieve sustainable coexistence with society by working to reinforce management based on ESG (Environment, Social, and Governance), primarily reflecting development of new treatments for intractable diseases and the supply of medicines to patients, and development of high-value-added consumer supplements
4.	Creation of organizational climate in which every employee can flourish	·Based on the concept that "unique products are the product of unique people," maintain respect for employee diversity free from discrimination based on gender, nationality or cultural background, and create an organizational climate where every employee can play a significant role and flourish by providing opportunities for individuals to take on challenges and grow
5.	Active use of AI and adoption of IT	·Support sustained creation of new value through aggressive adoption of AI, RPA and information technologies to allow faster product development, help streamline operations, and boost productivity
6.	Further strengthening of management base	·To achieve sustainable growth within a highly unpredictable and fast-changing environment, pursue greater profitability, improve management of costs and make effective use of resources while rebuilding management systems

3. Increase in corporate value by strengthening ESG management

We are working to raise corporate value through a strengthened focus on management based on ESG (Environmental, Social and Governance) aspects. This includes business activities such as creating treatments for intractable diseases to help patients, and providing high-value-added supplements for consumers. In January 2020, we signed the United Nations Global Compact (UNGC). By adhering to "The Ten Principles" of the UNGC, our aim is to build and maintain the trust of all stakeholders in Japan and abroad. Moreover, the announcement illustrates our commitment to working proactively as a corporate citizen to address societal issues.

4. Creation of organizational climate in which every employee can flourish

Since October 2019, we have introduced flextime arrangements across the company aimed at raising productivity by giving individuals more choice in terms of workstyle. In response to the COVID-19 outbreak, we have created conditions to facilitate smoother operational processes using staggered work times and ICT-based telework. Our plan for the post-COVID workplace is to realize more diverse working styles tailored to individual needs rather than insisting on a return to pre-pandemic norms.

Going forward, we will continue to respect the diversity of employees and seek to provide every individual with opportunities to grow by facing challenges proactively. In this way, we will ensure the organizational climate allows everyone to play a significant role and to flourish.

5. Active use of AI and adoption of IT

In fiscal 2019, we introduced Robotic Process Automation (RPA) across 13 divisions to improve productivity by boosting process efficiency and reducing costs. During this initial phase, the RPA project successfully generated annual savings of around 10,000 hours through automation of fixed processes and other improvements.

Looking ahead, we plan to extend this initiative on a larger scale across the company, while utilizing the time saved through greater process efficiency for creative purposes so that we can translate the gains into sustained growth. Moreover, through more active use of AI and adoption of IT, our policy is to boost productivity based on faster new product creation and streamlined operations.

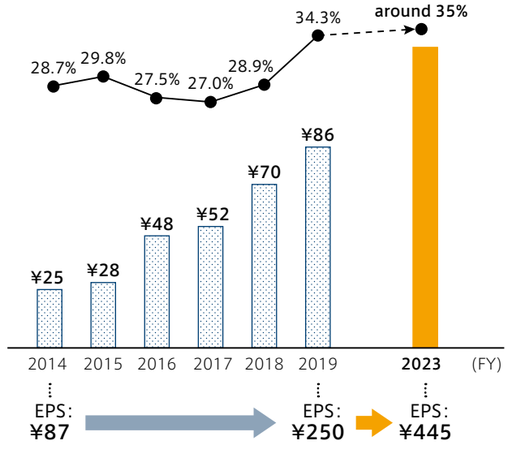
6. Further strengthening of management base

As mentioned earlier, we made steady progress in fiscal 2019 by increasing sales and profits as we work to achieve the performance targets in the 6th Five-Year Medium-term Management Plan.

To achieve sustained growth, we are continuing to strengthen our management base by maintaining a consistent focus on efforts to rebuild management systems, utilize management resources effectively, manage costs, and find ways to improve business profitability.

Over the period of the 6th Five-Year Medium-term Management Plan, we aim to utilize performance-linked dividends to boost the consolidated payout ratio to around 35%, with increases in EPS helping to grow total dividends per share.

Dividend per share / Payout ratio



Aspiring to be a "company with a meaningful existence in the healthcare field"

Outlook for FY2020, second year of 6th Five-Year Medium-term Management Plan

Our aim in fiscal 2020 is to set fresh records by growing sales and profits further.

In fiscal 2020, we are expecting an 8.9% increase in net sales to ¥110.7 billion. In pharmaceuticals, while we expect a negative impact from the NHI price revision, the advent of generic competition for Zalutia and the erectile dysfunction treatment Cialis, and other COVID-related impacts, we think these will be offset by several factors. In addition to higher sales of new products such as Uptravi, Gazyva and Defitelio, we are expecting growth in royalty income associated with overseas sales of Uptravi, higher co-promotional sales revenue, and a sales contribution from the launch of Viltepso. In functional food, we are expecting an increase in sales of 2.0% to ¥15.3 billion due to a sharp focus on the development and launch of new products, coupled with reinforced initiatives relating to core products. Overall, we expect consolidated net sales for the Nippon Shinyaku Group to increase 8.0% to ¥126.0 billion.

In terms of profit, we project year-on-year gains at every level, setting new records alongside net sales. We expect operating income of ¥25.0 billion (up 15.4%), ordinary income of ¥25.5 billion (up 13.6%), and net income attributable to owners of the parent of ¥19.0 billion (up 12.6%).

In R&D, we will focus on enhancing our pipeline, mainly targeting our core therapeutic areas, based on the three pillars of in-house drug discovery, in-licensing and PLCM. At the same time, we will continue working to launch drugs in our existing pipeline. Elsewhere, we have started R&D into potential nucleic acid treatments for COVID-19. We will also review the positioning of our current drug portfolio and development pipeline.

In fiscal 2020 to date, we have made a steady start as we work toward achieving the targets in the 6th Five-Year Medium-term Management Plan. We will continue to focus on realizing this plan.

Looking to prosper for another century

We are working to maintain the trust of every stakeholder and to be held in esteem as a vital enterprise.

We celebrated our 100th anniversary as a company in 2019. We cannot realize the sustained growth needed to prosper for another 100 years within a rapidly changing pharmaceutical industry unless we continue to produce distinctive products that take originality to new heights. Since we focus on the development of treatments for intractable and rare diseases with small patient populations, this is an area where we can deliver particularly original value. In addition, our aim is to maintain the trust of every stakeholder and to be held in esteem as a vital enterprise, not only by fulfilling our mission to patients and medical professionals, but also by contributing to the achievement of the Sustainable Development Goals (SDGs) through our enriched ESG initiatives.

Moving forward, we will aspire to be a "company with a meaningful existence in healthcare" based on realizing sustained growth through the efforts of all employees boldly taking up the challenge of achieving our goal to pursue originality and create distinctive products.

S. maekawa

Shigenobu Maekawa
President

Feature Progress with the 6th Five-Year Medium-term Management Plan

1 Creation of New Value Through R&D

First Antisense Oligonucleotide Discovered in Japan

Viltepso

Generic name: viltolarsen

One of the R&D challenges faced by Nippon Shinyaku is to develop therapies for intractable and rare diseases with no established treatment. We have been researching nucleic acid drugs at the Discovery Research Laboratories in Tsukuba for more than 20 years.

Societal issues in developing treatments for intractable and rare diseases

Total intractable/rare disease patients (Japan)

7.5 – 10 million

Over 6,000–7,000 types of intractable and rare diseases have been identified worldwide, with total patient numbers estimated at 7.5–10 million in Japan. Inherited disorders account for roughly 70% of the total, or 4,000–5,000 diseases. No effective treatments exist for many inherited disorders. Muscular dystrophy is an inherited intractable disease, with **Duchenne muscular dystrophy (DMD)** accounting for the bulk of cases. Since DMD is a serious and progressive neuromuscular condition for which no therapies other than symptomatic treatment have been established, the development of new treatments has been eagerly awaited.

The genetic cause of many intractable and rare diseases makes them especially difficult to treat with conventional drugs such as small molecules or antibodies. Small patient cohorts also make it difficult to gather sufficient epidemiological data or establish a clinical evaluation methodology. It is often unclear whether drug development will be economic for such conditions due to the high costs involved, and many pharmaceutical firms hesitate before committing to development.

What is Duchenne muscular dystrophy (DMD)?

Number of patients in Japan

Approx. 5,000

DMD inheritance follows an X-linked recessive pattern. It predominantly affects boys, with an incidence of about one case per 3,500 births. The estimated DMD patient population in Japan is about 5,000. In muscular dystrophies, the muscle fibers undergo degeneration and necrosis, which leads to progressive muscle weakness and a range of pathological changes. DMD is the most prevalent of the muscular dystrophies, generally causing weakness in or near the central trunk of the body. Muscular dystrophies were designated as intractable diseases in Japan in July 2015.

DMD is caused by a mutation in the gene coding for dystrophin, a protein that plays an essential role in maintaining the structural integrity of the cells as muscle tissue regenerates. Patients lose the ability to produce dystrophin. The deficiency weakens the membranes surrounding the cells in muscle tissue, causing progressive weakening of muscles as normal regeneration is blocked. This leads inexorably to loss of various capabilities, notably motor function.

Clinical symptoms of DMD

	Proximal muscle atrophy → Trunk muscle atrophy		
	Age 1–2 years (Onset)	Age 3–6 years	Age 10 years
Progression	Inherited at birth (X-linked recessive)	• Initial weakness in lower limbs, later spreading to upper limbs	• Rapid progression: most patients unable to walk by age 10 • Without assisted ventilation, most patients die from complications from late teens to early 30s
Clinical symptoms	Walking slightly delayed compared with healthy children	• Frequent falls • Waddling gait • Positive Gowers' sign*1	• Difficulty walking • Paralysis except for hands (can operate electric wheelchair) • Spinal deformities • Respiratory failure • Equinovarus foot*2 • Cardiac failure

Source: Byouki ga Mieru ("Atlas of Disease") Vol. 7 (Brain and Nerves) p. 374 (Medic Media, 2017)

*1 Gowers' sign: due to weakness in the pelvic muscles, the patient can only get off the floor by first rising to all fours and then "walking" hands up the knees
*2 Also known as clubfoot, a deformity where the instep extends and the heel does not touch the floor when standing or walking

1 Creation of New Value Through R&D

Nippon Shinyaku's Approach

Viltepso (generic name: viltolarsen)

(NS-065/NCNP-01)

Makeup of oligonucleotide drug Viltepso

DNA includes regions with genetic information for making proteins (exons) and regions that are non-coding (introns). The genetic information in the DNA is first **transcribed into a precursor of messenger RNA** (pre-mRNA) that contains exons and introns Fig. 1. The **final mRNA strand is then created** by linking together just the protein-encoding exons Fig. 2. Next, **the protein is synthesized** from the instructions contained in the mRNA template Fig. 3. It is hoped oligonucleotide drugs can be developed to treat previously intractable inheritable diseases, since they can act directly on the genes causing the conditions with a high degree of specificity.

Without Viltepso, the absence of exons upstream of exon 53 leads to a misalignment of the mRNA reading frame, and the dystrophin protein cannot be synthesized. As an antisense oligonucleotide, Viltepso binds to exon 53, enabling the cellular transcription machinery to skip over exon 53. The reading frame is realigned and dystrophin protein is made. Genetic testing can establish whether patients have a form of DMD amenable to treatment based on exon 53 skipping.

Although the dystrophin protein produced with exon 53 skipping is shorter than normal, it is expected to have sufficient functionality to help alleviate or restrict the muscle weakness in DMD patients.

Viltepso mechanism of action

Fig. 1

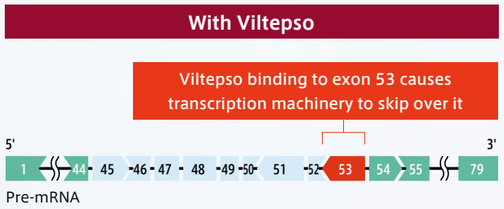
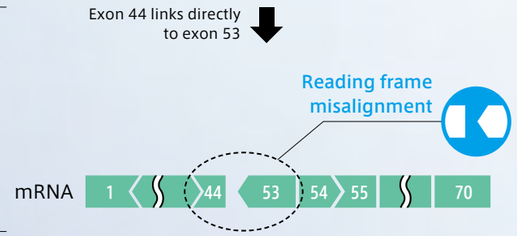


Fig. 2



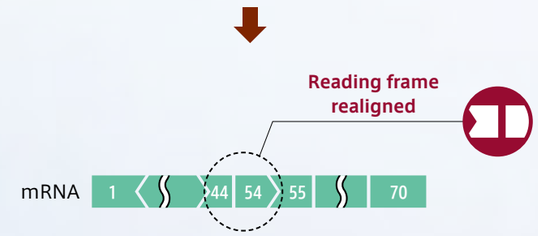


Fig. 3

Dystrophin protein not formed

Shorter, two-ended structure enables folding of protein and dystrophin expression

Source: Yoshitsugu Aoki et al., Journal of Clinical and Experimental Medicine, Recent Developments in Muscular Dystrophy, Ishiyaku Pub, Inc. (p. 6, 2017)

History of Viltepso development to regulatory approval

March 2020

Manufacturing and marketing approval (Japan)

* Marketing approval gained in US in August 2020

Until now, there has not been an approved DMD therapy in Japan to treat the underlying disease and reverse progressive muscle weakness or loss of motor function. We initiated a joint research project with the National Center of Neurology and Psychiatry (NCNP) in 2009 and discovered the exon 53 skipping drug NS-065/NCNP-01. It was first administered to human subjects in June 2013 in a physician-led study conducted by the NCNP. The trial met its primary endpoints of safety and expression of dystrophin. Using these results, we conducted Phase I/II studies in Japan and Phase II studies overseas. The clinical trials demonstrated dystrophin expression via exon 53 skipping. No serious adverse events were noted in any of the clinical trials.

Based on these results, we filed an NDA for regulatory approval in Japan in September 2019. In March 2020, MHLW granted manufacturing and marketing approval for viltolarsen for the indication of Duchenne muscular dystrophy in patients amenable to exon 53 skipping therapy, having earlier designated the drug as applicable for conditional early approval.

The US FDA also granted regulatory approval in August 2020.

Timeline of Viltolarsen development to simultaneous NDA filings in US/Japan

Development milestones

- Viltolarsen synthesized
- System used to discuss clinical trial strategy, non-clinical studies package and investigational drug quality issues
- Good tolerability and dystrophin expression demonstrated

US/Japan development history	
2009	Nippon Shinyaku initiates joint research with NCNP (Japan)
2011	Pharmaceutical Affairs Consultation on R&D Strategy system introduced by PMDA (Japan)
2013	Early-stage exploratory (physician-led) clinical studies initiated by NCNP (Japan)
Oct. 2015	"Sakigake" designation received from MHLW (Japan)
2016	**Phase I/II studies initiated (Japan)***
	Phase II studies initiated (US)*
Oct. 2016	Fast-track designation by FDA (US)
Jan. 2017	Orphan drug designation (US) Rare Pediatric Disease designation (US)
Feb. 2019	Rolling submission of NDA initiated (US)
Aug. 2019	Orphan drug designation (Japan)
Sep. 2019	**Regulatory applications filed (Japan/US)**

Regulatory milestones

- Regular discussions with the PMDA-appointed concierge enable efficient project management and resolution of pre-filing issues, accelerating development
- **NDA filings based on clinical trial results from US and Japan**
- Multiple rounds of discussion held with US FDA on clinical/non-clinical work and quality issues prior to rolling submission of NDA based on Phase II trial data from US and Japan
- Near-simultaneous filing in US and Japan
  Regulatory review process in Japan shortened to 6 months due to "Sakigake" designation

★ Results of P I/II studies (Japan)

Target	DMD patients (Japan): 16
Method	24-week administration schedule at 40 or 80 mg/kg
Results	Significant dystrophin expression in 14 out of 16 enrolled patients; no serious adverse events

★ Results of P II studies (US)

Target	DMD patients (US/Canada): 16
Method	20- or 24-week administration schedule at 40 or 80 mg/kg
Results	Dystrophin expression in all 16 enrolled patients; no serious adverse events

Market for nucleic acid medicines expected to grow

Projected global market size in 2030

Approx. ¥2,100 billion

Nucleic acid drugs are expected to be the next major therapeutic modality after antibody drugs. The global market for nucleic acid medicines is projected to reach ¥2,100 billion by 2030. As of December 2019, only 11 such products were on the market around the world. Of these, five have been launched since 2018. The pace of R&D into oligonucleotide drugs is accelerating, led by efforts to find therapies for intractable and rare diseases.

Besides the exon 53 skipping drug Viltepso, we are developing multiple exon skipping drugs to target DMD using a similar mechanism of action to Viltepso. This would allow us to offer therapy to more DMD patients. We are also looking at nucleic acid medicines as potential therapies for conditions that are intractable to conventional drugs such as small molecules and antibodies. As well as neuromuscular and other rare genetic conditions, we aim to develop distinctive new treatments across a range of therapeutic areas, including cancer and coronavirus infections.

1 Creation of New Value Through R&D

Kazuchika Takagaki
Corporate Officer
Department Manager,
Discovery Research Laboratories

On the R&D Frontline

Technology and experience gained from nucleic acid medicine development

There was no predetermined R&D path since it was the first nucleic acid drug discovered in Japan, and the process involved repeated trial and error. Our Discovery Research Laboratories in Tsukuba had been researching oligonucleotides for a long time, and so we had the basic technology platform for nucleic acid synthesis and evaluation at the time of development. However, Viltepso was a type of modified nucleic acid known as a morpholino that was quite different chemically from natural oligonucleotides. This made it hard for us from the start of R&D to synthesize even tiny sample quantities, and evaluation was just as difficult. We managed to find candidate sequences finally through painstaking sequence optimization after identifying the regions of high bioactivity.

We utilized a general solid-phase synthesis for supplying the quantities of drugs required in the non-clinical and clinical trials during early-stage development, but the yields were unacceptably poor when we tried to scale-up the production process. We teamed up with an external partner to develop a production method for large-scale synthesis. The method we developed was not only scalable and reliable, but was also better in that the yield was sufficiently high to translate into a reduced need for nucleic acid monomer.

Guaranteeing the quality of any investigational compound based on analysis is an indispensable part of the safety assurance process. Since there were hardly any examples of oligonucleotide drug development in either Japan or overseas for our reference, we had limited information. Lacking an established safety evaluation method for nucleic acid drugs, we held extremely detailed discussions with regulators under the "Sakigake" designation. To solve the technical issues required cooperation between our internal departments responsible for analysis/QC, production, pharmacokinetics and product safety.

DMD is a rare disease. The number of patients who can be treated is further restricted if we can only select those whose condition is amenable to exon 53 skipping. Our clinical development team recruited patients for the trial from around Japan after the National Center of Neurology and Psychiatry granted us access to their patient database. In contrast, in the US, our Group subsidiary NS Pharma had been working since 2014 with Head Office and local trial design consultants, as well as prominent researchers in the field, to ensure we had an integrated trial strategy from the outset. Since we also needed to confirm higher intracellular dystrophin concentrations after administration of the investigational drug to gauge its efficacy, our clinical development teams worked to solve this issue in collaboration with NS Pharma and the Discovery Research Laboratories in Tsukuba.

Future development

While we all hope that Viltepso will alleviate the suffering of DMD patients and their families, only about 8% of DMD patients stand to benefit from the drug. We want to develop other nucleic acid medicines to treat more patients with DMD by targeting other exons. In addition, we plan to continue R&D into nucleic acid drugs to help develop effective treatments for other diseases where conventional pharmaceutical therapies have not demonstrated sufficient efficacy.

Looking ahead, we will continue listening to patients and research physicians as we pursue R&D into medicines with improved efficacy that can help to treat more patients.

2 Development of Global Business

An Increasing Pace of Global Development

From R&D to production, logistics and sales, we are building an organization completely geared to the development of global business as we seek to supply our distinctive products worldwide. The pace of development in global operations built under the 5th medium-term management plan and other previous plans is now accelerating.

The concept espoused by Hisomu Ichinose when he founded Nippon Shinyaku was that Japanese would prefer the medicines they take to be made in Japan. Santonin, an anthelmintic that was the company's first domestically produced success, was later exported overseas. Ever since, Nippon Shinyaku has been an R&D-oriented pharmaceutical company making medicines not only for Japan, but overseas markets as well.

The development of global business is one of the "six actions" we defined as part of the 6th Five-Year Medium-term Management Plan that began in fiscal 2019 to achieve our corporate vision by realizing sustained development. It was a theme on which we focused in the 5th Five-Year Medium-term Management Plan as well. Our global growth in recent years has been spearheaded by Uptravi, a treatment for pulmonary arterial hypertension that we discovered in-house. Uptravi is on the way to becoming a blockbuster product due to the sales efforts of our global partner Actelion Pharmaceuticals Ltd, a Janssen Pharmaceuticals company of Johnson & Johnson across 55 countries worldwide.

Boosted in confidence by Uptravi's success, we are expecting to develop another global product in Viltepso, a treatment for Duchenne muscular dystrophy (DMD). Viltepso is gaining attention as an oligonucleotide, a class of drugs that forms a new treatment modality. Its discovery was the product of nucleic acid synthesis and sequencing technologies that we have developed over many years. In Japan, we received manufacturing and marketing approval from MHLW for Viltepso in March 2020, and we started sales and detailing activities in May. In the US, local subsidiary NS Pharma has led the clinical development of Viltepso. Our NDA application was received by the US FDA in February 2020, and we gained marketing approval for the drug in August. NS Pharma has now begun sales and detailing activities in the US. Besides the US, we hope to make Viltepso available to patients in more countries worldwide, starting with Europe and China. We are also developing other treatments for DMD to succeed Viltepso, which treats forms of DMD amenable to exon 53 skipping, with the focus on developing other oligonucleotide drugs that could enable skipping at different exons to help treat more DMD patients.

The Global Business Division that I lead exports not only Uptravi, but a range of other products we have developed in-house. These include the synthetic antibiotic prulifloxacin; the gastritis and gastric ulcer treatment Gaslon N; Trisenox, a treatment for relapsed and refractory acute promyelocytic leukemia; and Erizas, a treatment for allergic rhinitis. Our successful development of our export business has led to sales in Europe, the Middle East and Asia. In-licensing activities around the world are another major focus for the Global Business Division as we work to expand our development pipeline.

Global development is the basic assumption of our in-house drug discovery going forward – as seen with NS-018, our myelofibrosis treatment that is currently in US clinical trials. We will continue to work to provide patients worldwide with products in our main specialist areas, most notably intractable and rare diseases.

Toru Nakai
Director,
Head of Global Business