Message from the President

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

Shigenobu Maekawa
President

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% 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 ¥116,637 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.

<table>
<thead>
<tr>
<th>6th Five-Year Medium-term Management Plan Numerical targets for FY2023</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Consolidated)</td>
</tr>
<tr>
<td>Net sales</td>
</tr>
<tr>
<td>Pharmaceuticals</td>
</tr>
<tr>
<td>Functional Food</td>
</tr>
<tr>
<td>Operating income</td>
</tr>
<tr>
<td>Net income attributable to owners of the parent*</td>
</tr>
<tr>
<td>EPS*2</td>
</tr>
<tr>
<td>ROE*3</td>
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</tbody>
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*1 CAGR: Compound Annual Growth Rate  *2 EPS: Earnings Per Share  *3 ROE: Return On Equity

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

 Already launched (as of August 20, 2020)

<table>
<thead>
<tr>
<th>In-house</th>
<th>Viltepso (generic name: viltolarsen) Duchenne muscular dystrophy (DMD)</th>
</tr>
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<tbody>
<tr>
<td>In-licensed</td>
<td>Defitelio (generic name: defibrotide sodium) Sinusoidal obstruction syndrome (treatment)</td>
</tr>
</tbody>
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Regulatory approval targeted by FY2023

<table>
<thead>
<tr>
<th>In-house</th>
<th>Exon 44 skipping drug DMD</th>
</tr>
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<tbody>
<tr>
<td>In-licensed</td>
<td>NS-018 (lignatinib) Myelofibrosis</td>
</tr>
<tr>
<td>PLCM</td>
<td>NS-32 (ferri desferal) Iron deficiency anemia</td>
</tr>
<tr>
<td>NS-304 (selipexa) Chronic thromboembolic pulmonary hypertension</td>
<td></td>
</tr>
<tr>
<td>Macitentan (selected for development) Chronic thromboembolic pulmonary hypertension</td>
<td></td>
</tr>
<tr>
<td>NS-17 (azacitidine) Acute myeloid leukemia</td>
<td></td>
</tr>
</tbody>
</table>

Early regulatory approval targeted from FY2024

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

DMD treatments other than Viltepso and exon 44 skipping drug
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 N5 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 myofibrosis 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.
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 flexible 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 by 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

<table>
<thead>
<tr>
<th>Year</th>
<th>EPS (¥)</th>
<th>Payout ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014</td>
<td>¥87</td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td>¥25</td>
<td>28.8%</td>
</tr>
<tr>
<td>2016</td>
<td>¥48</td>
<td>27.5%</td>
</tr>
<tr>
<td>2017</td>
<td>¥52</td>
<td>27.0%</td>
</tr>
<tr>
<td>2018</td>
<td>¥70</td>
<td>28.9%</td>
</tr>
<tr>
<td>2019</td>
<td>¥86</td>
<td>34.3%</td>
</tr>
<tr>
<td>2023 (FY)</td>
<td></td>
<td>around 35%</td>
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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 ¥10.7 billion. In pharmaceuticals, while we expect a negative impact from the NHK 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 Viltropo. 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 intractable and rare 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.

Aspiring 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.

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.

Shigenobu Maekawa
President
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.

**Societal issues in developing treatments for intractable and rare diseases**

**Total intractable/rare disease patients (Japan)**

7.5 – 10 million

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**What is Duchenne muscular dystrophy (DMD)?**

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**

<table>
<thead>
<tr>
<th>Age 1–2 years</th>
<th>Age 3–6 years</th>
<th>Age 10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inherited at birth (X-linked recessive)</td>
<td>Initial weakness in lower limbs, later spreading to upper limbs</td>
<td>Rapid progression: most patients unable to walk by age 10</td>
</tr>
<tr>
<td>Walking slightly delayed compared with healthy children</td>
<td>Frequent falls</td>
<td>Paralysis except for hands (can operate electric wheelchair)</td>
</tr>
<tr>
<td><em>Gowers’ sign</em>&lt;sup&gt;1&lt;/sup&gt;</td>
<td>&quot;Waddling gait&quot;</td>
<td>Respiratory failure</td>
</tr>
</tbody>
</table>

<sup>1</sup> *Gowers’ sign*: due to weakness in the pelvic muscles, the patient can only get off the floor by first stooping with both hands and then "walking" hands up the knees.

*Also known as equinovarus foot, a deformity where the calf extends and the heel does not touch the floor when standing or walking.*

**Number of patients in Japan**

Approx. 5,000

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.

**Viltepso**

Generic name: viltolarsen

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**First Antisense Oligonucleotide Discovered in Japan**

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**Viltepso (generic name: viltolarsen)**

(ns-065/ncnp-01)

**Viltepso mechanism of action**

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.

**Timeline of viltepso development to simultaneous nDA filings in us/japan**

- **2009** Nippon Shinyaku initiates joint research with NCNP (Japan)
- **2011** Pharmaceutical Affairs Consultation on R&D strategy initiated by PMDA (Japan)
- **2013** Early stage exploratory (physician initiated) clinical studies initiated by NCNP (Japan)
- **2016** Phase I/II/III studies initiated (Japan)
- **2016** Fast-track designation received from MHLW (Japan)
- **2017** Orphan drug designation (US)
- **2017** Rare Pediatric Disease designation in Japan
- **2018** Noting submission of NDA initiated (US)
- **2019** Orphan drug designation (Japan)
- **2019** Regents skalbita designation received from MHLW (Japan)

**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.
ANNUAL REPORT 2020

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 modified type of 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 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.