Nippon Shinyaku Co., Ltd.

FY2025 R&D Meeting

March 2, 2026

Event Summary

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Toru Nakai	Representative Director, President
Takanori Edamitsu	Director, Business Management & Sustainability Division
Keiichi Kuwano	Director, Research & Development
Manabu Beppu	Corporate Officer, Head of R&D Planning and Administration Div.
Hideyasu Takechi	Corporate Officer, Department Manager, Corporate Planning Dept.

Presentation

Takechi: It is time to commence the FY2025 R&D Meeting of Nippon Shinyaku Co., Ltd.

Prior to the presentation, we would like to introduce today's speakers. From the left, facing you, Mr. Nakai, Representative Director, President. Mr. Kuwano, Director, Research & Development. Mr. Edamitsu, Director, Business Management & Sustainability Division. Mr. Beppu, Corporate Officer, Head of R&D Planning and Administration Division, and I am the moderator, Takechi, Corporate Officer, Department Manager, Corporate Planning Dept. Thank you.

The content of today's presentation will be available on our website as an on-demand video streaming and script, so please be aware of this before speaking at the question-and-answer session after the presentation.

Now, Mr. Nakai, please go ahead.

Nakai: I am Toru Nakai, Representative Director, President of Nippon Shinyaku. Thank you very much for taking time out of your busy schedules today to participate in our FY2025 R&D Meeting. We appreciate your participation.

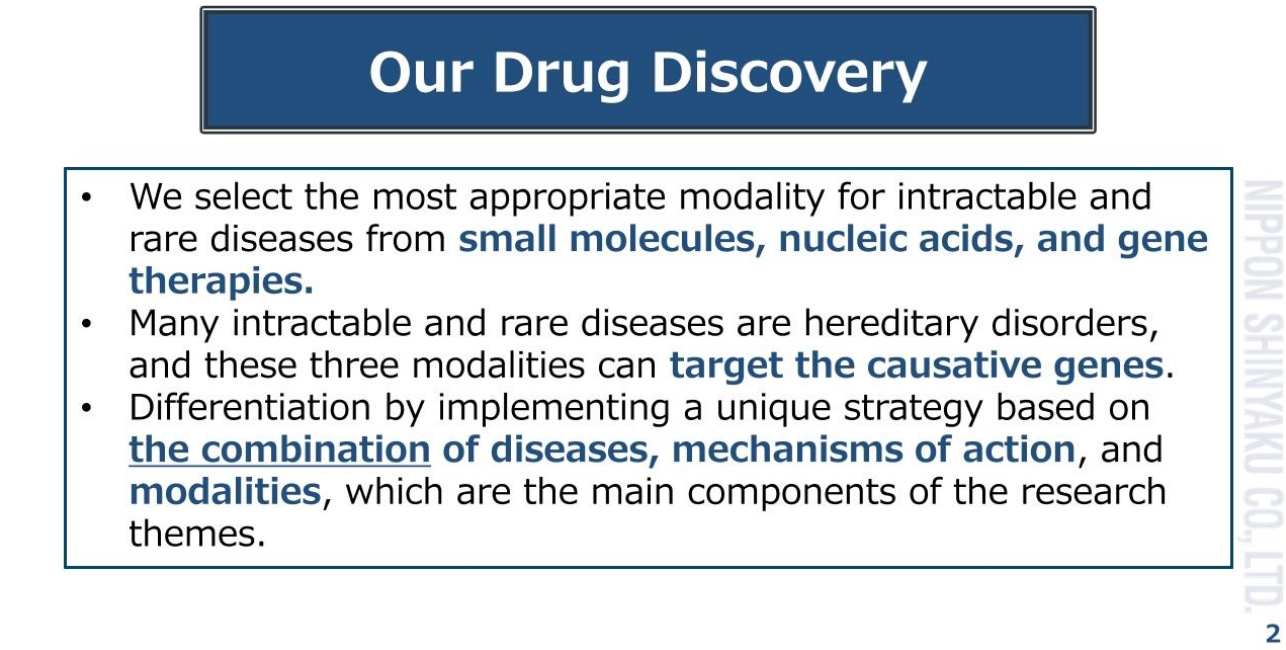
In the first part of the presentation, Mr. Kuwano, who assumed the position of director in charge of R&D in June last year, will explain the direction of drug discovery that we are aiming for and the characteristics of the pipeline that we are currently developing.

After a 10-minute break, the second part of the meeting will be an IR meeting.

First, I will introduce the main results to date for FY2025, as well as the latest outlook for the market launch target in the mid-term management plan.

Unlike our usual financial results briefings, today's meeting will allow more time for dialogue with you. We hope that lively discussions will provide you with an opportunity to deepen your understanding of our company.

Now, Mr. Kuwano, in charge of research and development, will give an explanation of the drug discovery we are aiming for.



Kuwano: I am Keiichi Kuwano, Director, Research & Development.

After presenting the direction of drug discovery that we are aiming for, we will have time for a question-and-answer session.

This is the essence of the drug discovery that Nippon Shinyaku is aiming for. We hope to promote drug discovery for intractable and rare diseases by freely selecting the most appropriate modality from small molecules, nucleic acids, and gene therapies. Many intractable and rare diseases are hereditary, and we believe that these three modalities are very reasonable approaches in the sense that they can act on the etiological genes. There are three main components of research themes: disease, mechanism of action, and modality, and we intend to implement a highly unique and differentiated strategy by successfully combining these components.

I would like to explain the focus areas.

These are the focus areas of Nippon Shinyaku, which we have been showing you for some time. We have four therapeutic areas: hematology, intractable and rare diseases, urology, and gynecology. In the area of intractable and rare diseases, in particular, we have made progress in the modality of in-house drug discovery such as Uptravi, successful small-molecule drug, and Viltepso which was successfully launched with nucleic acid. I would like to be more specific about the intractable and rare diseases that represent these focus areas.

Intractable and Rare Diseases

85% of our development pipeline targets intractable or rare diseases.

- The average ratio of intractable and rare diseases is 28% among 69 companies with sales over 100 billion yen and more than 10 products under development.
- Nippon Shinyaku's ratio is 85%, **ranked at the top in both domestic and global markets.**

Ratio of Intractable and Rare Diseases in Pharmaceutical Companies' Development Pipelines

Japan			
#	Company name	%	# of products
1	**Nippon Shinyaku**	**85**	**11**
2	Company A	47	20
3	Company B	43	9
4	Company C	43	3
5	Company D	38	5

Global			
#	Company name	%	# of products
1	**Nippon Shinyaku**	**85**	**11**
2	Company E	70	7
3	Company F	60	6
4	Company G	58	14
5	Company H	50	38

Source: Evaluate Pharma® 9 2025, analysis for the first indication, ©Evaluate Ltd 5

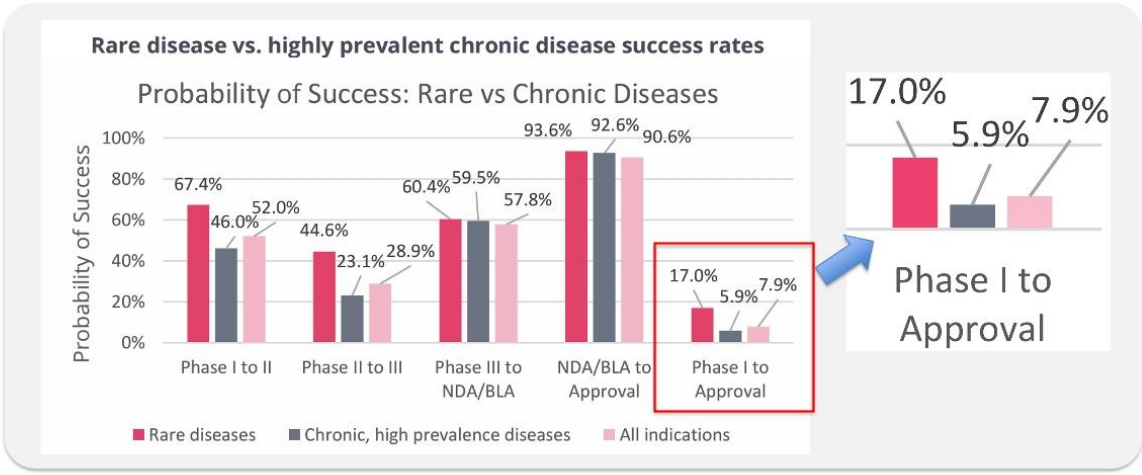
We are actually promoting drug discovery in this field, and this is reflected in the figures. In aggregating the data of 69 companies with sales of more than JPY100 billion and products under development more than 10, the average percentage of products under development in the field of intractable and rare diseases is approximately 28%, while the percentage of our company is remarkably high at 85%.

Even among domestic companies, ours is the highest, with no other company exceeding 50%, and globally, although the number of items under development is smaller than that of the major companies, the ratio is outstandingly high, at 85%.

Why Rare Diseases?

Success rates in development for rare diseases are relatively high

- Probability of success from P1 to approval is about 3x higher than for chronic diseases.
- Depending on requirements, regulatory pathways for Accelerated Approval may be available.



Source: "Clinical Development Success Rates and Contributing Factors 2011-2020", Rare disease vs. highly prevalent chronic disease success rates

There are a number of reasons why we are working in the area of intractable and rare diseases, but one reason is that the probability of success in rare diseases is relatively high, as shown here.

The graph below shows the data from Phase I to Phase II, Phase II to Phase III, Phase III to NDA, and finally Phase I to approval, which includes rare diseases, chronic diseases, and all indications. In this way, the total Phase I to approval results show that the probability of success is about three times higher for rare diseases than for chronic diseases.

In addition, as you know, there is a possibility of accelerated approval for intractable and rare diseases, depending on the requirements, and in some cases it may be possible to skip certain development steps.

Our Pipeline and Disease Areas

Disease area		Development pipeline
Hematology		NS-401, LY3527727, NS-917
Immunology		GA101, NS-229
Neuromuscular		ZX008, CAP-1002, NS-089, NS-035, NS-050, NS-051
Pulmonary hypertension (PH)		NS-863, NS-421
Specialty	Congenital metabolism	RGX-121, RGX-111
	Ophthalmology	ATSN-101

Black: small molecule, Orange: nucleic acid, Green: gene therapy, Blue: other

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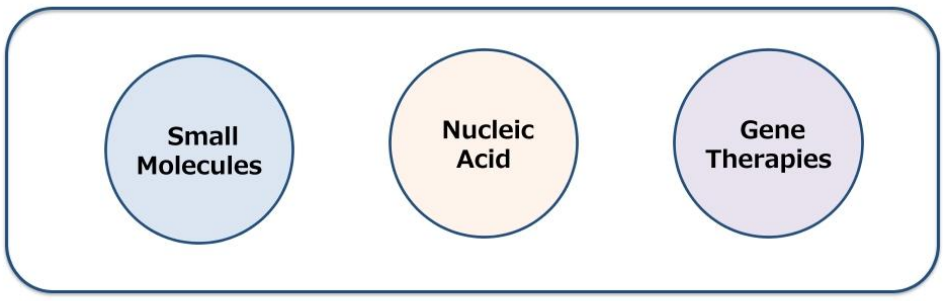
Under such development policy, our pipeline is mainly for intractable and rare diseases, but we also have pipelines for hematology, immunology, neuromuscular, and pulmonary hypertension.

Types of Modalities

We are advancing our research and development activities centered on the following three core modalities.



Nippon Shinyaku leverages three modalities capable of acting on genes, with strength in selecting the optimal modality for disease-causing genes.

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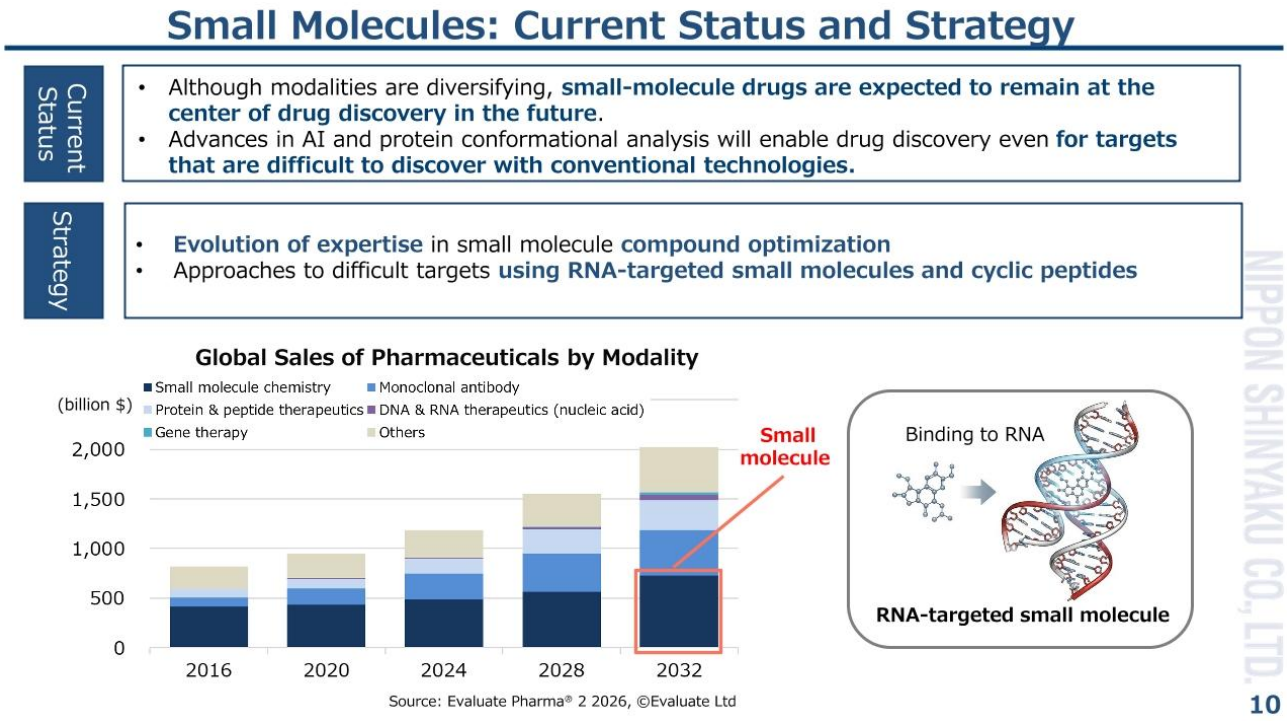
I would like to continue talking about modalities.

As I mentioned at the beginning, we have already conducted and will continue to promote research activities based on the three modalities shown here.

While major global companies are working on various modalities such as cells and antibodies in addition to these three modalities, I am aware that there are very few companies of our size that are developing drug discovery focusing on these three modalities.

As I mentioned at the beginning, these three modalities are easy to approach disease-causing genes, and by selecting the optimal modality, we can aim for optimal drug discovery.



Let me discuss each modality.

First, as for small molecule drugs, some people have suggested that small molecule drug discovery is running out of targets amidst the diversification of modalities.

However, as shown in the graph below, small molecule drugs are still expected to be at the center of drug discovery, accounting for about half of future sales.

I think this is due to the fact that the development of technology in recent years has made it possible to do more and more of the things that are difficult to create drugs with conventional technology.

For example, AI and protein conformational analysis have made great progress, making drug discovery possible.

We have been active in small molecule drug discovery for a long time, and we believe that we have expertise and strength in compound optimization, which we intend to further develop. In addition, we would like to work on small molecules that target not only proteins but also RNA, and we would like to use cyclic peptides, which are more advanced from small molecules, to approach difficult targets.

Nucleic Acid Drugs: Current Status and Strategy

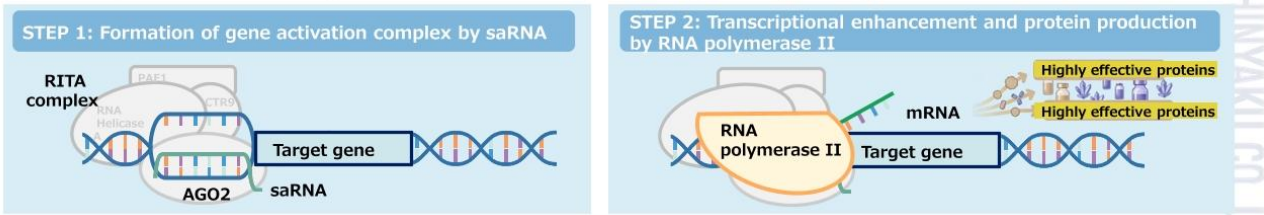
Current Status

- **Patent competition for nucleic acid drugs is intensifying**, and **securing in-house patents** is an important issue.
- Limited therapeutic effect due to lack of tissue transferability

Strategy

- **Potential for patent acquisition**: Application of expression-enhanced nucleic acids to loss-of-function diseases
- Beginning with central local administration, expanding to intravenous administration using DDS technology

Gene expression-enhancing nucleic acids: Small activating RNA (saRNA)



DDS : drug delivery system
RITA : RNA-induced transcriptional activation

Next is nucleic acid drugs, which, given the state of the world, are experiencing intensified patent competition.

Of course, small molecules also require patents, but nucleic acids are a world where patents are even more important than small molecules, and if conceptual patents are suppressed, research and development will not be able to proceed.

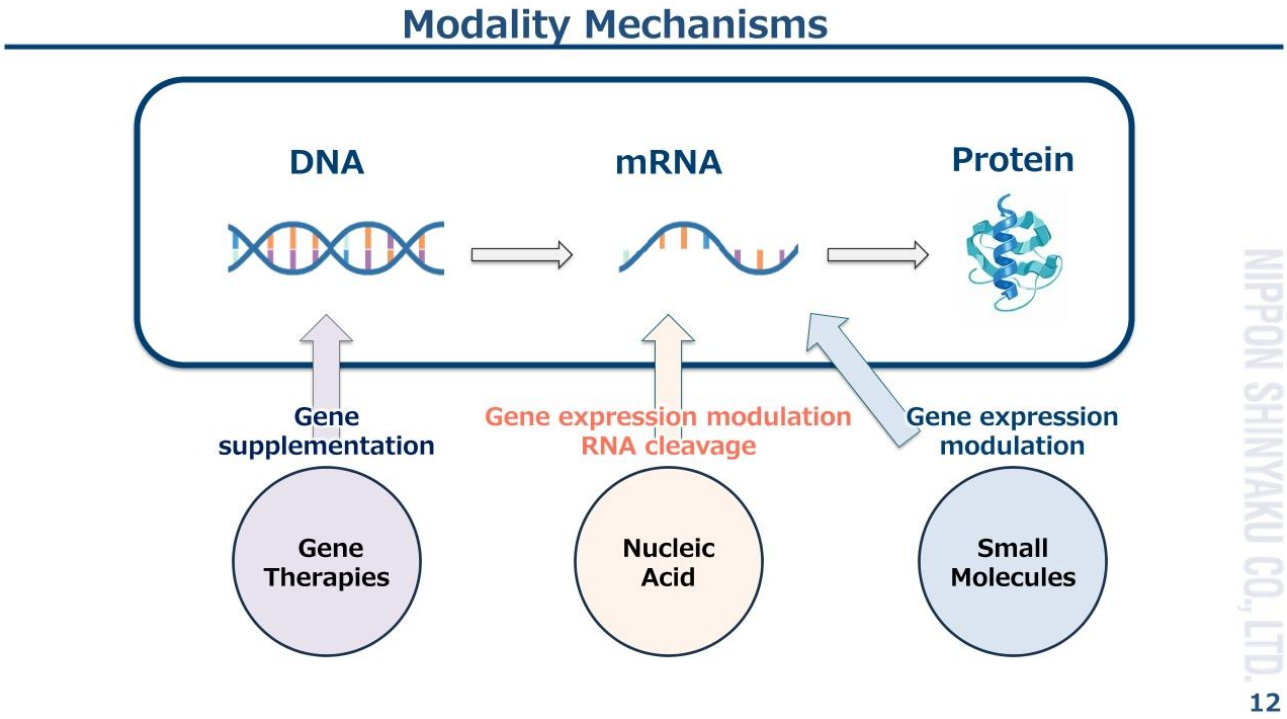
Then there is the issue of the need for DDS due to lack of tissue transferability compared to small molecules.

We must have high expectations for the development of this area, but there is a problem of how to overcome the limited therapeutic effect.

Therefore, we would like to work on expression-enhanced nucleic acids, for which we believe there is still room for patent acquisition.

By working on this, we hope to apply it to loss-of-function diseases and approach diseases that we have not been able to research and develop in the past.

We would also like to work on central nervous system diseases, starting with central local administration, which does not yet require DDS, or drug delivery system innovations, and then expand to intravenous administration using DDS technology.



This page shows modality mechanism.

Three modalities made it easier to approach intractable and rare diseases and genetic diseases. For example, in the case of gene therapy, the approach could be to replenish the gene, and in the case of nucleic acids and small molecules, the approach could be to control the expression of mRNA, or in the case of nucleic acids, to suppress the expression of RNA by cutting it.

Of course, small molecules can also act on proteins to develop drugs that contribute to intractable and rare diseases.

So by freely selecting these three things, we hope to promote innovative drug discovery.

Open Innovation in Progress

Target Search	• Search for novel disease-causing genes • Disease mechanism elucidation by AI
Modality Technology	• Gene expression enhancing nucleic acids targeting loss-of-function diseases • RNA-targeted small molecules for genetic diseases
Seeds introduction	• Acquisition of innovative therapeutic seeds • Enhancement of pipeline by seed supplementation

Advancing open innovation in areas where we can leverage our strengths, aligned with our drug discovery strategy

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Next, I would like to move on to open innovation.

We have identified three axes of our open innovation.

One is target search.

Then there is the technology represented by modalities, and furthermore, the introduction of seeds.

The target discovery will be presented in more detail later in this presentation, but we are looking forward to collaborating with Boston Children's Hospital, for example, in the search for novel etiologic genes.

We will also be working on elucidating disease mechanisms through AI.

In terms of modalities, we have already entered into a partnership with MiNA Therapeutics for gene expression enhancing nucleic acids for loss-of-function diseases, as I mentioned earlier, and we intend to promote more and more of these modalities.

We would also like to work on RNA-targeted small molecules for genetic diseases, including partnerships.

As we move forward with these matters, we hope to promote open innovation in areas where we can demonstrate our strengths in accordance with our drug discovery strategy.

Strategic Alliance with Boston Children's Hospital (BCH)

The No.1 children's hospital in the U.S.

- World-class medical institution with outstanding clinical and research achievements
- 3,000 researchers and 3,000 peer-reviewed papers per year

Affiliated with Harvard Medical School

- A center for cutting-edge medical research and education

Seeking research proposals with social impact from BCH's researchers

- Nippon Shinyaku entered into a strategic alliance with BCH in June 2025.
- With an eye toward establishing a long-term partnership with BCH in the rare disease areas, we select themes that are expected to yield positive effects for our own research.

July 1 2025, Announcement of Strategic Alliance with Boston Children's Hospital 15

This is in regard to the strategic alliance with Boston Children's Hospital in the US that I mentioned earlier.

Needless to say, this is one of the largest children's hospitals in the US, and it is also renowned for its excellence in research.

The hospital is also affiliated with Harvard Medical School and is a center for cutting-edge medical research and education.

We have already entered into a strategic partnership with them last year and would like to collaborate with specific laboratories on specific research projects.

We have almost finished picking up those areas and hope to move forward with specifics in this area in the next fiscal year. From here I would like to discuss the specific pipeline.

Pipeline (1/2)

Stage	Code No. (Generic name)	Origin	Indications	Schedule	Country	ID#
Launch P3	NS-065/NCNP-01 (viltolarsen)	Co-development with National Center of Neurology and Psychiatry	Duchenne muscular dystrophy	—	Japan	jRCT2080224893
				—	U.S.	NCT04060199
Preparation for launch	NS-401 (tagraxofusp)	In-license The Menarini Group	blastic plasmacytoid dendritic cell neoplasm	Study completion : FY2026	Japan	jRCT2031220023
Filed	CAP-1002 (deramiocel)	Partnership Capricor Therapeutics, Inc.	Duchenne muscular dystrophy cardiomyopathy	—	U.S.	NCT03406780[1]
						NCT05126758[2]
Filed	RGX-121 (clemidsogene lanparvovec)	Partnership REGENXBIO Inc.	mucopolysaccharidosis type II	Under clinical hold[3] CRL[4]	U.S.	NCT03566043
P3	ZX008 (fenfluramine hydrochloride)	Distribution partnership UCB S.A.	CDKL5 deficiency disorder	Study completion : FY2026	Japan	jRCT2041230015
	GA101 (obinutuzumab)	In-license Chugai Pharmaceutical Co., Ltd.	lupus nephritis	Projected submission : CY2026	Japan	jRCT2011210059
			pediatric nephrotic syndrome	Projected submission : CY2026	Japan	NCT05627557
			extra renal lupus	Projected submission : CY2027	Japan	jRCT2071230031
	CAP-1002 (deramiocel)	Partnership Capricor Therapeutics, Inc.	Duchenne muscular dystrophy	—	U.S.	NCT05126758
	LY3527727 (pirtobrutinib)	Alliance agreement Eli Lilly Japan K.K.	mantle cell lymphoma	—	Japan	jRCT2021210026
			chronic lymphocytic leukemia	—	Japan	jRCT2011210061
						jRCT2041210150
						jRCT2021220024
Preparation for P3	NS-304 (selexipag)	In-house	arteriosclerosis obliterans	Study start : FY2025	Japan	jRCT2071250134

1. Phase II (HOPE-2)
2. Phase III trial (HOPE-3 trial)
3. Clinical hold received from the FDA in January 2026
4. Complete Response Letters (CRLs) are issued directly to product sponsors when the FDA completes its review cycle and determines that it cannot grant an approval of an application in its current form.

*Schedule is based on trial end dates, etc. from jRCT or ClinicalTrials.gov.

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I will now explain three items from these two pipeline slides.

NS-304, selexipag, is at the bottom of this table and is indicated for the treatment of arteriosclerosis obliterans.

Pipeline (2/2)

Stage	Code No. (Generic name)	Origin	Indications	Schedule	Country	ID#
P2	NS-580 (friluglanstat)	In-house	endometriosis	Temporarily suspended	Japan	jRCT2031210685
			chronic prostatitis/ chronic pelvic pain syndrome	Temporarily suspended	Japan	jRCT2031230134
	NS-089/NCNP-02 (brogidirsen)	Co-development with National Center of Neurology and Psychiatry	Duchenne muscular dystrophy	Study completion : FY2026	Japan	jRCT2041250028
					U.S.	NCT05996003
	NS-229	In-house	eosinophilic granulomatosis with polyangiitis	Study completion : FY2026	Japan	jRCT2031230526
					U.S.	NCT06046222
Preparation for P2	NS-035	In-house	Fukuyama congenital muscular dystrophy (FCMD)	Study start : FY2026	Japan	In preparation
	NS-863	In-house	pulmonary arterial hypertension	Study start : FY2026	Japan	In preparation
					U.S.	NCT07441200
			pulmonary hypertension associated with interstitial lung disease		Japan	In preparation
					U.S.	NCT07441278
P1/2	NS-050/NCNP-03	Co-development with National Center of Neurology and Psychiatry	Duchenne muscular dystrophy	Study completion : FY2027	Japan	jRCT2041240060
					U.S.	NCT06053814
	ATSN-101	In-license Atsena Therapeutics	GUCY2D-associated Leber congenital amaurosis	Study completion : FY2027	U.S.	NCT03920007
	RGX-111	Partnership REGENXBIO Inc.	mucopolysaccharidosis type I	Under clinical hold[1]	U.S.	NCT03580083
P1	NS-917 (radgocitabine)	In-license Delta-Fly Pharma, Inc.	relapsed/refractory acute myeloid leukemia	Study completion : FY2026	Japan	jRCT2031210452
	NS-025	In-house	urological diseases	Study completion : FY2024	Japan	jRCT2031220474
	NS-245	In-house	Inframmatory diseases	Study completion : FY2026	Japan	jRCT2071250086

*Schedule is based on trial end dates, etc. from jRCT or ClinicalTrials.gov.

1. Clinical hold received from the FDA in January 2026

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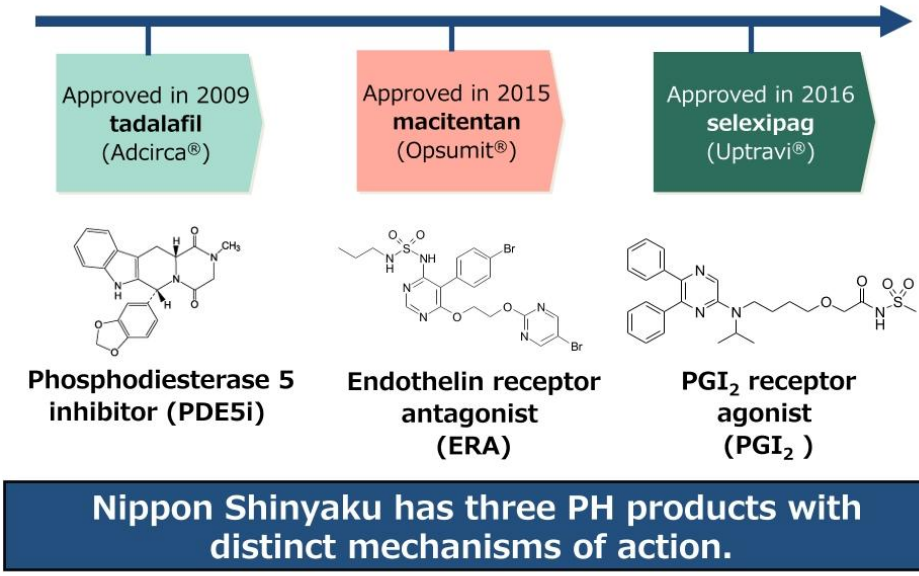
The next table shows NS-035, a therapeutic agent for Fukuyama congenital muscular dystrophy. I would also like to introduce NS-863, which was revealed today for the first time as a treatment for pulmonary hypertension.

Our Product Line for Pulmonary Hypertension (PH)



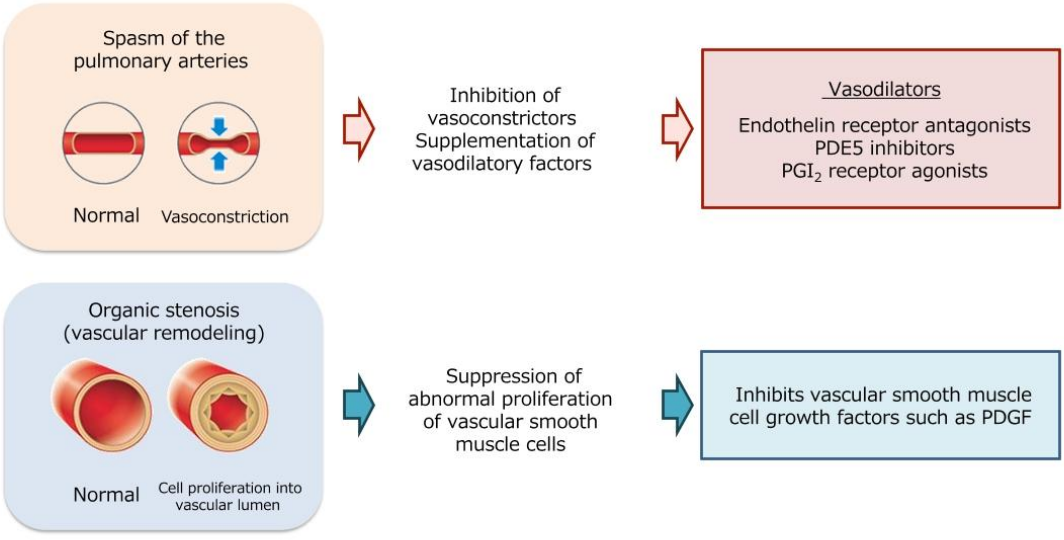
Nippon Shinyaku has three PH products with distinct mechanisms of action.

PGI_2 : prostacyclin

First on NS-863. We have been working on a number of drugs for pulmonary hypertension, mainly these three. We have developed our business with tadalafil, macitentan, and selexipag.

Vascular Lesions in Pulmonary Hypertension (PH)

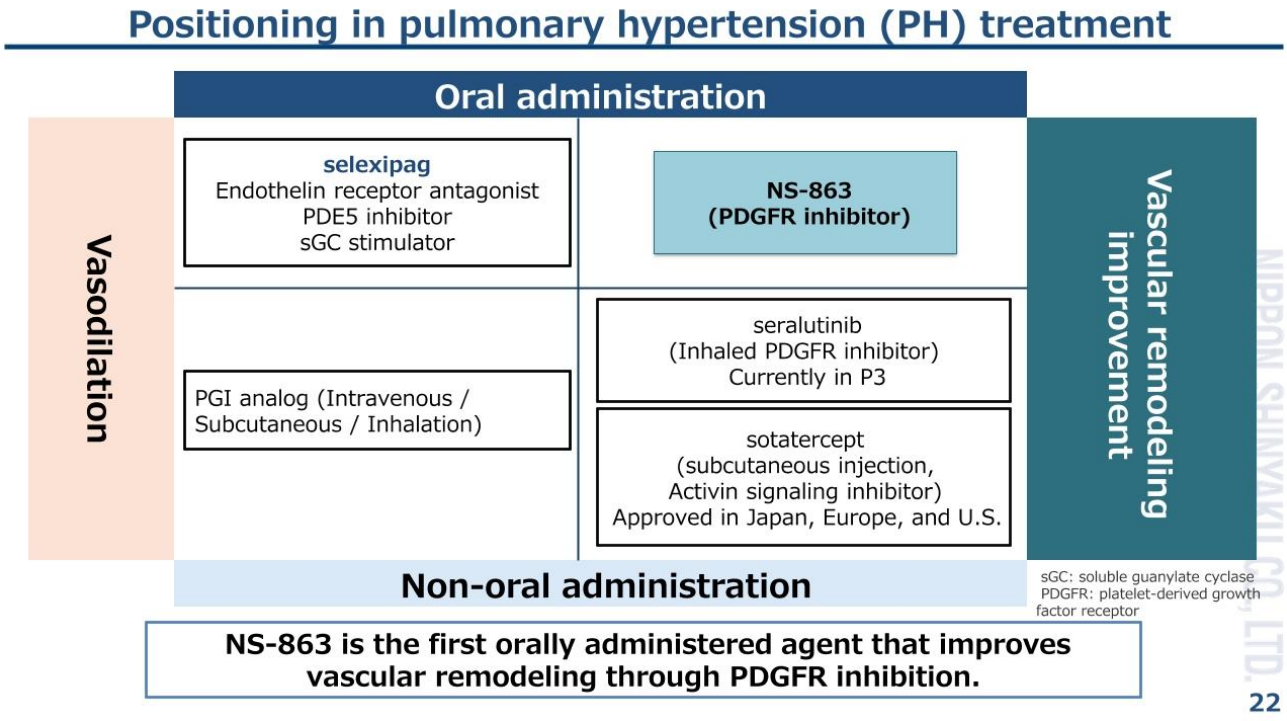
Pulmonary hypertension (PH) involves pulmonary artery spasm or organic stenosis.



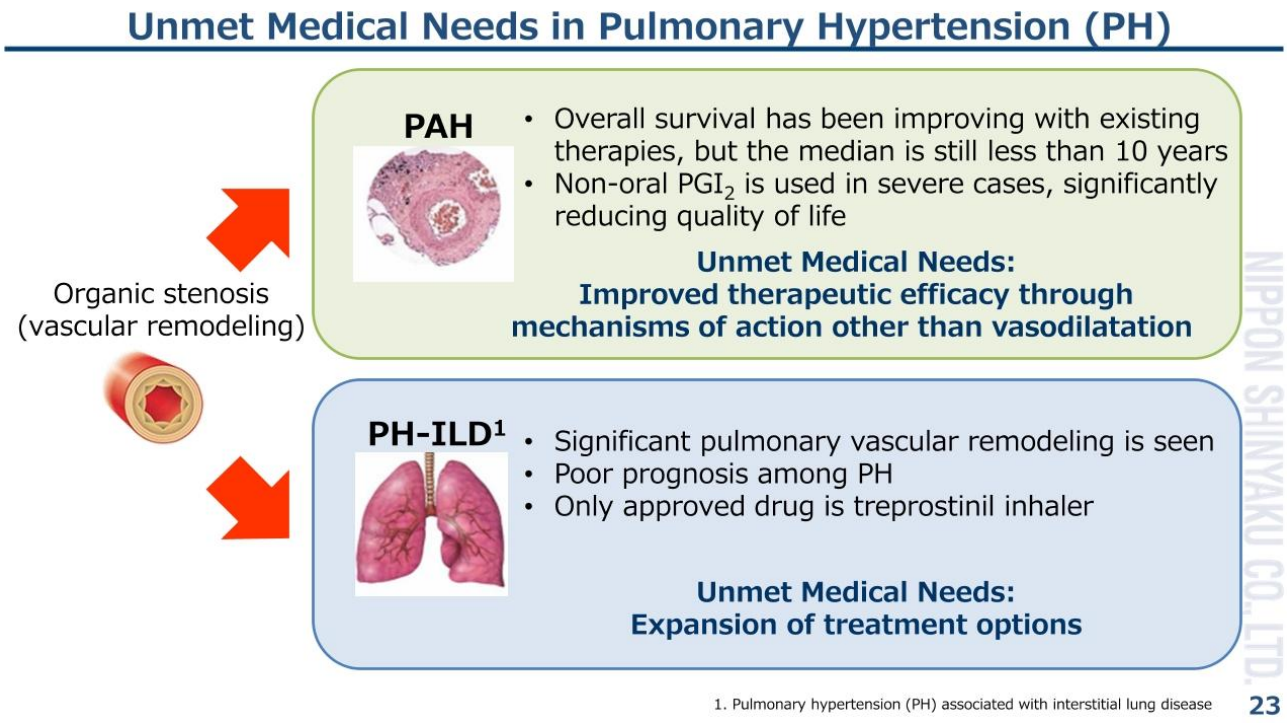
PDGF: platelet-derived growth factor

Here is a description of vascular lesions in pulmonary hypertension. The three drugs I just showed you are positioned as vasodilators, which means vasoconstriction, as you can see above. The medicinal effect is in improving the narrowing of the blood pathway by shrinking it. Some of these drugs also seem to work partially on vascular remodeling, as shown on the bottom of slide 21, but there have not been many drugs

that primarily act on vascular remodeling. We have developed NS-863, which inhibits the receptor for a growth factor called PDGF, and we hope to develop an effective drug for vascular remodeling.



Slide 22 shows drugs on two axes: oral administration or not, and vasodilation or vascular remodeling. In the gap, NS-863 is a drug that can be orally administered to improve vascular remodeling, and I would like to develop it as a uniquely positioned drug in the future. NS-863 is an orally available, selective agent for PDGFR that improves vascular remodeling.



As to where to apply this drug, one is PAH (pulmonary arterial hypertension), which has been promoted in the past. Although many drugs have been developed for PAH, and the prognosis has improved considerably, it is said at academic conferences that there are still issues to be addressed. We would like to develop more effective drugs for these areas. In addition, pulmonary hypertension associated with interstitial lung disease, known as PH-ILD, is a third group of diseases for which there are few therapeutic agents available, making it a very unmet medical need. We believe that vascular remodeling inhibitors may be effective in this area as well, and we would like to develop these two diseases.

NS-863: Summary

Indications	PAH (pulmonary arterial hypertension) PH-ILD (pulmonary hypertension associated with interstitial lung disease)
Mechanism of action	Selective inhibition of platelet-derived growth factor receptor (PDGFR)
Form of development	In-house development
Dosage form	Oral
Characteristics	• Unlike pulmonary vasodilators, NS-863 improves pulmonary vascular obstruction (vascular remodeling). • It is expected to be a highly convenient oral treatment for pulmonary hypertension.

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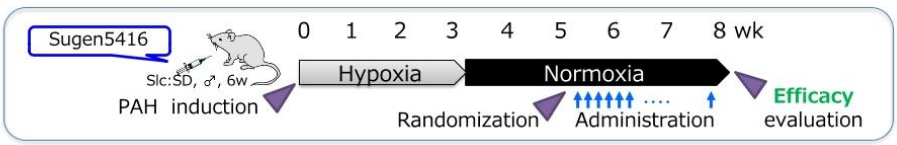
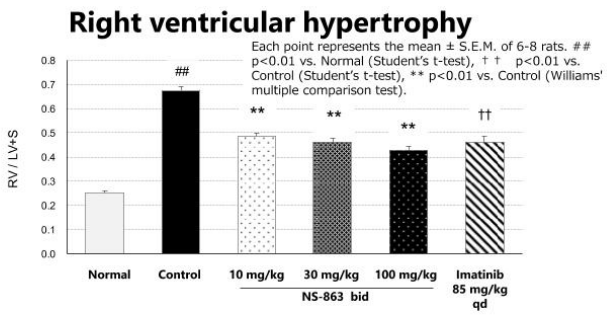
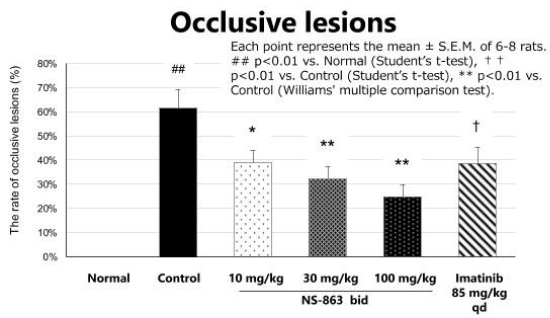
This is an overview of NS-863, the applicable diseases are shown above, and the mechanism of action is as I mentioned earlier. We will continue to develop the drug in-house for the time being, and it will be a drug that exhibits the characteristics I just mentioned.

NS-863: Non-clinical study in SuHx-induced PAH Rat Model







NS-863 (10 mg/kg, twice daily) improved right ventricular hypertrophy and vascular remodeling as much as imatinib (85 mg/kg, once daily).

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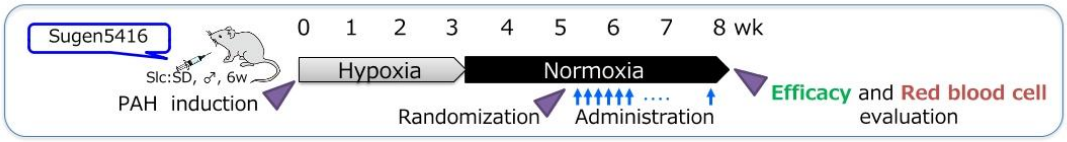
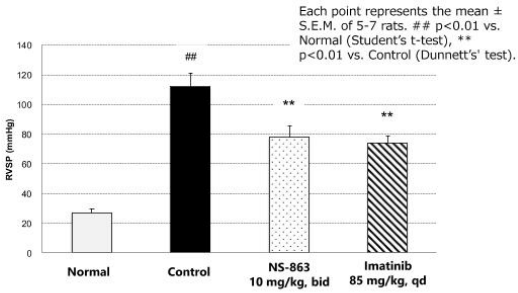
I will show you a little data. This is a nonclinical, but efficacy evaluation using the Sugen/hypoxia model, a pulmonary hypertensive rat model. In both cases, NS-863 shows efficacy in a concentration-dependent manner and is comparable to imatinib, which has the same mechanism of action.

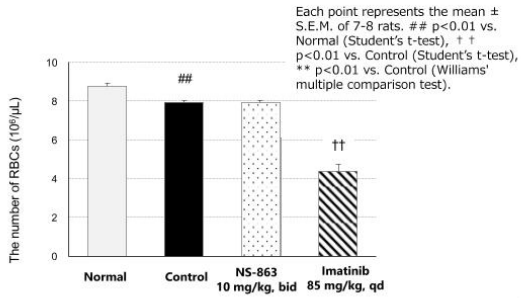
NS-863: Non-clinical study in SuHx-induced PAH Rat Model



Right ventricular systolic pressure（RVSP）



Red blood cell (RBC) number



NS-863 (10 mg/kg, twice daily) did not affect RBC count and decreased RVSP.

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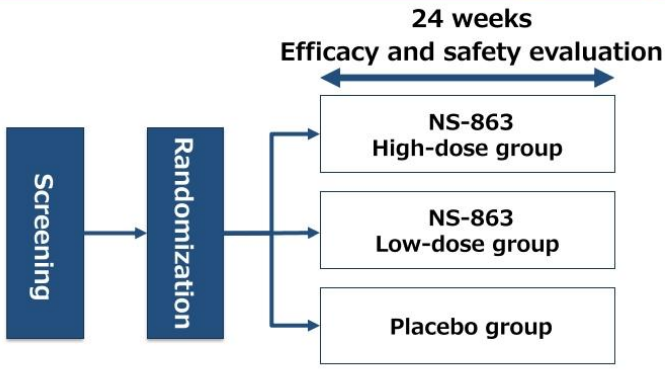
In the same animal model, we measured right ventricular systolic pressure and found that a dose of 10 mg/kg was as effective as imatinib. We believe that this drug has a high selectivity, which mitigates hematologic toxicity. The graph on the right shows this. Imatinib reduces red blood cell number somewhat at doses, but there are data on NS-863 that show no effect on red blood cell number under conditions that reduce right ventricular systolic pressure.

NS-863: Global P2 Study Design



	NS863A-P2-01	NS863B-P2-01
Target patients	PAH patients	PH-ILD patients
Number of participants	135	177
Primary Endpoint	Pulmonary vascular resistance and safety	Pulmonary vascular resistance and safety
Planned start date	July 2026	July 2026

*This slide is based on our current assumptions and the final study design will be determined after further discussions with the authorities.

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We hope to start this trial in July and these are the two study designs. We would like to proceed with a 3-arm study in 2 diseases: a high-dose group, a low-dose group, plus a placebo group. As I mentioned earlier, we are planning to start in July of this year.

NS-035: Fukuyama Congenital Muscular Dystrophy (FCMD)

Characteristics

- Congenital muscular dystrophy
  (1,000-2,000 patients in Japan)
- Hereditary disease whose patients are predominantly Japanese
- Muscle atrophy and CNS abnormalities

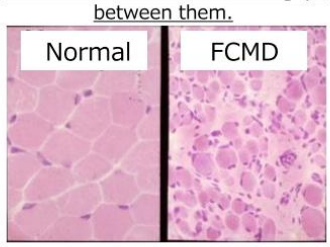
Symptoms

- Seating posture is acquired at an average age of 2 years
- Most patients are non-ambulatory and **bedridden around the age of 10**
- **Decreased swallowing and breathing muscles**
  - Deaths from aspiration pneumonia or respiratory failure in the teens
- Brain malformation, mental retardation

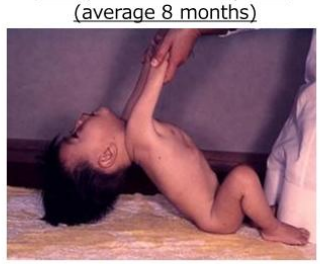
Treatment

- Symptomatic treatment only
  - physiotherapy, respiratory support, cardiac countermeasures, anticonvulsants

Muscle cells in FCMD patients are smaller than normal and have gaps between them.



Delayed neck development (average 8 months)



Source: The Japan Muscular Dystrophy Association

NIPPON SHINYAKU CO., LTD.

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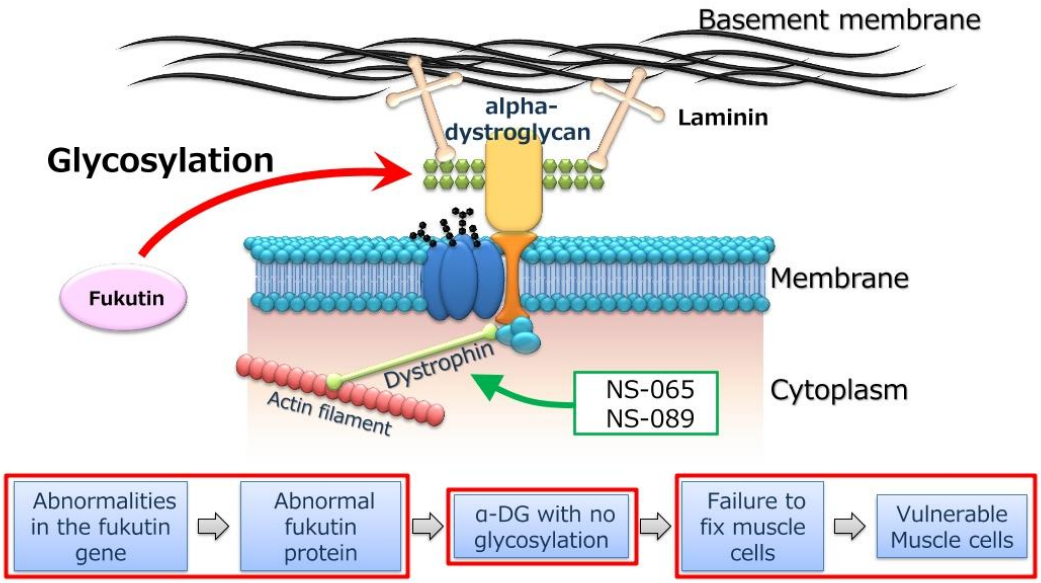
Next, I will introduce NS-035, a therapeutic agent for Fukuyama congenital muscular dystrophy.

This disease is a congenital muscular dystrophy and is estimated to affect 1,000 to 2,000 people. It is a genetic disease that is particularly common in the Japanese population. The pathological image is shown on the right. Compared to normal, the Fukuyama type on the right has smaller cells and larger intercellular spaces, and the muscle tissue is more fragile. It is also associated with progressive muscle atrophy and central abnormalities.

Symptoms of this disease include the average age at which patients are able to sit up, many are unable to walk, and many die of aspiration pneumonia and respiratory failure in their teens. The only treatment is targeted therapy.

Pathogenesis: Abnormalities of fukutin



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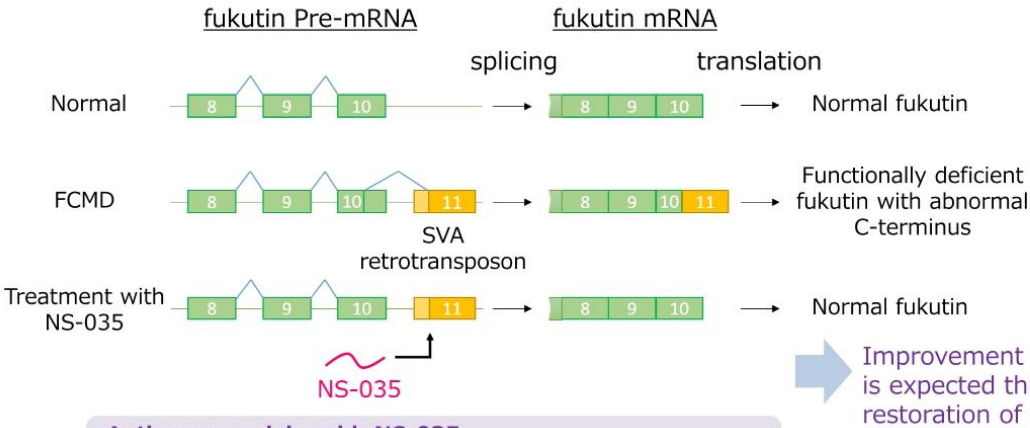
To understand why this disease occurs, here is a schematic of the image around the muscle. In the lower center, there is dystrophin, which is the key part of the muscles to be treated in DMD, but in Fukuyama muscular dystrophy, the enzyme protein called fukutin on the left side is the target. The alpha-dystroglycan is found at the top, and it is necessary for this protein to bind to laminin and other proteins to firmly form muscles, and the sugar chains attached to the alpha-dystroglycan are needed for this. Fukutin is necessary for the addition of these sugar chains, but when the enzymatic activity of fukutin is lost, the alpha-dystroglycan cannot be modified with sugar chains, and the muscle becomes fragile, resulting in this type of disease.

NS-035: Therapeutic Mechanism

By inhibiting exon trapping occurring in fukutin mRNA precursors, we aim to restore normal fukutin expression and improve muscle function through the recovery of α-dystroglycan (α-DG) glycan chains.



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I will show you the mechanism of FCMD. In healthy individuals, splicing is normal and normal fukutin is produced. However, in the pathological condition, the transposon enters the 11th exon at the end, resulting in the loss of normal fukutin and the loss of enzyme activity. NS-035, which we are developing, binds to this part of the transposon, suppressing the addition of extra exons and increasing normal fukutin. The mechanism of the drug is to improve muscle fragility and restore muscle strength by doing so.

NS-035: P2 Study (Japan)

Study design	Multi-center, parallel-group/single-group
Target patients	Typical FCMD patients between 5 and 9 years of age
Number of participants	12 or more cases
Dosage and administration	Intravenous infusion **Double-blind period** • NS-035 group: NS-035 (40 mg/kg) and D-mannitol (500 mg/kg) once a week for 12 weeks • Placebo group: Placebo and D-mannitol (500 mg/kg) once a week for 12 weeks **Open-label period** • NS-035 (40 mg/kg) and D-mannitol (500 mg/kg) once weekly
Primary Endpoint	Gross Motor Function Measure (GMFM-88) total score
Key secondary endpoints	• Glycosylation rate of α-DG • Expression of glycosylated α-DG • Exon trapping inhibition efficiency • Serum CK level • Activities of daily living (ADL) assessment • Clinical general improvement (CGI-I)
Planned start date	April 2026

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Here is the domestic P2 test plan. We expect to start next month and the primary endpoint is motor function.

NS-304: Arteriosclerosis obliterans (ASO)

ASO is a disease in which blood vessels in the legs become narrowed or occluded due to atherosclerosis.

Treatment (Guideline on the Management of Peripheral Arterial Disease[1])

1. Exercise: Improvement of QOL and symptoms of intermittent claudication
2. Drug treatment
    1. Antiplatelet agents/anticoagulants (prevention of cardiovascular events)
    2. Cilostazol (improvement of ischemic symptoms such as ulcer, pain, and cold sensation based on ASO)
3. Surgical treatment: revascularization (EVT[2] , surgical revascularization)

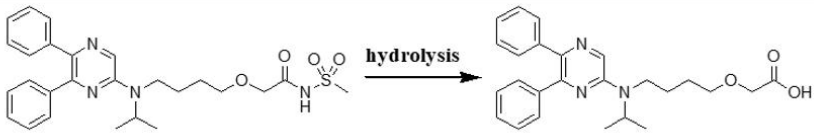
There is no drug which has indication and evidence of improvement for walking difficulties due to intermittent claudication, resulting an unmet medical need.

1. JCS/JSVS 2022 Guideline on the Management of Peripheral Arterial Disease
2. EVT : endovascular therapy

Finally, I would like to introduce NS-304 as the third one.

This product is already on the market for pulmonary hypertension, and we would like to add an indication for the same ingredient for a disease called arteriosclerosis obliterans, or ASO. ASO is a disease in which lesions form on the legs due to atherosclerosis, making it difficult to walk, causing ulcers, or in some cases, necrosis. Exercise therapy is the primary treatment option, but it can also be accompanied by drug therapy or surgical treatment. We would like to develop a drug for the symptom of intermittent claudication in Japan, but there is no drug that has evidence and a specified indication for improving intermittent claudication, and we believe that there is an unmet medical need for this drug.

NS-304: Overview

Generic name	selexipag
Proprietary name	Uptravi
Structural formula	 NS-304 (prodrug) MRE-269 (active form)
Mechanism of action	Prostacyclin (PGI_2) receptor agonist
Origin	In-house
Dosage form	Film-coated tablet
Indications	Uptravi® Tablets 1) Pulmonary arterial hypertension (PAH) 2) Chronic thromboembolic pulmonary hypertension (CTEPH) **Currently under preparation for P3 for arteriosclerosis obliterans (ASO)**
Dosage and administration	Oral twice daily (Dose: 0.2 to 1.2 mg/dose)

NS-304, as you may know, is the profile shown here. The prodrug NS-304 undergoes hydrolysis in vivo and its active body is converted to MRE-269. It is a prostacyclin receptor agonist, and the same ingredient is already indicated for pulmonary hypertension as Uptravi tablets.

NS-304 for ASO

Department/Clinical Specialty	Cardiovascular Surgery, Cardiology, Internal Medicine, Orthopedics, Diabetes/Metabolism/Endocrinology
Origin	In-house
Dosage form	Tablet
Indication	Improvement of intermittent claudication associated with arteriosclerosis obliterans (ASO)
Dosage and administration	Oral administration Dosage starts at 200 μg/dose and is titrated up to a maximum of 1,200 μg/dose, twice daily
Efficacy	• The active metabolite, MRE-269, has selective and sustained agonist activity at the IP receptor. • Improvement of the pathological condition of a rat model of ASO disease
Safety	• No adverse findings in non-clinical toxicity studies • The most frequently observed side effects in clinical studies were headache, nausea, vomiting, and jaw pain.

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The department of treatment is slightly different from that of pulmonary hypertension, and additional departments such as cardiovascular surgery, orthopedics, and diabetes, metabolism, and endocrinology may be required. The dosage and administration is basically the same as for pulmonary hypertension: oral administration twice a day. There are some differences in the upper limit, but it is basically the same dosage and administration.

NS-304: P3 Study for ASO (Japan)

P3 study has started after favorable results of P2 study

Study design	Randomized, double-blind, placebo control, parallel assignment
Target patients	Patients with intermittent claudication associated with arteriosclerosis obliterans (ASO)
Number of participants	194 cases
Dosage and administration	NS-304 or placebo orally twice daily. Dosing will start at 200 μg/dose and titrate up to a maximum of 1200 μg/dose depending on tolerability. The maintenance dose for each subject will be determined and administered for 16 weeks.
Primary Endpoint	Change from baseline in Natural log transformed peak walking time (ln PWT)
Key secondary endpoints	Claudication onset time (COT), Resting Ankle-Brachial Index (ABI), WIQ scores, SF-36 scores
Start date	March 2026

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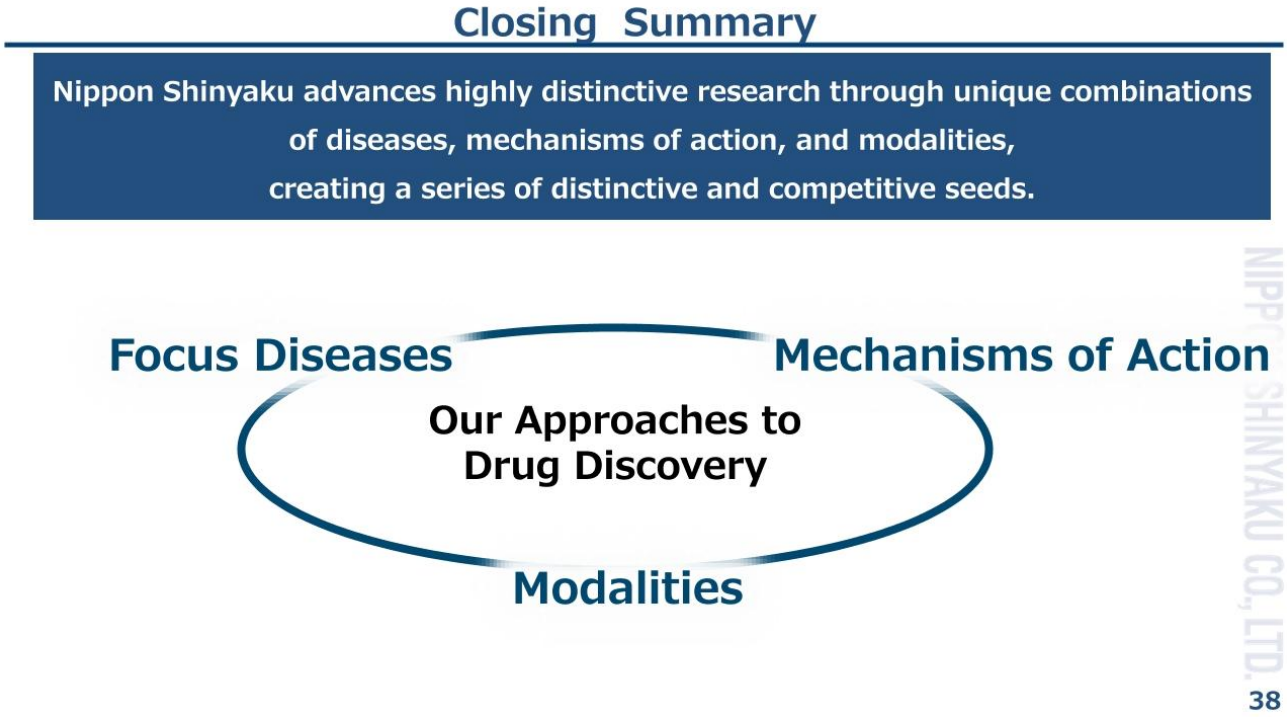
So far, we have been conducting the P2 study, but now that we have obtained good results here, we would like to start the P3 study. In fact, that means starting this month. A Phase III study is expected to enroll 194 patients in Japan, with the primary endpoint being the change from baseline in log-transformed maximum walking time.



As I indicated at the beginning, we would like to conduct research and development in three modalities, focusing on intractable and rare diseases. In doing so, we will combine disease, mechanism of action, and modality in a highly unique way, promote research to differentiate ourselves, and create new seeds one after another. Thank you for your attention today.

Question & Answer

Takechi [M]: We will now begin the question-and-answer session. When asking questions, please state the name of the company and your name before speaking.

We will first take questions from the audience. We will then take questions online. Thank you.

Mr. Hashiguchi, please go ahead.

Hashiguchi [Q]: My name is Hashiguchi from Daiwa Securities. I would like to ask again how you think about the risk-return balance by focusing on intractable and rare diseases.

As for the current market size, I think it is very dependent on the US compared to other types of diseases. This is due to the fact that the cultural characteristics of the US are different from those of other regions, but the US is also changing in terms of what kind of data should be used for approval and the way of thinking about drug prices. I can't deny the impression that the goalposts have been moved with regard to REGENXBIO's gene therapy RGX-121.

In this context, I would like to ask again what you think about the balance of risk and return by concentrating limited resources in this area.

Nakai [A]: Thank you for your question. Let me answer. As you pointed out, if we focus on intractable and rare diseases, we cannot ignore the US from the standpoint of marketability, and I think you are right that the importance of the US will become very important.

When the CRL was issued to RGX-121 and we checked the contents, we found that the surrogate endpoint was the one we had originally discussed with the FDA when we submitted the application, but we experienced some doubts about it in the review process.

We must learn from the experience of our partners in the future, but I think that, above all, if we are to go through a pathway such as the one mentioned on the previous slide, which is to obtain expedited approval, we must have a clear understanding of the surrogate endpoints and the need to establish them in advance. We believe that we should not proceed unless we have a firm agreement with the authorities on the surrogate endpoints.

Inevitably, there has been some experience with DMD, such as the expression of dystrophin in morpholinonucleic acid, and this experience has really proceeded with agreement in the form of surrogate endpoints that have been properly confirmed scientifically.

The current stance of the US authorities is, after all, to do a solid Phase III, and then approve it as soon as possible, to broaden the range of such options. If we were to go faster, we would agree on a proper surrogate endpoint. We believe that the balance between risk and return is achieved by conducting research while considering the diseases and drugs to be targeted based on the surrogate endpoints for each of these diseases.

In terms of returns, we believe that the impact on the budget of each payer is not so significant for intractable and rare diseases, and in that sense, they are very generous with this area. We would like to make sure that we are successful in this area.

Hashiguchi [Q]: Thank you. One more point, in your explanation of the strategy for the development of nucleic acid drugs, you mentioned starting with central local administration and then intravenous administration with DDS technology. What is the reason not to do this in parallel? Of course, I think that using DDS after confirming the efficacy of the drug centrally would reduce the risk.

If your company starts development, there are many companies that will follow in your footsteps, and they are getting faster than in the past. I think that the risk can be mitigated if you do it in parallel. In fact, I think it may be possible to reduce some of the risks. Can you tell us about the aims of this kind of strategy?

Kuwano [A]: Thank you for your question. It might have been misleading, but it is not that we always do it in order, and will do what we can do first. If it is possible to add more value to nucleic acids by modifying them in some way, and if they are ready, we would like to start from that first.

However, rather than delay development by waiting for DDS, if there is an effective nucleic acid sequence, we would rather proceed with development with it. After that, if we can make something with even higher added value, we want to bring that kind of thing further into the market, and that is the way we think.

Hashiguchi [M]: Understood. Thank you.

Takechi [M]: Next, Mr. Tanaka, please go ahead.

Tanaka [Q]: This is Tanaka from Mizuho Securities. Thank you.

Today, I understand that the results of the physician-led trial for NS-035 cannot be explained by your company because it is a physician-led trial. However, I haven't seen much proper data, so I would really appreciate a better explanation.

In the meantime, there was some data presented at the World Muscle Society and other conferences that suggested effectiveness, showing girls descending stairs, but I would like to ask you to explain a little more about what the overall data was.

Kuwano [A]: Thank you for your question. We wish we could have presented the data today, but since the doctors are preparing to make presentations at conferences and in papers, we would like to leave that to them and hope that you will take a look at the data.

As for efficacy, of course, we are only going to proceed with the P2 trial, so our judgment is that it is effective. The number of cases is also limited, so it is difficult to say the definite thing from its average value.

Looking at the individual data, we found that almost all of the patients showed improvement in motor function, as mentioned earlier, and that there was also a dose-response effect, so we decided to start the study based on our belief that this is a drug worthy of development.

Tanaka [Q]: Understood. I believe there were 8 cases of physician-led clinical trials, and since there are more than 12 cases this time, I believe that the market launch date is already set for FY2029. Is this test supposed to be OK with the Japanese authorities?

Kuwano [A]: After talking with PMDA, of course, we have settled on 12 cases in several exchanges regarding the number of cases, and we consider this to be a so-called pivotal trial.

Tanaka [Q]: Understood. So, you explained NS-863 this time with small molecules, but I think this inhaler seralutinib on page 22 has missed its primary endpoint in February. On the other hand, I remember Merck's WINREVAIR, which is shown below that, and it has great data, and I feel that it is not quite safe to go in from

here anymore. Of course there may be the advantage of its oral formulation, but what are your thoughts on that?

Kuwano [A]: We have also seen that seralutinib has not performed well in a recent trial. For one thing, I have a feeling that maybe the dosage was not high enough. I don't want to speak too much about other companies, but it seems that there were no problems with safety, so I think that if they add a little more dosage, the efficacy of the drug with this mechanism will be strong.

As you said, we have launched three oral drugs, and the next one will also be an oral drug. I believe that oral drugs are the ones that will benefit patients the most, and we would like to offer such drugs.

As for the comparison with sotatercept, I think the profile is also different because of the different mechanism. For example, the safety profiles of the two products are very different, so we believe that we can sufficiently differentiate them from each other in this respect. They are also different in terms of oral and injectable formulations, and we believe we are able to compete in the market sufficiently with such positioning that I talked about today.

Tanaka [Q]: Lastly, about Uptravi. Thanks to its royalties earned, you were able to spend a lot of money on R&D, but looking from outside, I understand that negotiations with the FDA concerning current development products have not progressed very well. Of course, I understand that there have been many changes due to political changes in the U.S. administration.

I would like to know about the people in your company who are involved in such negotiations with the authorities, or the NS Pharma team, and whether you have already made any changes in this regard, or how you are planning to change it in the future.

Nakai [A]: Thank you. In terms of the members who are currently working on development in the US and negotiating with the authorities, local staff who are active in the US during the regulatory phase have been recruited as career hires.

One of the reasons why we had not been able to make progress in negotiations with the authorities in the past was that we did not have an MD or a regulatory affairs on an internal basis, while using outside consultants. That kind of in-house production, or in the sense of hiring staff inside, has been enhanced.

As for the hiring of the MD, I mentioned that he finally joined us at some point in the current fiscal year, and that he was in charge of PH development in his previous position and DMD drug development at a different company. We finally announced today about PH drug, but I hope you will understand that we have hired a person who will contribute to the advancement of NS-863 and DMD drugs in the US.

Tanaka [M]: Understood. Thank you.

Takechi [M]: Next, Mr. Yamaguchi from Citigroup Global Markets, please go ahead.

Yamaguchi [Q]: Thank you. I am Yamaguchi from Citi. To continue with the current question, this NS-863, the previous one is Actelion, I think, although you took it out in the middle of the process. In this case, the question of how far to go and where to release the product is a little different from the R&D meeting. What is your thought?

Nakai [A]: We are aware that we are not in a situation where we can spend R&D expenses without limit. After all, it is management that is appropriate for one's stature and size, and then, capability. We have a variety of options, such as working with a company that is capable of global development in PH if we can find a partner, rather than doing it in-house.

At the moment, we are preparing to proceed with the development of these two indications in Phase II, but at the same time, we have already started activities to find a partner for NS-863.

Therefore, we would like to consider the best time to work with a partner, based on our future budget, speed, and subsequent sales.

Yamaguchi [Q]: Normally, I would think that we could just give it to the place where we are currently working, but that is not necessarily the case. It would be generic there.

Nakai [A]: I understand that you were referring to Johnson & Johnson. Now, that company has their own situation. Looking at the situation of companies with PH area in their pipeline, there are no visible items in the pipeline for the PH area. Therefore, I think it depends on the timing and situation of the partners.

Yamaguchi [Q]: This NS-863 potency, you are comparing it to imatinib, but imatinib is not used as PAH, right? But this remodeling is so strong that you are doing this to some indicator. Is that what you are saying?

Kuwano [A]: Actually, imatinib has been clinically tested in pulmonary hypertension. The data showed very good efficacy, but unfortunately the side effects were more severe, so it did not reach commercialization.

Yamaguchi [Q]: The potential was confirmed, so based on that, if you can secure the safety, you will be able to go ahead. Is this the right thinking?

Kuwano [A]: Yes, that's right. We believe we have a PoC for clinical effectiveness.

Yamaguchi [Q]: Also, this PDGFR is being done here and there by various companies for various indications, so it's a little difficult to see the whole picture. Is your company the only one doing this PAH? Are there any other companies?

Kuwano [A]: Seralutinib is the inhaled PDGFR inhibitor that you asked about earlier. This is used for PAH.

Yamaguchi [Q]: Not much else?

Kuwano [A]: Yes, that's right. I don't think so.

Yamaguchi [Q]: Understood. Thank you. Just one more, sorry. In the area of rare diseases, I see that rare diseases are popular among other pharmaceutical companies in their mid-term plan. Although your company is a little different globally, especially in Japan, with DMD, it seems to be getting crowded as various companies are bringing in various products one after another from all over the place.

Despite that, you have determined to do it, although competitive situation is like this now. In terms of Japanese pharmaceutical companies, because of the clinical gap, or maybe it's not a gap, I forgot how to say it, but that's one of the reasons why there are so many development going on now. But is it correct that you do not mind about it?

Kuwano [A]: There are many kinds of intractable and rare diseases. As you know, though. Among them, we have been working for a long time in the areas I have mentioned today. Moreover, we have always been conscious of the need to adopt a differentiation strategy, and not just for rare and intractable diseases. I think we just need to do an extension of what we have been doing, which is to create something that makes a difference and differentiates us from the competition, regardless of whether there is competition or not.

Yamaguchi [M]: Thank you.

Takechi [M]: Mr. Wakao, please go ahead.

Wakao [Q]: Thank you. I am Wakao from JPMorgan Securities. Please allow me to ask you a few questions about NS-863.

If the drug is successfully marketed, it will be used as an add-on to existing drugs, but I would like to know if the combined effect of the two drugs has been confirmed in animal models, etc.

Also, in terms of development, clinical trials, you mentioned P2 safety, but for Phase III, do you want to do another severe endpoint like worsening of disease or death like Uptravi, or do you want to get approval first with something like 6-minute walk?

I guess it depends on future data, but what is the current trend or current thinking?

Kuwano [A]: First of all, we have seen an additive effect in the non-clinical phase. We have been collecting some of those data. I think your question was about the P3 study, but that was only after seeing the P2 study, and we are not making the same assumption of worsening of the disease as we did with the UPTRAVI from the beginning. While keeping the 6-minute walking distance in mind, we would like to decide on the evaluation items that will best utilize the features of this product, and on clinical trials that will add value.

Wakao [Q]: Is it correct to think that the add-on is for all existing drugs that are still available? I think Merck's WINREVAIR is highly effective, so I think it is important whether or not we can see the added effect there.

Kuwano [A]: I don't think we had done it with sotatercept yet. We do have data on the use of this in combination with existing vasodilators.

Wakao [Q]: Understood. The second is development. Your company's overall development speed has been an issue in the past, or perhaps it still is, and I think you have been working on various ways to speed up the process.

However, from what I have seen over the past year, especially from the outside, it does not appear that the Company is speeding up its development activities. Could you tell me what the President thinks about it and how you are going to improve the issue, if there is one?

Nakai [A]: Thank you. The top management of R&D has been replaced by Mr. Kuwano June last year. Mr. Kuwano is the inventor of selexipag. From the outside, he might appear to be a drug discovery specialist, but he also played a role in the development of Uptravi, as a project manager. Therefore, he has a great deal of experience in development management.

Although Mr. Wakao said that the progress is not visible, since Mr. Kuwano took charge of the project in June, I have been able to confirm by participating in the same sessions with him that he has been managing the development team in great detail. He is a man who is very strict about deadlines and schedules, so I feel that development is progressing with a sense of speed under his leadership.

Wakao [Q]: I understand very well. I'm sorry, I forgot to ask one thing, but the Phase II of NS-863 that is about to start, and ClinicalTrials.gov says it will be at the end of 2028. What do you currently see the timing of the end of Phase II?

Kuwano [A]: Sorry, I don't have the exact end date at the moment. How about it, Secretariat?

Beppu [M]: I will check and let you know later.

Wakao [M]: That is all.

Takechi [M]: Mr. Wada, please go ahead.

Wada [Q]: This is Wada from SMBC Nikko Securities, Thank you.

I would like to ask you what you consider to be the areas of focus for rare diseases, since you mentioned that rare diseases cover a wide range of medical specialties.

Looking at the pipeline, I think it is basically concentrated in the areas of hematology, pulmonary hypertension, and pediatric neurology, which are your company's priority themes. The range of rare diseases are broad including immune system and hereditary. The challenges in rare disease drug discovery are that there are no models, and if the range is too broad, you may face challenges in the marketing to new department. From this perspective, I would like to ask you what you think of rare disease departments or disease areas.

Kuwano [A]: As you can see on page seven of the slide I showed you today, we are focusing on hematology, immunology, neuromuscular, and pulmonary hypertension, as you just pointed out.

In addition, we have learned a lot about inborn errors of metabolism and eye diseases through in-licensed products, which we were not familiar with in the past. I would like to promote in-house drug discovery in this area as well.

If we do too broadly and extensively, it will result in the dispersion of resources, but at the same time, we are willing to boldly take on new projects where we think they are promising. So, I think it is possible that as we move forward with research and development, we may be shifting our axis more and more with regard to that.

Wada [Q] Secondary, I would like to ask about modalities, especially about nucleic acid. I am still thinking that DDS is a trend now. I think the current trend is to conjugate with antibodies like AOC for drug delivery.

Could you tell me what is DDS technology that you are thinking?

Kuwano [A]: Of course, eventually it will be innovative, but for the time being, I think it would be good if we could use things that we pay attention to in clinical practice, such as anti-transferrin receptor antibodies, to some extent, and produce something that are novel and revolutionary in terms of sequence, and make delivery by using things that are taken for granted, and evolve further from there.

Wada [Q]: I also would like to ask about NS-863. Imatinib, indeed, has PDGFR inhibitory activity, so there has always been talk that it works in pulmonary hypertension, but it has not shown much efficacy, including seralutinib. I think that PDGFR has a history of failure because it cannot be made specific in terms of selectivity after all.

As for your NS-863, does that mean that it is quite selective in terms of kinase inhibitory activity? Can you please tell us about this high degree of specificity?

Kuwano [A]: Thank you for your question. This is a question that we appreciate your asking as you asked about what we want to tell. As you know, with regard to imatinib, besides PDGFR inhibition, of course the main thing is inhibition of Abl, and I think there is also c-Kit.

For our NS-863, this Abl and c-Kit inhibition is almost non-existent and the data is quite selective for PDGFR. As I mentioned in my presentation today, I believe that we excel at optimizing and improving selectivity, and I am proud to say that our expertise in this area has been put to good use in this new product. Thank you.

Wada [M]: Thank you.

Takechi [M]: Mr. Lee, can you ask your question?

Lee [Q]: This is Lee from Morgan Stanley MUFG Securities. Thank you. You mentioned that you will continue to promote small molecule drugs. On the other hand, there is a lot of competition, and I think it is becoming a red ocean.

In this context, I would like to ask what kind of strategy your company will use, and what differentiates your company from others. In addition, you mentioned that you will work hard on gene therapy in the future, but unfortunately, there is no track record yet, and the progress of introduced products is not good.

What kind of strategy will you take on this point as well? I understand that you are working with some other company, as I recall, but progress has not been forthcoming, so I would like to hear any updates.

Kuwano [A]: I think you asked first about small molecules. As I answered earlier, I think that the key here is how to differentiate ourselves. For example, I have a feeling that we may be able to target a different area than what other companies are targeting, just by choosing where to target the applicable diseases.

For example, we have an R&D product called NS-229, which is a JAK1 inhibitor, so if we were to take the high road, we would probably focus on major diseases such as rheumatoid arthritis. However, we are not doing so and start from where other company does not handle such as rare diseases. We would like to continue to do so for future items, and to promote our differentiation strategy more and more.

As for gene therapy, as you have pointed out, we feel sorry that we are not able to tell you about in-house drug discovery yet, but we are moving forward with this area as well. In order to differentiate our products as much as possible, we would like to come up with something that is not just about raising gene expression, but something that puts a twist on it. If there is an opportunity to talk to you again, we would be happy to show you our work. That is all.

Lee [Q]: Thank you**.** I see on page 10 of this presentation, in the small molecule section, there was a comment this time on RNA. I believe you partnered with MiNA Therapeutics in 2024. Have there been any updates and progress in this area? I would like to hear an update on this part of the RNA, including the partnership with MiNA.

Kuwano [A]: We have been working with MiNA on the research and have received reports that it is progressing quite well, but I have heard that in the final stage, there is one hurdle that needs to be overcome. Naturally, we are hoping to see this one in the pipeline as well. This one is not a small molecule but saRNA. That is all.

Lee [Q]: Thank you. Finally, I also would like to ask about NS-863. I am sorry to be uninformed, but was it correct that this was planned to be developed as a single agent? In addition, I have the impression that it could be a growth driver to replace this Uptravi.

Is there this kind of potential for future sales of USD1 billion to USD2 billion, although it may not be the question for R&D Meeting. I would appreciate if you could tell. This is the last one.

Kuwano [A]: NS-863 is a single agent in a small molecule drug.

Nakai [A]: I once asked Mr. Kuwano how much market potential there was, given that sotatercept was already on the market, and this is also the kind of discussion we have when we move from one phase to another.

Mr. Kuwano said that the vasodilator drug has also grown from EPO and injectable to an oral drug called Uptravi, and Uptravi has already become a blockbuster. Mr. Kuwano commented that if the drug is able to

produce proper efficacy, sotatercept, which is a subcutaneously administered drug, can be expected to be so convenient that it cannot be ignored as oral administration is possible.

Therefore, we are planning to develop and enroll 300 patients for both indications in this Phase II study, and we are very hopeful that we will be able to develop a drug of a reasonable size, and that we will be able to develop a drug of a large size on our own. We hope that you will understand this.

Lee [M]: Very clear. Thank you.

Takechi [M]: Any other questions from the audience? Now, if you are online and have any questions, please press the raise your hand button. Since there seem to be no questions, I will end the question-and-answer session. Finally, the secretariat will answer your earlier question.

Beppu [A]: I will now respond to the question Mr. Wakao asked earlier. The P2 study of NS-863 for PAH will end in November 2028. And for PH-ILD, the P2 study is scheduled to end in December 2028. That is all.

Takechi [M]: This concludes the FY2025 R&D Meeting. Thank you for your participation.

The IR meeting will be held after this. Please feel free to participate if time allows.

We will now take a 10-minute break.

[END]