FY2025
R&D Meeting

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Nippon Shinyaku Co., Ltd.

NIPPON SHINYAKU CO., LTD.

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Our Drug Discovery

- We select the most appropriate modality for intractable and rare diseases from **small molecules, nucleic acids, and gene therapies.**
- Many intractable and rare diseases are hereditary disorders, and these three modalities can **target the causative genes**.
- Differentiation by implementing a unique strategy based on **the combination of diseases, mechanisms of action**, and **modalities**, which are the main components of the research themes.

Focus Areas

Our Focus Areas

Main Products **(Indications, Year of launch)**	**Jaypirca®** r/r-MCL r/r-CLL 2025	**Uptravi®** PAH 2016 CTEPH 2021 Pediatric PAH 2025	**Erleada®** Prostate cancer 2019	**MonoVer®** Iron deficiency anemia 2023
	Vyxeos® High-risk AML 2024	**Viltepso®** DMD 2020		
Main pipeline	**NS-401** **LY3527727** **etc.**	**CAP-1002** **NS-863** **etc.**	**NS-025**	**NS-580**

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	38	5
5	Company D	38	9

Global

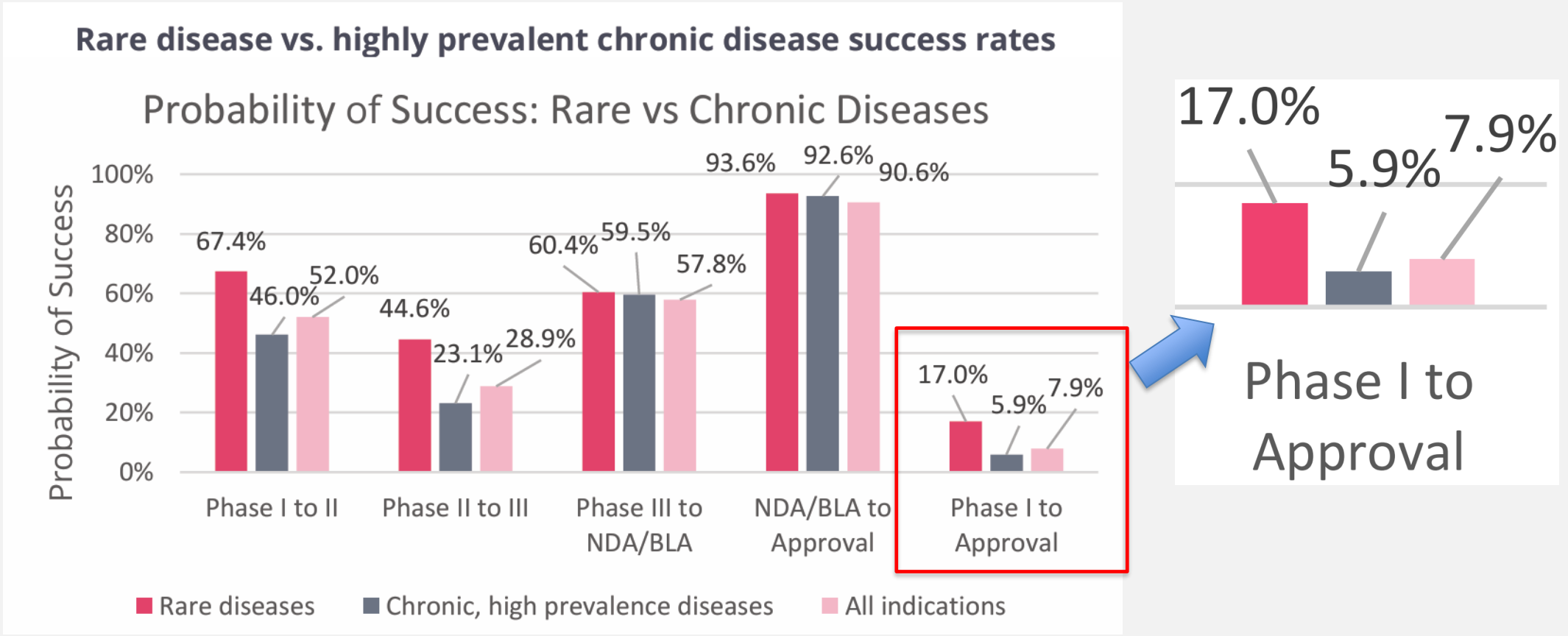
#	Company name	%	# of products
1	**Nippon Shinyaku**	**85**	**11**
2	Company E	70	7
3	Company F	60	6
4	Company G	58	14
5	Company H	50	38

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

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

Our Pipeline and Disease Areas

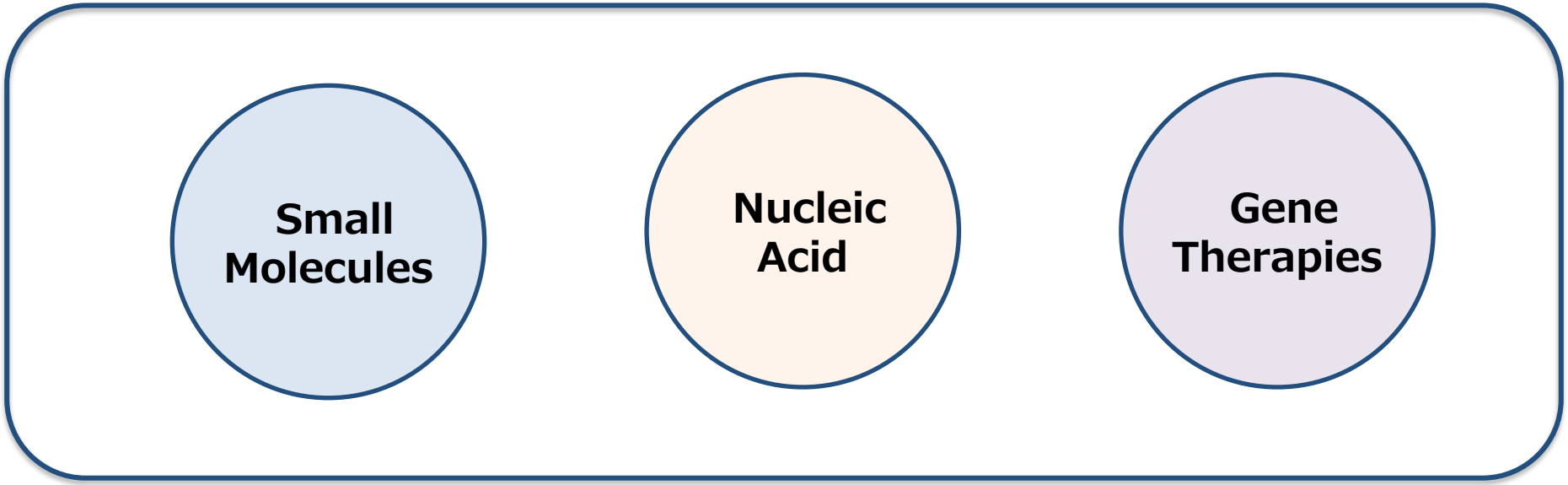
Disease area		Development pipeline
Hematology		NS-401, LY3527727, NS-917
Immunology		GA101, NS-229
Neuromuscular		ZX008, CAP-1002, NS-089, NS-035, NS-050, NS-051
Pulmonary hypertension (PH)		NS-863, NS-421
Specialty	Congenital metabolism	RGX-121, RGX-111
	Ophthalmology	ATSN-101

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

Modalities

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.

Small Molecules: Current Status and Strategy

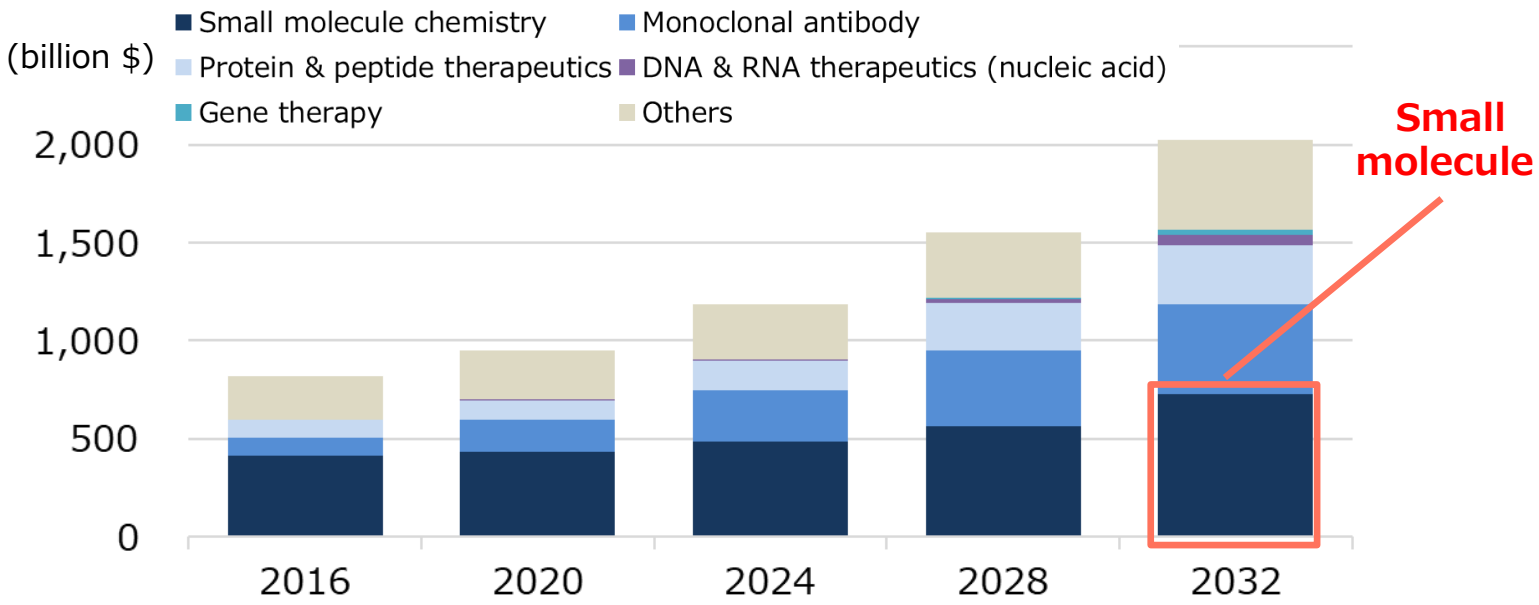
Current Status

- Although modalities are diversifying, **small-molecule drugs are expected to remain at the center of drug discovery in the future**.
- Advances in AI and protein conformational analysis will enable drug discovery even **for targets that are difficult to discover with conventional technologies.**

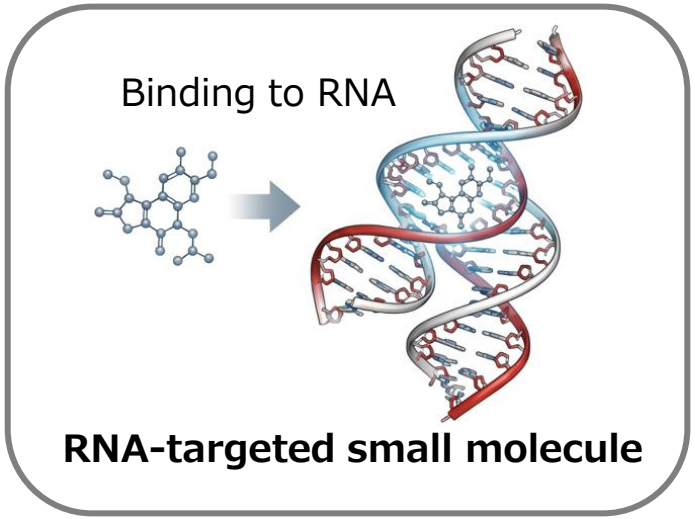
Strategy

- **Evolution of expertise** in small molecule **compound optimization**
- Approaches to difficult targets **using RNA-targeted small molecules and cyclic peptides**

Global Sales of Pharmaceuticals by Modality



Source: Evaluate Pharma® 2 2026, ©Evaluate Ltd



Nucleic Acid Drugs: Current Status and Strategy

Current Status

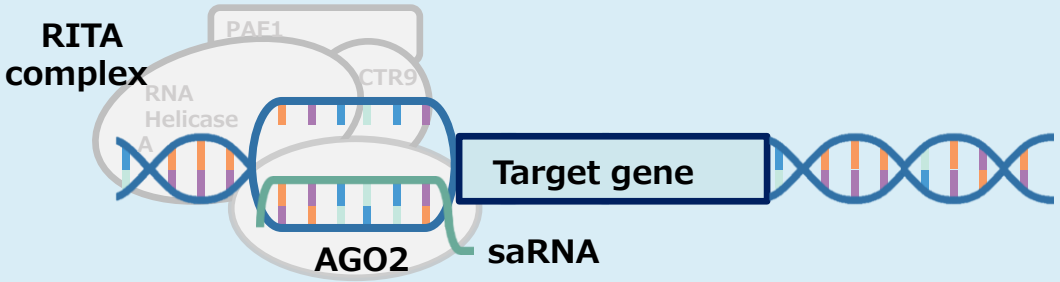
- **Patent competition for nucleic acid drugs is intensifying**, and **securing in-house patents** is an important issue.
- Limited therapeutic effect due to lack of tissue transferability

Strategy

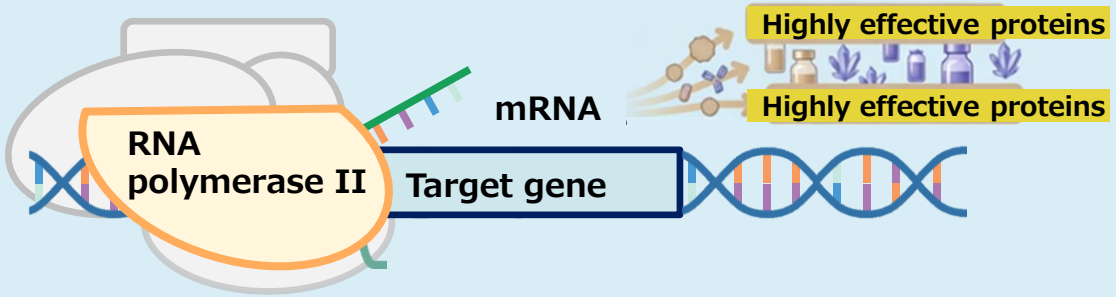
- **Potential for patent acquisition**: Application of expression-enhanced nucleic acids to loss-of-function diseases
- Beginning with central local administration, expanding to intravenous administration using DDS technology

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

STEP 1: Formation of gene activation complex by saRNA

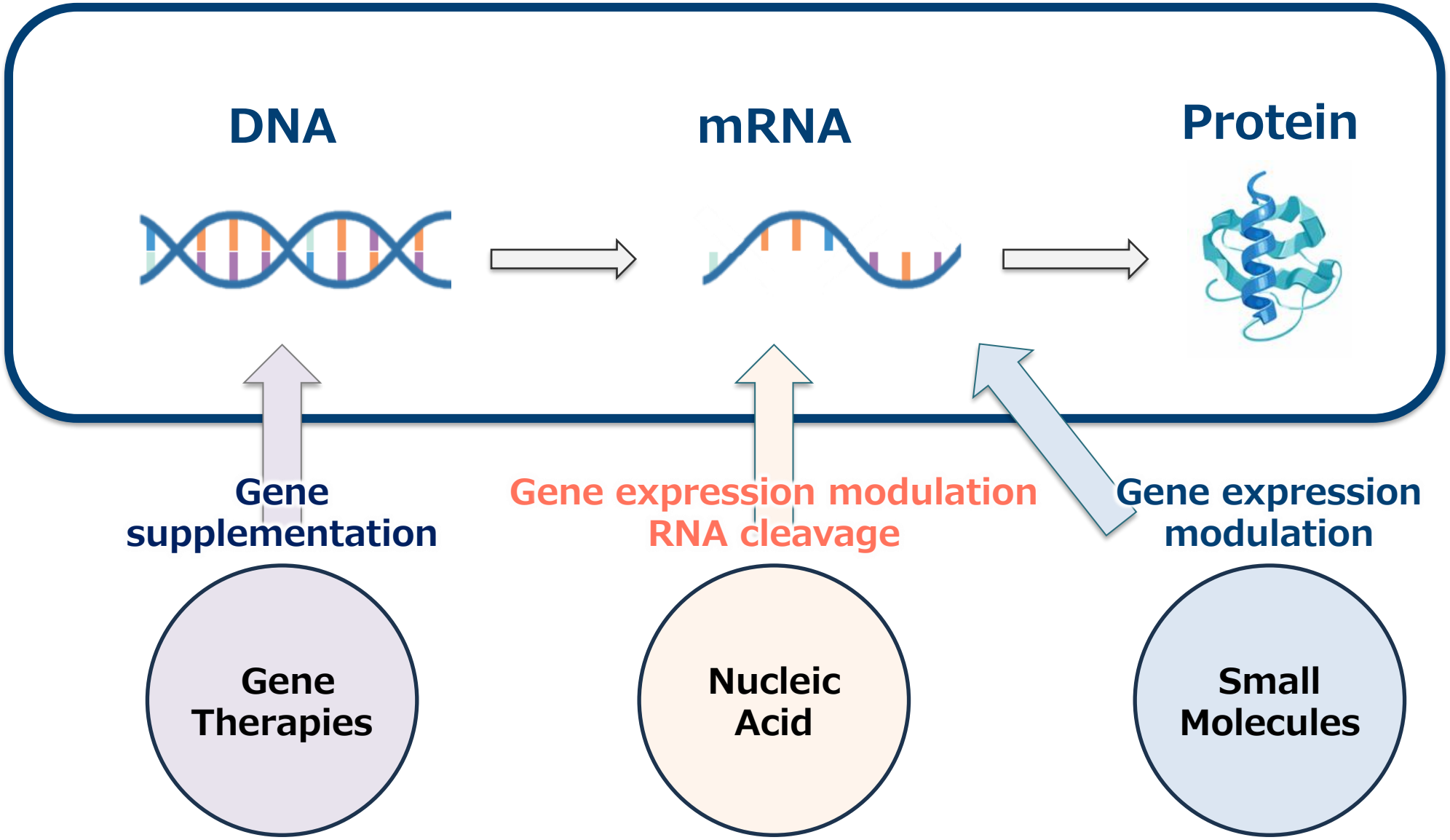


STEP 2: Transcriptional enhancement and protein production by RNA polymerase II



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

Modality Mechanisms



Open Innovation

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

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

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.

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

NS-863

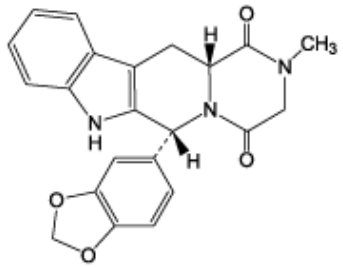
PAH (pulmonary arterial hypertension)
PH-ILD (pulmonary hypertension associated with interstitial lung disease)

Our Product Line for Pulmonary Hypertension (PH)

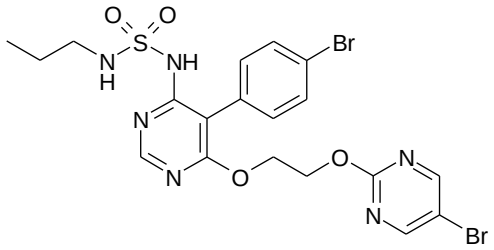
Approved in 2009
tadalafil
(Adcirca®)

Approved in 2015
macitentan
(Opsumit®)

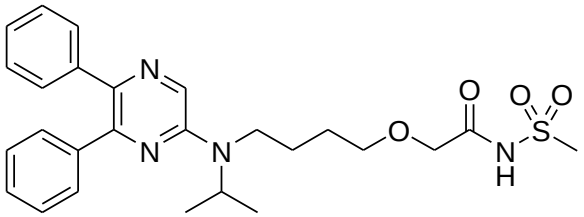
Approved in 2016
selexipag
(Uptravi®)



Phosphodiesterase 5 inhibitor (PDE5i)



Endothelin receptor antagonist (ERA)



PGI_2 receptor agonist (PGI_2)

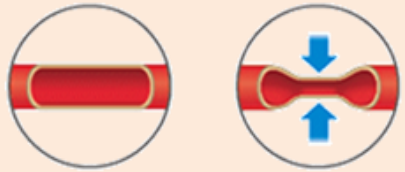
Nippon Shinyaku has three PH products with distinct mechanisms of action.

PGI_2 : prostacyclin

Vascular Lesions in Pulmonary Hypertension (PH)

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

Spasm of the pulmonary arteries



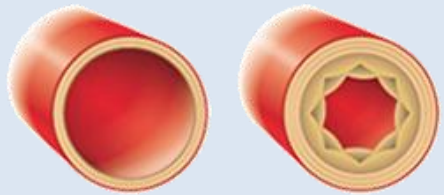
Normal　Vasoconstriction

Inhibition of vasoconstrictors
Supplementation of vasodilatory factors

Vasodilators

Endothelin receptor antagonists
PDE5 inhibitors
PGI_2 receptor agonists

Organic stenosis (vascular remodeling)



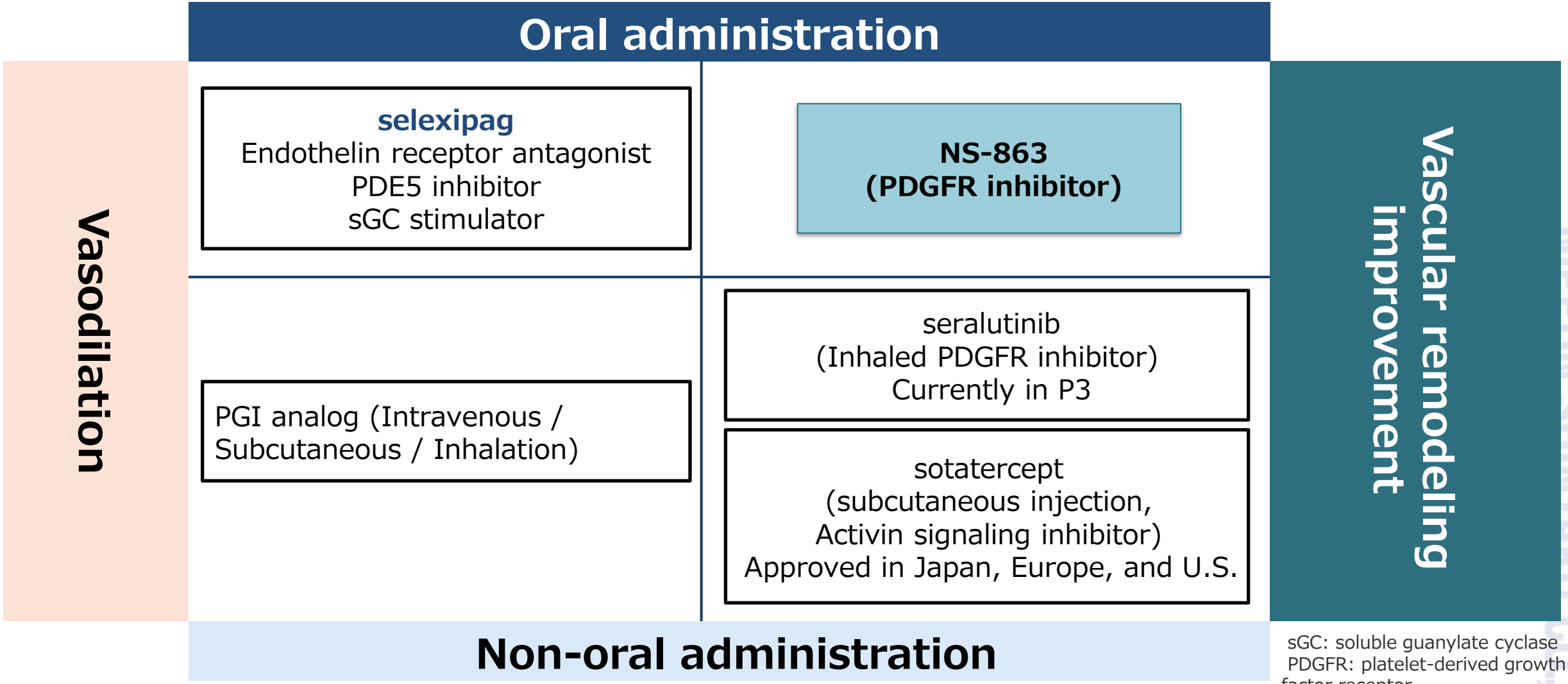
Normal　Cell proliferation into vascular lumen

Suppression of abnormal proliferation of vascular smooth muscle cells

Inhibits vascular smooth muscle cell growth factors such as PDGF

PDGF: platelet-derived growth factor

Positioning in pulmonary hypertension (PH) treatment



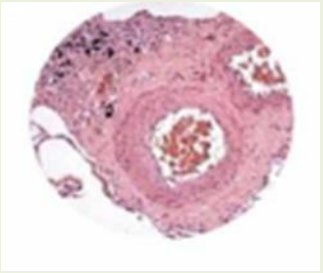
sGC: soluble guanylate cyclase
PDGFR: platelet-derived growth factor receptor

NS-863 is the first orally administered agent that improves vascular remodeling through PDGFR inhibition.

Unmet Medical Needs in Pulmonary Hypertension (PH)

Organic stenosis
(vascular remodeling)

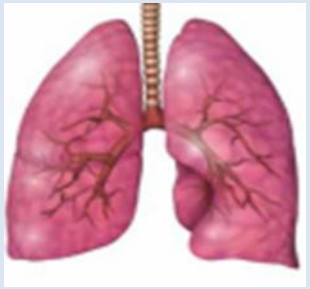
PAH



- Overall survival has been improving with existing therapies, but the median is still less than 10 years
- Non-oral PGI_2 is used in severe cases, significantly reducing quality of life

Unmet Medical Needs:
Improved therapeutic efficacy through mechanisms of action other than vasodilatation

PH-ILD[1]



- Significant pulmonary vascular remodeling is seen
- Poor prognosis among PH
- Only approved drug is treprostinil inhaler

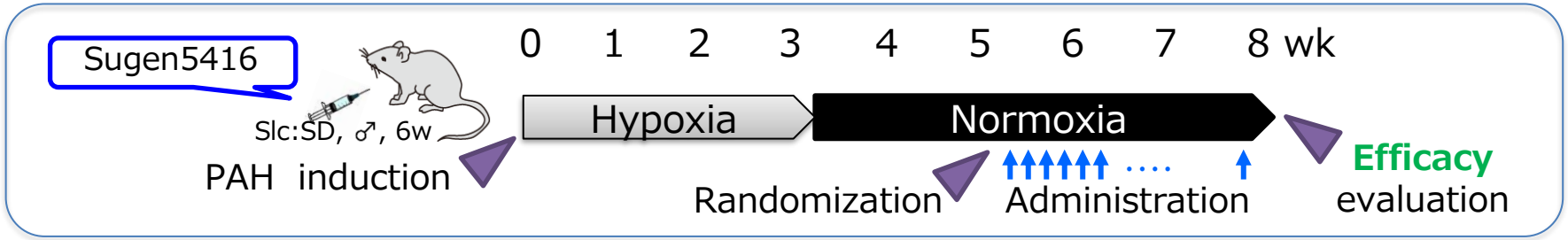
Unmet Medical Needs:
Expansion of treatment options

1. Pulmonary hypertension (PH) associated with interstitial lung disease

NS-863: Summary

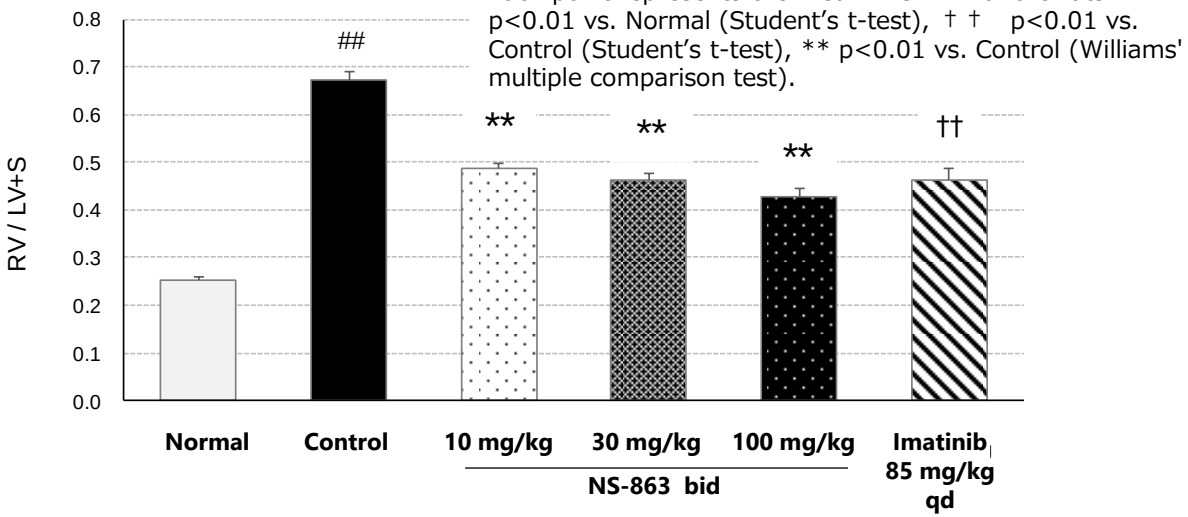
Indications	PAH (pulmonary arterial hypertension) PH-ILD (pulmonary hypertension associated with interstitial lung disease)
Mechanism of action	Selective inhibition of platelet-derived growth factor receptor (PDGFR)
Form of development	In-house development
Dosage form	Oral
Characteristics	• Unlike pulmonary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

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



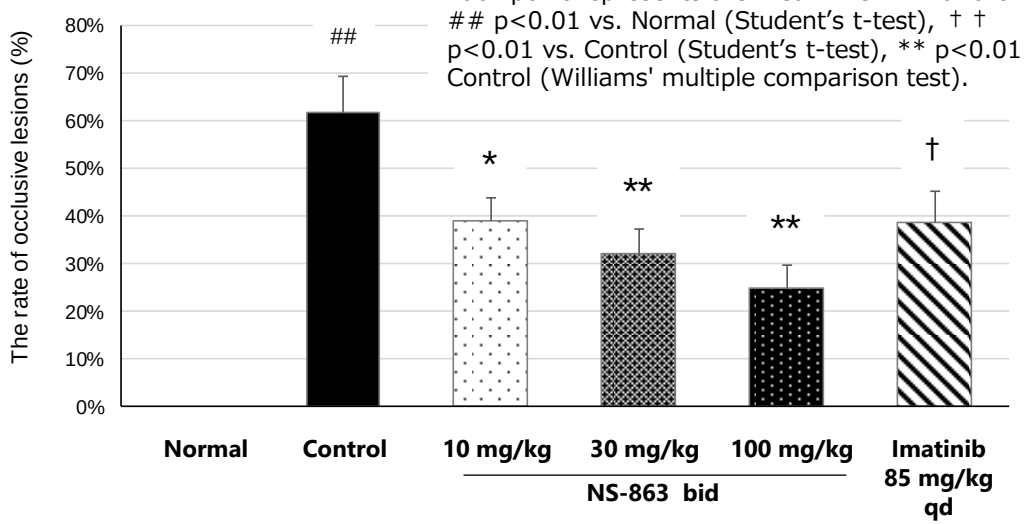
Right ventricular hypertrophy

Each point represents the mean ± S.E.M. of 6-8 rats. ## p<0.01 vs. Normal (Student's t-test), † † p<0.01 vs. Control (Student's t-test), ** p<0.01 vs. Control (Williams' multiple comparison test).



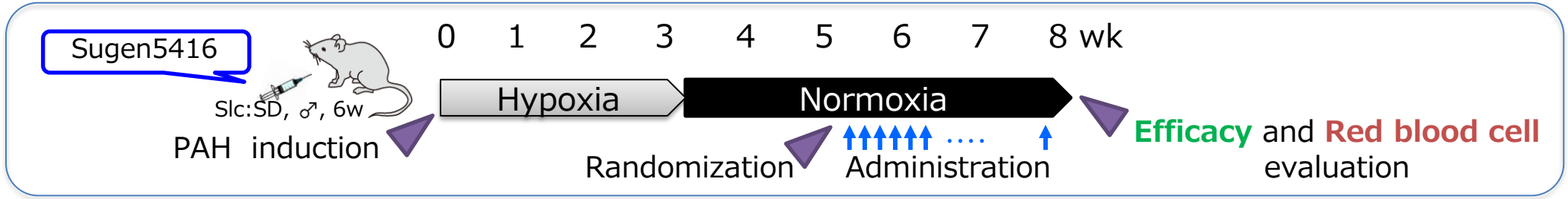
Occlusive lesions

Each point represents the mean ± S.E.M. of 6-8 rats. ## p<0.01 vs. Normal (Student's t-test), † † p<0.01 vs. Control (Student's t-test), ** p<0.01 vs. Control (Williams' multiple comparison test).



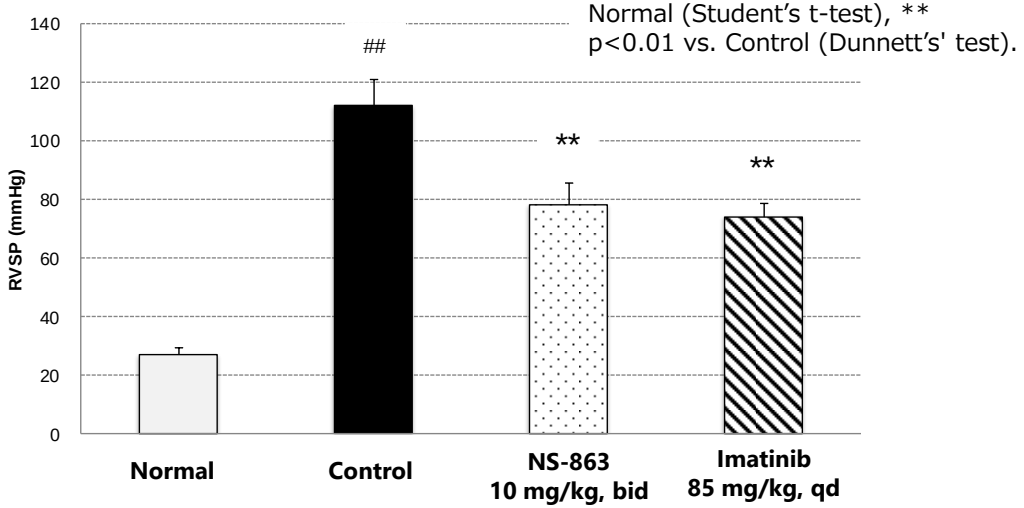
NS-863 (10 mg/kg, twice daily) improved right ventricular hypertrophy and vascular remodeling as much as imatinib (85 mg/kg, once daily).

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



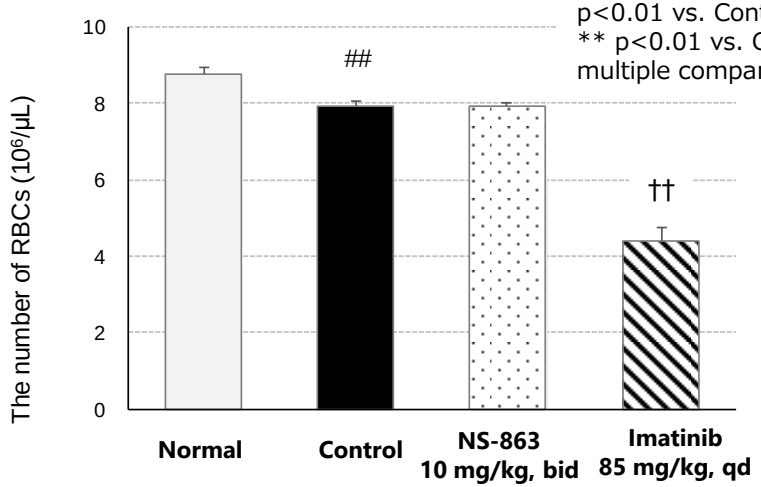
Right ventricular systolic pressure（RVSP）

Each point represents the mean ± S.E.M. of 5-7 rats. ## p<0.01 vs. Normal (Student's t-test), ** p<0.01 vs. Control (Dunnett's' test).



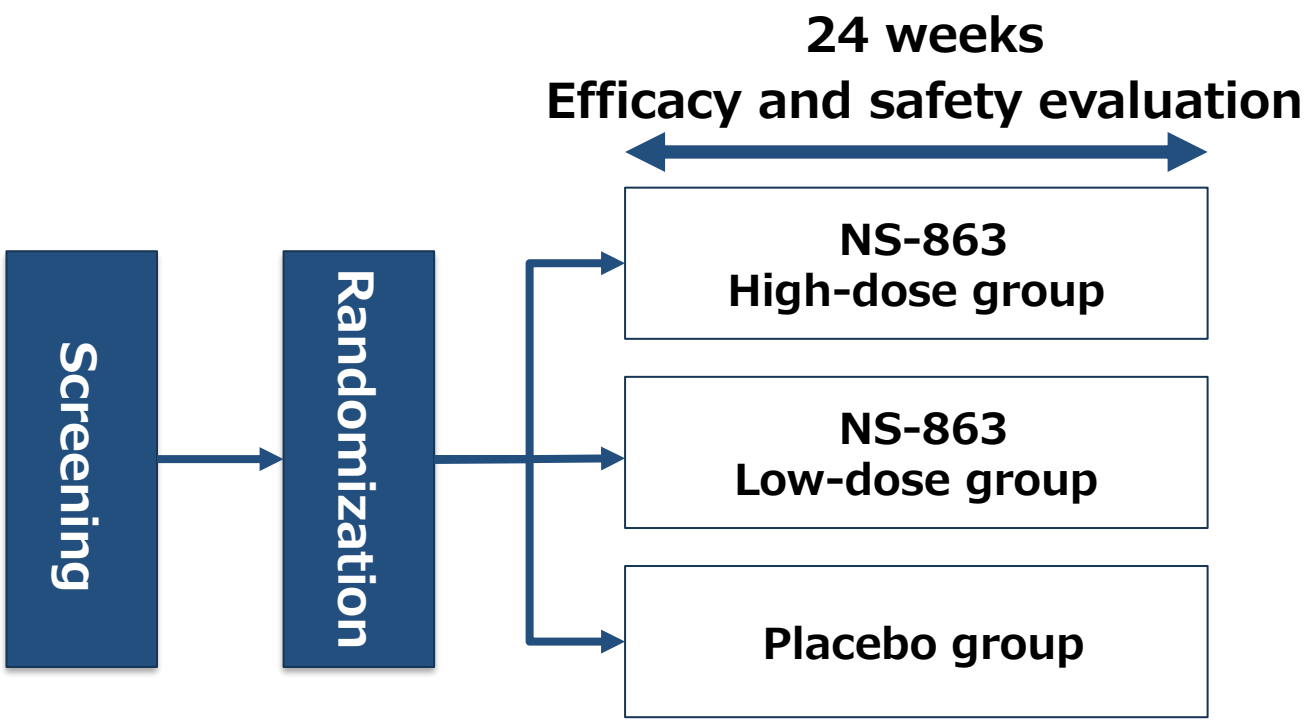
Red blood cell (RBC) number

Each point represents the mean ± S.E.M. of 7-8 rats. ## p<0.01 vs. Normal (Student's t-test), †† p<0.01 vs. Control (Student's t-test), ** p<0.01 vs. Control (Williams' multiple comparison test).



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

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.

NS-035
Fukuyama Congenital Muscular Dystrophy (FCMD)

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

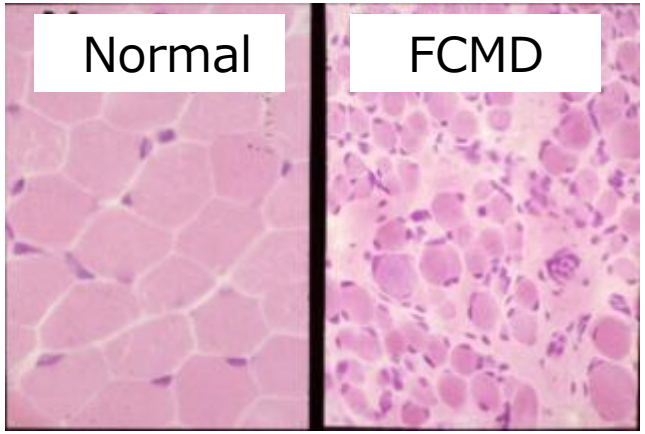
Symptoms

- 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

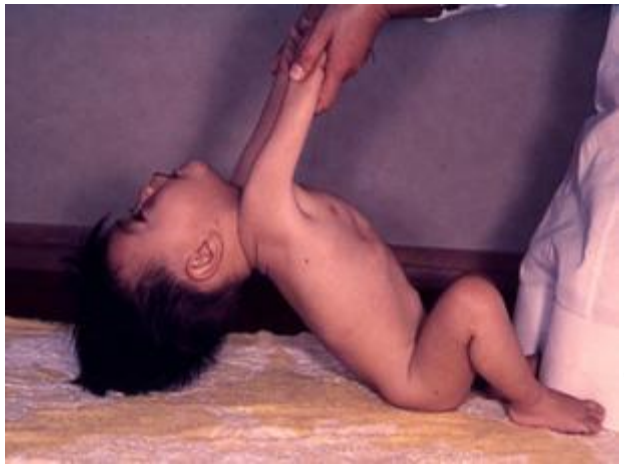
Treatment

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

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

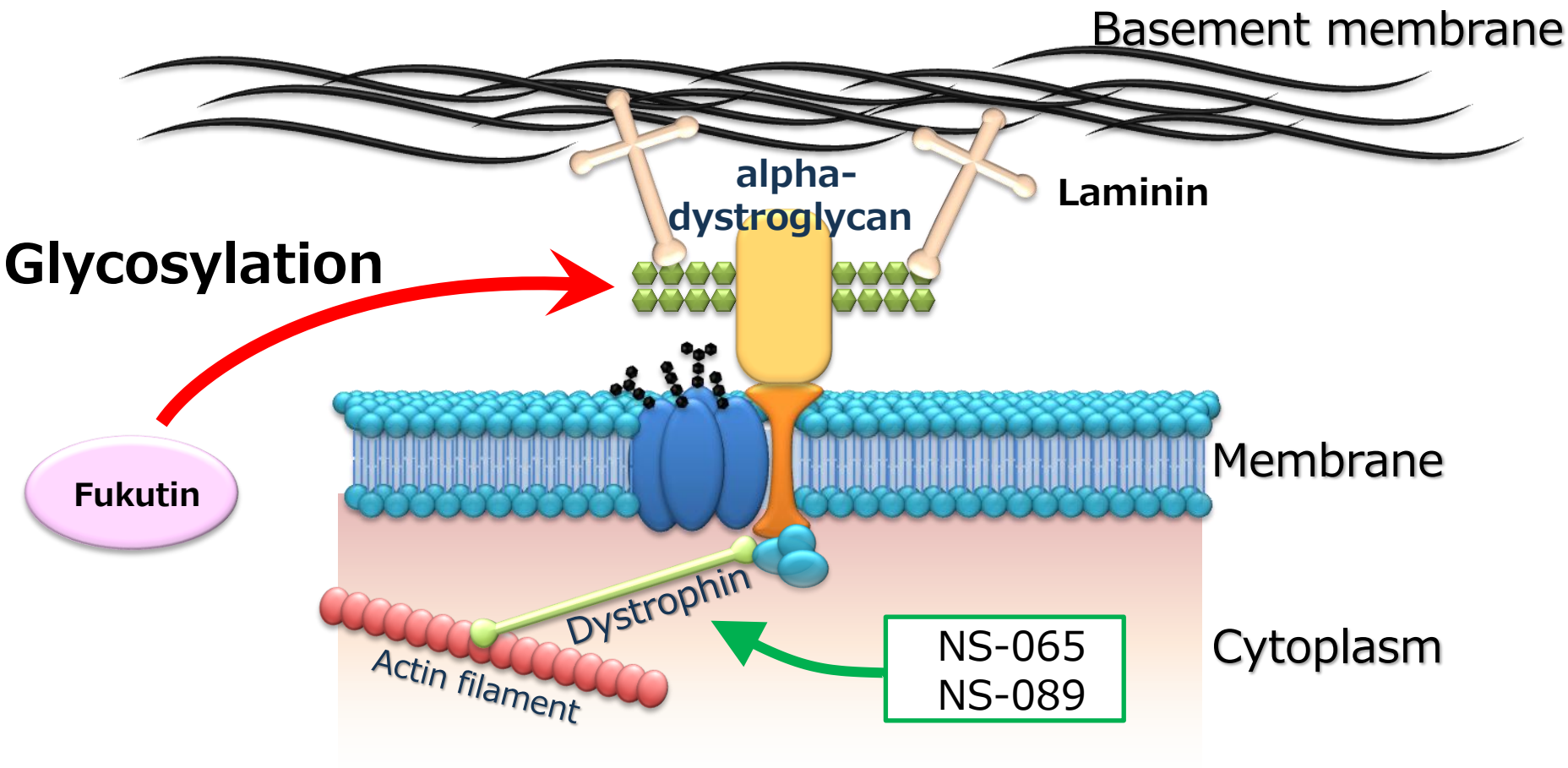


Delayed neck development (average 8 months)



Source: The Japan Muscular Dystrophy Association

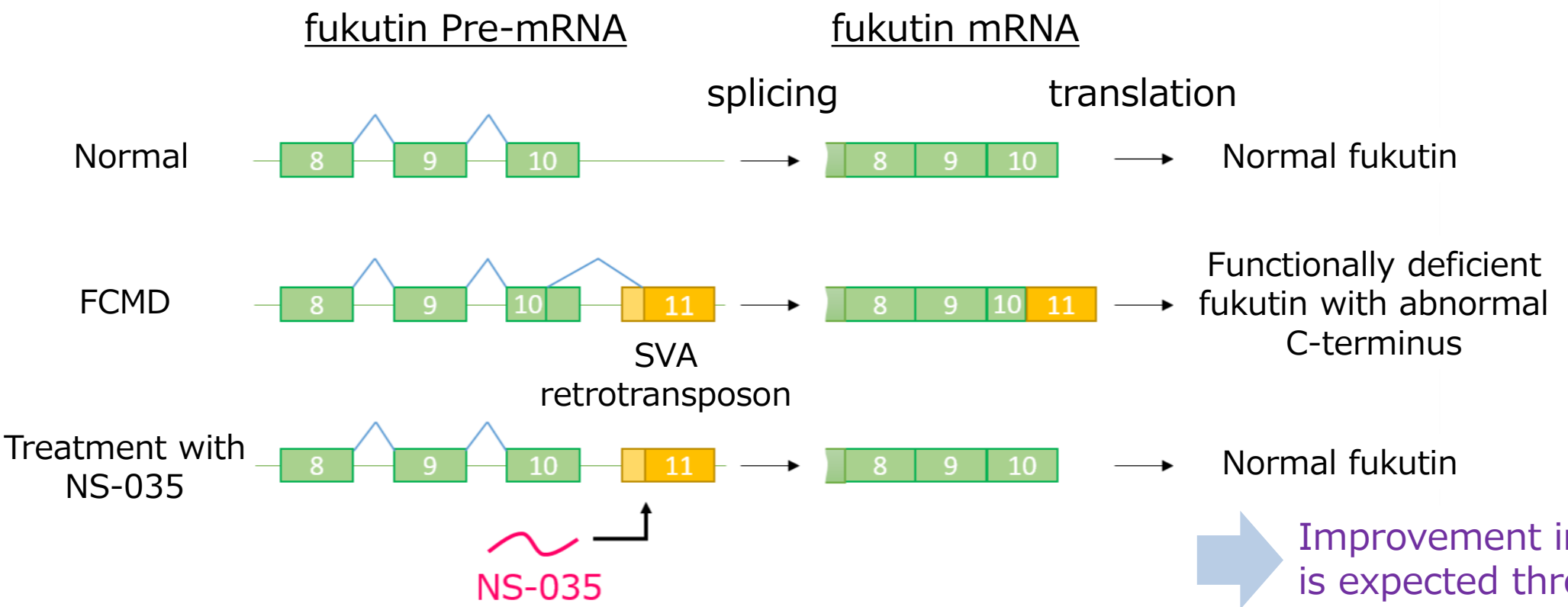
Pathogenesis: Abnormalities of fukutin



Abnormalities in the fukutin gene → Abnormal fukutin protein → α-DG with no glycosylation → Failure to fix muscle cells → Vulnerable Muscle cells

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.



Antisense nucleic acid: NS-035

Binds to the splice acceptor site of SVA retrotransposon

Improvement in muscle function is expected through the restoration of α-dystroglycan glycan chains.

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

Product Life Cycle Management (PLCM) Initiatives

NS-304 (selexipag)
for the treatment of arteriosclerosis obliterans

NS-304: Arteriosclerosis obliterans (ASO)

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

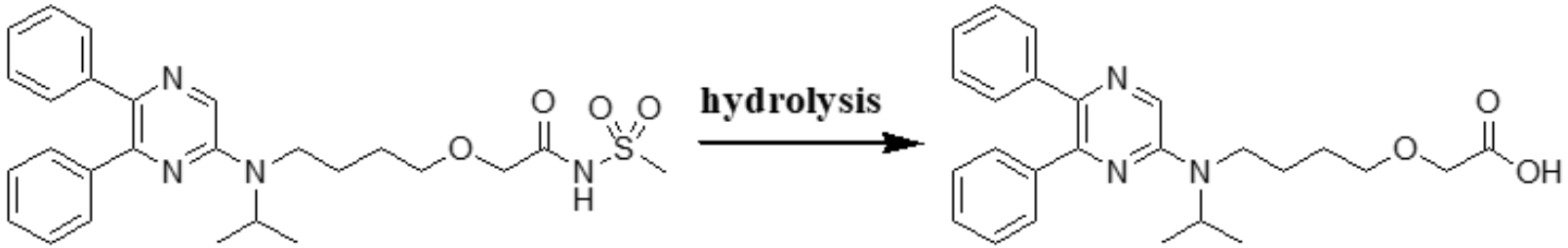
Treatment (Guideline on the Management of Peripheral Arterial Disease[1])

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

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 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.

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

Closing Summary

Nippon Shinyaku advances highly distinctive research through unique combinations of diseases, mechanisms of action, and modalities, creating a series of distinctive and competitive seeds.

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