FY2024
R&D Meeting

February 18th, 2025
Nippon Shinyaku Co., Ltd.

NIPPON SHINYAKU CO., LTD.

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AGENDA

01

Introduction

Toru Nakai
Representative Director, President

02

R&D activities

Kazuchika Takagaki
Director, Research & Development

03

Q&A

Introduction

Toru Nakai
Representative Director, President

Key Theme III : Continuous Pipeline Expansion

Licensing in products in the clinical stage and strengthen in-house drug discovery by leveraging open innovation and AI drug discovery system to continuously expand the pipeline.

Modified from May 27, 2024
The 7th Five-Year Medium-Term Management Plan (FY2024 - FY2028)
-For Global Growth Beyond the Cliff-p.31

In-house drug discovery

- Promotion of nucleic acid drug discovery
  - DMD
  - Central nervous system
- Promote small molecule drug discovery
  - Hematology
  - Intractable/rare diseases
  - Urology and Gynecology

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New / Outside Technology

- Utilization of open innovation and new drug discovery modalities
- Promote research and development using AI

Continuous Pipeline Expansion

In-licensing

- Activities with attention to priority
- Strengthening negotiation capabilities
- Acquire more than 1 item every year

PLCM

- Consider clinical trials for secondary indications simultaneously to maximize the value of the product

Establishing a Foundation for Growth Overcoming the Patent Cliff

❶Speed and success probability in clinical development

- Delay of start of the studies for NS-089/NCNP-02 and NS-050/NCNP-03
- Prolonged clinical trials and termination of development for NS-018
- Termination of the development for NS-161

❷R&D speed for new modalities

- The length of time for development of next-generation nucleic acid drugs and gene therapeutics

Major issues identified in the 6th Medium-Term Management Plan

❸Marketing capabilities overseas

- Delay of initial sales growth of Viltepso in the U.S.
- Struggling to increase market share 3 years after launch of Viltepso in the U.S.

During the 7th Medium-Term Management Plan, we will resolve issues identified in the 6th Medium-Term Management Plan.

Modified from May 27, 2024
The 7th Five-Year Medium-Term Management Plan (FY2024 - FY2028) -For Global Growth Beyond the Cliff-p.6

Business Strategy for Pharmaceutical Segment

Business Strategy

Launching an average of two or more new products per year through the three pillars of in-house drug discovery, in-licensing, and PLCM, prioritizing response to the patent cliff.

■ In-house drug discovery, PLCM	Focusing on nucleic acid and small molecule drug discovery, concentrate management resources on diseases and areas where we can aim for global expansion In particular, nucleic acids will be focused on DMD and non-DMD diseases, with the aim of bringing products for non-DMD diseases to market by 2035
■ In-licensing	Focused as much as in-house drug discovery
■ Sales	Based on global marketing, consider and promote the best way to proceed with out-licensing, self-sales, etc. in each country to quickly launch products in each region and increase market share

Pharmaceutical Business Segment Targets

	FY2028
Revenue	203 billion yen
Operating profit	28.2 billion yen
ROIC	≧ 9%

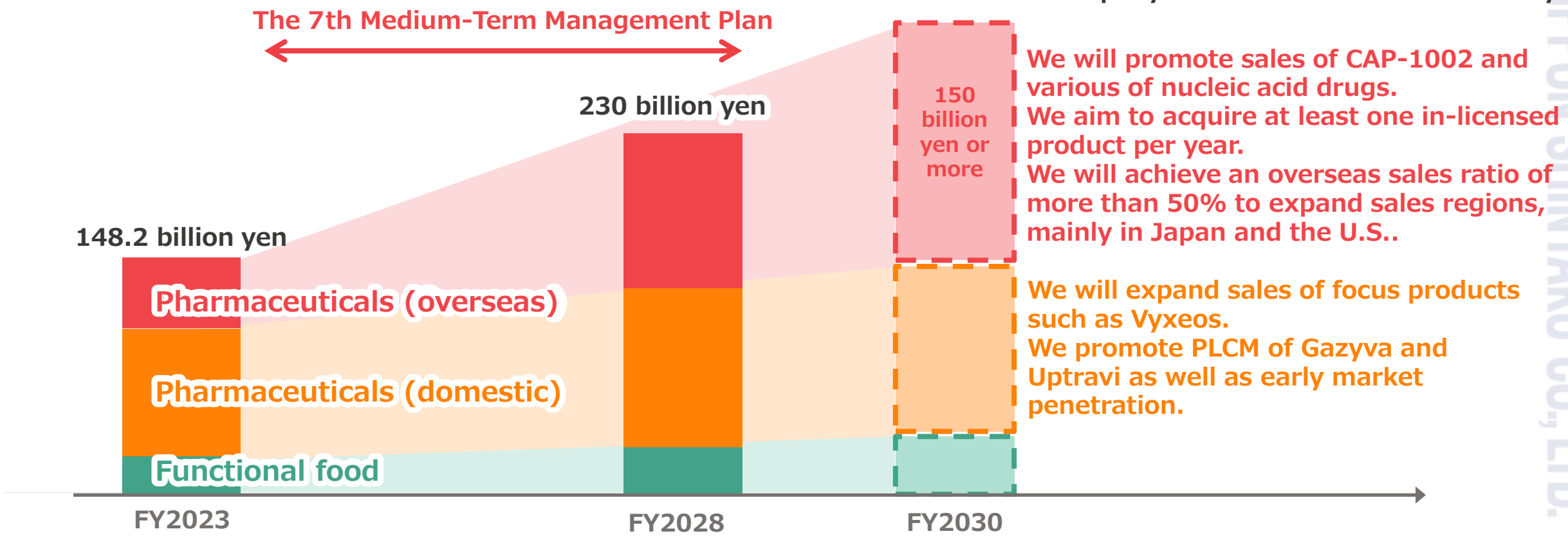
Modified from May 27, 2024
The 7th Five-Year Medium-Term Management Plan (FY2024 - FY2028) -For Global Growth Beyond the Cliff-p.21

Establishing a foundation for growth overcoming the patent cliff

We plan to achieve revenues of 300 billion yen in FY2030 by promoting investment in R&D pipeline, in-licensed products, M&A, etc. during the 7th Medium-Term Management Plan period.

Modified from May 27, 2024
The 7th Five-Year Medium-Term Management Plan (FY2024 - FY2028) -For Global Growth Beyond the Cliff-p.18

< Image of revenue development >



We will promote sales of CAP-1002 and various of nucleic acid drugs.
We aim to acquire at least one in-licensed product per year.
We will achieve an overseas sales ratio of more than 50% to expand sales regions, mainly in Japan and the U.S..

We will expand sales of focus products such as Vyxeos.
We promote PLCM of Gazyva and Uptravi as well as early market penetration.

FY2024 R&D milestones to date

2024 Apr	Research alliance with MiNA Therapeutics
May	Launch of Vyxeos (Japan)
Aug	Launch of Jaypirca (Japan)
Nov	Exclusive strategic collaboration for ATSN-101 (U.S. and Japan) Start of co-promotion activities for Yuvanci (Japan)
Dec	Additional indication (pediatric PAH) for Uptravi (Japan) Approval for Uptravi tablets for pediatric 0.05 mg (Japan) CAP-1002 BLA submission (U.S.)
2025 Jan	Exclusive partnership for RGX-121/RGX-111 (U.S. and Asia) Option agreement for commercialization of Tadekinig alfa (U.S.)

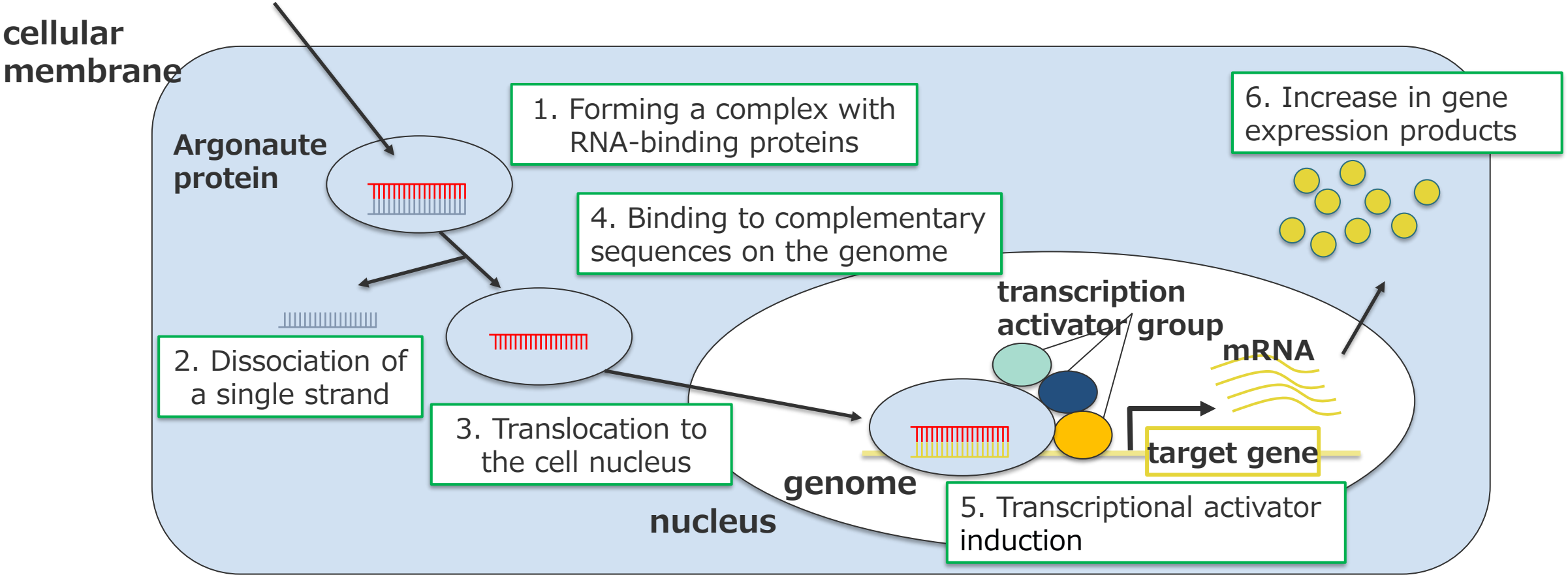
R&D activities
- For continuous pipeline expansion -

Kazuchika Takagaki
Director, Research & Development

New / outside technology

Small molecule activated RNA: Research collaboration with MiNA

saRNA is a type of nucleic acid that enhances gene expression
Chemically synthesized double-stranded RNA of 21 bases (similar to siRNA)



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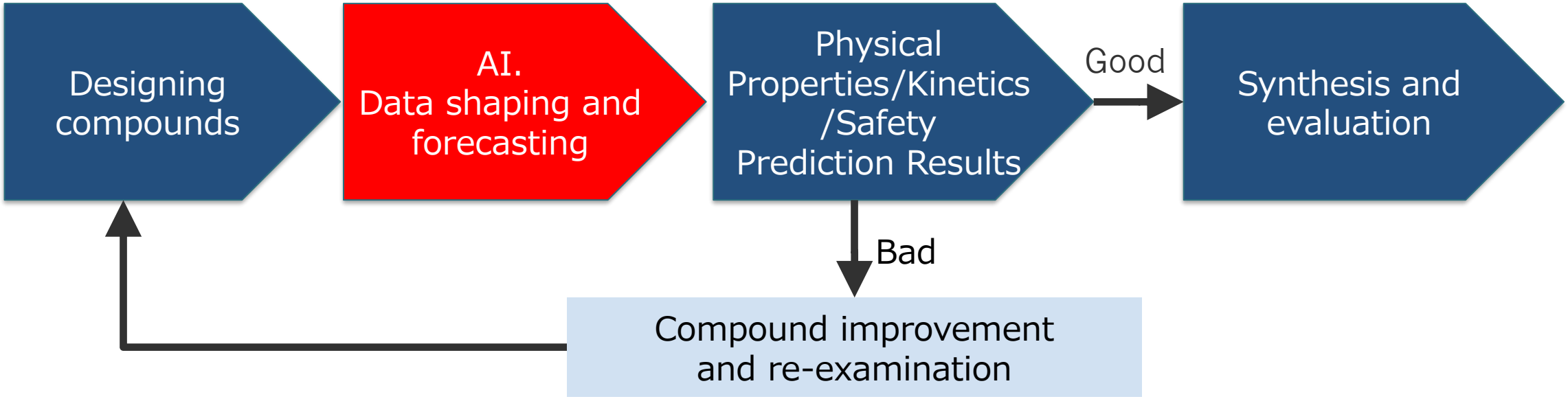
Enhancing the expression of target genes by 1.2 to 15 times

April 4, 2024 company press release Announcement of Research Alliance with MiNA Therapeutics in the Field of Central Nervous System
https://www.nippon-shinyaku.co.jp/file/download.php?file_id=7500

AI Drug Discovery

Workflow aimed at the Discovery Research Laboratories

- Design compounds that bind to target molecules (known/unknown structure) using AI
- Predict the physical properties, kinetics, and safety of compounds before synthesisPredicts physical properties/kinetics/safety of compounds before synthesis
- Allows prioritization of compounds to be synthesized



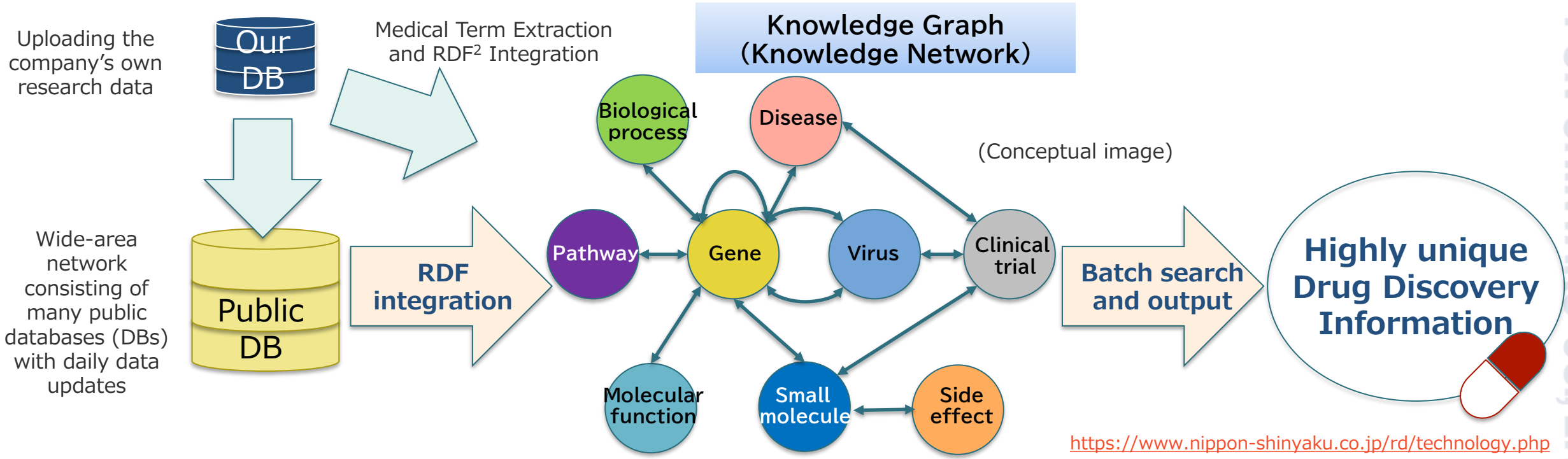
Usage example: AI application in non-clinical safety

- Early prioritization at the compound design stage removes the source of toxicity will **increase the probability of success and speed up drug discovery**

AI Drug Discovery

Information Creation of highly unique drug discovery by building a knowledge network system that integrates public and in-house data

- Comprehensive acquisition of drug discovery information from disease names to patents, clinical, genetic mutations, target molecule groups, existing compounds, etc.
- Greatly reduces information retrieval time by searching multiple databases at once.
- MeSH term expansion[1] and AI keyword generation for non-human, objective and exhaustive information retrieval
- Obtain the latest and competitive information through frequent data updates



https://www.nippon-shinyaku.co.jp/rd/technology.php

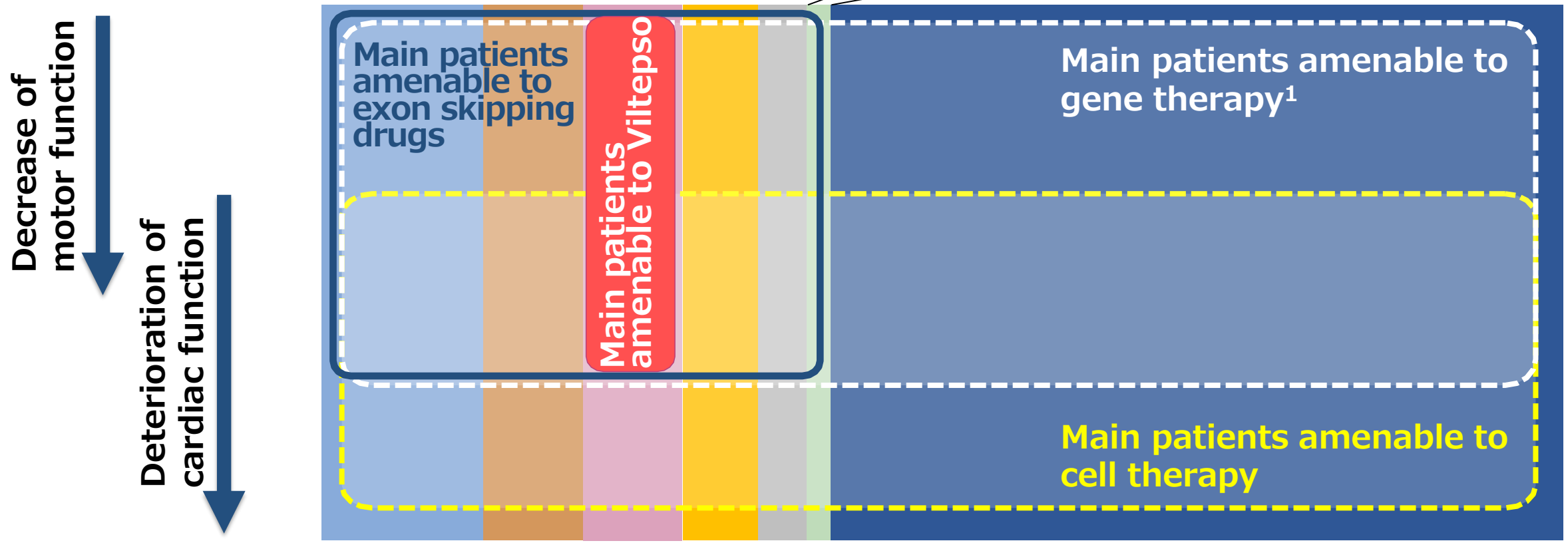
1. MeSH (Medical Subject Headings) is a glossary of medical terms that unifies the shaky notation of medical terms. MeSH term expansion is used to search for words of the same concept (e.g., cancer, neoplasms, etc.) at the same time.
2. RDF (Resource Description Framework) is a data format that defines a generic method for describing information about information (meta information/metadata).

In-licensing

Deramiocel (CAP-1002)
for the treatment of DMD-cardiomyopathy by cell (exosome) therapy

Positioning in the DMD treatment options

Our product and pipeline								
	Nucleic acid drug (Exon skipping)			Viltepso	NS-089	NS-050		
	Cell (exosome) therapy	CAP-1002						
Exon skipping		51	45	53	44	50	55	
% in DMD population		13%	8%	8%	6%	4%	2%	59%



(conceptual diagram)

1. Currently marketed gene therapy is indicated for patients aged 4 years and over. It is is contraindicated in patients with any deletion in exon 8 and/or exon 9 in the DMD gene and not recommended in patients with elevated anti-AAVrh74 total binding antibody titers (≥1:400).

Duchenne Muscular Dystrophy (DMD)

What is DMD?

Due to a genetic mutation that causes dystrophin to be lost, the structure that connects the cytoskeleton actin and basement membrane to reinforce the muscle cell membrane is not formed, and muscle cells become fragile. The broken muscle cells are regenerated by stem cells, but as the patient ages, muscle regeneration becomes unable to keep up, and muscle strength gradually declines. The incidence rate is 1 in 3,500-5,000 male births. The estimated number of patients is 3,500 (Japan) and 19,500 (Europe and the U.S.).

Symptoms and prognosis

DMD is a progressive muscular atrophy. At 3-5 years of age, abnormalities related to ambulation and cardiac dysfunction start at 8- 10 years of age, patients lose the ability to ambulate and live in a wheelchair. After 20 years of age, death from respiratory and heart failure occurs. (Advances in treatment for respiratory failure have extended life expectancy into the 30s.)

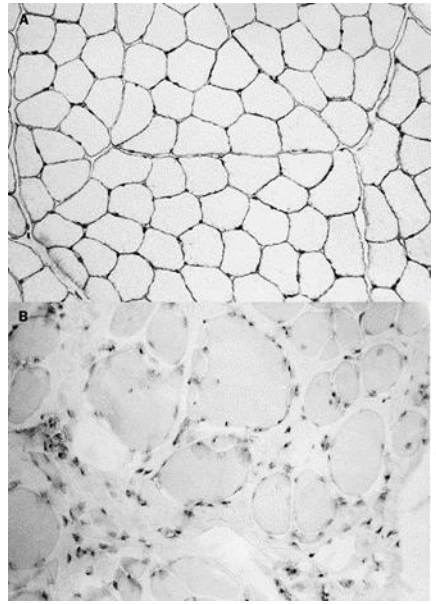
Cause

Deficiency of dystrophin protein due to abnormalities in the dystrophin gene (deletion/duplication of exons, etc.), X-linked

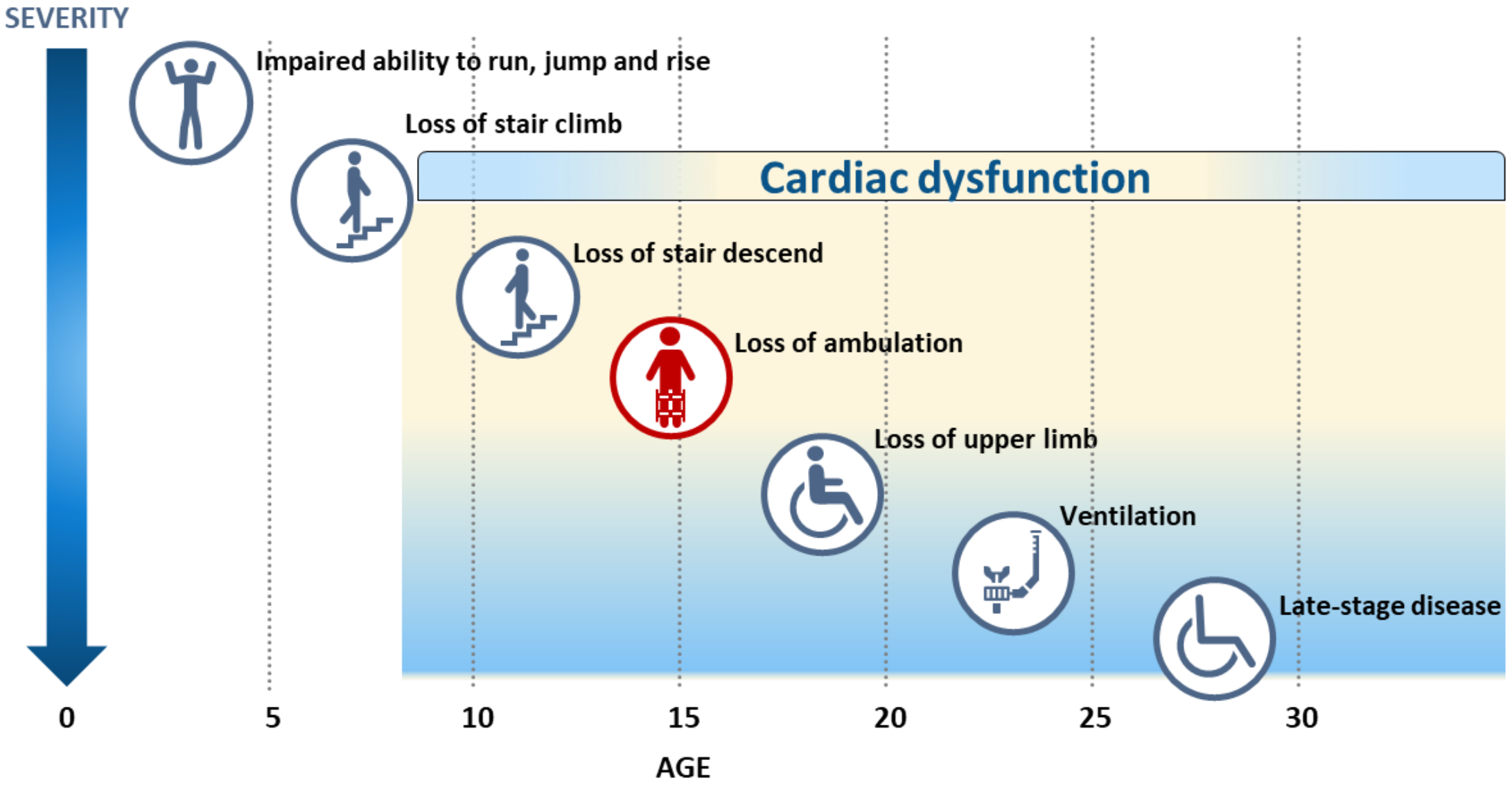
Existing treatment

Symptomatic treatment is the mainstay of treatment, and treatment that approaches the cause of the disease is eagerly awaited.

- corticosteroids (effective in preventing disease progression)
- occupational therapy
- respiratory care (ventilator)
- cardiac function protection (ACE inhibitors, beta-blockers)



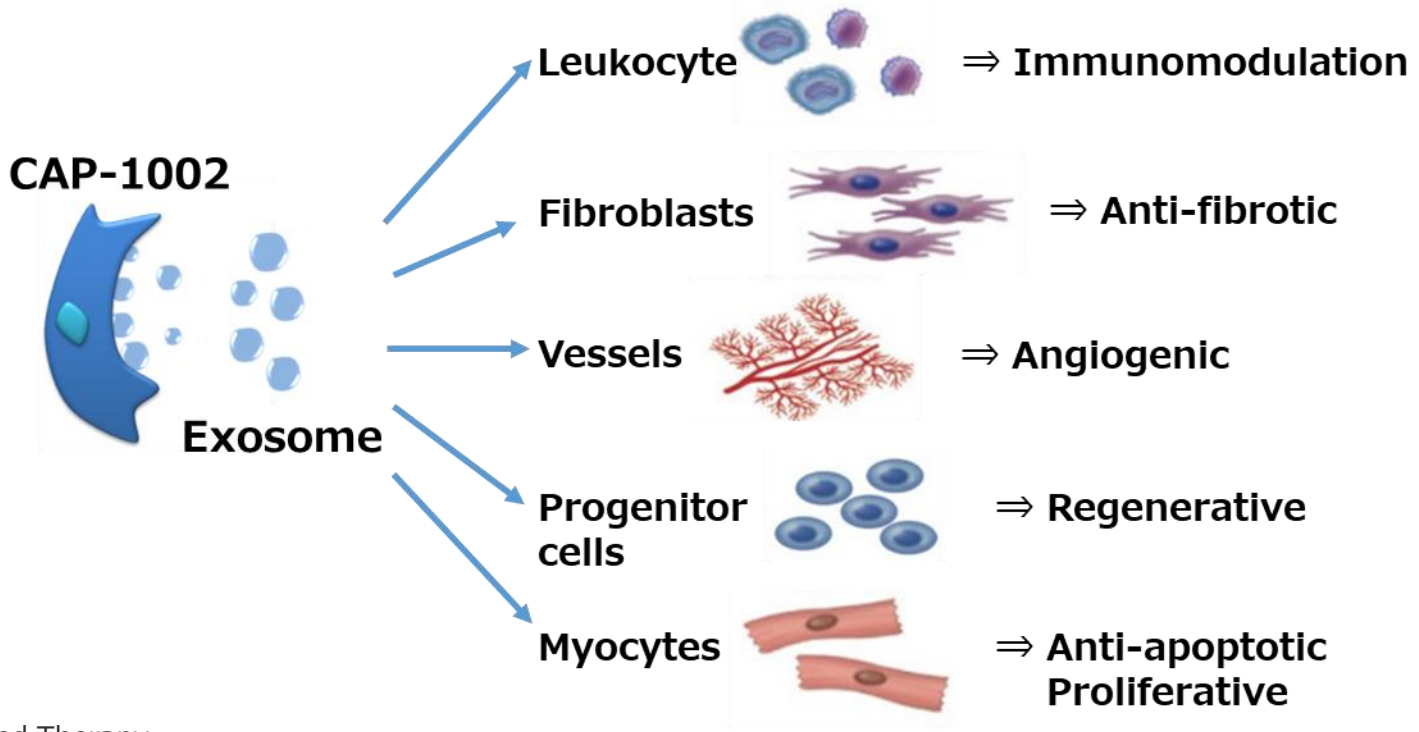
Duchenne Disease Trajectory



Source: Materials provided by Capricor Therapeutics

Deramiocel (CAP-1002): Cell therapy for the expected indication of DMD-cardiomyopathy

- Cell therapy derived from transplant-qualified human hearts (allogeneic sources).
- Exosomes (extracellular vesicles) secreted from CAP-1002 are expected to reduce oxidative stress, inflammation, and fibrosis, and increase cellular energy and muscle cell production, thereby reducing the decline in motor function and cardiac function.
- In the U.S., BLA submission was completed with data from the P2 study (HOPE-2) and the P2 open-label extension study (OLE) completed, and full approval is expected in 2025 2H.
- After the FDA approval, Capricor is aiming for indication expansion in DMD skeletal muscle myopathy based on data from the P3 study (HOPE-3) which is currently underway.
- Orphan Designation (US and EU), RMAT Designation[1] (US), ATMP Designation[2] (EU), Rare Pediatric Disease Designation (US)



1. Regenerative Medicine Advanced Therapy
2. Advanced Therapy Medical Products

Source: Materials provided by Capricor Therapeutics

Production of deramiocel (CAP-1002)

Deramiocel
Manufacturing Facility

San Diego, California

Capricor receives **qualified human heart**

Explants derived from **cardiac tissue**

EDC expansion & **MCB** formulation

Cardiosphere Formation

CDC Expansion

RNA characterization

Deramiocel

Doses of **deramiocel** are **cryopreserved**

Doses of **deramiocel shipped** to infusion sites

Deramiocel thawed and **administered i.v.**

150 million cells
4x per year

EDC : explant-derived cell
MCB : master cell bank
CDC : cardiosphere-derived cell

Source: Materials provided by Capricor Therapeutics

Deramiocel (CAP-1002): Clinical Trials

	P2 study (HOPE-2)	P2 Open-label extension study (HOPE-2 OLE)
Testing period	March 2018 - March 2020	July 2020 - ongoing
Number of cases	Total 20 cases 8 active drug (7 cases of non-ambulatory) 12 placebo (11 cases of non-ambulatory)	13 cases (all non-ambulatory)
Trial design	multicenter, randomised, double-blind, placebo-controlled trial.	multicenter open-label trial
Trial sites	7 sites in the U.S.	5 sites in the U.S.
Target patients	DMD patients aged 10 years and older with reduced upper arm function If ambulatory, 10m walking speed < 1m/sec Continuous steroid administration in the last 12 months	Eligible patients who completed the HOPE-2 study
Dosage and administration	Placebo or active drug (150 million cells) intravenous (IV) infusion every 3 months	Active drug (150 million cells) intravenous (IV) infusion every 3 months
Duration of administration	12 months (4 doses in total)	~4 years (16 doses in total) Currently, data are available up to 3 years after the first dose

https://clinicaltrials.gov/study/NCT03406780

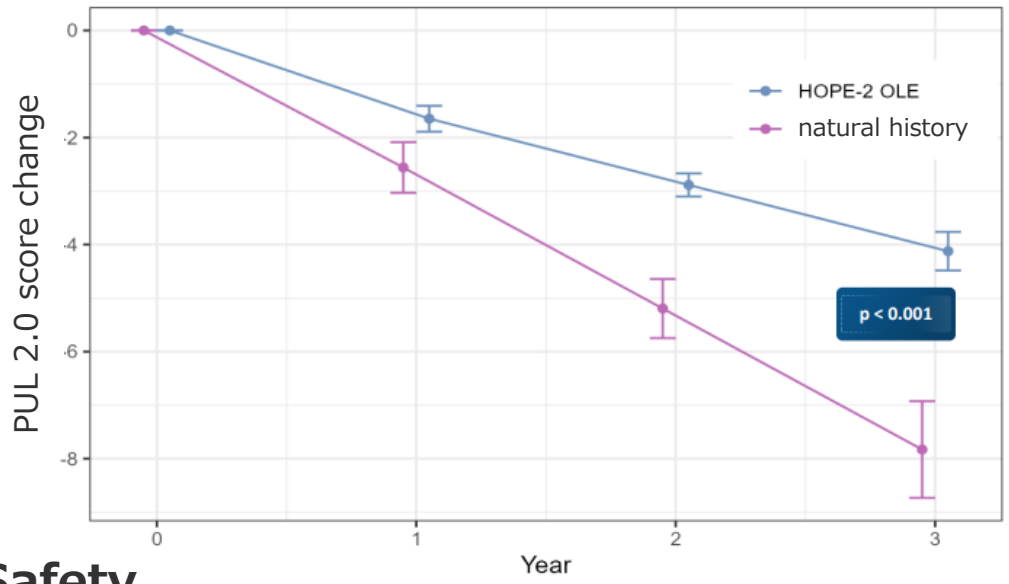
https://clinicaltrials.gov/study/NCT04428476

Sources: Clinicaltrials.gov and materials provided by Capricor Therapeutics

Deramiocel (CAP-1002): HOPE-2 OLE study 36 months data

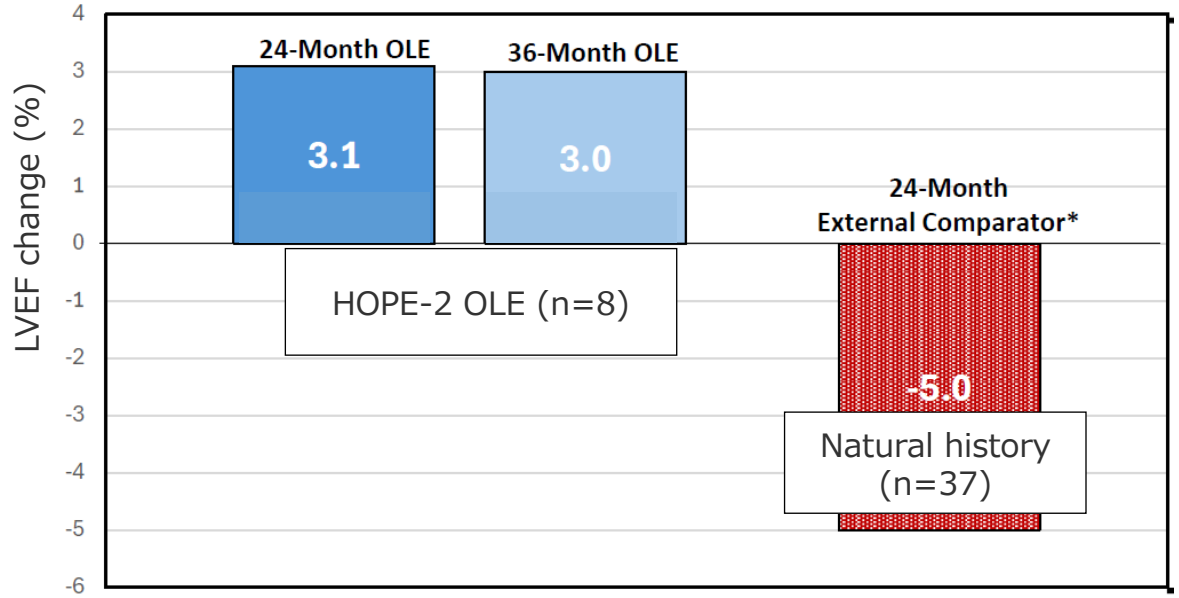
Skeletal Muscle Endpoint
Change in PUL 2.0 score [1]

At 3 years post-treatment, deramiocel (CAP-1002) (n=13) significantly reduced the decline in PUL 2.0 scores[2] compared to the natural history group (n=30).



Cardiac Endpoint
Median change in left ventricular ejection fraction (LVEF)
Baseline LVEF >45%

While LVEF worsened by 5.0% over 2 years in the natural history data of patients who had not yet lost cardiac function, it improved by 3.1% at 2 years, an improvement of 8.1 points compared to the natural history data. This efficacy was also observed at 3 years (3.0% improvement in LVEF).



Safety

- Of TEAE[3] that occurred up to 3 years after the administration of this product, there were 9 cases (69.2%) that were considered to be related to the administration of investigational products, all were mild to moderate.
- There were no significant TEAEs related to the administration of CAP-1002.

1. Performance of the upper limb
2. 3.7 point (47%) suppression vs. natural history, p<0.001
3. Treatment emergent adverse event

Source: modified from 2024 The World Muscle Society, Poster 721LBP

Deramiocel (CAP-1002): Development timeline and partnership

NS Pharma, a U.S. subsidiary of Nippon Shinyaku, is currently preparing for the product launch.

BLA submission	completed in December 2024
Expected PDUFA (FDA approval date)	2025 2H
Expected type of approval	full FDA approval with data of HOPE-2 and HOPE-2 OLE in comparison with natural history
Indication	cardiomyopathy in patients with DMD

Source: https://www.capricor.com/investors

Partnership between Nippon Shinyaku and Capricor Therapeutics

	Territory	Signed date	Developed by	Development timeline	Distributed by
Commercialization and distribution of CAP-1002 for the Treatment of DMD	U.S.	January 2022	Capricor	In application	Nippon Shinyaku group
	Japan	February 2023		To be decided	
	Europe	Under discussion			

Gene therapy

Gene therapy : In-Licensed products

Code name	ATSN-101	RGX-121	RGX-111
Origin	Athena Therapeutics, Inc.	Regenex Bio Inc.	
Indication	GUCY2D-associated Leber congenital amaurosis (LCA1)	Mucopolysaccharidosis type II (MPS II; Hunter syndrome)	Mucopolysaccharidosis type I (MPS I)
AAV serotype	AAV5	AAV9	AAV9
Promoter (the region in DNA that controls gene transcription)	hGRK1 (human rhodopsin promoter)	CMV-chicken beta-actin fusion	CMV-chicken beta-actin fusion
GOI (gene of interest)	Guanylate cyclase 2D (GUCY2D)	Isuronic acid-2-sulfatase (*IDS*)	alpha-L-isuronidase (IDUA)
RoA (route of administration)	Single dose of $1x10^{11}$ vg per eye, subretinal administration	2.9×10^{11} vg/g brain into CNS administration	into CNS administration (dose to be determined)

ATSN-101
for the treatment of GUCY2D-associated Leber congenital amaurosis (LCA1)

ATSN-101 : Summary of expected indications

What is LCA?[1,2]

LCA (Leber congenital amaurosis) is a family of diseases caused by mutations in ~20 different genes. The estimated number of patients is around 10,000 (Japan)[3] and just under 50,000 (USA) [4]. All forms of LCA are inherited in autosomal recessive fashion and, together, account for the leading cause of blindness in children. GUCY2D-associated LCA1 is one of the most prevalent forms and is estimated to account for around 10% of cases of LCA[5].

Symptoms/Prognosis of LCA

The main symptoms are night blindness, where it becomes difficult to see in dark places, visual field narrowing, where the field of vision narrows, and reduced eyesight. If left untreated, it can lead to blindness.
The condition is characterized by severe visual impairment at birth or immediately after birth, and the visual impairment tends to worsen over time.

Cause of the disease of LCA1

When the GUCY2D gene is mutated, the photoreceptors of the rods (which sense light and dark) and cones (which sense color) become chronically activated, and their photoreceptor function declines.

Existing treatment of LCA1

There is no fundamental treatment, and the following symptomatic treatments are used.

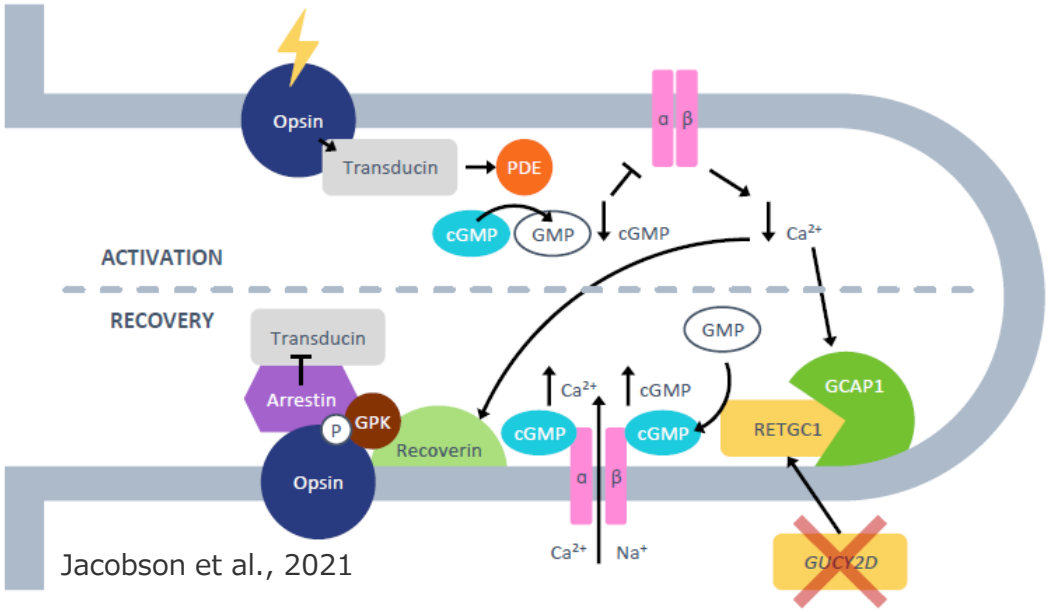
- Wearing glasses to improve eyesight as much as possible.
- Wearing goggles to prevent actions such as pressing or rubbing the eyes.

1. https://medlineplus.gov/genetics/condition/leber-congenital-amaurosis/#causes
2. https://rarediseases.org/rare-diseases/leber-congenital-amaurosis/
3. レーベル遺伝性視神経症（指定難病３０２） – 難病情報センター
4. Leber congenital amaurosis | About the Disease | GARD
5. Leber congenital amaurosis: Genes, proteins and disease mechanisms - ScienceDirect

Features of ATSN-101

Modality	Gene therapy
Development stage	P1/2
Dosage and administration	1×10^{11} vg per eye administered as a single subretinal injection
Dosage form	Vial
Designations	RMAT designation, orphan designation, rare pediatric disease designation by the U.S. FDA

Mechanism of action



Jacobson et al., 2021

The GUCY2D gene encodes retinal guanylate cyclase (RETGC1), which plays an important role in the recycling of cGMP during the recovery period after light stimulation in the phototransduction pathway.

This is a gene therapy in which the human GUCY2D gene is incorporated into an AAV5 vector, and by administering it under the retina, it expresses the normal GUCY2D gene and restores photoreceptor function.

Source: materials from Atsena Therapeutics

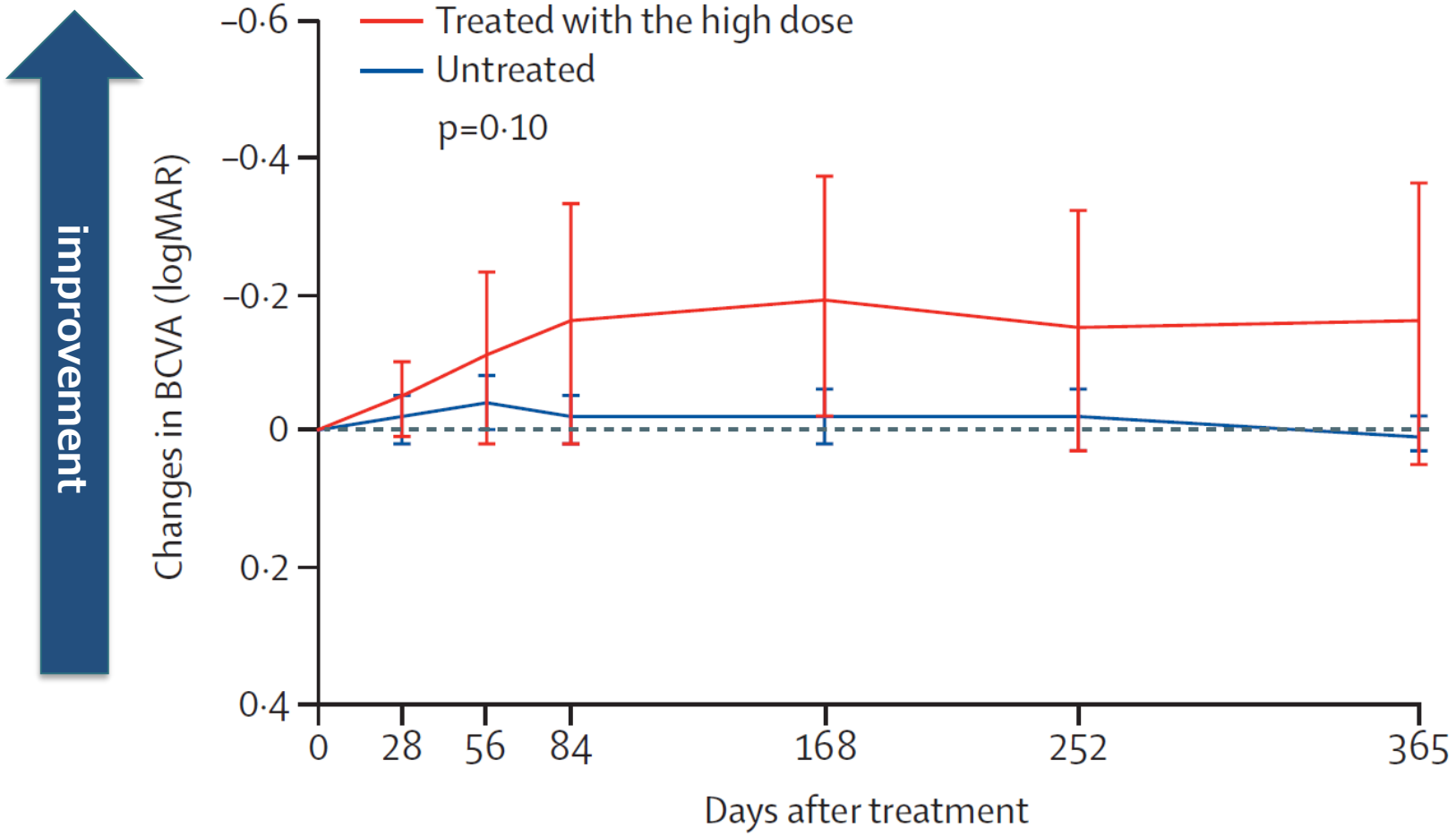
ATSN-101: U.S. P1/2

Testing period	September 2019 - May 2027
Number of cases	15
Trial design	Multicenter open-label single eye dose escalation study
Trial sites	2 sites in the U.S.
Target patients	• 18 years and older (cohorts 1-4), 6-17 years (cohort 5) • Genetically diagnosed with Leber's congenital cataract • All of the following findings are confirmed 1. GUCY2D mutation in both alleles 2. best-corrected visual acuity (BCVA) ≤ 20/200 (Snellen, cohorts 1-3) or ≤20/80 (Snellen, cohorts 4, 5) 3. optical coherence tomography confirms the structure of photoreceptors in the outer retinal granular layer
Dosage and administration	Single subretinal dose per eye at the following doses Cohort 1: 1.0 x 10^{10} vg (low dose) Cohort 2: 3.0 x 10^{10} vg (medium dose) Cohort 3: 1.0 x 10^{11} vg (high dose)
Duration of administration	One-time use only (no re-administration)

Source: https://clinicaltrials.gov/study/NCT03920007

ATSN-101: Efficacy evaluation of U.S. P1/2 clinical trial

Efficacy: BCVA (best-corrected visual acuity)

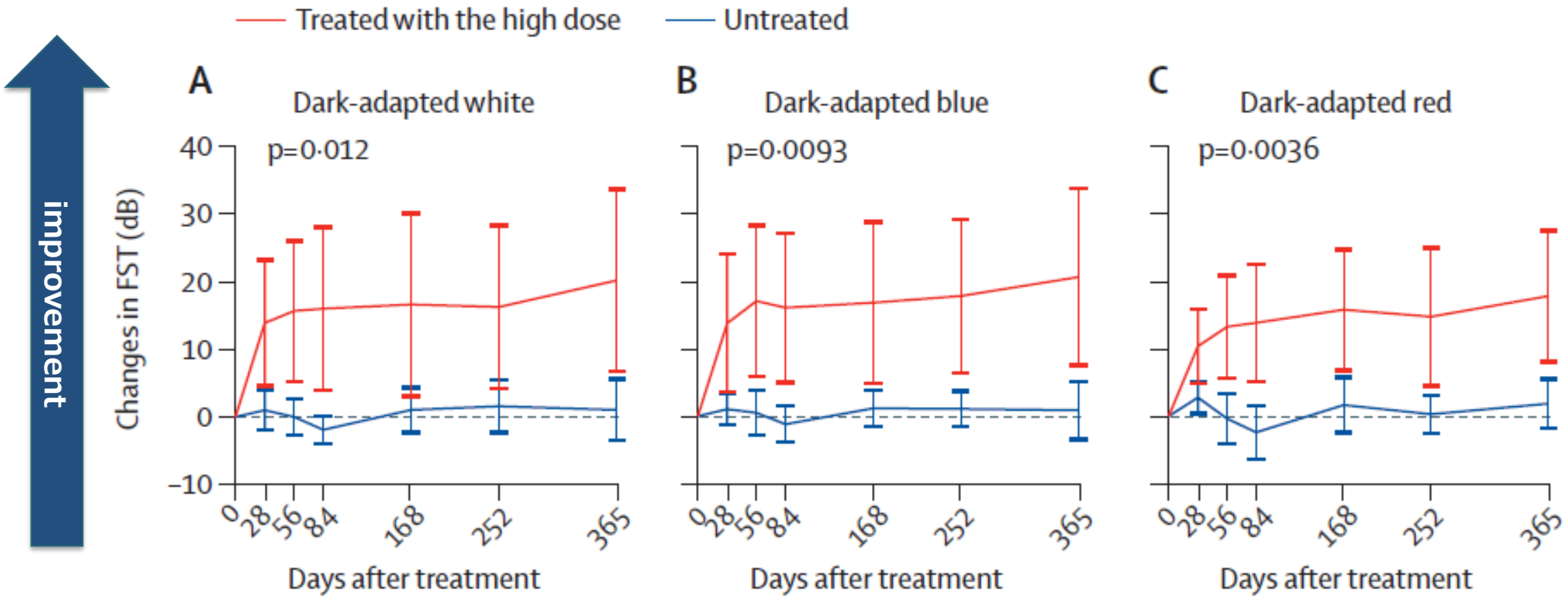


Improvement trend was observed.

Source: Figure 5, The Lancet Volume 404, Issue 10456, 7-13 September 2024, Pages 962-970
Safety and efficacy of ATSN-101 in patients with Leber congenital amaurosis caused by biallelic mutations in GUCY2D: a phase 1/2, multicentre, open- label, unilateral dose escalation study

ATSN-101: Efficacy evaluation of U.S. P1/2 clinical trial

Efficacy: FST (full-field stimulus threshold)



In the high-dose group (1.0×10^{11} vg/eye), the response to light was significantly improved compared to that of the untreated group. The effect continued at the one-year point.

Source: Figure 3, The Lancet Volume 404, Issue 10456, 7-13 September 2024, Pages 962-970
Safety and efficacy of ATSN-101 in patients with Leber congenital amaurosis caused by biallelic mutations in GUCY2D: a phase 1/2, multicentre, open- label, unilateral dose escalation study

ATSN-101: Safety evaluation of U.S. P1/2 clinical trial

Safety: Treatment-Emergent Adverse Event (TEAE)

cohort		Total	1	2	3/4	5
Number of cases		15	3	3	6	3
Any TEAE		15 (100%)	3 (100%)	3 (100%)	6 (100%)	3 (100%)
Any serious TEAE		2 (13%)	0	1 (33%)	0	1 (33%)
Severity	1	15 (100%)	3 (100%)	3 (100%)	6 (100%)	3 (100%)
	2	5 (33%)	0	0	4 (67%)	1 (33%)
	3-5	0	0	0	0	0
Related to ATSN-101		4 (27%)	0	0	4 (67%)	0
Related to Surgical Procedure		15 (100%)	3 (100%)	3 (100%)	6 (100%)	3 (100%)

No drug-related serious SAEs reported. No study discontinuation or death was observed from the study due to AE.

The three serious TEAEs that occurred in two patients were macular hole, endophthalmitis, and retinal detachment (one each), all related to surgical procedure. Two events of ocular inflammation (subretinal inflammation and vitritis) noted, both Grade 2 in severity and resolved with steroid.

Source: materials from Atsena Therapeutics

RGX-121/111
for the treatment of Mucopolysaccharidosis Type II and Mucopolysaccharidosis Type I, respectively

RGX-121/111 : Summary of expected indications

What is Mucopolysaccharidosis?

Mucopolysaccharidoses (MPS) are a group of rare inherited metabolic diseases, classified within a larger group of disorders called lysosomal disorders, and involve the deficiency of enzymes that breakdown of mucopolysaccharides, more commonly known as glycosaminoglycans (GAGs). In the severe or neuronopathic forms, the buildup of GAGs cause permanent, progressive cellular damage that affects the person's appearance, physical abilities, organ and system functioning, and, in most cases, cognitive development. The prevalence per 100,000 people in Japan and the U.S. is 1.53 and 1.2 for MPS overall, 0.84 and 0.29 for MPS II, and 0.23 and 0.34 for MPS I[1].

1. https://pmc.ncbi.nlm.nih.gov/articles/PMC7916572/#diagnostics-11-00273-t002

Cause of the disease

Mucopolysaccharidosis type II (MPS II) is characterized by deficiency in the enzyme iduronate 2-sulfatase (IDS), while mucopolysaccharidosis type I (MPS I) is characterized by congenitally deficient in alpha-L-iduronidase (IDUA), respectively, and in both diseases, accumulation of the glycosaminoglycans (GAGs), heparan sulfate (HS) and dermatan sulfate (DS) are in various organs in the body.

Existing treatment

Current treatments include hematopoietic stem cell transplantation (for MPS I) and enzyme replacement therapy (ERT, for both MPS I and II), but the ERT currently on the market in the US and Europe (Elaprase® for MPS II and Aldurazyme® for MPS I) is a weekly intravenous formulation that does not cross the blood-brain barrier (BBB).

Therefore, treatment options with high convenience and the potential to address efficacy against CNS symptoms have been eagerly awaited.

In the following pages, we will explain RGX-121,
which is currently undergoing a rolling BLA submission in the U.S.

Features of RGX-121

Modality	gene therapy
Development stage	rolling BLA (submission expected to be completed in 1Q of CY2025)
Dosage and administration	2.9 x 10^{11} copies/g brain administered into CNS
Dosage form	frozen liquids in vials

RGX-121 is an investigational gene therapy that is designed to use the NAV® AAV9 vector to deliver the human iduronate-2-sulfatase (*IDS*) gene to the central nervous system (CNS).
By administering the drug directly into the cerebrospinal fluid, the *IDS* gene is delivered to the central nervous system cells, causing them to produce the enzyme.

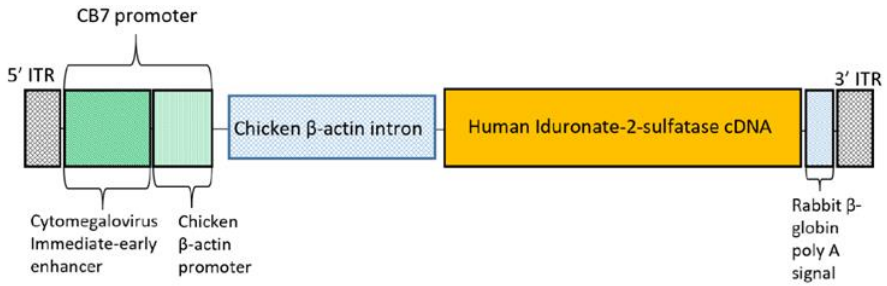


Figure S.1.2-1 Schematic Representation of the RGX-121 Vector Genome

- It is expected that a single dose will have a sustained effect, and that it will be effective against central nervous system symptoms that are not recognized by existing ERTs.
- As RGX-121 can be administered from the age of 4 months, compared to other products[1] under development, it is expected that this drug will be used preferentially for the treatment of newborns.

1. The minimum age for administration of Tividenofusp Alfa in P1/2 is 22 months of age (Barbara K Burton et al., Interim analysis of a phase 1/2 study of weekly intravenous tividenofusp alfa in mucopolysaccharidosis type II), and P3 for Izcargo is 30 months of age or older (NCT04573023). Both products are ERT.

Source: Materials provided by REGENXBIO

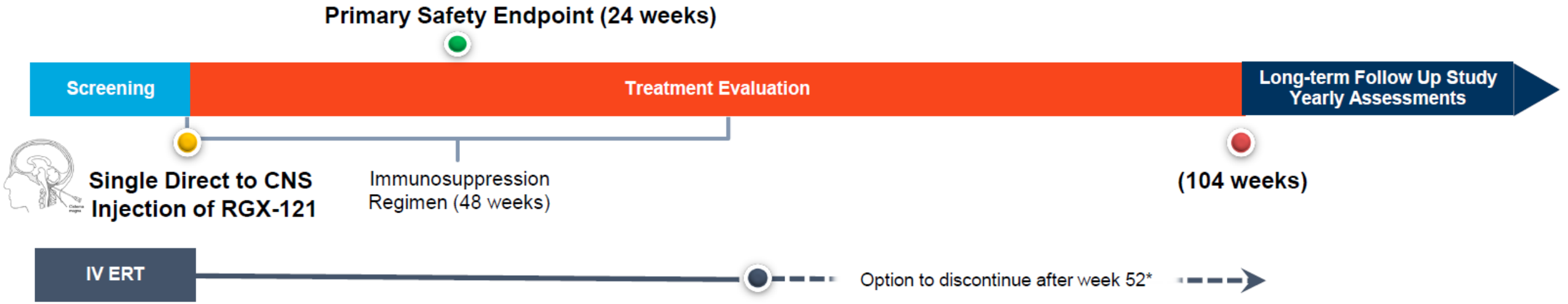
RGX-121: P1/2/3 clinical study

Number of cases	Part1: 15 cases, Part2: 10 cases
Eligible age	4 Months to 5 Years
Trial design	Open-label, single-arm, open-label study
Trial sites	4 sites in the U.S., 1 site in Brazil
Dosage and administration	Single, intracisternal (IC) administration. If the approach is difficult due to bony deformity or tendon abnormalities at the site of administration, intraventricular (IVR) administration was chosen as an alternative route. Three doses were explored in Part 1, and Dose 3 was chosen for Part 2. Dose 1: 1.3 x 10^{10} copies/g brain (Part 1: 3 cases) Dose 2: 6.5 x 10^{10} copies/g brain (Part 1: 7 cases) Dose 3: 2.9 x 10^{11} copies/g brain (Part 1: 5 cases, Part 2: 10 cases) The following immunosuppressive agents are used in conjunction with the administration of the drug. oral sirolimus (Day -2 ~ Week 48) methylprednisolone IV (Day 1) oral prednisolone (Day 2 ~ Week 12) tacrolimus Oral (Day 2 ~ Week 32)
Duration of administration	single dose

https://clinicaltrials.gov/study/NCT03566043

RGX-121: P1/2/3 clinical study

Part 1: Study Design



The primary endpoint was safety at 24 weeks. Evaluation period of 104 weeks, followed by transition to long-term follow-up.
Both patients receiving ERT (13 cases) and patients not receiving ERT (2 cases) were entered, and in the case of patients receiving ERT as a baseline therapy, a discontinuation option was available after 52 weeks[1].

1. May 2022 protocol update changes the discontinue option to 24 weeks

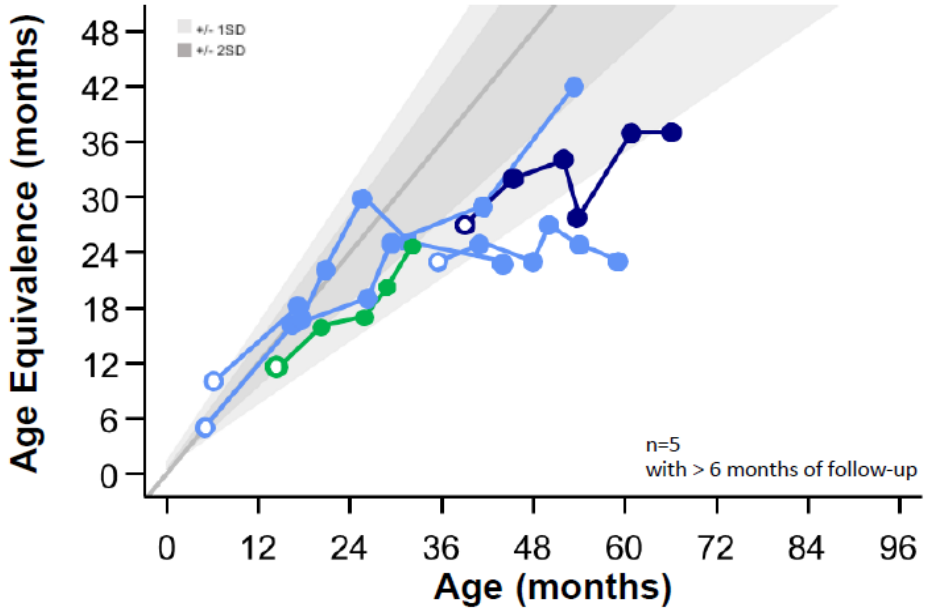
Source: Materials provided by REGENXBIO

RGX-121: P1/2/3 clinical study

Part 1: Results Neurodevelopmental Assessments Demonstrate Continued Skill Acquisition or Stability in the Majority of CAMPSIITE® Dose-Finding Participants

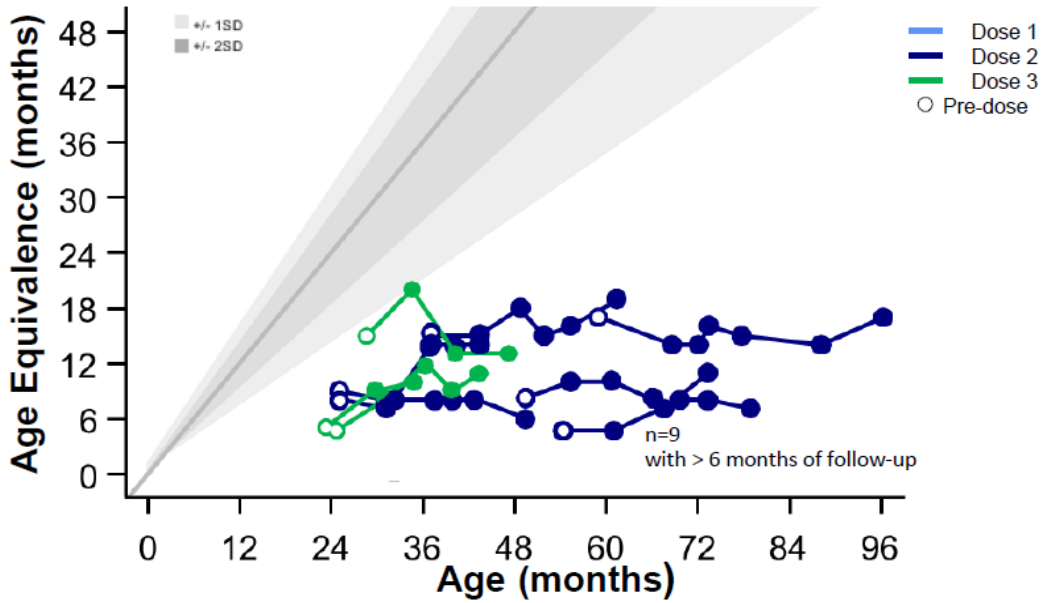
Majority of Participants Continued to Gain Skills

Baseline BSID-III Cognitive Functior ≧-2SD



Majority of Participants Gained at Least 3 Months of Skills in AEq or Stabilized

Baseline BSID-III Cognitive Function < -2SD



In the Neurodevelopmental Assessments of the Bayley Scales of Infant Development (BSID-III), patients with good cognitive function at baseline ≧-2SD of normative mean) showed continued cognitive development at the same level as healthy people, while patients with developmental delays (<-2SD of normative mean) showed reduced cognitive deterioration.

Source: Materials provided by REGENXBIO

RGX-121: P1/2/3 clinical study

Part 2: Study Design

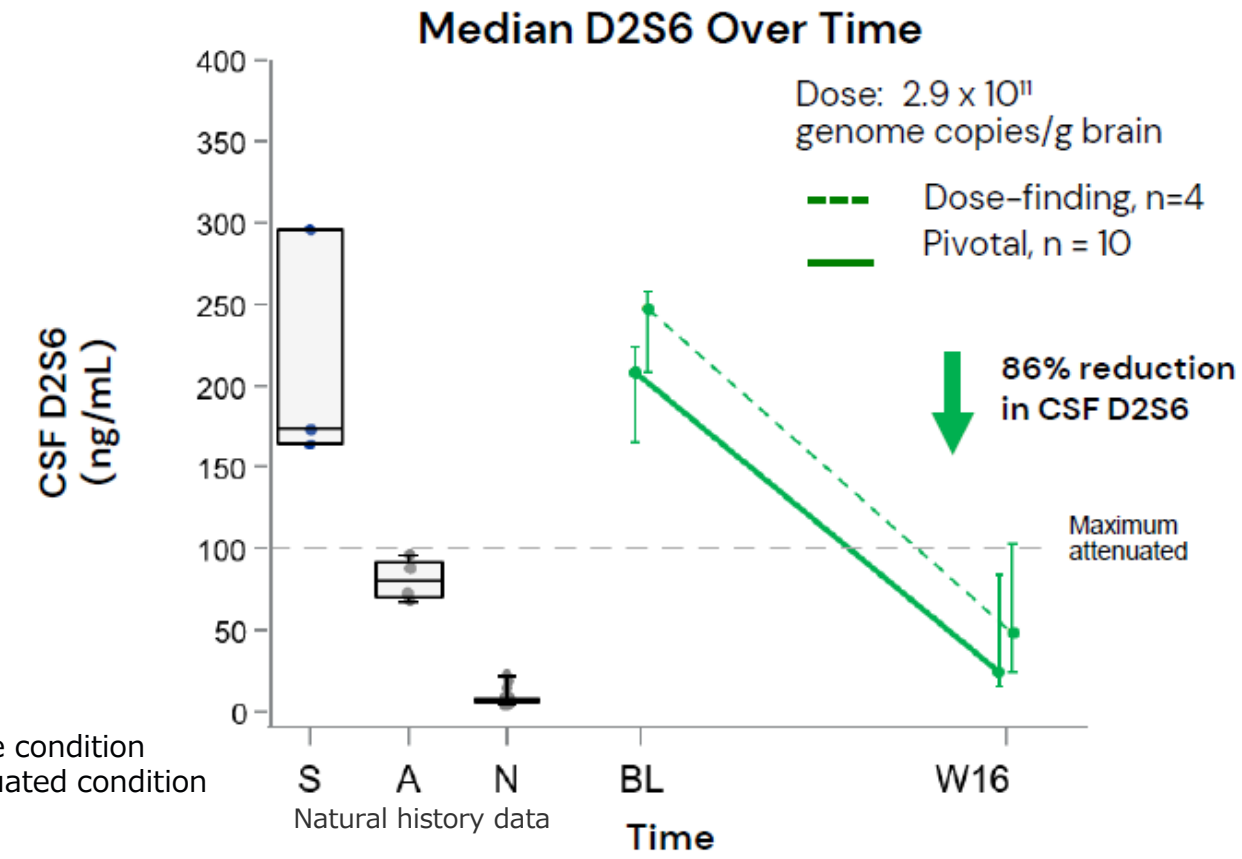
- The primary efficacy endpoint of Part 2 is the proportion of patients at 16 weeks compared to baseline achieving a reduction in CSF HS D2S6 levels to at or below the upper limit detected in attenuated MPS patients(100 ng/ml)[1]. An immunosuppressive regimen was followed for 48 weeks.

1. additional efficacy data included BSID, VABS, ERT withdrawal, auditory as well as safety

Source: Materials provided by REGENXBIO

RGX-121: Clinical P1/2/3 study

Part 2: Results



S = Patients with severe condition
A = Patients with attenuated condition
N = Normal people

16 weeks after treatment administration, the level of HS D2S6 in the CSF decreased by 86%, and primary endpoint was met: i.e. 8 of 10 cases, the levels of CSF D2S6 fell below the maximum level measured in a group of attenuated MPS II patients (p=0.0016). The HS D2S6 levels of the remaining two cases also decreased by 55% and 85%, respectively.

Source: Materials provided by REGENXBIO

Pipeline overview

NS-065/NCNP-01 (viltolarsen)

- Treatment for Duchenne muscular dystrophy -

Development Phase	・Japan : Launch ・U.S. : Launch ・Global : P3 open-label extension study in progress
Origin	Co-development : National Center of Neurology and Psychiatry
Development	Nippon Shinyaku
Mechanism of action	Exon 53 Skipping
Indication	Duchenne muscular dystrophy
Dosage form	Injection
Feature	・Improvement in symptoms and prevention of the disease progression by recovery of dystrophin protein expression ・Morpholino based oligonucleotide with possible high safety profile and maximized activity

NS-304 (selexipag)

- Treatment for pulmonary hypertension, arteriosclerosis obliterans -

Development Phase	Japan : P2b (ASO) Japan : Uptravi® tablets 0.2 mg and 0.4 mg for the additional indication of pediatric pulmonary arterial hypertension (PAH) Uptravi® tablets for pediatric 0.05 mg approved and preparing for launch
Origin	Nippon Shinyaku
Development	Nippon Shinyaku
Mechanism of action	Selective IP receptor agonist
Indication	arteriosclerosis obliterans (ASO) pediatric pulmonary arterial hypertension (pediatric PAH)
Dosage form	Tablet
Feature	Long-acting oral drug

CAP-1002 (deramiocel)

- Treatment for Duchenne muscular dystrophy -

Development Phase	U.S. : P3 (Duchenne muscular dystrophy) U.S. : BLA Filing (Duchenne muscular dystrophy cardiomyopathy)
Origin	[Jan. 2022] Partnership for commercialization in U.S. [Feb. 2023] Partnership for commercialization in Japan : Capricor Therapeutics, Inc.
Development	Capricor Therapeutics, Inc.
Mechanism of action	Exosomes released from cardiosphere-derived cells
Indication	Duchenne muscular dystrophy cardiomyopathy Duchenne muscular dystrophy
Dosage form	Injection
Feature	・Exosomes released from this drug are expected to reduce oxidative stress, inflammation, fibrosis, and increase cell energy and myocyte generation, resulting in improvement of motor and cardiac functions. ・ Its broad applicability makes it suitable for patients regardless of the type of genetic mutation.

RGX-121 (clemidsogene lanparvovec)

- Treatment for Mucopolysaccharidosis Type Ⅱ -

Development Phase	U.S. : Rolling submission
Origin	[Jan. 2025] Partnership for commercialization in U.S., Japan and other Asian countries : REGENXBIO Inc.
Development	REGENXBIO Inc.
Mechanism of action	Iduronate-2-sulfatase Gene therapy
Indication	Mucopolysaccharidosis Type Ⅱ
Dosage form	Injection
Feature	・An investigational gene therapy using adeno-associated virus (AAV) 9 to deliver the iduronate-2-sulfatase (*IDS*) gene to the central nervous system using intracisternal or intraventricular administration ・Transduced cells produce the missing *IDS* protein ・A single dose is expected to lead to sustained production of *IDS* leading to the attenuation of CNS manifestations in MPS II patients

ZX008 (fenfluramine hydrochloride)

- Treatment for rare intractable epilepsy -

Development Phase	Japan : Launch (Dravet syndrome) Japan : Launch（Lennox-Gastaut syndrome) Japan : P3 (CDKL5 deficiency disorder)
Origin	[Mar. 2019] Distribution partnership in Japan : UCB S.A. (former Zogenix, Inc.)
Development	UCB S.A. (former Zogenix, Inc.)
Mechanism of action	5-HT (serotonin) releaser with agonist activity at several 5-HT receptors
Indication	Dravet syndrome Lennox-Gastaut syndrome CDKL5 deficiency disorder
Dosage form	Oral liquid agent
Feature	・Effective for Dravet syndrome, Lennox-Gastaut syndrome and CDKL5 deficiency disorder patients refractory to existing treatment options ・ZX008 can be used in combination with other drugs, as standard of care for intractable epilepsy based on combination therapy.

GA101 (obinutuzumab)

- Treatment for lupus nephritis, pediatric nephrotic syndrome, extra renal lupus -

Development Phase	Japan : P3（LN） Global : P3（PNS） Japan : P3（ERL）
Origin	[Nov. 2012] Licensed-in from : Chugai Pharmaceutical Co., Ltd.
Development	Co-development : Chugai Pharmaceutical Co., Ltd.
Mechanism of action	Anti-CD20 monoclonal antibody
Indication	lupus nephritis (LN) pediatric nephrotic syndrome (PNS) extra renal lupus (ERL)
Dosage form	Injection
Feature	Anti-CD20 monoclonal antibody, increased antibody-dependent cellular cytotoxicity (ADCC) activity and direct cytotoxicity

LY3527727(pirtobrutinib)

- Treatment for Mantle cell lymphoma, Chronic lymphocytic leukemia -

Development Phase	・Launch (for patients with relapsed or refractory mantle cell lymphoma who are resistant or intolerant to other BTK inhibitors) ・P3 (MCL and CLL)
Origin	[Mar. 2024] Alliance agreement in Japan : Eli Lilly Japan K.K.
Development	Eli Lilly Japan K.K.
Mechanism of action	A reversible non-covalent BTK inhibitor
Indication	mantle cell lymphoma (MCL) chronic lymphocytic leukemia (CLL)
Dosage form	Oral agent
Feature	・A highly selective, non-covalent (reversible) inhibitor of the enzyme Bruton's tyrosine kinase (BTK), with having a novel binding mechanism.

NS-580

- Treatment for endometriosis, Chronic prostatitis/Chronic pelvic pain syndrome -

Development Phase	Japan : P2b (endometriosis) Temporarily suspended Japan : P2a (CP/CPPS) Temporarily suspended
Origin	Nippon Shinyaku
Development	Nippon Shinyaku
Mechanism of action	Inhibition of membrane-associated prostaglandin E synthase-1
Indication	endometriosis chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS)
Dosage form	Oral agent
Feature	・Treatment for endometriosis without hormonal effect and with possible analgesic potency ・Treatment for CP/CPPS with high safety and long-term pain control

NS-089/NCNP-02（brogidirsen）

- Treatment for Duchenne muscular dystrophy -

Development Phase	Global : P2
Origin	Co-development : National Center of Neurology and Psychiatry
Development	Nippon Shinyaku
Mechanism of action	Exon 44 Skipping
Indication	Duchenne muscular dystrophy
Dosage form	Injection
Feature	・Improvement in symptoms and prevention of the disease progression by recovery of dystrophin protein expression ・Morpholino based oligonucleotide with possible high safety profile and maximized activity

NS-229

- Treatment for Eosinophilic granulomatosis with polyangiitis -

Development Phase	Global : P2
Origin	Nippon Shinyaku
Development	Nippon Shinyaku
Mechanism of action	JAK1 inhibitor
Indication	eosinophilic granulomatosis with polyangiitis (EGPA)
Dosage form	Oral agent
Feature	・Potent and highly selective JAK1 inhibitor ・High efficacy and good safety profiles are expected in the treatment for EGPA

NS-401 (tagraxofusp)

- Treatment for blastic plasmacytoid dendritic cell neoplasm -

Development Phase	Japan : P1/2
Origin	[Mar. 2021] Licensed-in from: The Menarini Group
Development	Nippon Shinyaku
Mechanism of action	Induction apoptosis of cells by inhibiting protein synthesis by specifically targeting cancer cells expressing CD123
Indication	blastic plasmacytoid dendritic cell neoplasm (BPDCN)
Dosage form	Injection
Feature	・Composed of diphtheria toxin (DT) fusion protein and recombinant human IL-3 ・Novel targeted therapy directed to CD123 on tumor cells ・IL-3 binds to CD123-expressing tumor cells and delivers the cytotoxic diphtheria toxin to the cells, resulting in the blockage of protein synthesis in the cell and causing cell death in CD123-expressing cells

NS-050/NCNP-03

- Treatment for Duchenne muscular dystrophy -

Development Phase	Global : P1/2
Origin	Co-development : National Center of Neurology and Psychiatry
Development	Nippon Shinyaku
Mechanism of action	Exon 50 Skipping
Indication	Duchenne muscular dystrophy
Dosage form	Injection
Feature	・Improvement in symptoms and prevention of the disease progression by recovery of dystrophin protein expression ・Morpholino based oligonucleotide with possible high safety profile and maximized activity

ATSN-101

- Treatment for GUCY2D-associated Leber congenital amaurosis -

Development Phase	**US : P1/2**
Origin	**[Nov. 2024] Partnership for commercialization in U.S. Development and sales license agreement in Japan : Atsena Therapeutics, Inc.**
Development	**Atsena Therapeutics, Inc.**
Mechanism of action	**GUCY2D Gene therapy**
Indication	**GUCY2D-associated Leber congenital amaurosis (LCA1)**
Dosage form	**Injection**
Feature	**• A first-in-class, investigational gene therapy for the treatment of LCA1 • A gene therapy using adeno-associated virus (AAV) 5, incorporating the human GUCY2D gene into the AAV5 vector. • Subretinal administration to express the normal GUCY2D gene and restore photoreceptor function.**

RGX-111

- Treatment for Mucopolysaccharidosis Type Ⅰ -

Development Phase	Global : P1/2
Origin	[Jan. 2025] Partnership for commercialization in U.S., Japan and other Asian countries : REGENXBIO Inc.
Development	REGENXBIO Inc.
Mechanism of action	Alpha-L-iduronidase Gene therapy
Indication	Mucopolysaccharidosis Type Ⅰ
Dosage form	Injection
Feature	・An investigational gene therapy using adeno-associated virus (AAV) 9 to deliver the alpha-L-iduronidase (IDUA) gene to the central nervous system using intracisternal or intraventricular administration ・Delivery of the IDUA gene within the cells in the central nervous system could provide a permanent source of secreted IDUA beyond the blood-brain barrier, allowing for long-term cross-correction of cells throughout the CNS ・With a single dose, potential to prevent the progression of cognitive deficits

NS-917 (radgocitabine)

- Treatment for relapsed or refractory acute myeloid leukemia -

Development Phase	Japan : P1
Origin	[Mar. 2017] Licensed-in from : Delta-Fly Pharma, Inc.
Development	Nippon Shinyaku
Mechanism of action	DNA strand-break by incorporating itself into DNA
Indication	relapsed or refractory (r/r) acute myeloid leukemia (AML)
Dosage form	Injection
Feature	・Significant anti-leukemic activity with unique mechanism of action from other nucleoside analogs at low dose continuous infusion ・Tolerable safety profile available to elderly patients with r/r AML

NS-025

- Treatment for urological diseases -

Development Phase	Japan : P1
Origin	Nippon Shinyaku
Development	Nippon Shinyaku
Mechanism of action	–
Indication	Urological diseases (to be determined)
Dosage form	Oral agent
Feature	–

NS-863

- Treatment for cardiovascular diseases -

Development Phase	Japan : P1
Origin	Nippon Shinyaku
Development	Nippon Shinyaku
Mechanism of action	–
Indication	Cardiovascular diseases (to be determined)
Dosage form	Oral agent
Feature	–

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