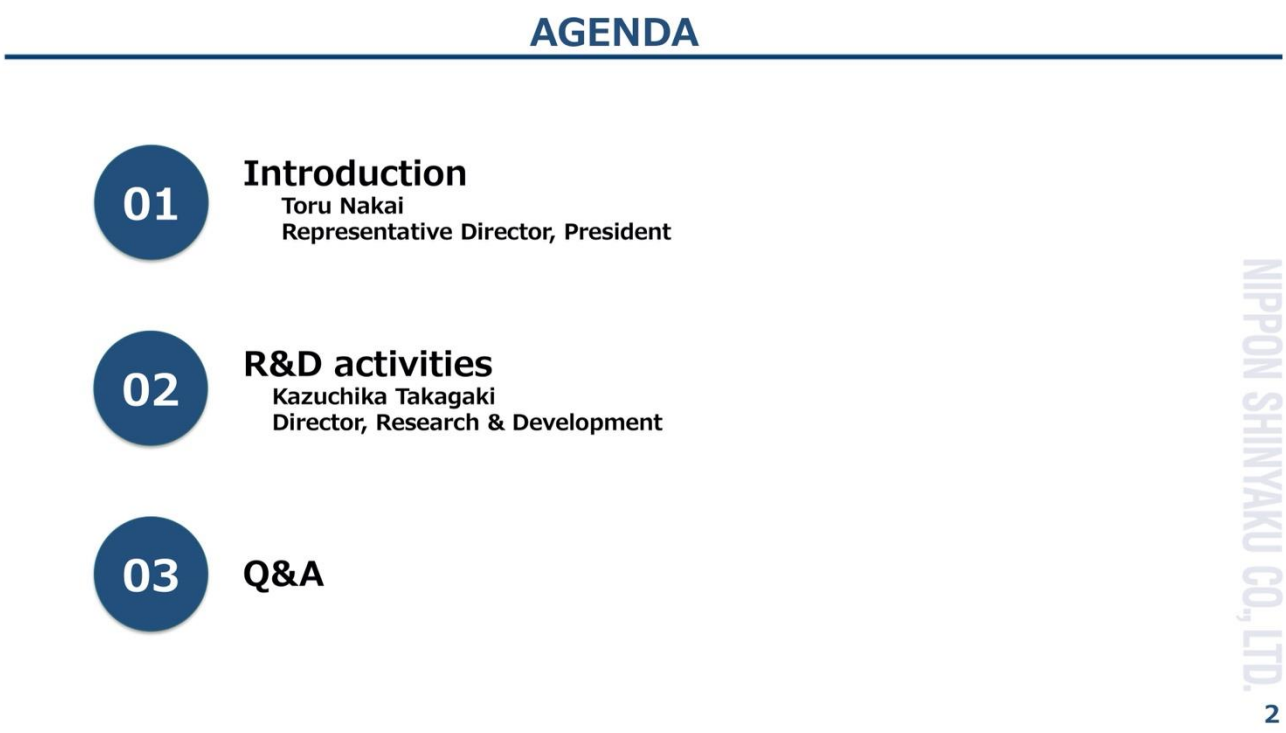
Nakai: I am Toru Nakai, President Nippon Shinyaku Co., Ltd. Thank you very much for joining our R&D presentation today. I appreciate it very much.

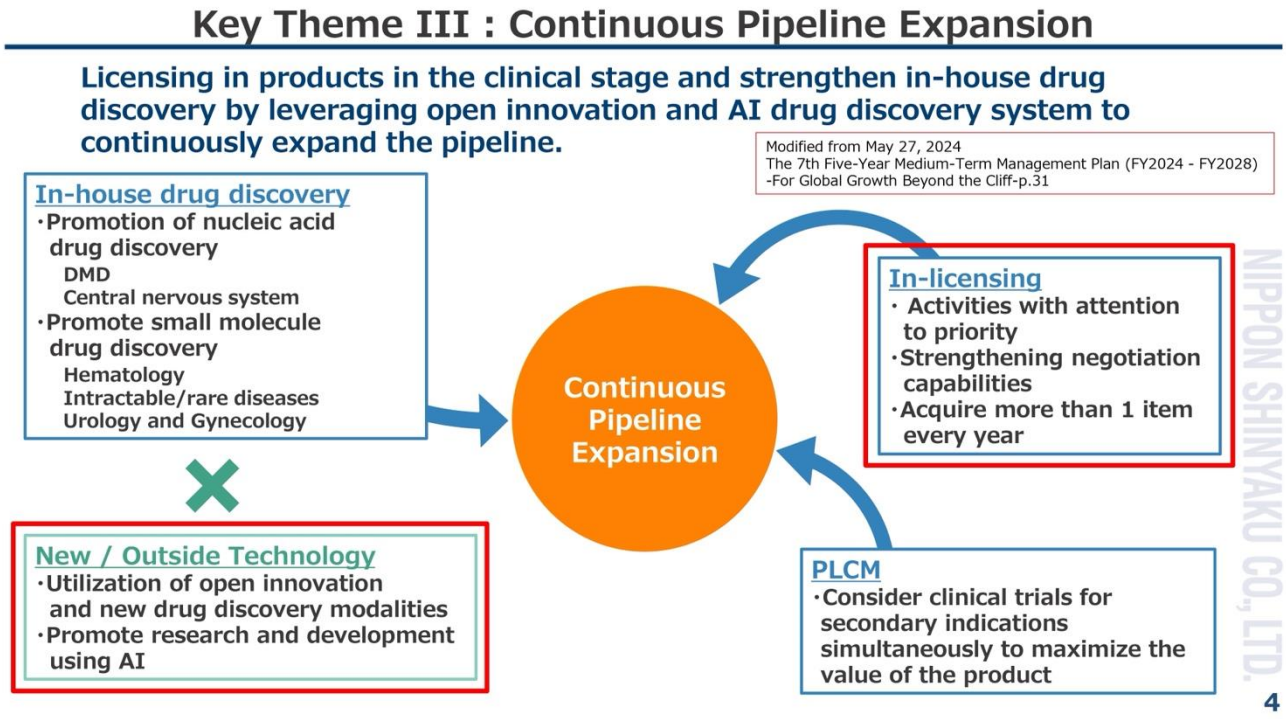


Here are today's contents.

As an introduction, I would like to reiterate some of the points that I have picked up regarding the Seventh Medium-Term Management Plan.

Next, Takagaki, Director in charge of R&D, will explain about one of the key themes of the Seventh Medium-Term Management Plan, "Continuous Pipeline Expansion," including the most recently in-licensed product candidates from our pipeline.

Finally, there will be a Q&A session, totaling 60 minutes.



I will now explain our Seventh Medium-Term Management Plan.

As we have already announced, we have started the Seventh Medium-Term Management Plan from this fiscal year, and one of the three key themes of the plan is "Continuous Pipeline Expansion."

The Company's policy is to continuously expand its pipeline by acquiring in-licensed products at the clinical stage and beyond, as well as by strengthening in-house drug discovery through the use of open innovation and AI drug discovery.

Among the three pillars of in-house drug discovery, in-licensing, and PLCM, today we will especially discuss in-licensed products, in which we aim to acquire at least one product per year, open innovation, and AI drug discovery.

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

In the Sixth Medium-Term Management Plan, issues such as "Speed and success probability in clinical development" and " R&D speed for new modalities" were clarified, and in the Seventh Medium-Term Management Plan, efforts are being made to resolve these issues.

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

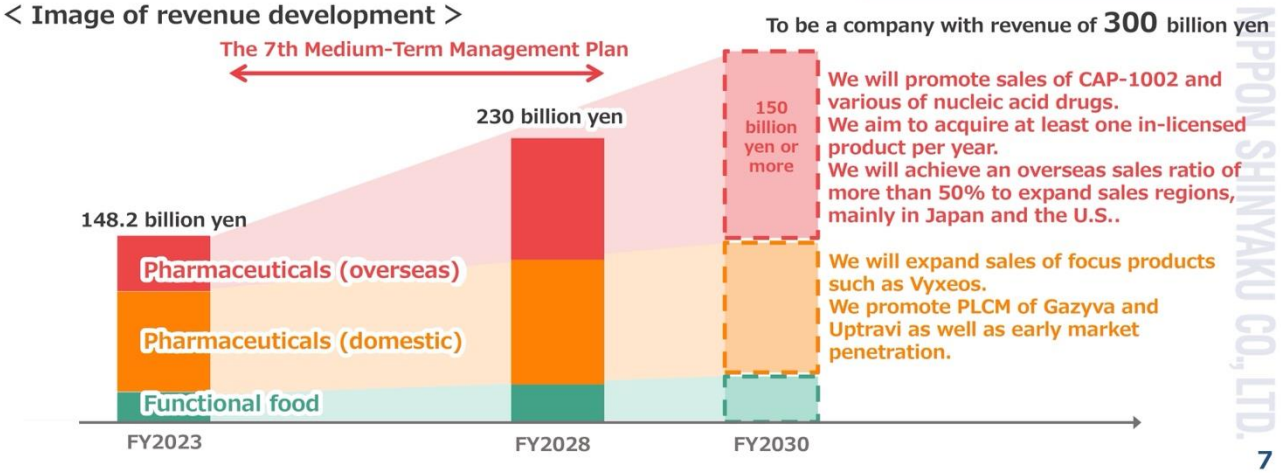
We had informed you that our business strategy for the pharmaceuticals business is to launch an average of at least two new products per year through the three pillars of in-house drug discovery, in-licensing, and PLCM, and that our priority is to respond to the patent cliff of Uptravi. We are executing our strategy by concentrating our management resources on diseases and areas where we can aim for global expansion, particularly nucleic acid and small molecule drug discovery.

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

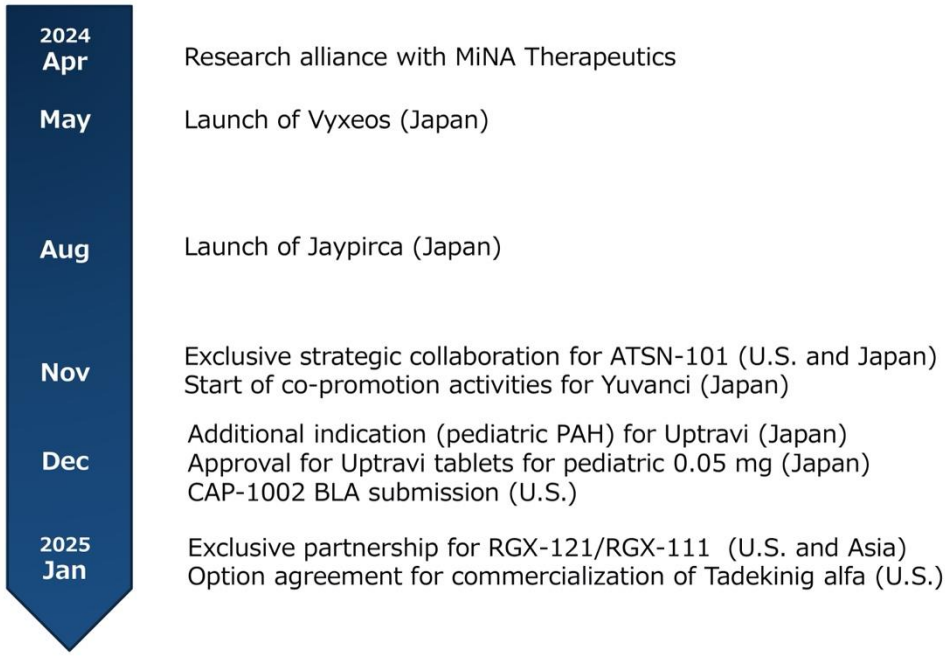
< Image of revenue development >



During the Seventh Medium-Term Management Plan period, we will invest in R&D, acquisition of in-licensed products, and M&A, and beyond that, we envision a scenario in which we will reach JPY300 billion in sales revenue by FY2030.

By promoting sales of CAP-1002 and the nucleic acid drug group and growing overseas sales more than domestic sales, we aim to achieve an overseas sales ratio of more than 50%.

FY2024 R&D milestones to date



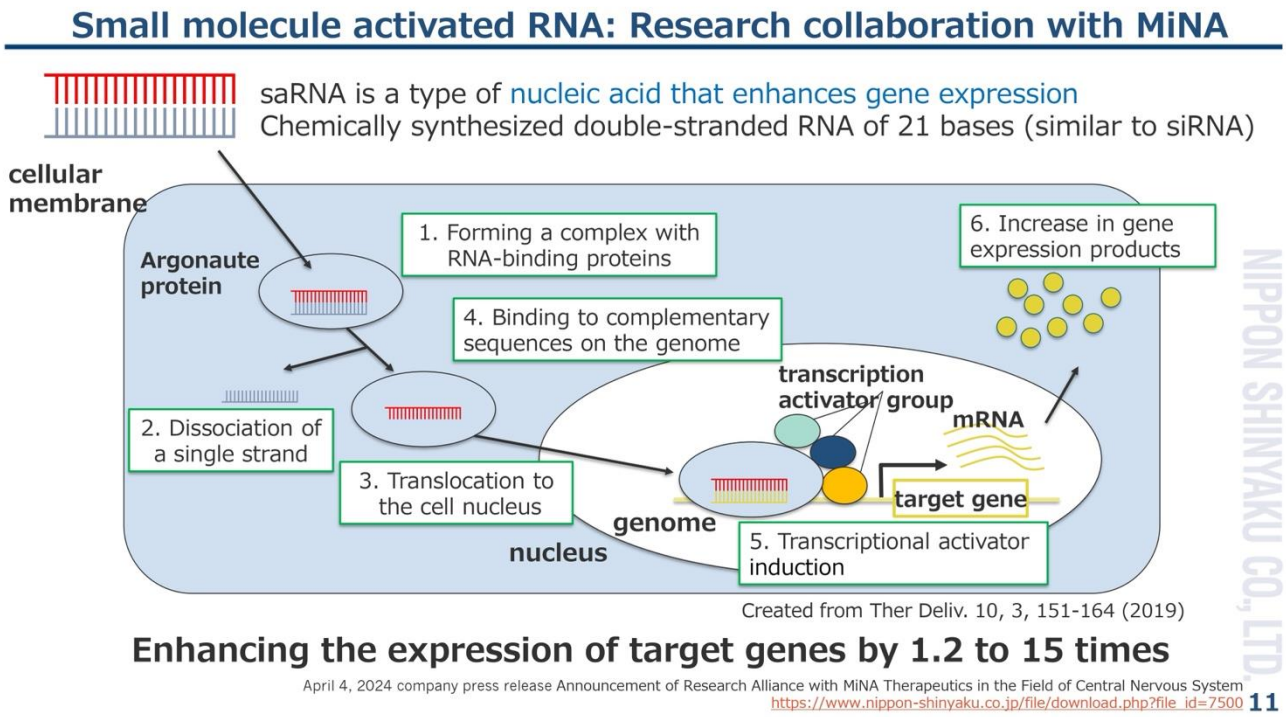
This slide shows our main achievements for the current fiscal year.

We achieved results such as research alliances, exclusive licensing agreements, and the launch of new products. Today, Takagaki, our R&D Director, will introduce the features of CAP-1002, whose BLA rolling submission has been completed for approval with the expected indication of DMD cardiomyopathy, and ATSN-101 and RGX-121/111, for which we have concluded exclusive licensing agreements.

We believe that these will contribute significantly to our future performance and will be critical to our ability to grow and overcome the patent cliff of Uptravi.

Takagaki: I am Takagaki, Director in charge of R&D. I will now continue with an explanation of our R&D efforts.

We will begin by explaining our open innovation and AI-based R&D initiatives.



As part of our efforts to utilize open innovation and new drug discovery modalities, in April last year, we entered into a research collaboration agreement with MiNA for the creation of expression-enhancing nucleic acid drugs that are expected to be indicated for the treatment of intractable and rare diseases in the field of central nervous system disorders.

Under the agreement, we will receive from MiNA nucleic acid sequences produced using their proprietary technology for creating small molecule-activated RNA (saRNA), i.e., nucleic acids that increase the transcription of target genes. saRNA is a type of nucleic acid that enhances gene expression. Chemically synthesized double-stranded RNA of 21 bases.

Unlike conventional nucleic acids, which often show expression suppression, it can generally enhance the expression of the target gene by 1.2 times to 15 fold. Because it acts on endogenous genes, unlike gene therapy, it can enhance the expression of genes, even those that are long and large in size.

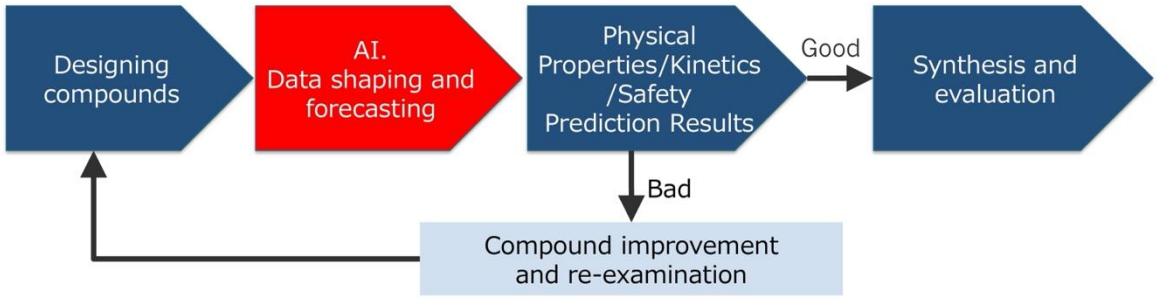
It also makes it possible to target and enhance the expression of target genes not by overexpression, but by targeting appropriate expression levels close to normal.

Through our research collaboration with MiNA, we are applying nucleic acid medicine technology to the central nervous system area as well, with the aim of delivering new medicines to patients suffering from intractable and rare diseases and we will continue to target specific diseases.

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**

From here, I would like to introduce the "promotion of efficient R&D utilizing AI" as presented in the Seventh Medium-Term Management Plan.

We utilize AI predictive models in the drug discovery phase, and by doing so, we are able to predict the physical properties, kinetics, and safety of compounds before they are synthesized, enabling us to prioritize them.

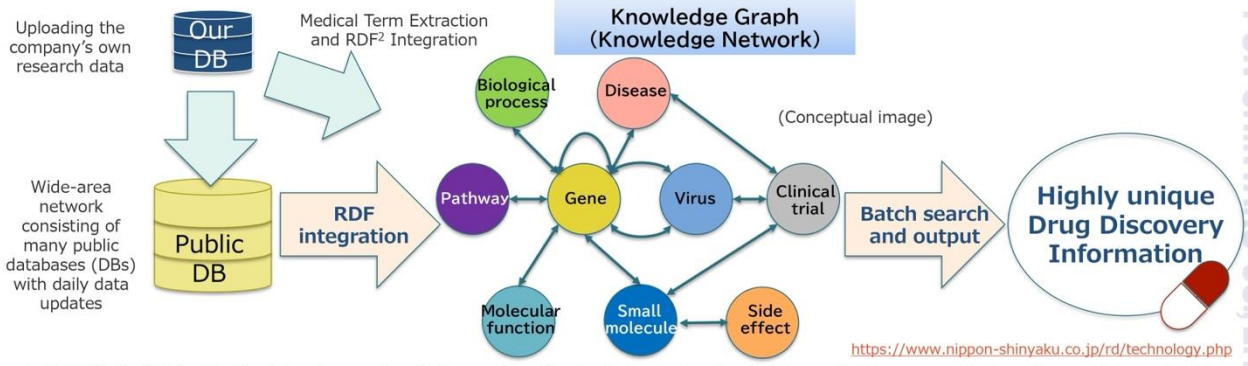
The ability to clarify priorities at the compound design stage allows us to focus resources more efficiently, leading to a higher probability of success and speed in drug discovery.

In fact, by utilizing AI, we have been able to efficiently identify one candidate in the neuromuscular disease area and one candidate in the blood cancer area and advance them to the non-clinical trial stage.

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



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 addition, in order to create highly unique drug discovery information, we have established a knowledge network system called the Knowledge Graph, which integrates public and in-house data.

The Knowledge Graph enables batch searches of numerous databases, making it possible to obtain the latest non-human, objective, and comprehensive information in a short period of time, leading to efficient R&D. This one is scheduled to complete its trial operation during this fiscal year and to start full-scale operation in the next fiscal year.

We will continue to further promote the use of AI to speed up drug discovery.

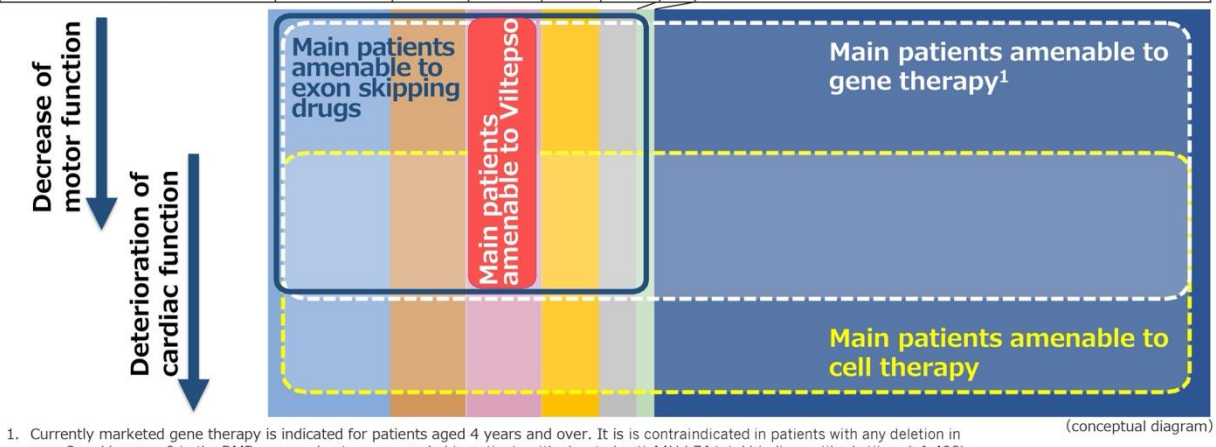
Deramiocel (CAP-1002) for the treatment of DMD-cardiomyopathy by cell (exosome) therapy

I would now like to explain about the most recently acquired in-licensed products in our pipeline.

First of all, I would like to introduce CAP-1002, a cell therapy drug, including its mechanism of action.

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).

Here is a diagram that summarizes our concept of DMD treatment.

Exon skipping drugs, gene therapy drugs, and cell therapy drugs each have their own advantages and disadvantages, and the optimal combination of treatments is expected to be based on the patient's genetic background, age, or symptoms.

Since patients whose symptoms have not yet progressed have an abundance of muscle stem cells, which means that muscle regeneration is active and DMD gene expression is high, it is desirable to use exon skipping drugs, which are nucleic acid drugs, to express a slightly shorter but functioning dystrophin protein to prevent muscle breakdown and to maintain muscle mass It is desirable to prevent muscle breakdown and maintain muscle mass.

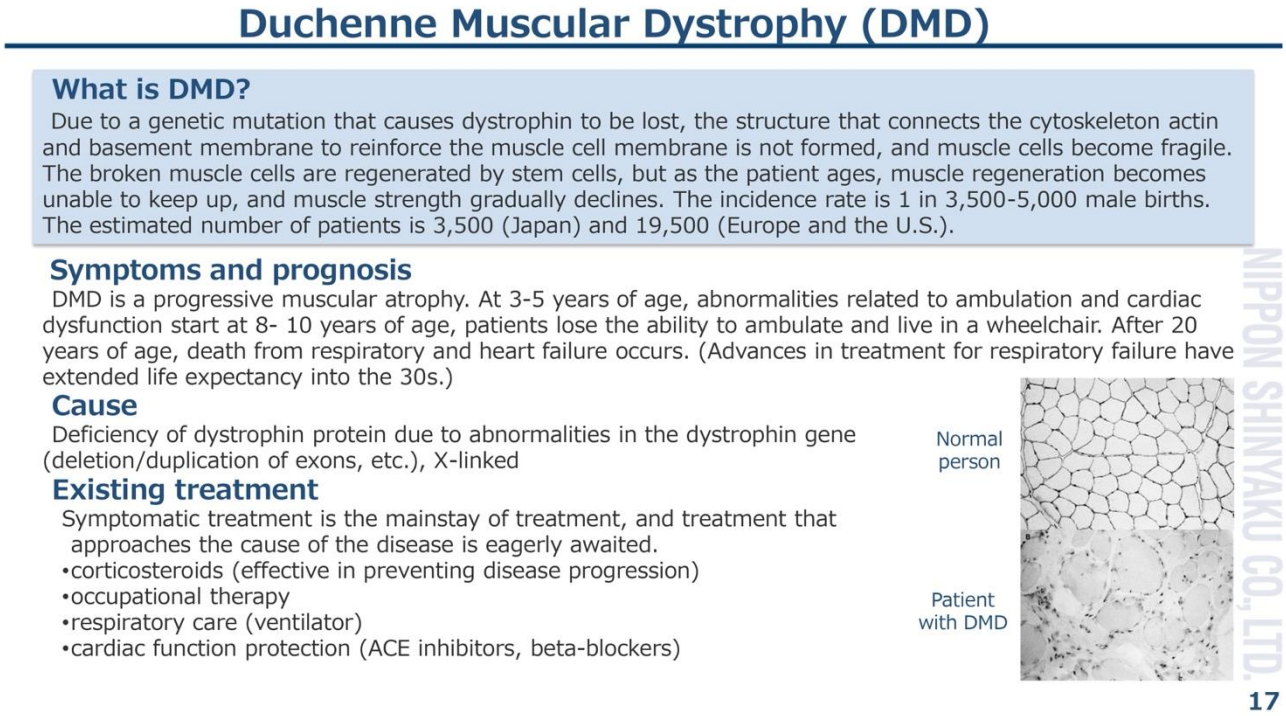
Elevidys has the full FDA approved for ambulatory patients 4 years of age and older but has the accelerated approval for non-ambulatory patients, and may overlap therapeutic targets with exon skipping drugs.

However, gene therapy drugs cannot be administered to about 14%-32% of patients with neutralizing antibodies and those with certain gene mutations.

It is also possible that exon skipping drugs may be used at a time when symptoms worsen, as theoretically it would be difficult to sustain the effect for a long period of time.

CAP-1002, a cell therapy, is expected to receive the full FDA approved for DMD cardiomyopathy, and may be used in combination with these therapies in patients who have received exon-skipping drugs or gene therapy and have begun to lose cardiac function.

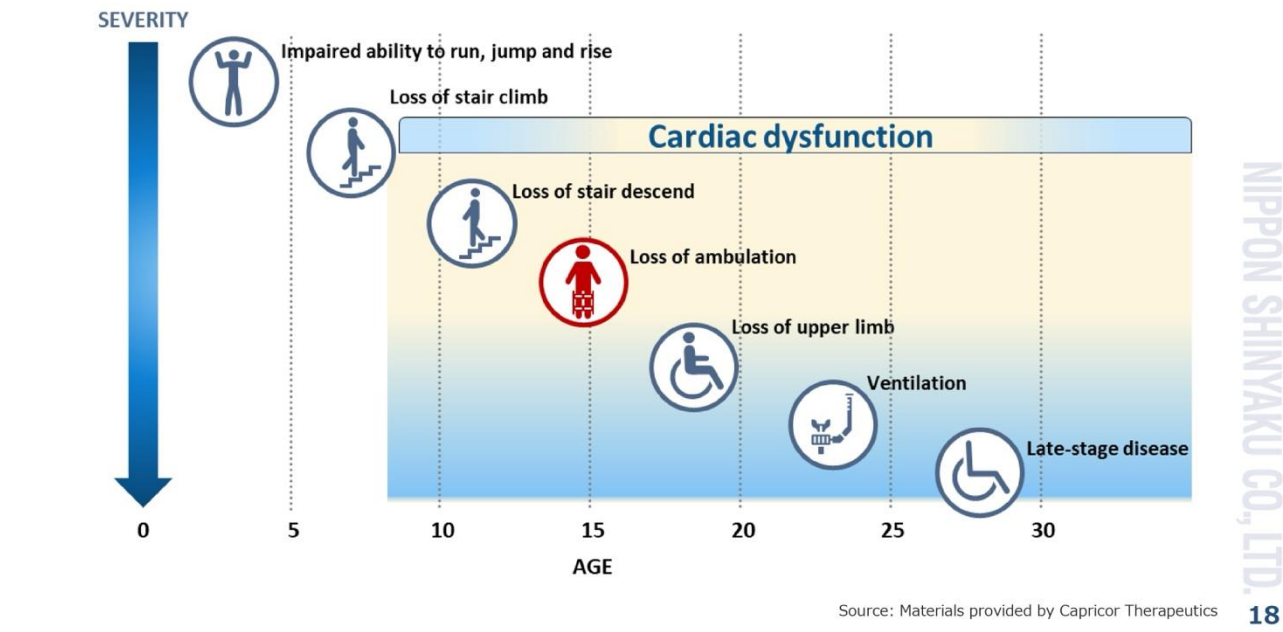
Thus, we believe that these three types of drugs are not in complete competition with each other but will coexist and be used differently depending on the patient's background and the progression of symptoms.



DMD is a disease in which a genetic mutation prevents the body from making dystrophin.

Deletion of dystrophin prevents the creation of structures that connect the actin of the cytoskeleton to the basement membrane and reinforce the muscle cell membrane, making muscle cells more fragile.

Broken muscle cells are regenerated by stem cells, but as we age, muscle regeneration cannot keep up and muscle strength gradually declines. As a result, cardiac, skeletal, and other muscles are unable to function properly, a very serious disease that eventually leads to death.



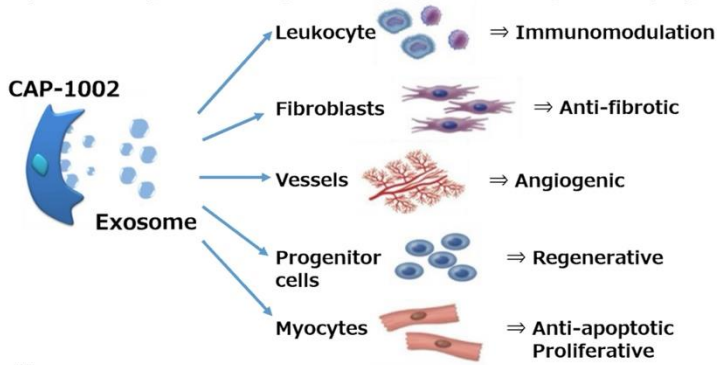
Here is a diagrammatic representation of the progression of DMD symptoms.

Normal DMD patients experience muscle weakness from the skeletal muscles and gradual loss of motor function, but about 50% to 60% of DMD patients have cardiac dysfunction and develop cardiomyopathy.

Cardiomyopathy is a major cause of death in DMD, but at this time there are no drugs marketed for DMD cardiomyopathy.

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)



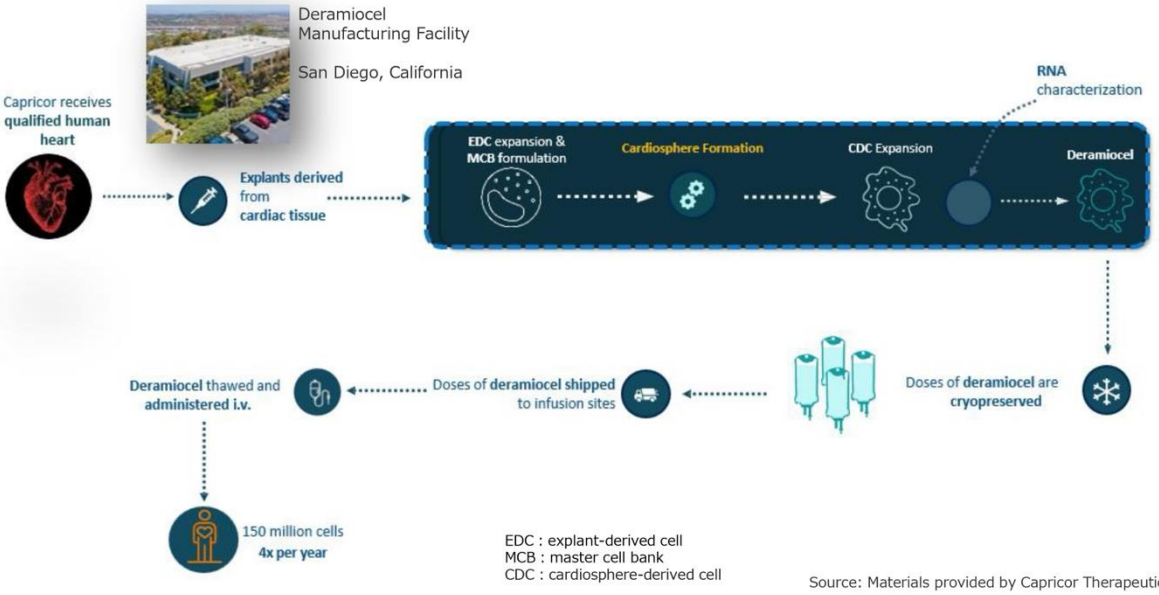
1. Regenerative Medicine Advanced Therapy
2. Advanced Therapy Medical Products

Source: Materials provided by Capricor Therapeutics

CAP-1002 is a cardiac-derived cell manufactured from human myocardium. Exosomes secreted from this drug are thought to reduce the decline in exercise and cardiac function by reducing oxidative stress, inflammation, and fibrosis and by promoting an increase in cellular energy and myogenesis.

Exosomes secreted by myocardium-derived cells are said to have cytoprotective effects on cardiomyocytes via an anti-apoptotic effect and are expected to be highly effective in treating patients with DMD cardiomyopathy.

Production of deramiocel (CAP-1002)



Source: Materials provided by Capricor Therapeutics

In fact, Capricor Therapeutics has an access to eligible human hearts, and its new manufacturing process has enabled them to produce multiple-dose allogeneic cell-based therapeutics.

Capricor is also building another manufacturing site in San Diego for commercial products and plans to expand its manufacturing capacity to further meet market demand.

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

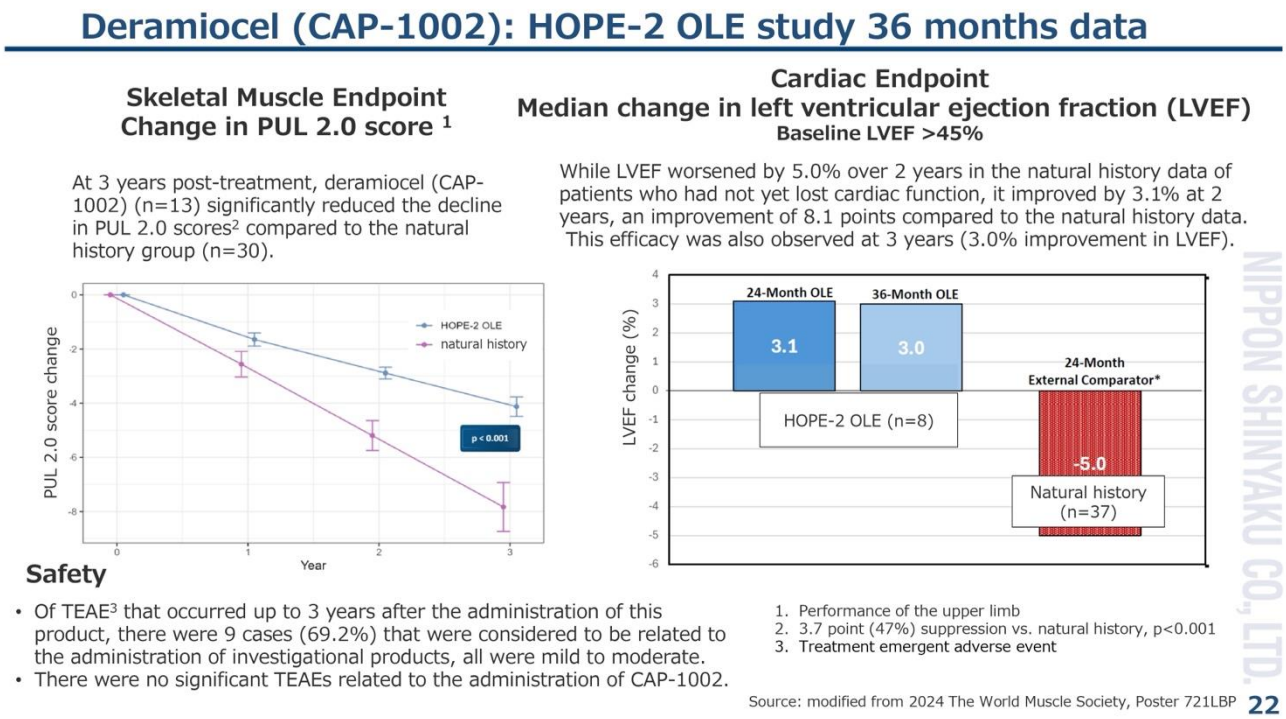
We will now discuss the HOPE-2 trial and its OLE study, the Tier II clinical trial that provided the basis for CAP-1002's application for phased approval in DMD cardiomyopathy.

The HOPE-2 trial was conducted at seven U.S. sites beginning in March 2018.

20 patients in total were enrolled, 8 of them were treated with the active drug once every three months for a total of four doses and compared to 12 patients in the placebo cohort.

The primary endpoint is efficacy in skeletal muscles, such as upper arm function, while the secondary endpoint is efficacy in left ventricular ejection fraction.

In the HOPE-2 OLE study, in which 13 patients who completed the HOPE-2 study were administered a total of 16 doses of the active drug over a four-year period, data were available for up to three years after the first dose.



Here we show data from the HOPE-2 OLE trial at 36 months.

The graph on the left side shows the results of the PUL2.0 score, which evaluates upper limb function, the primary endpoint of the study, showing a significant Inhibition of decline in the PUL2.0 score in the treatment group compared to the natural history group.

On the right is a graph looking at the amount of change in LVEF, the ejection fraction of the left ventricle.

While LVEF worsened by 5.0% over two years in patients with natural history of heart function not yet compromised, it improved by 3.1% after two years of treatment in patients treated with the drug.

This effect was also observed after three years of treatment.

Using these results, Capricor has completed the rolling BLA submission in the U.S.

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			

Here is the upcoming schedule for CAP-1002 and status of our partnership. As originally planned, Capricor completed the BLA submission at the end of last December for the expected indication of DMD cardiomyopathy and has requested a further priority review.

If priority review is granted, the review schedule will be reduced from the normal 10 months to 6 months from the date of acceptance by the FDA, with an expected PDUFA date in CY2025 2H.

In Europe, the Letter of Intent was signed in September 2024 that stipulates an exclusive negotiation period, and discussions are continuing regarding a commercialization and distribution agreement.

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 x 10^{11} vg/g brain into CNS administration	into CNS administration (dose to be determined)

I would now like to move on to some of our gene therapy drugs from our pipeline. Here is a list of gene therapy drugs that we will be introducing today.

We have successfully in-licensed multiple types of gene therapies, such as ATSN-101 and RGX-121/111, and we expect them not only to simply contribute to our business performance, but also to enhance our drug discovery capabilities for gene therapies targeting the central nervous system by utilizing information on R&D and regulatory filings for these products, which is expected to have a synergistic effect on our future R&D. We also expect synergistic effects on our future R&D activities.

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

Let me begin with ATSN-101, a gene therapy for hereditary retinal dystrophy caused by biallelic GUCY2D mutations, including Leber congenital amaurosis type 1, for which we signed an exclusive license agreement with Athena Therapeutics on November 13th of last year.

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

Leber congenital amaurosis are a group of diseases caused by mutations in at least 20 different genes.

The GUCY2D gene variant Leber congenital amaurosis (LCA1) is one of the most common types.

Mutations in GUCY2D result in a chronic state of activation of photoreceptors in rods, which sense light and dark, and cones, which sense color, leading to their function as photoreceptors decreases.

Symptoms include night blindness, which makes it difficult to see in the dark, narrowing of the visual field, and vision loss, which may progress to blindness.

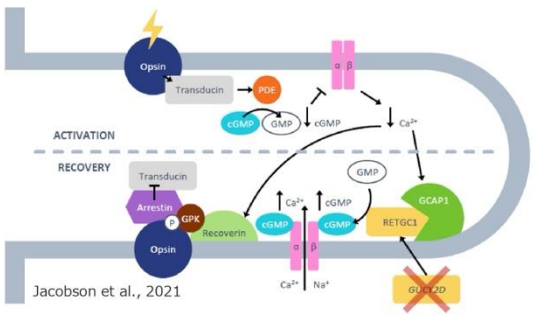
They suffer from severe visual impairment at or shortly after birth, and their visual impairment tends to worsen over time.

At present, there is no fundamental cure, and the only treatment is symptomatic treatment, such as vision correction with eyeglasses.

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



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 is a gene therapy drug that incorporates the human GUCY2D gene into the AAV5 vector, which is administered subretinally to induce normal GUCY2D gene expression and restore photoreceptor function.

A Phase I/II study for the expected indication of "biallelic GUCY2D mutant hereditary retinal dystrophy" has been completed in the U.S., and Phase III studies are now under preparation in the U.S., Europe and Japan.

The drug has also received RMAT designation, orphan designation, and rare pediatric disease designation from the FDA.

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

From here, we would like to introduce Phase I/II trials conducted overseas.

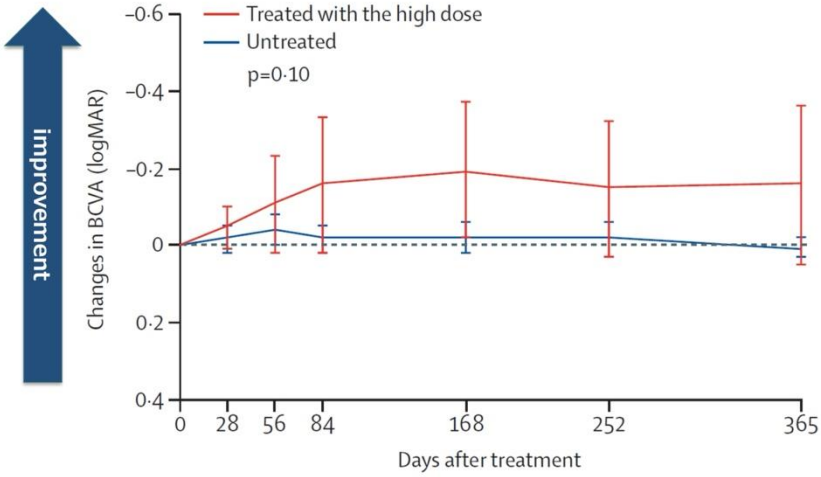
This clinical trial was a multicenter, open-label study of 15 patients genetically diagnosed with Leber's congenital cataract.

The safety and efficacy of a single dose of the drug has been confirmed by dividing the patients into five cohorts based on age and highest corrected visual acuity score.

This clinical trial has been published in *The Lancet*.

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

Efficacy: BCVA (best-corrected visual acuity)



Improvement trend was observed.

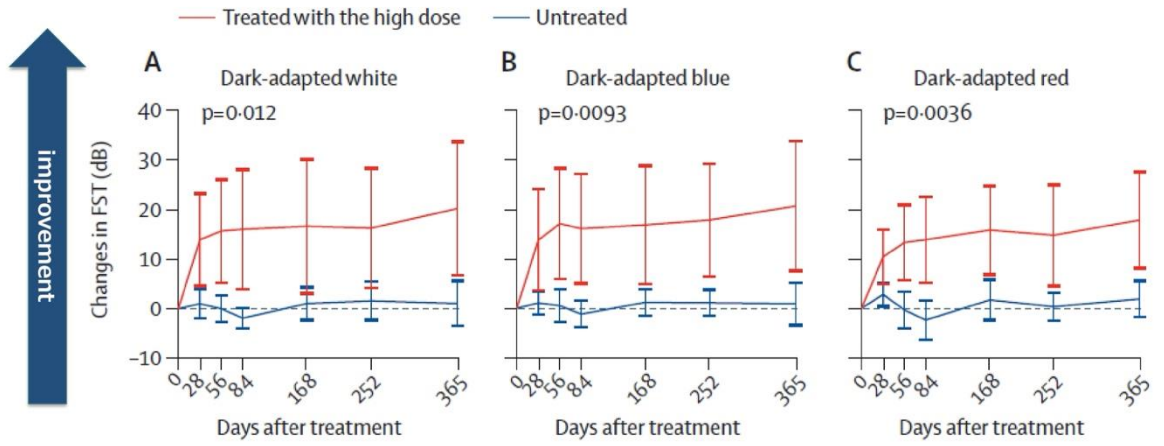
Source: Figure 5, The Lancet Volume 404, Issue 10456, 7-13 September 2024, Pages 962-970
Safety and efficacy of ATSN-101 in patients with Leber congenital amaurosis caused by biallelic mutations in GUCY2D: a phase 1/2, multicentre, open- label, unilateral dose escalation study

Here we show the results of BCVA, best-corrected visual acuity.

The high-dose group showed a trend toward improvement compared to the untreated group, and this effect was maintained over the course of the year.

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

Here we show the results of FST, full-field stimulus threshold.

The high-dose group showed significantly improved responses to various colors of light compared to the untreated group, and this effect continued at the one-year follow-up.

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

This slide shows the safety of the Phase I/II study that we have introduced so far.

No treatment-related adverse events leading to study discontinuation or death, including serious drug-related events, have been observed.

Thus, the efficacy and safety of this drug, including restoration of visual acuity and sensitivity to light, have been confirmed in Phase I/II studies, and we believe it will make a significant contribution to the treatment of Leber's congenital melanoma type I, for which there is currently no treatment available.

In the U.S., our subsidiary NS Pharma will commercialize and distribute CAP-1002.

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

Next, I would like to explain about RGX-121/111, a treatment for Mucopolysaccharidosis type II/Mucopolysaccharidosis type I, for which we signed an exclusive license agreement with REGENXBIO on January 14th.

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.

Mucopolysaccharidosis is a type of lysosomal disease in which a genetic abnormality causes a deficiency in the enzyme that degrades mucopolysaccharides, resulting in the accumulation of mucopolysaccharides in the body and a variety of symptoms.

Mucopolysaccharidosis type I and type II are congenitally deficient in α-L-isuronidase and isuronic acid-2-sulfatase, respectively, and in both diseases, the glycosaminoglycans dermatan sulfate and heparan sulfate are not broken down and accumulate in various organs in the body, resulting in systemic organ damage including the central nervous system in severe cases. The prognosis is 10 years to 15 years of age.

Current treatment options include hematopoietic stem cell transplantation as well as ERT, but the currently marketed ERT requires weekly intravenous infusions.

Because of challenges such as the inability to cross the blood-brain barrier, a drug that is both convenient and effective in treating CNS symptoms is desired.

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.

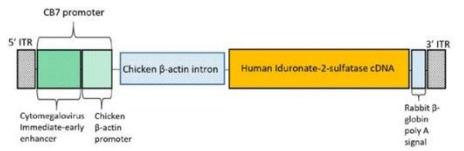


Figure S.1.2-1 Schematic Representation of the RGX-121 Vector Genome

- 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

From here, we will focus on RGX-121 for the expected indication of Mucopolysaccharidosis type II, also known as Hunter's syndrome, among the mucopolysaccharidoses.

Unlike ERT, which requires weekly intravenous infusions, RGX-121 is a gene therapy agent and can be administered as a one-time dose for continued efficacy.

It is also administered in the cerebrospinal fluid to deliver genes to central nerve cells to produce enzymes.

It is said to be important to intervene early in the treatment of mucopolysaccharidosis type II after diagnosis to control the progression of central symptoms. Unlike other agents, this drug can be administered from four months of age, and we believe that this drug is a priority in the neonatal period.

Currently, a phased approval application is under review in the U.S..

In addition, the drug has received orphan pediatric disease designation, advanced regenerative medicine approval, orphan drug designation, and fast-track designation from the FDA.

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 36

I will now explain the results of the Phase I/II/III study of RGX-121.

This clinical trial is an open-label, single-arm, open-label, two-part study. In Part One, 15 patients were treated in three doses. In Part Two, the highest dose of the Part One doses is selected for the 10 cases. In addition, all of these clinical trials were conducted as single doses.

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

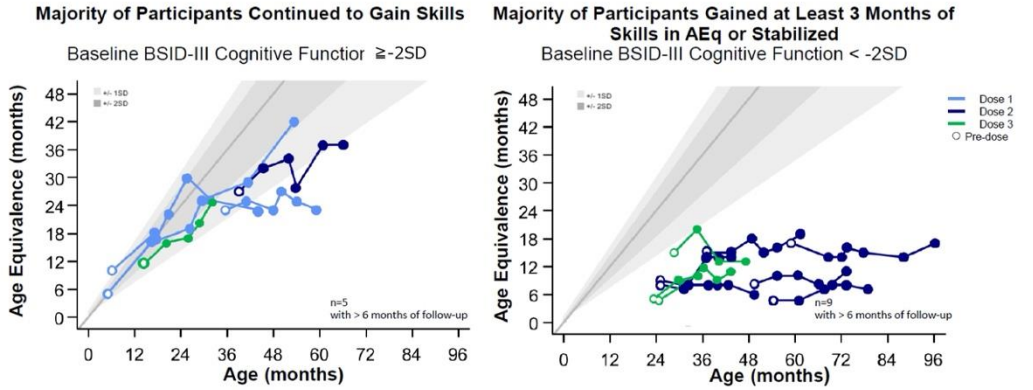
This is the trial design of Part One. The primary endpoint is safety at 24 weeks.

The efficacy evaluation period is 104 weeks, after which the patient moves to long-term follow-up.

Of the 15 patients treated, 13 were on ERT (enzyme replacement therapy) and were considered for withdrawal from ERT after 52 weeks of treatment with the drug.

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



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

This slide shows the results for the effectiveness of Part One.

In cognitive function assessments that evaluate the developmental age of infants and toddlers, patients with good cognitive function at baseline continue to show cognitive development comparable to that of healthy controls, while patients with developmental delay show less cognitive deterioration.

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

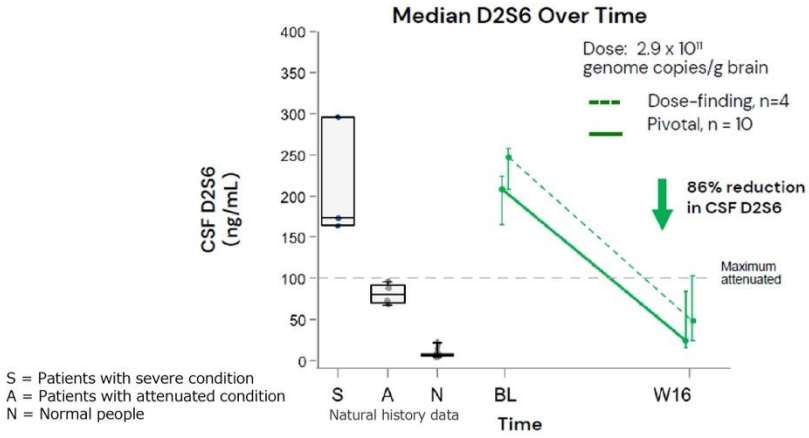
Here is the Part Two test design.

The primary endpoint was heparan sulfate concentration in cerebrospinal fluid at 16 weeks, followed by one year of safety and long-term follow-up.

Patients on immunosuppressive regimens for the first 48 weeks of treatment and on ERT did not change doses during the 16-week study.

RGX-121: Clinical P1/2/3 study

Part 2: Results



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

This slide shows the results of the effectiveness of Part Two. At 16 weeks of treatment, the concentration of HS D2S6, a metabolite of heparan sulfate, in the cerebrospinal fluid had decreased by approximately 86% and was below the maximum level of the mild form in 8 of the 10 patients. This is a one-time gene therapy, and the results of these clinical trials indicate that it is a first-in-class treatment for Mucopolysaccharidosis Type II.

Since this product can be administered earlier than ERT, and ERT can be administered after this product, we do not believe that this product will be an intrinsic competitor to existing therapies, including existing enzyme replacement therapies and formulations currently under development.

In the U.S., our U.S. subsidiary NS Pharma will conduct sales and promotional activities. We expect that the addition of this drug to our portfolio will contribute to the treatment of patients suffering from mucopolysaccharidosis.

In order to deliver groundbreaking new drugs to patients suffering from diseases as soon as possible, we will further increase the speed of our R&D and continuously expand our pipeline.

This concludes our presentation.

FY2024 R&D Meeting Q&A (summary)

February 18, 2025

No.	Question	Answer
1	The 7th Five-Year Medium Term Management Plan has a target of launching at least one new product per year. I suppose there is the cost burden of the three gene therapy products that were in-licensed since November last year. It seems that the pace of in-licensing is progressing faster than the original plan, but if the development of these products goes well, will your U.S. subsidiary NS Pharma (NSP) be able to handle all the commercialization and distribution?	As we were targeting late-stage development products that could be launched in time for the Uptravi patent cliff, we needed to acquire products for which we could conclude an exclusive contract within this fiscal year and expect an FDA BLA submission soon. Since it is not always possible to reach a successful agreement in a single negotiation, we were simultaneously negotiating with different partners on multiple items. We expect CAP-1002 and RGX-121 to be launched in 2H of FY2025, and NSP is preparing for them. Some investment was recorded in SG&A expenses this year, such as for increasing staff numbers. This is also planned for the next fiscal year. We believe that NSP will be able to handle without any problems. They believe that it is a good time to welcome new products since Viltepso was launched almost five years ago, and they are preparing for the launches in a positive mood.
2	How many more people will NSP need to hire to launch the two products, CAP-1002 and RGX-121?	Of the 120 people working at NSP, 50 are in the commercial and medical teams. There are currently plans to increase the number of commercial staff by 20 to 30.
3	How many patients are eligible for CAP-1002? I think there are various issues regarding FDA approval and insurance, but is the age on the label limited to 10 years old or older, which was the eligibility age for clinical trials? Also, will payers include cardiomyopathy symptoms in the conditions for reimbursement?	Capricor Therapeutics, Inc. (Capricor) estimates that 70% of all DMD patients are eligible for CAP-1002, but we think the figure is around 50-60%. Since cardiomyopathy progresses independently of motor function, it is necessary for a pediatric cardiologist to diagnose a tendency toward decreased cardiac function. I think that a certain threshold will be set for the treatment.

4	What criteria were used to calculate that 50-60% of all DMD patients are eligible for treatment? Was it LVEF (left ventricular ejection fraction)?	The scale of the number of patients to be administered the drug will depend on the outcome of discussions with the FDA, but there are thought to be around 15,000 DMD patients in the US, and around half of these are thought to have some form of heart function impairment, so in the broadest sense, we think that this is the target patient group for CAP-1002 as a treatment for DMD-cardiomyopathy. The target patients are not being narrowed down by specific LVEF values. Capricor is trying to discuss the label with the FDA on the premise that there are no age restrictions on patients who can be administered the drug. The inclusion age for the HOPE-2 study was 10 years or older, but Capricor's view is that the fastest possible medication will benefit patients because the function of the heart will irreversibly worsen.
5	Given that 50-60% of all DMD patients have some kind of cardiomyopathy, will the definition of cardiomyopathy be used to narrow down the target patients?	That's correct. For example, we believe that LVEF could be used a reference.
6	Is Capricor negotiating the label with the FDA to include patients with an LVEF of 45% or higher?	The answer is no. The inclusion criteria for the HOPE-2 study only cut off patient entry based on LVEF and did not attempt to determine the patients eligible for the product.
7	The number of subjects in the HOPE-2 trial is small, but will the FDA approve with this number of subjects?	Although the number of patients in the clinical trial was small, the FDA proposed a BLA for Capricor that included natural history data. I heard that the FDA looked at the HOPE-2 trial data and suggested to Capricor that it might be better to proceed with a BLA for cardiomyopathy rather than upper limb function. We think the probability of approval is high.

8	Will there be an Advisory Committee*? *Advisory Committees are open to the public and are held when the FDA reviews a pharmaceutical product. The pharmaceutical company and the FDA each give a presentation on the risk/benefit of the product under review, and the Advisory Committee, which is made up of experts in various fields, deliberates, taking into account public opinion, and then votes on whether to recommend the product or not.	We are expecting the acceptance of the BLA at the end of this month or the beginning of next month, and we have heard that it will also be notified of whether or not there will be an Advisory Committee at that time. At this point, we and Capricor believe that there will not be an Advisory Committee, but we are preparing just in case.
9	I think CAP-1002 is a drug with high potential, depending on the approved label and it must have seemed like a promising product for Sarepta Therapeutics too, which has the distribution channels in the U.S., just like NSP. Could you tell us the background to your acquisition of CAP-1002?	I think that CAP-1002 was met with some skepticism in the U.S. back then due to the nature of cell (exosome) therapy. We found that the product had very strong data and at the same time, both of us were a very good fit in terms of corporate culture. The management teams of our company and Capricor communicate closely with each other, and we can exchange opinions freely. Although we cannot speculate on our competitors, we believe that we were able to identify a promising product at the right time, quickly move forward with negotiations, and sign a contract with economic terms that suited our company.
10	Were there any competitors at the time of the in-license negotiations?	According to Capricor, they were also considering other proposals.
11	I think the CAP-1002 application will be accepted by the FDA soon, but there are concerns about manufacturing due to the new modality. At the meeting in March last year, the FDA reportedly decided that RNA sequencing assays and anti-fibrotic assays were acceptable. Are allogeneic cells really bioequivalent?	Capricor is working with us to prepare the manufacturing line for the launch of the product. They have established a highly reproducible, systematized process. There are no particular problems with production. Clinical trials for cohorts A and B have also been conducted, and we believe that bioequivalence can be confirmed through RNA profiling and anti-fibrosis assays. The product is made from eligible human heart, so we believe there is no concern about quality stability or efficacy. We would like to work together to improve the manufacturing process with the aim of mass-producing a product of equivalent quality.

12	I would like to know how you ensure the lot-to-lot consistency of CAP-1002 and the efficacy of the drug product. Looking at today's presentation material, it says that RNA characterization is performed after CDC (cardiosphere-derived cell) expansion. I think that Capricor has defined a certain amount of RNA that is considered to be effective, and I suspect that they are profiling the amount of this RNA to determine the appropriateness of each CDC. What kind of RNA is it? Capricor also says that there is a risk that CAP-1002 will be replaced by exosome drug discovery, which is said to be the next promising modality, but I would like to know how much is known about the molecules in exosomes that can define their effectiveness based on that.	The details of the RNA profiling are not shared with us. We imagine that it is not distinguishing by a few types, but by a large number of RNA expression patterns. In the future, there is a possibility that exosome therapy will rise in place of cell therapy, but the commercial opportunity risk for CAP-1002 will change depending on when that happens. Capricor also thinks that the trend will move in the direction of exosome therapy, but also thinks that it will take some time.
13	Are the lots for the HOPE-2 and HOPE-3 trials different?	The lots for Cohort A in the HOPE-2 and HOPE-3 trials are the same, but those for Cohort B were made at a different manufacturing facility.
14	How do they check for lot-to-lot variation?	The bioequivalence of lots made at different manufacturing facilities was confirmed in preclinical studies.
15	I understand that REGENXBIO is in the process of rolling BLA submission for RGX-121 and that the submission is scheduled to be completed by the end of March, but will the drug be approved based solely on surrogate endpoints from the current P1/2/3 Part 2 trials? I think that the data on cognitive function that was observed in Part 1 will be released at a later date.	The Part 2 trial is being conducted at the maximum dose of Part 1. Gene therapy has a simple mechanism of action and is highly reproducible, and we expect to see the same good results in the Part 2 trial.
16	Will the results of the Part 2 be available while the FDA is reviewing the BLA?	The FDA will decide whether the current data is sufficient for accelerated approval or whether further data is required.

17	Regarding the strategic positioning of the two in-licensing deals, ATSN-101 and RGX-121/111, I would like to know whether you are seeking added value beyond acquiring the rights in exchange for cash and securing sales figures. Are you considering developing gene therapy in the future based on the technology you have acquired this time? The release by Atsena included some wording that implied future collaboration with you. It seems that Atsena expects to receive a priority review voucher, which could be used for your development activities.	We are currently working on nucleic acid medicine for neuromuscular diseases, and we are considering the central nervous system (CNS) as our next target area. Among CNS diseases, there are some that are suitable for nucleic acid medicine approaches and others that are suitable for gene therapy approaches. We also hope to promote gene therapy as one of these approaches. The knowledge and expertise in gene therapy that we will gain through this partnership, including CMC and U.S. clinical regulatory/development, will be extremely important in promoting the development of gene therapy aimed at the CNS area. It may be a bit of an exaggeration, but we think it will be a big plus because we will gain the same amount of knowledge as if we had developed one candidate product ourselves.
18	By accumulating knowledge and expertise in gene therapy through RGX-121/111, are you aiming to develop a gene therapy or orphan drug for lysosomal diseases?	We thought that local administration and gene therapy were good. As with ATSN-101, local administration requires a smaller dose than systemic administration, and there are also advantages in terms of production. In addition, local administration requires a smaller amount of vector to be introduced into the body at one time than systemic administration, and although steroid care is still necessary due to side effects, we think that there are advantages in this point too.
19	Was the reason for in-licensing not for a product for lysosomal diseases, but for a gene therapy with local administration?	That’s correct.
20	Are you considering acquiring Atsena? Is this in-licensing partnership the starting point of that?	As we promote technical exchange through our partnership, we will confirm Atsena's technical capabilities, as well as their operations and manufacturing capabilities in the U.S. If, as we talk about future collaboration, it becomes clear that it would be better for us to be in the same group, then acquisition may become an option, but there are no concrete plans at the moment.

21	Both CAP-1002 and RGX-121/111 are seeking approval outside of the true endpoints, but in the end it will be up to the FDA and CBER (Center for Biologics Evaluation and Research) to decide. With the change of government in the U.S., do you think there is a risk that the supportive stance of CBER in the review process may change due to personnel changes, or that Dr. Peter Marks (Director of CBER) may leave the current position?	There was a report today that the new administration is planning to reduce the number of FDA staff. While it is possible that the change in the system in the US could have a slightly negative impact on the difficulty of obtaining approval, we do not believe that the ongoing application process will be dramatically overturned. At present, the FDA is supportive of the CAP-1002 and RGX-121 approval applications. In particular, with regard to CAP-1002, the FDA suggested to Capricor that they should move forward with an application for DMD-cardiomyopathy as the expected indication, based on a comparison with natural history data. This was led by Dr. Peter Marks' department. Development of RGX-121 is also progressing based on similar supportive discussions.
22	It would be best if CAP-1002 and RGX-121 were approved in six months to a year's time. Otherwise, you will need to consider Plan B as the LOE（Loss of Exclusivity） for Uptravi is approaching. In that case, how will you use the current cash of around 60 billion yen?	Of the 60 billion yen, we have already spent some on the in-licensing activities. There is a strategic allocation of 100 billion yen, and we will look for other business opportunities within that. There are also other in-licensing opportunities currently under negotiation, and we will make decisions flexibly while looking at our cash on hand and the costs of future projects.
23	As the conclusion of today's discussion, to what extent will taking on the challenge of new modalities increase the probability of overcoming the Uptravi patent cliff?	In our 7th Five-Year Medium Term Management Plan, we announced that we would make up for the patent cliff of Uptravi by increasing sales of our pediatric neurology, hematology, and pulmonary hypertension products. We understand that there is concern about what products will actually sell for how much. Today, we explained the progress of our pipeline this year by introducing the status of CAP-1002 and other in-licensed products under development. We hope that today's presentation has increased your certainty and awareness of our growth beyond the patent cliff.