FY2022
R&D Meeting: Part I

December 15, 2022
NIPPON SHINYAKU CO., LTD.

NIPPON SHINYAKU CO., LTD.

Current and Future Treatment for Dravet Syndrome

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FY2022
R&D Meeting: Part II

December 15, 2022
NIPPON SHINYAKU CO., LTD.

NIPPON SHINYAKU CO., LTD.

Promoting patient-centric business activity

Three commitments to fulfill our corporate philosophy

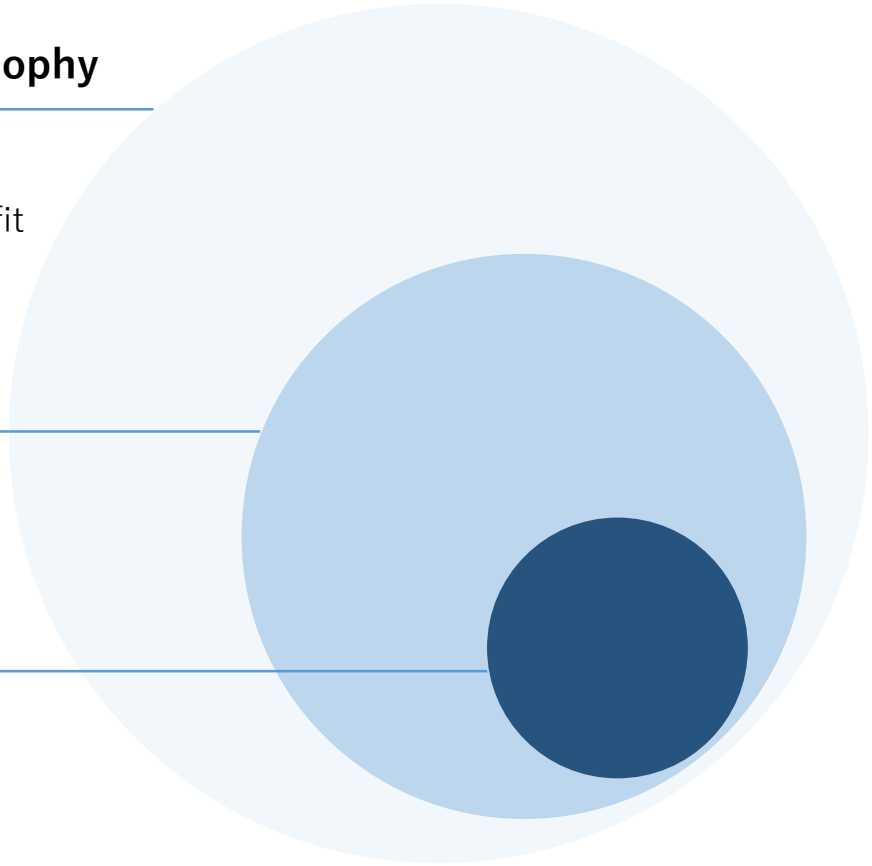
Continue to launch at least one unique product each year
Generate at least 50% of consolidated sales from overseas
Target at least more than twice in net sales and operating profit

Corporate philosophy

Helping People Lead Healthier, Happier Lives

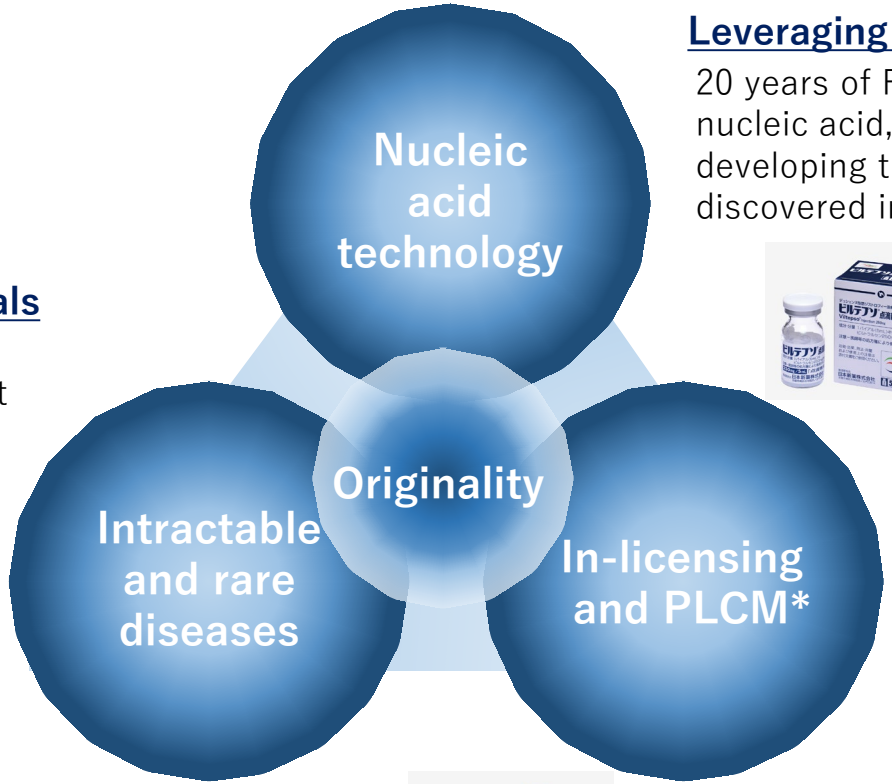
Identity

To produce new drugs



Regardless of the size of the market, we will continue to contribute to society by creating and delivering innovative new drugs for patients suffering from diseases.

Leveraging our acquired strengths



Leveraging our technical superiority

20 years of R&D activity in the field of nucleic acid, results to success of developing the first nucleic acid drug discovered in Japan

Viltepso

Generic name: Viltolarsen
In-house discovered drug by Nippon Shinyaku.
This treatment for Duchenne muscular dystrophy is an morpholino antisense oligonucleotide.

Doing one's all for individuals

Promote unique R&D in areas where other companies are not involved

Uptravi

Generic name: Selexipag
Treatment for pulmonary arterial hypertension /chronic thromboembolic pulmonary hypertension developed in-house by Nippon Shinyaku.
A global blockbuster product marketed in more than 70 countries.

Vidaza

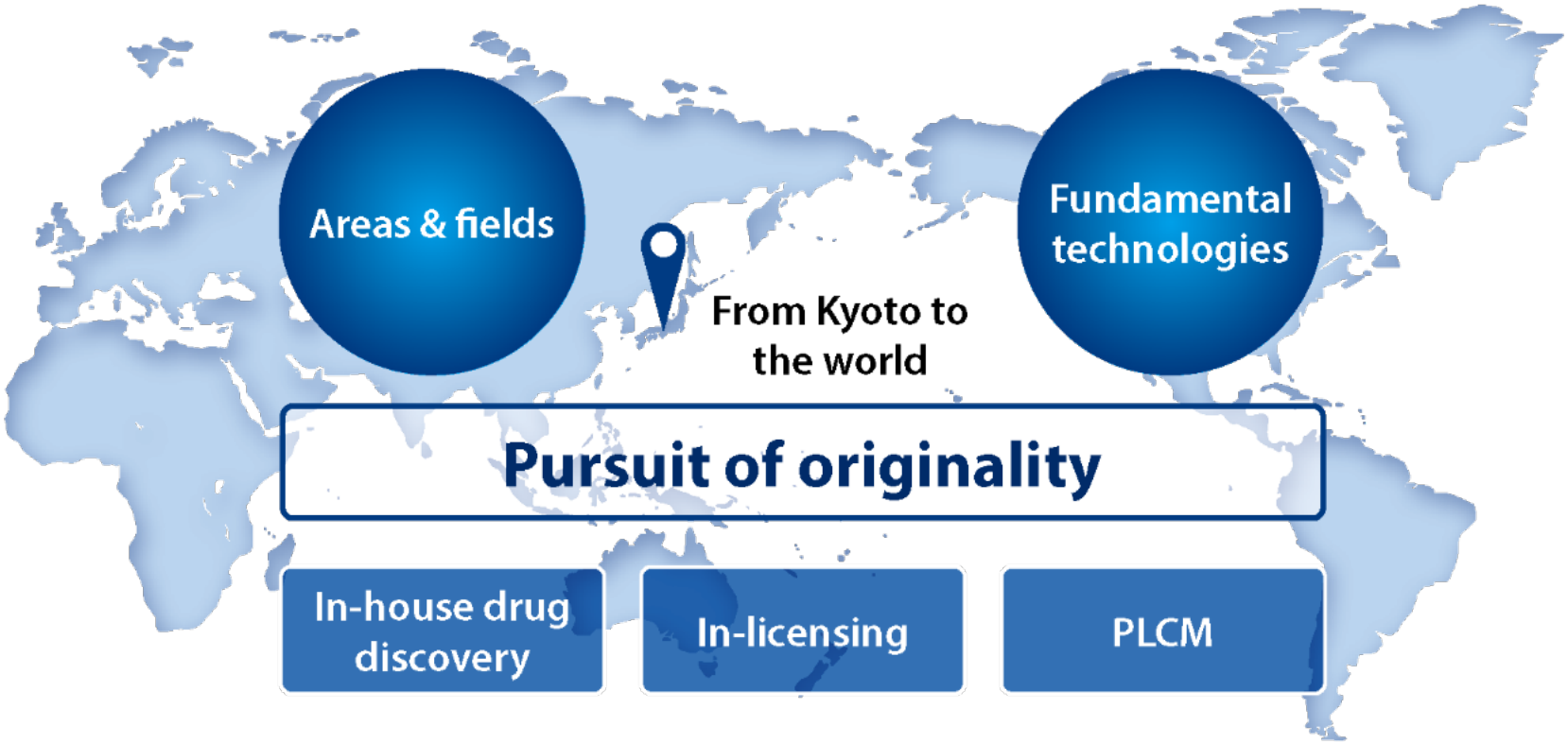
Generic name: Azacitidine
Introduced through a licensing agreement with Celgene corporation.
Treatment for myelodysplastic syndrome / acute myeloid leukemia treatment.

Maximizing product value

Enhanced development pipeline and marketed an average of 1 or more new products per year

*PLCM: Product life cycle management

R&D strategy



We aim to become a company with a meaningful existence in the global healthcare field.

Research and Development Activities

NIPPON SHINYAKU CO., LTD.

R&D approach

As a slogan for our R&D division, we aim for "The creation of new drugs to be used worldwide." Therefore, we will continue to create highly unique and distinctive new drugs.

With a sense of speed and to increase the probability of success in mind, research will be conducted to expand our product pipeline by continuously creating unique research themes through three approaches, "Strategy for Therapeutic Focus Area" and "Strategy for Modality," and "Open Innovation."

Progress of nucleic acid DMD pipeline

Program	Target	% of DMD patients	Pre clinical	PI	PI／II	PII	PIII	Launch
NS-065/NCNP-01 (Viltolarsen)	Exon 53	8%					PIII in progress	
NS-089/NCNP-02	Exon 44	6%						
NS-050/NCNP-03	Exon 50	4%						
NS-051/NCNP-04	Exon 51	13%						
Exon 45 Skipping	Exon 45	8%						
Exon 55 Skipping	Exon 55	2%						

Nippon Shinyaku owned DMD pipeline can cover approximately 40% of all DMD patients

Progress of nucleic acid product (NS-065/NCNP-01)

Study no.	Study description	Estimated primary completion date*
Study 202 (Long-term study from P2 study (Study 201))	P2, open Week 217, 16 patients	**Complete** 2021/11
Study 502 (Registry from Study 202).	Long-term follow-up 10 years, ~16 cases	2032/9
Study 301-RACER53 (Global P3 Study)	P3, double-blind, placebo-controlled 48 weeks, 74 patients, 4-7 years	2024/12
Study 302-RACER53-X (Long-term study from Study 301)	P3, open 2 years	2026/6
Study 211-Galactic53 (advanced cases)	P2, open 48 weeks, 20 patients, 8 years or older ambulatory (8 patients)/non-ambulatory (12 patients).	2023/8

*Primary Completion Date on ClinicalTrials.gov

Clinical study updates

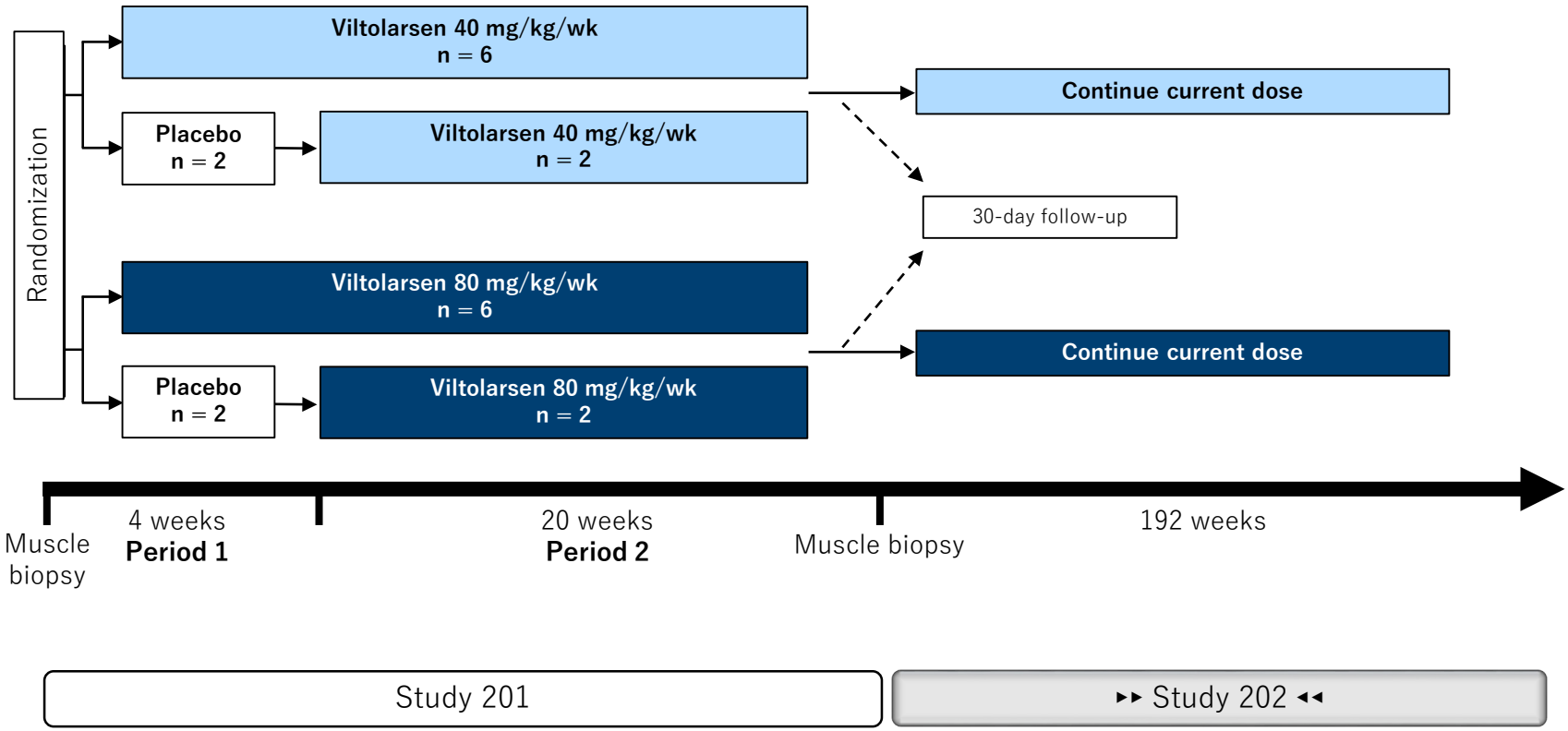
- NS-065/NCNP-01 phase 2 extension study
- NS-089/NCNP-02 investigator-initiated clinical study

Clinical study updates

- NS-065/NCNP-01 phase 2 extension study
- NS-089/NCNP-02 investigator-initiated clinical study

NS-065/NCNP-01　phase 2 extension study

【Study Design of Study 201 and 202】

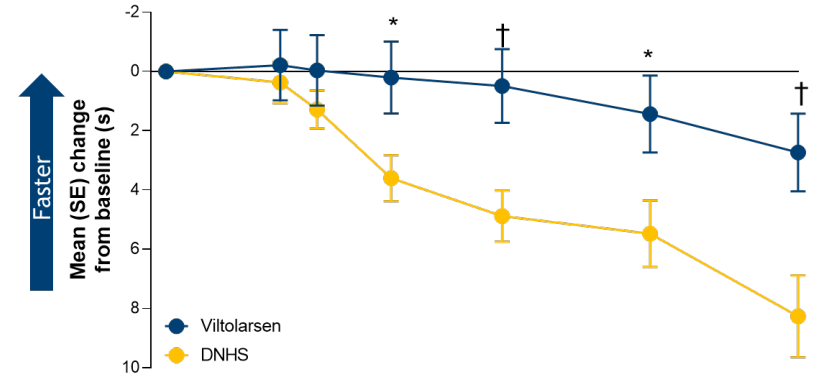


*wk, week.

NS-065/NCNP-01　phase 2 extension study

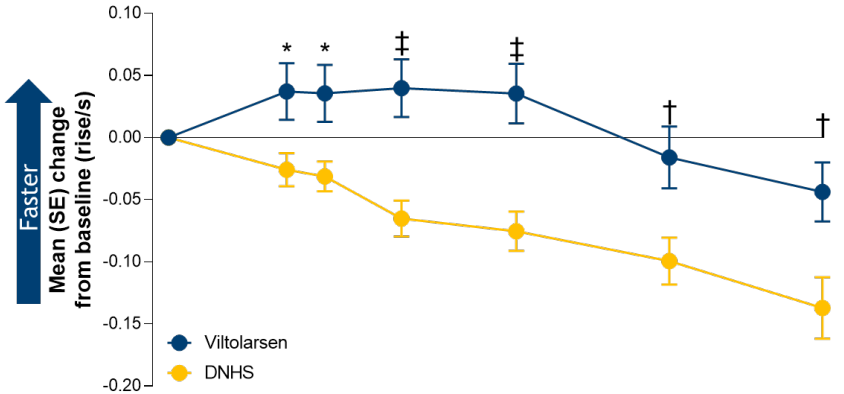
【TTSTAND CFB vs Natural History Controls】

Seconds



	Baseline	37w	49w	73w	109w	157w	205w
Viltolarsen, n	16	16	15	14	14	11	13
DNHS, n	65	31	57	24	24	14	10

Velocity

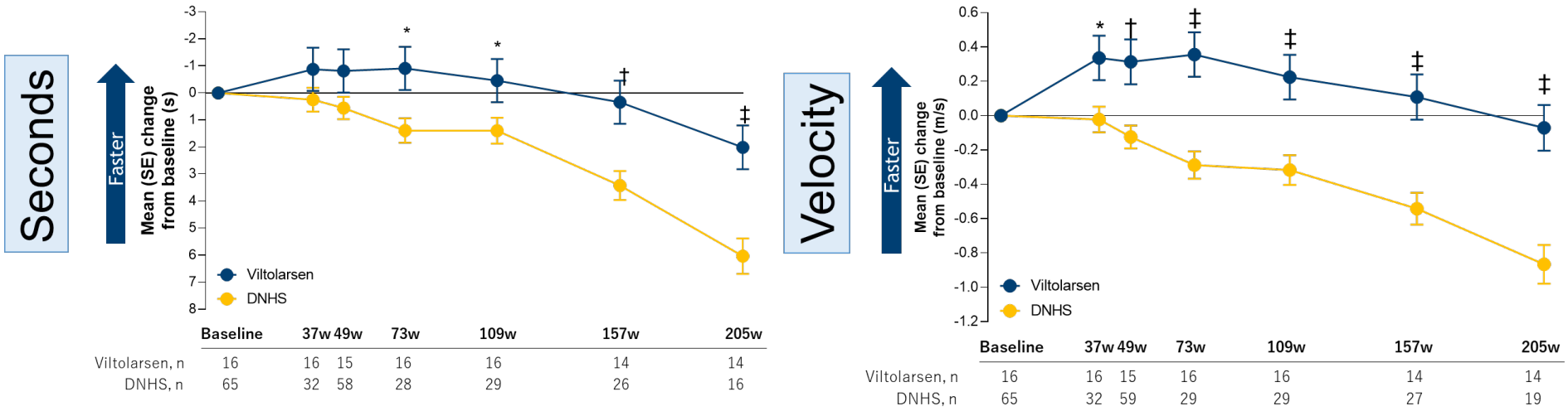


	Baseline	37w	49w	73w	109w	157w	205w
Viltolarsen, n	16	16	15	14	14	11	14
DNHS, n	65	31	58	28	28	20	12

*P <0.05; † P <0.01; ‡ P ≤0.001.
CFB, change from baseline; DNHS, Duchenne Natural History Study（DMD natural history control group）;
s, seconds; SE, standard error; TTSTAND, time to stand from supine; w, weeks.

NS-065/NCNP-01　phase 2 extension study

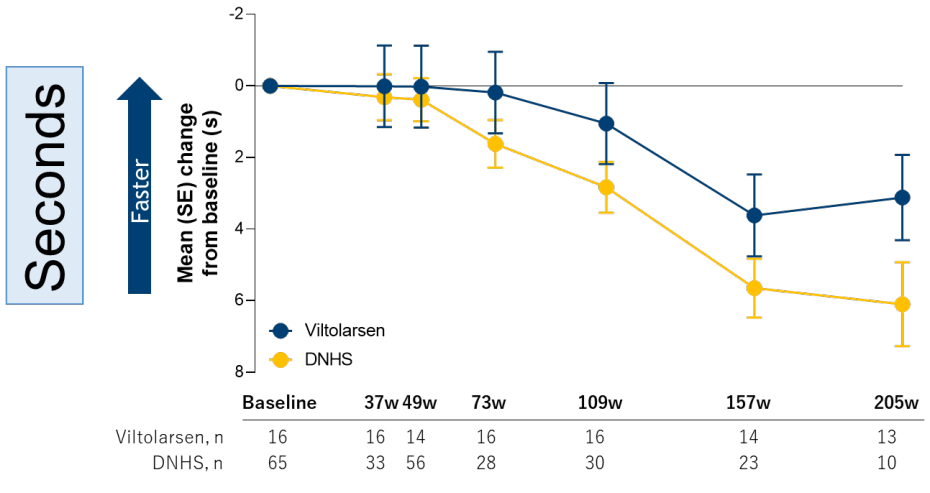
【TTRW CFB vs Natural History Controls】



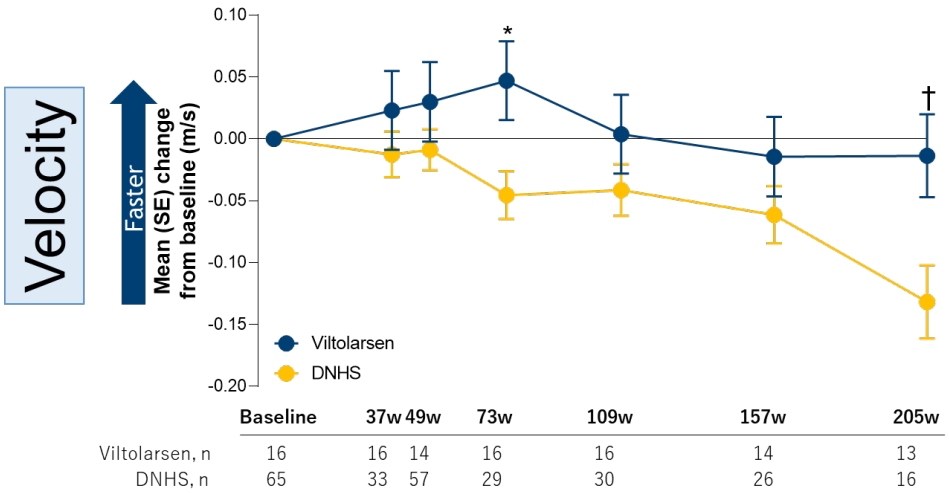
*P <0.05; † P <0.01; ‡ P ≤0.001.
CFB, change from baseline; DNHS, Duchenne Natural History Study（DMD natural history control group）;
s, seconds; SE, standard error; TTRW, time to run/walk 10 meters; w, weeks.

NS-065/NCNP-01　phase 2 extension study

【TTCLIMB CFB vs Natural History Controls】



	Baseline	37w	49w	73w	109w	157w	205w
Viltolarsen, n	16	16	14	16	16	14	13
DNHS, n	65	33	56	28	30	23	10



	Baseline	37w	49w	73w	109w	157w	205w
Viltolarsen, n	16	16	14	16	16	14	13
DNHS, n	65	33	57	29	30	26	16

*P <0.05; † P <0.01; ‡ P ≤0.001.
CFB, change from baseline; DNHS, Duchenne Natural History Study（DMD natural history control group）;
s, seconds; SE, standard error; TTCLIMB, time to climb 4 stairs; w, weeks.

NS-065/NCNP-01　phase 2 extension study

【 Safety Assessment / Common TEAEs (Preferred Term in ≥25% of Participants)】

	Viltolarsen participants		
Participants with:	**40 mg/kg/wk (n = 8)**	**80 mg/kg/wk (n = 8)**	**Total (N = 16)**
Any TEAE, n (%)	8 (100)	8 (100)	16 (100)
Any drug-related TEAE, n (%)	0	1 (13)	1 (6)
Any serious treatment-related AE, n (%)	0	0	0
Study drug discontinuation due to TEAE, n (%)	0	0	0
Death, n (%)	0	0	0
	Viltolarsen participants		
TEAEs（Preferred Term in ≥25% of Participants）	**40 mg/kg/wk (n = 8)**	**80 mg/kg/wk (n = 8)**	**80 mg/kg/wk (n = 8)**
Cough, n (%)	5 (63)	5 (63)	10 (63)
Nasopharyngitis, n (%)	4 (50)	5 (63)	9 (56)
Insect bite, n (%)	4 (50)	2 (25)	6 (38)
Rash, n (%)	2 (25)	4 (50)	6 (38)
Vomiting, n (%)	3 (38)	3 (38)	6 (38)
Fever, n (%)	2 (25)	3 (38)	5 (31)
Fall, n (%)	4 (50)	1 (13)	5 (31)
Headache, n (%)	3 (38)	2 (25)	5 (31)
Nasal congestion, n (%)	3 (38)	2 (25)	5 (31)
Influenza, n (%)	3 (38)	1 (13)	4 (25)

- The most frequently reported TEAEs (reported by ≥25% of participants) were cough and nasopharyngitis.

Conclusion

- Participants treated with viltolarsen for an additional 192 weeks (up to 216 weeks or 4 years) showed maintenance of function over the first 2 years and significantly delayed disease progression over the following 2 years in timed function tests compared with CINRG DNHS controls, which declined over this same time period.

- Viltolarsen was well tolerated over 192 weeks, with most reported TEAEs being mild or moderate; with no study drug discontinuations or deaths reported.

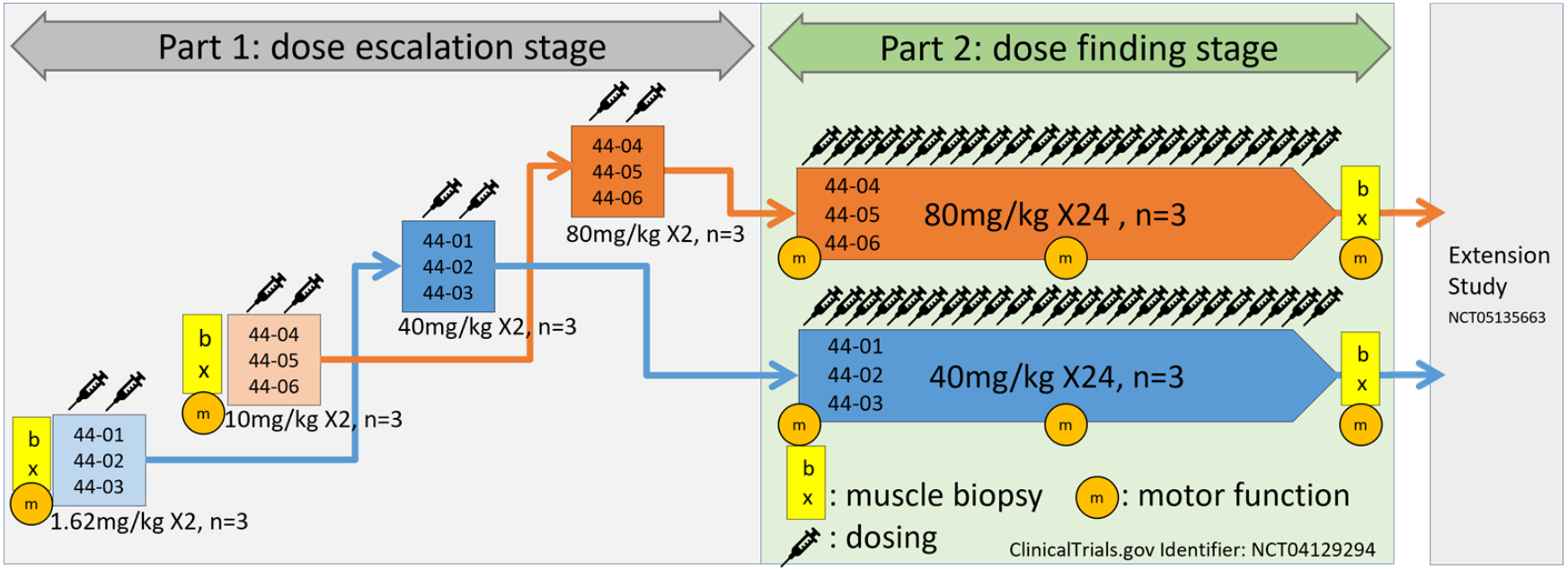
- Viltolarsen should be considered an important part of the treatment strategy for patients with DMD who are amenable to exon 53 skipping.

Clinical study update

- NS-065/NCNP-01 phase 2 extension study

- NS-089/NCNP-02 investigator-initiated clinical study

NS-089/NCNP-02
Study design of Phase 1/2 Study（First-in-human, Open label study）



MDA, March 2022

Key inclusion Criteria

- Age : 4-17 years
- Ambulant
- Amenable to exon 44 skipping

Primary Objectives

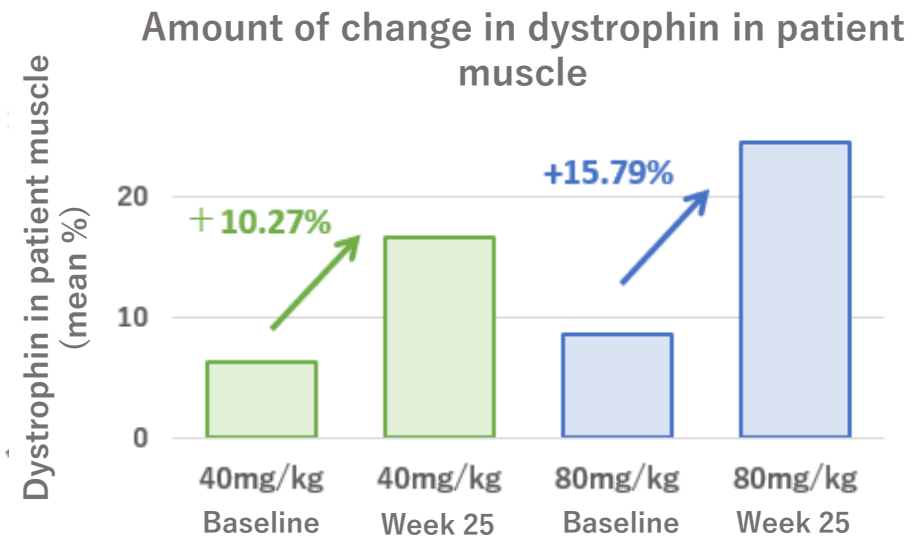
- Safety and tolerability

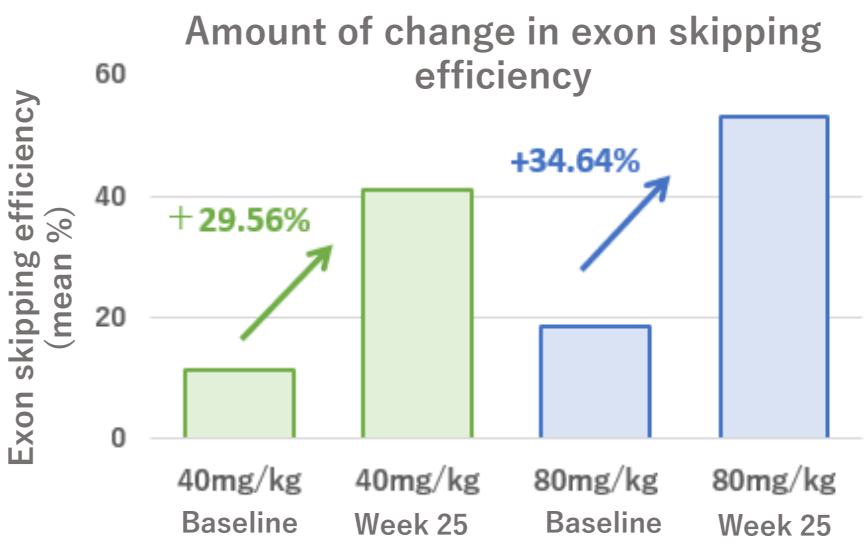
Secondary Objectives

- Dystrophin protein expression
- Motor function assessments*
- Exon 44 skipping levels
- Pharmacokinetics
- Serum CK levels
- In vitro assays

＊Motor function assessments : NSAA (North Star Ambulatory Assessment), TTSTD (Time to stand from supine), TTRW (10-meter walk), 6MWT (6-minute walk), 2MWT (2-minute walk), TUG (Timed Up and Go), PUL (Performance of Upper Limb), Muscle strength assessment

NS-089/NCNP-02
Study design of Phase 1/2 Study（First-in-human, Open label study)





MDA, March 2022

	Mean change from baseline in dystrophin expression %（SD)	Mean change from baseline in exon skipping efficiency %（SD)
40mg/kg(n=3)	10.27 (1.88)	29.56 (8.77)
80mg/kg(n=3)	15.79 (6.44)	34.64 (9.56)
Mean(%)	13.03 (5.21)	32.10 (8.71)

- After 24 weeks of 6 cases tested, a significant increase of dystrophin expression and exon skipping efficiency from baseline were observed. Also, NS-089/NCNP-02 was safe and well tolerated.
- Function assessment in the dose finding stage show a tendency of recovery and increase in motor function.
- The limitations of this study include the small number of participants and lack of placebo control arm, thus the observed effectiveness of NS-089/NCNP-02 in inducing endogenous dystrophin expression and stabilization of motor function needs further verification.

Status of developing DMD pipelines

	Development stage	Contents
NS-065/ NCNP-01	Approved in Japan and US P3 study in progress	● P3 study, Study 502 (long-term follow-up study), and Study 211 (study in ambulant and non-ambulant boys with DMD) in progress.
NS-089/ NCNP-02	Preparation for P2 study in Japan and US	● Investigator-initiated clinical trial in Japan has been completed, and an extension study is ongoing. ● Throughout discussion with the FDA to begin P2 study in Japan and the United States, FDA commented on the result of nonclinical safety study and asked for a third-party expert meeting. During this year, a meeting with a third-party expert is expected to be completed and by the end of this fiscal year, we will renegotiate with the FDA.
NS-050/ NCNP-03	Preparation for P1/2 study in Japan and US	● Throughout discussion with the FDA to begin P1/2 study in Japan and the US, FDA requested an additional genotoxicity study to be conducted, which we are currently proceeding. We expect genotoxicity study to be completed during this fiscal year and submit results to the FDA.
NS-051/ NCNP-04	Preparation for P1/2 study in Japan and US	● We are currently discussing with PMDA, to initiate clinical study. We are also planning to have pre-IND meeting with the FDA, within this fiscal year.
Exon 45 skipping	Preclinical	● We have selected candidate sequeces and nonclinical studies are underway.
Exon 55 skipping	Preclinical	● We have selected candidate sequeces and nonclinical studies are underway.

Next-generation modalities

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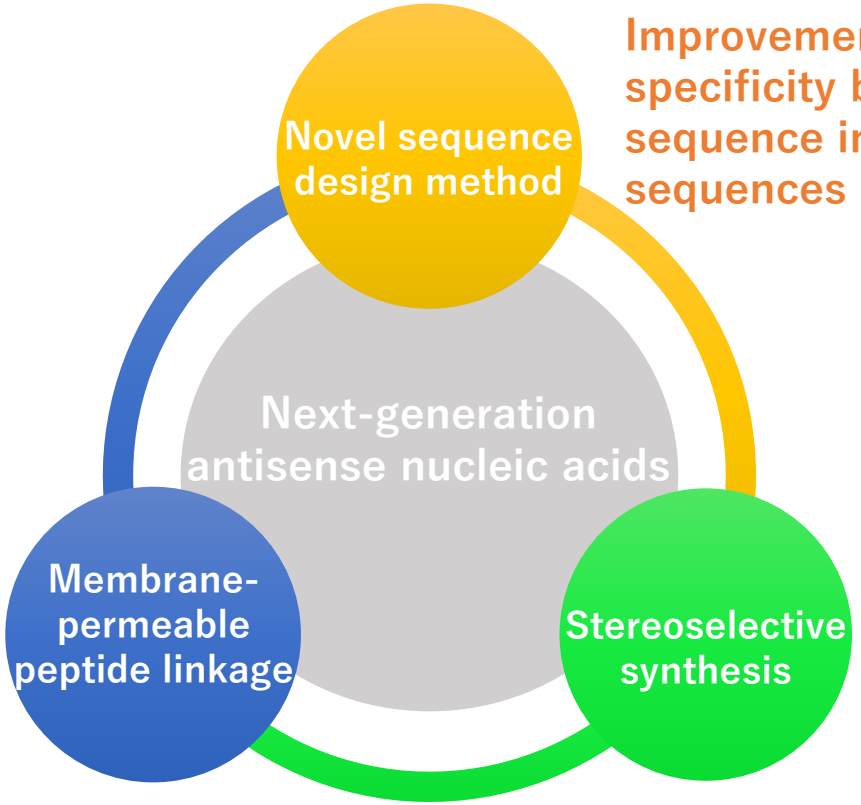
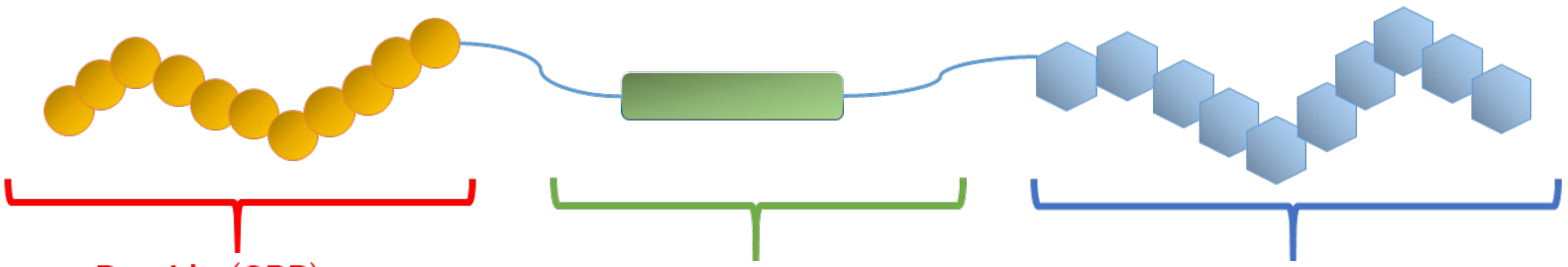
Development of next-generation antisense nucleic acids



Next generation antisense nucleic acids can improve distribution, efficacy (persistence and activity), safety, and physical properties compared to current antisense nucleic acids. This expands the application of nucleic acid drug to other diseases.

Peptide-conjugated nucleic acid

PPMO（Peptide-conjugated phosphorodiamidate morpholino oligomer）



Peptide（CPP）
A short peptide of 30 or fewer amino acids with high cell membrane permeability at low concentrations

Linker
Important for activity and stability of molecule

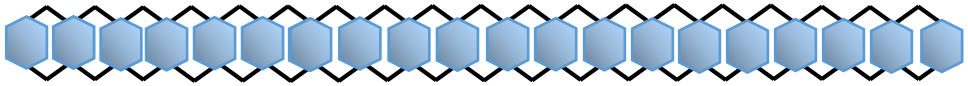
Phosphorodiamidate morpholino oligomer (PMO)
Highly activity PMO such as Viltepso and NS-089

We are developing PPMO in which CPP is bound to morpholino nucleic acid as DDS technology to improve the pharmacokinetics of nucleic acid drugs by enhanced cell membrane permeability. As a result, we aim to improve the drug efficacy and reduce the frequency of administration using PPMO.

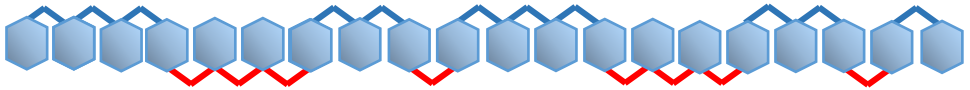
Selection of optimal peptide (Completed) → Optimize linker (Completed) → Highly active PMO sequence (Selected) → Selection of PPMO candidate (Completed) → Pre-clinical Studies (In progress)

Stereoselective synthesis

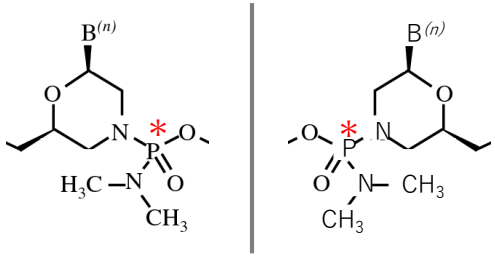
Conventional PMO (a mixture of stereoisomers)



Stereocontrol (single-stereoisomers)



mirror

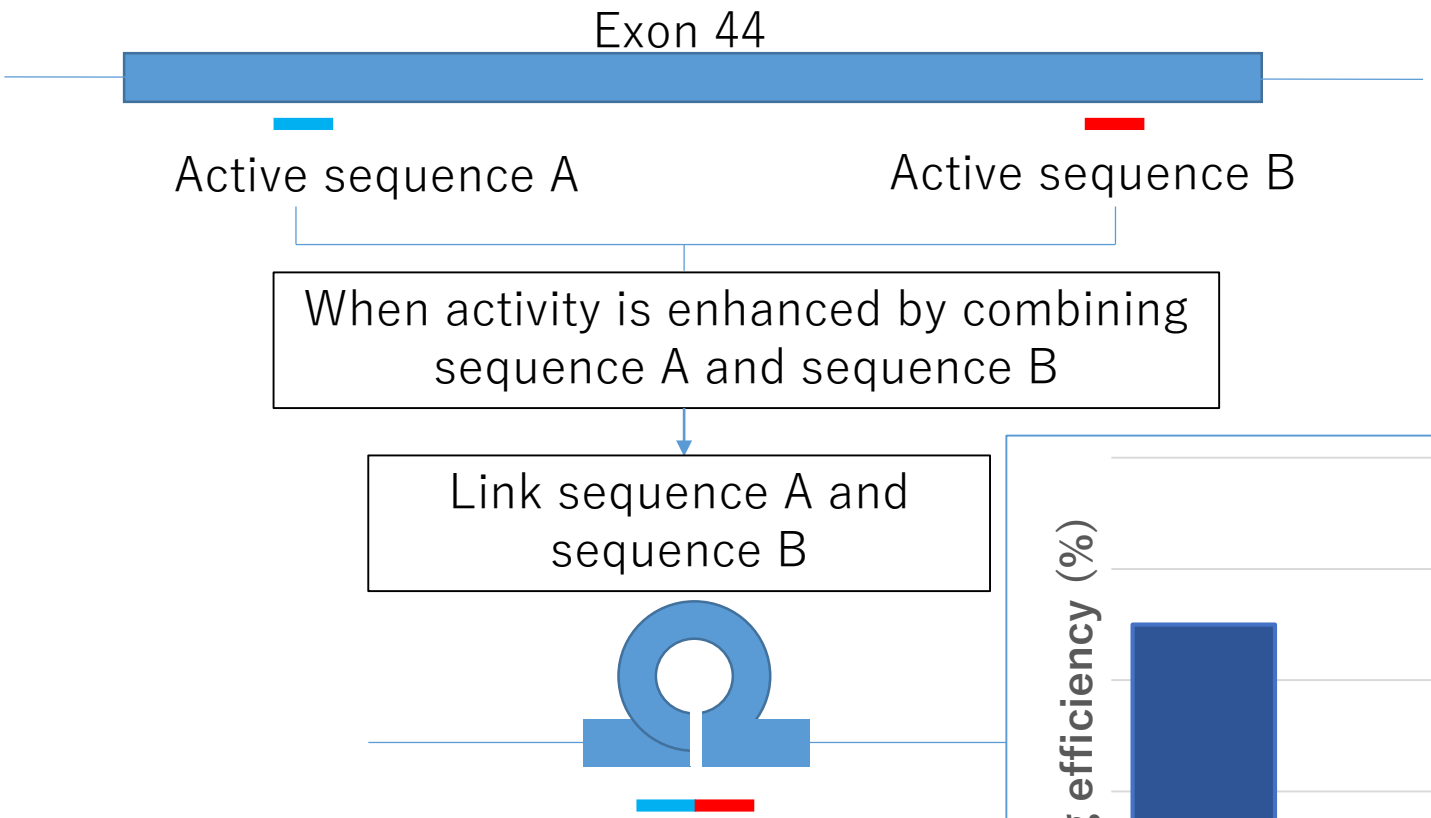


Monomer has chirality and PMO is a mixture of stereoisomer.

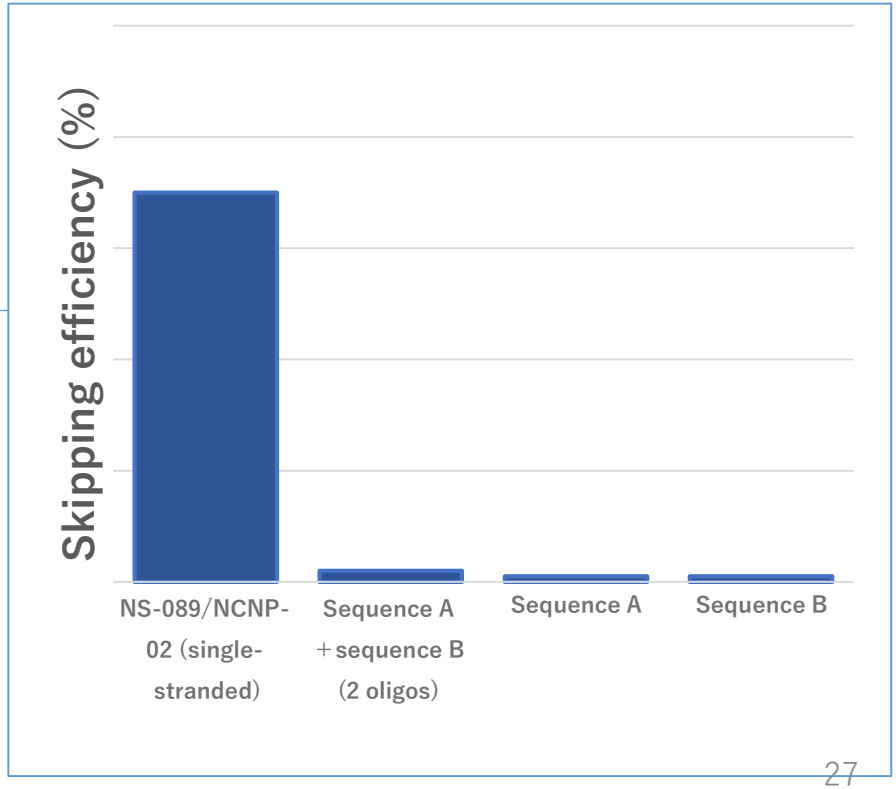
Stereocontrolled synthesis of optimized modified nucleic acids create new added value (such as improvement of physical properties and activity)

Synthesis of Stereo-controlled PMO (Success) → Improvement of physical properties and activities (Success) → Reproducibility and regularity with sequence changing (In progress) → Selection of Stereo-controlled PMO candidate → Pre-clinical Studies

Novel sequence design method (NS-089/NCNP-02)



Strong skipping activity is obtained.



Several types of approach for DMD

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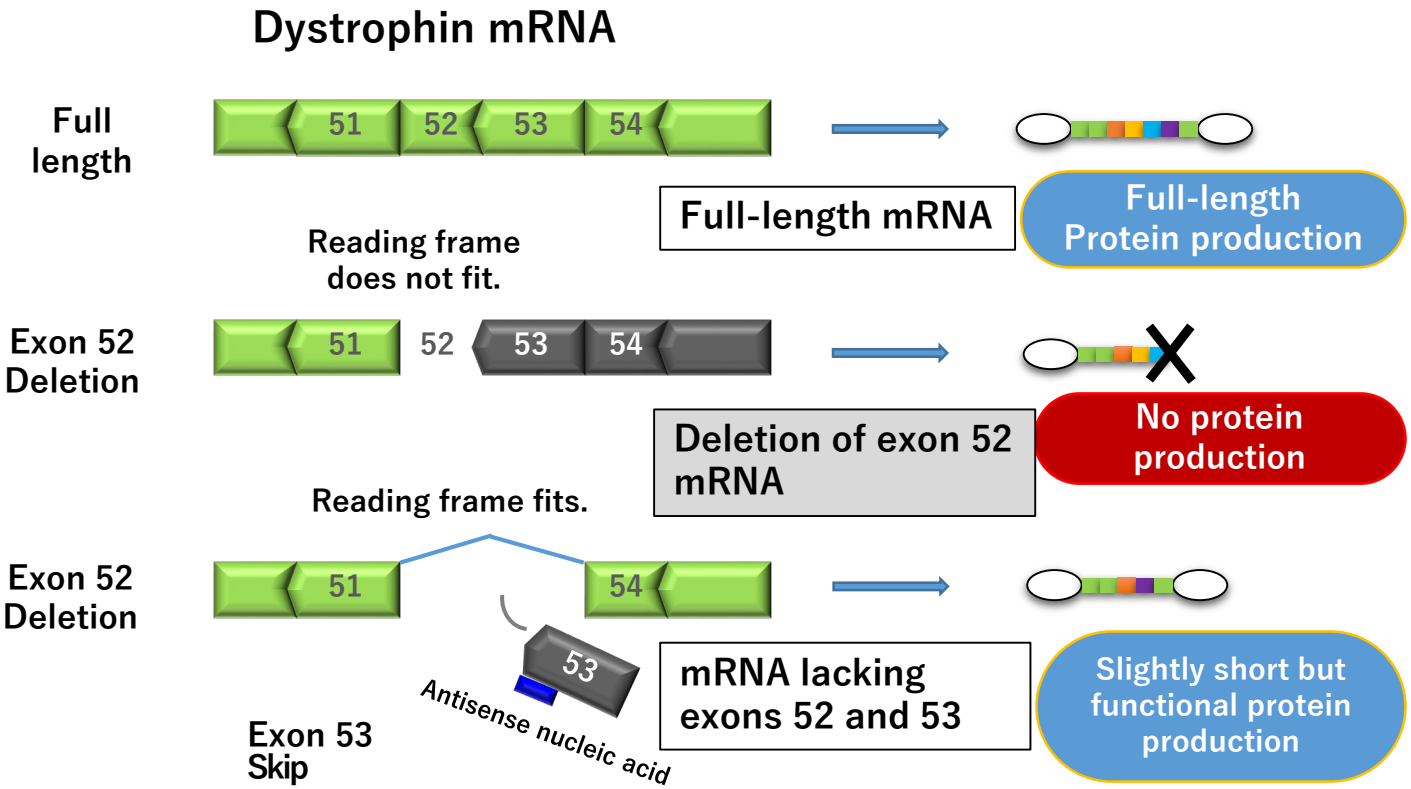
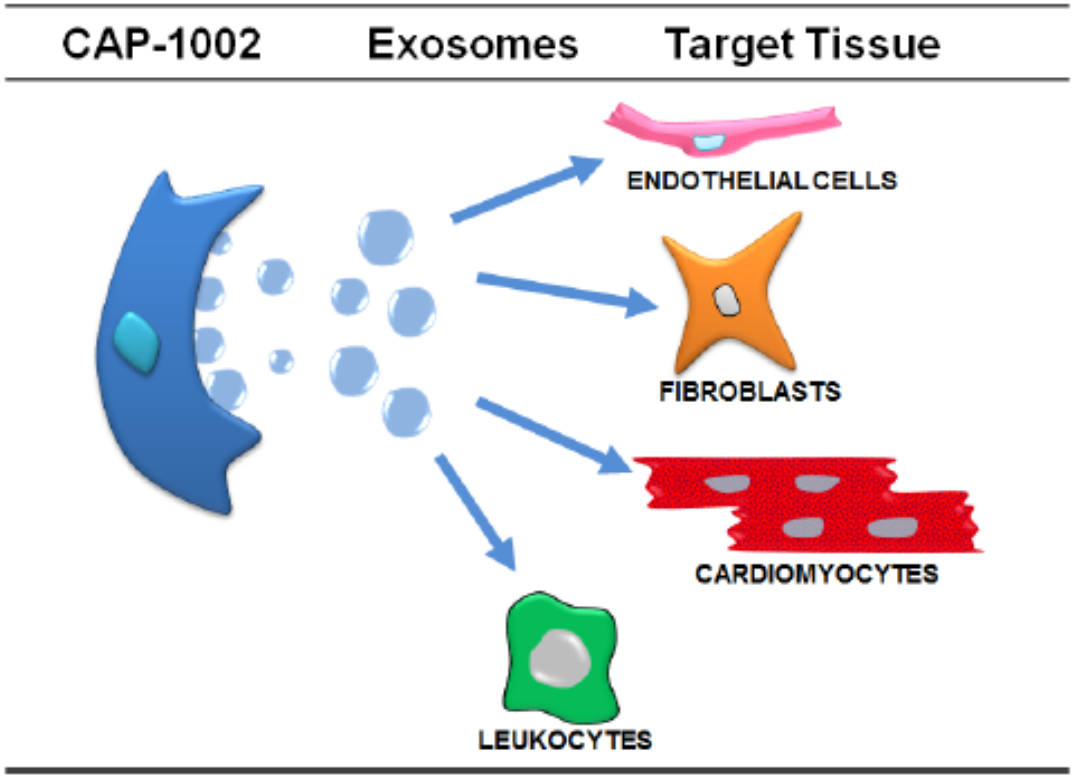
Nucleic acid drug (exon skipping)



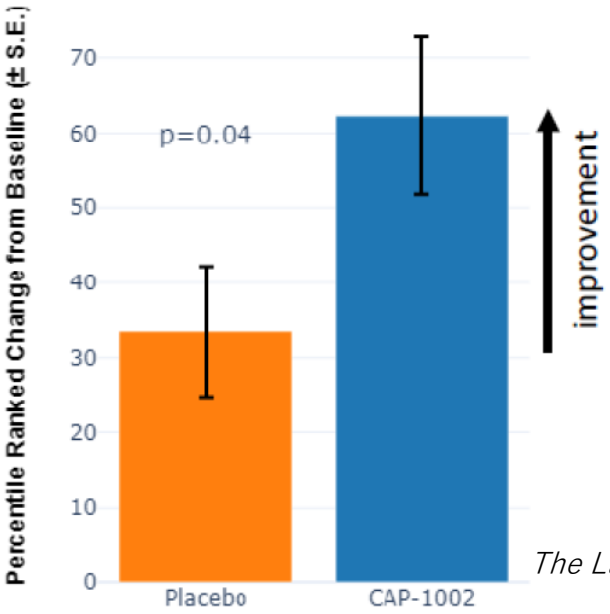
Cell therapy CAP-1002

Cardiosphere-derived cell therapeutic.
Exosomes (extracellular vesicles) released from this drug are expected to reduce oxidative stress, inflammation, fibrosis, and increase cell energy and myocyte generation, resulting in reducing deterioration of motor and cardiac functions.



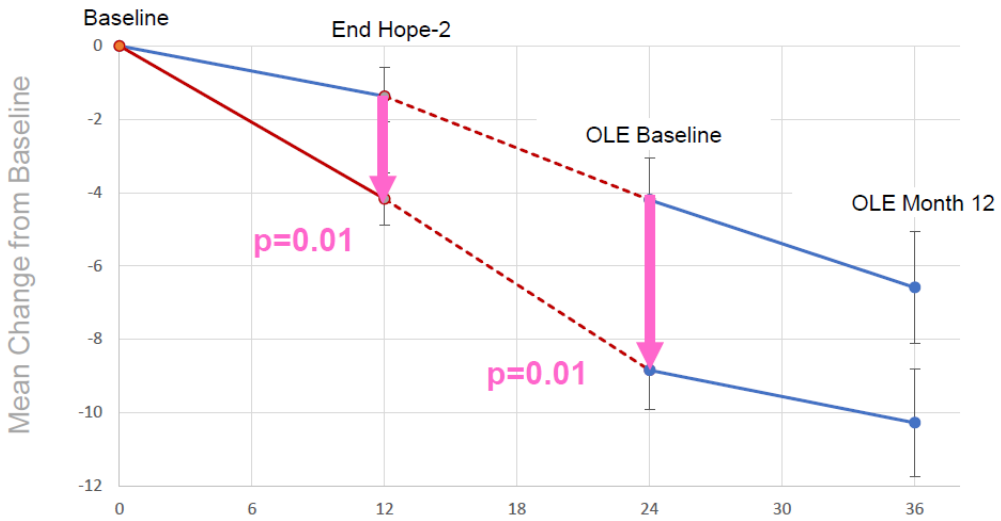
Cell therapy CAP-1002:HOPE-2 study + OLE study

Δ=1.8 points in CAP-1002 vs. placebo at 12-months



The Lancet, March 2022

DB Phase | Gap Phase | OLE Phase



WMS, October 2022

HOPE-2 DB: PUL scoring

Key inclusion criteria

- **Age: 10 years or older**
- **Non-ambulant or late ambulant (10MWT>10S)**
- **PUL entry item score 2-5 (loss of full overhead reach but retained hand-to-mouth function)**

HOPE-2 DB+OLE: PUL scoring

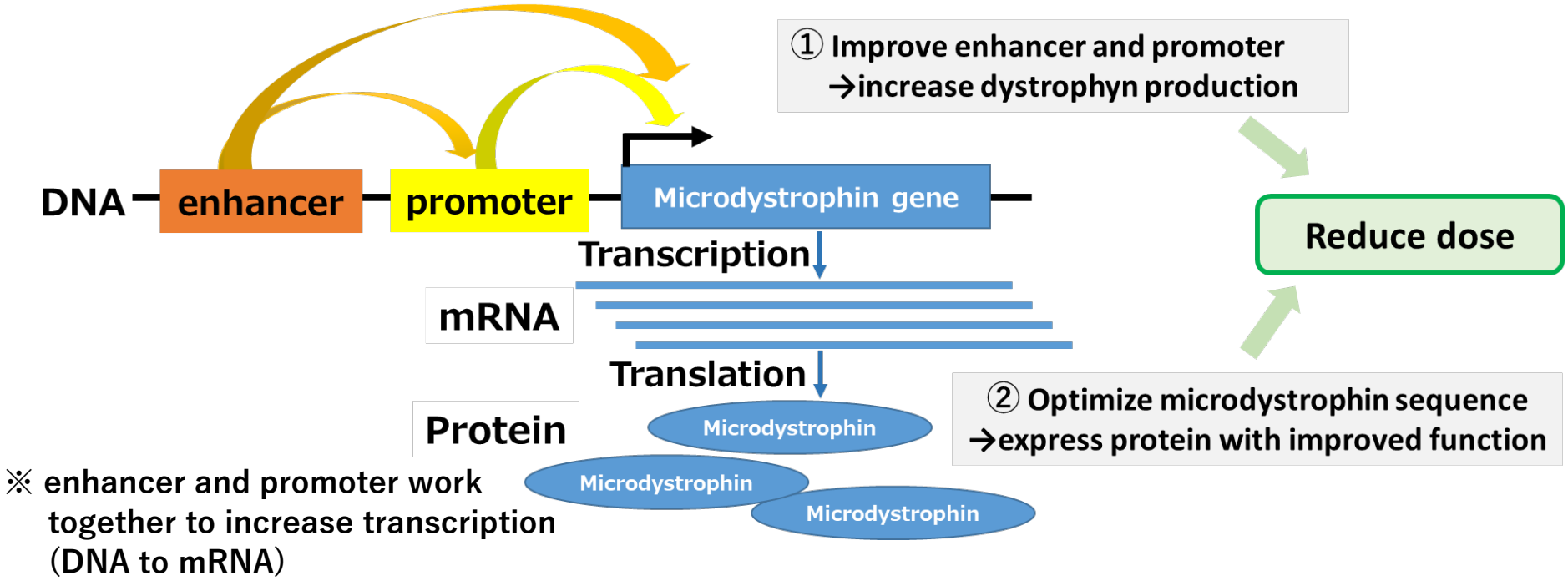
Duration of treatment

- **DB Phase: CAP-1002 or placebo was given once every 3 months for 4 doses**
- **Gap Phase: Off treatment due to COVID-19 pandemic**
- **OLE Phase: CAP-1002 was given once every 3 months for 2 years**

As a result, CAP-1002 slowed decline of upper limb function for long period of time.

Gene therapy (our activity)

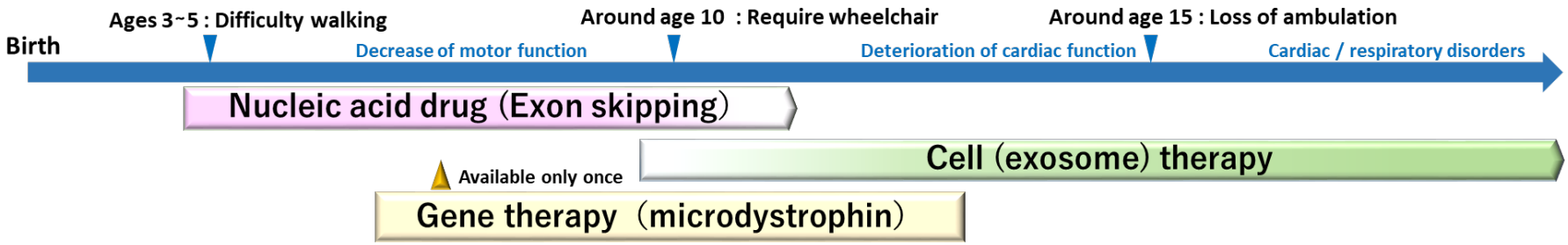
Challenges of microdystrophin products: Serious adverse events associated with high-dose and systemic administration



Concept: Microdystrophin gene therapy with equivalent or higher efficacy and higher safety profile than developing drug.

Position within the three treatments

	Advantage	Disadvantage
Nucleic acid drug (Exon skipping)	・Multiple doses are possible ・Long-term safety and efficacy data are available	・Target patients are limited ・Therapeutic effects only towards skeletal muscle
Cell (exosome) therapy	・Potentially effective not only for skeletal muscle, but also for the heart ・Can improve upper limb function in patients who are non-ambulant	・Effect towards ambulant patients have not been examined. ・Difficulty in cell specification and distribution
Gene therapy (microdystrophin)	・Potentially effective not only for skeletal muscle but also for the heart ・May be available to DMD patient who is not amenable to exon skipping.	・High and systemic dose resulting to immunotoxicity ・Currently difficult to administer multiple doses. ・Not clear whether short-chain dystrophin adequately improves motor function



We believe that there is an optimal combination of treatments depending on the patient's genetic background, medical (health) condition and timing.

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R&D Meeting

December 15, 2022

Presentation

Moderator: I will now introduce today's speakers. From the left, Toru Nakai, President.

Nakai: Hello. Thank you.

Moderator: Kazuchika Takagaki, Director, Research and Development.

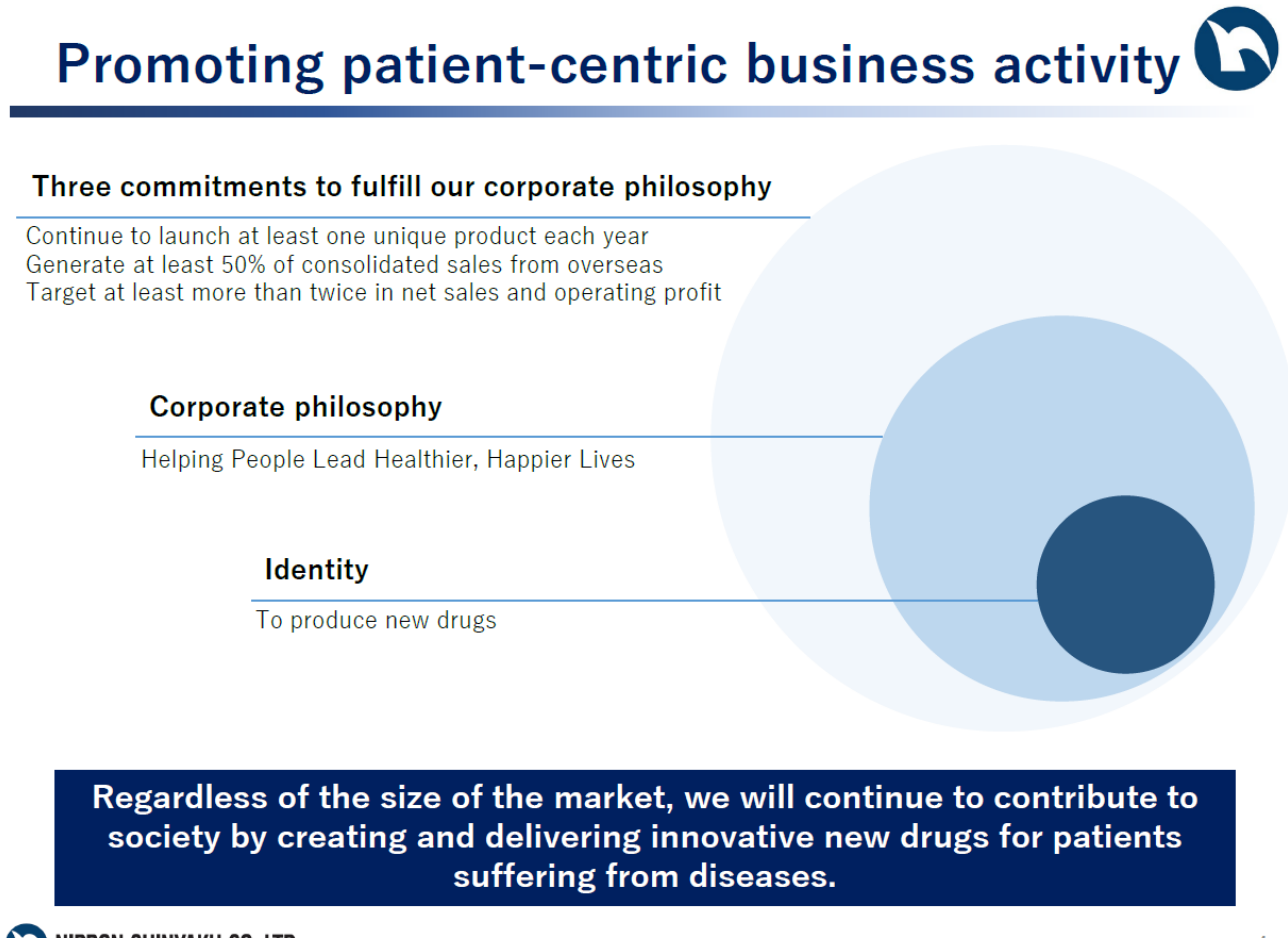
Takagaki: Hello. Thank you.

Moderator: Takanori Edamitsu, Director, Business Management and Sustainability.

Edamitsu: Hello. Thank you.

Moderator: I will now hand over to the president to begin the presentation.

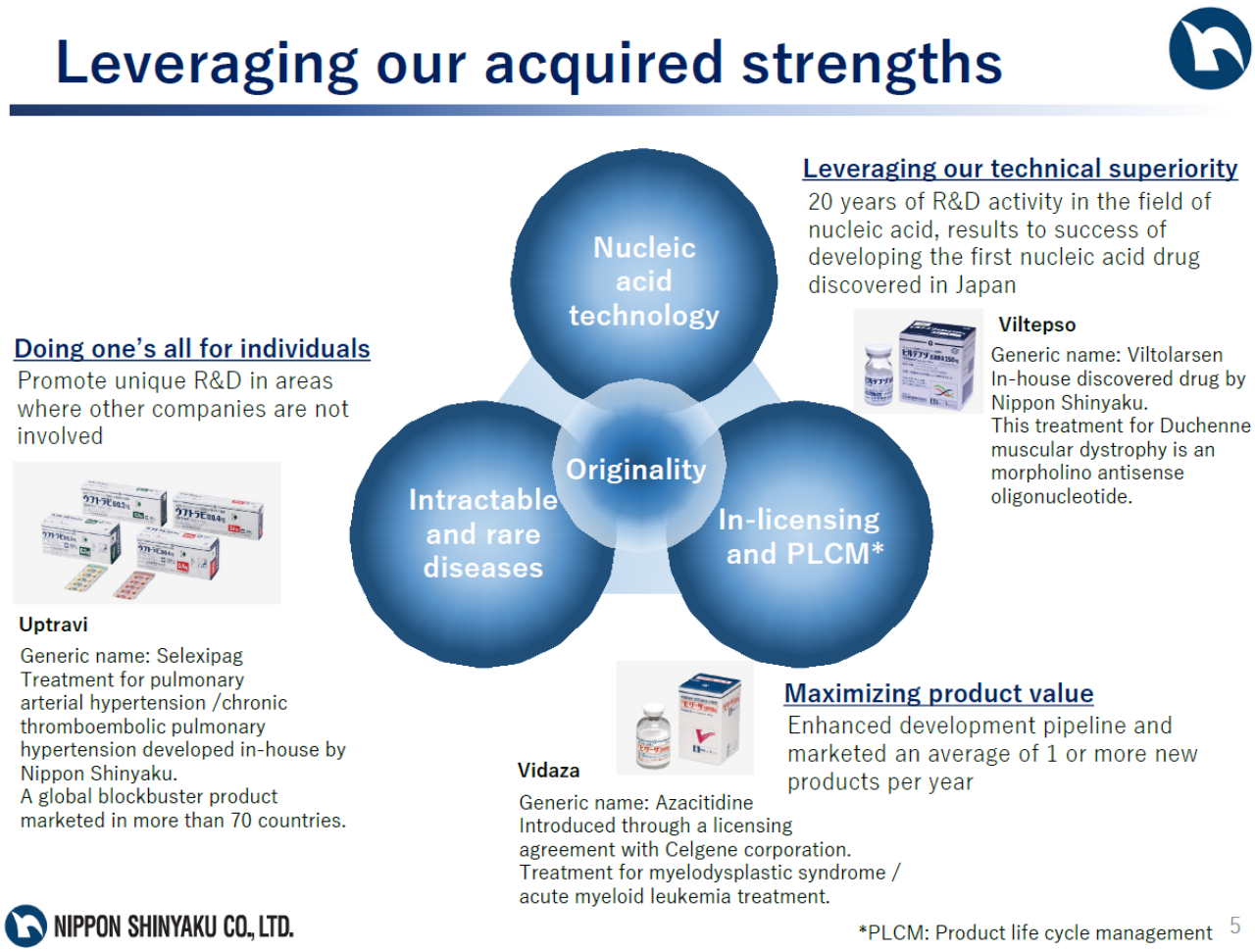
Nakai: My name is Toru Nakai, President of Nippon Shinyaku.



First, let me explain Nippon Shinyaku's R&D strategy.

Since our company was established, our identity has been to create new medicines. To us, that means we are pursuing our corporate philosophy, which is Helping People Lead Healthier, Happier Lives through the provision of high quality and distinctive products.

To this end, all of our employees have the desire to put patients and their families first and foremost. We will promote research and development to create as many products as possible and as soon as possible. Our goal is to help each and every patient who is suffering from a disease to get the appropriate treatment, regardless of the size of the market. As a result, we hope to achieve to continue to launch an average of at least one unique product each year.

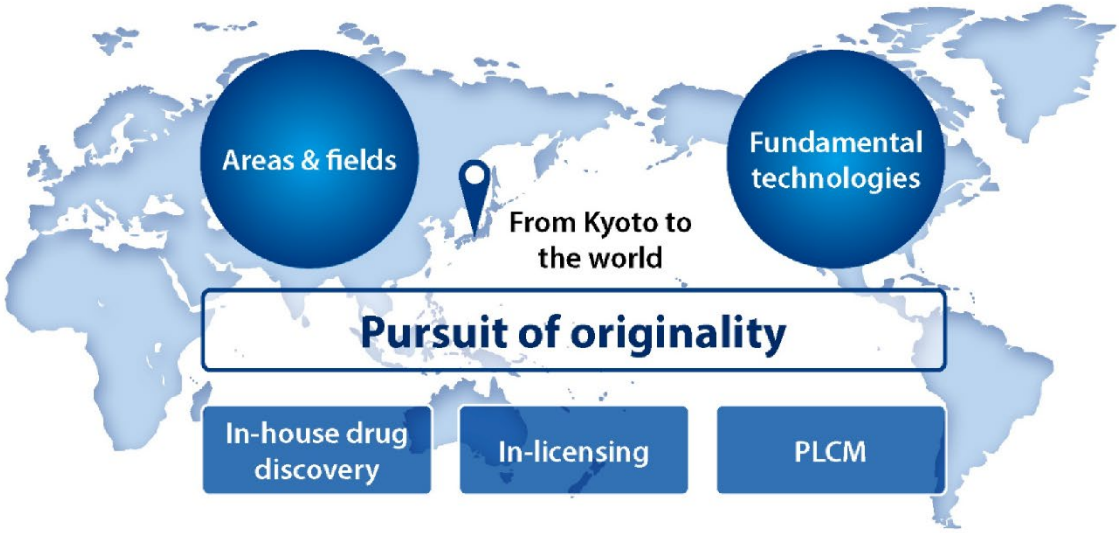


For more than 100 years, we have been engaged in the creation of distinctive drugs as a research-based pharmaceutical company.

We believe that we have a number of strengths, which we have built up over the years. One is our technological superiority in nucleic acid technology, which we have been working on for more than 20 years. Another is our spirit of challenge in actively tackling therapeutic areas and diseases that other companies are not working on. Another strength is our efforts in in-licensing activities and product life cycle management to maximize the value of our products.

We will continue to engage in research and development in pursuit of originality by making the most of the strengths we have built up.

R&D Strategy



We aim to become a company with a meaningful existence in the global healthcare field.

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Our R&D strategy is to promote research and development with a sense of urgency in our four focus therapeutic areas of urology, hematology, intractable and rare diseases, and gynecology. Our approach is based on the three pillars of in-house drug discovery, in-licensing, and product lifecycle management.

In addition, we will continue to develop and promote our business in the US, Europe, China, and other regions in order to develop globally needed drugs and provide them to patients, aiming to become a company with a meaningful existence in the global healthcare field.

Today, Mr. Takagaki will explain our specific R&D activities centered on nucleic acid technology, which is indispensable for us to become a meaningful existence in the global healthcare field.

Takagaki: Hello, I am Takagaki, Director, Research and Development.

Our approach to research and development is to continuously create highly unique and distinctive new drugs to be used worldwide.

With an eye to speeding up the development process and increasing the probability of success, we are conducting research to expand our pipeline through continuously creating distinctive research themes. We will proceed using three approaches: Strategy for Therapeutic Focus Area, Strategy for Modality, and Open Innovation.

Progress of nucleic acid DMD pipeline

Program	Target	% of DMD patients	Pre clinical	PI	PI／II	PII	PIII	Launch
NS-065/NCNP-01 (Viltolarsen)	Exon 53	8%					PIII in progress	
NS-089/NCNP-02	Exon 44	6%						
NS-050/NCNP-03	Exon 50	4%						
NS-051/NCNP-04	Exon 51	13%						
Exon 45 Skipping	Exon 45	8%						
Exon 55 Skipping	Exon 55	2%						

Nippon Shinyaku owned DMD pipeline can cover approximately 40% of all DMD patients

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Here is our DMD pipeline.

We have viltolarsen, NS-065, targeting exon 53, NS-089 targeting exon 44, NS-050 targeting exon 50, NS-051 targeting exon 51 and exon 45 and exon 55 skipping agents.

The percentage of DMD patients covered by viltolarsen is 8%, by exon 44 is 6%, by exon 50 is 4%, by exon 51 is 13%, by exon 45 is 8%, and by exon 55 is 2%. We will be able to cover about 40% of all DMD patients with our DMD pipeline.

Later on, we will explain the progress of each compound.

Progress of nucleic acid product (NS-065/NCNP-01)

Study No.	Study Description	Estimated primary completion date*
Study 202 (Long-term study from P2 study (Study 201))	P2, open Week 217, 16 patients	**Complete** 2021/11
Study 502 (Registry from Study 202).	Long-term follow-up 10 years, ~16 cases	2032/9
Study 301-RACER53 (Global P3 Study)	P3, double-blind, placebo-controlled 48 weeks, 74 patients, 4-7 years	2024/12
Study 302-RACER53-X (Long-term study from Study 301)	P3, open 2 years	2026/6
Study 211-Galactic53 (advanced cases)	P2, open 48 weeks, 20 patients, 8 years or older ambulatory (8 patients)/non-ambulatory (12 patients).	2023/8

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*Primary Completion Date on ClinicalTrials.gov

First, I would like to explain the current progress of NS-065, viltolarsen.

At the top is Study 202, an extension study of Phase II study. This was completed in November 2021. The results will be presented later on.

We also have Study 502, an extension study from Study 202. This is a long-term follow-up study for 10 years.

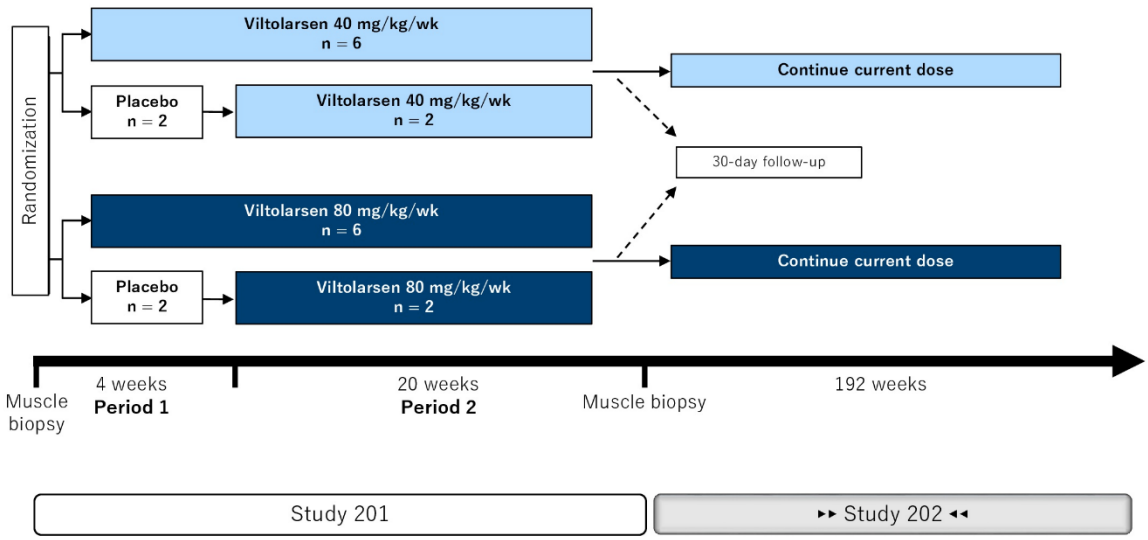
The next is Study 301, which is a Phase III randomized, double-blind, placebo-controlled study. The duration is 48 weeks, with 74 patients aged four to seven years. All patients have registered, and the trial is currently progressing well.

Next is Study 302, an extension Study of Study 301.

At the bottom of the list is Study 211, which is a study in advanced cases. In addition to ambulatory patients, the study includes a certain number of non-ambulatory patients.

NS-065/NCNP-01　Phase 2 Extension Study

【Study Design of Study 201 and 202】



*wk, week.

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Now, I would like to continue with clinical study updates.

First, I would like to explain the results of the Phase II extension study of NS-065, viltolarsen.

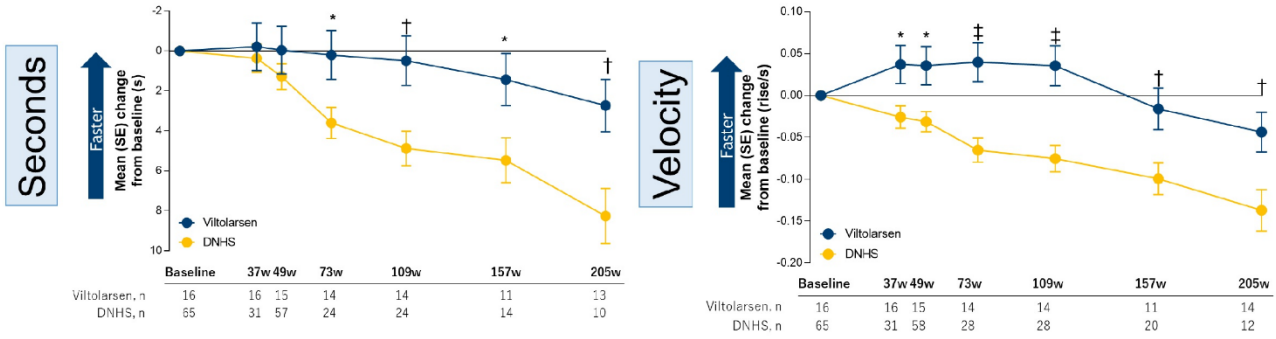
Here is a description of the design of Study 201 and Study 202.

In Study 201, viltolarsen at 40 mg/kg and 80 mg/kg was administered. Initially, some patients received placebo for 4 weeks. After confirming safety, patients on placebo also received 40 mg/kg or 80 mg/kg of viltolarsen. This is Study 201.

I will like to introduce the results of Study 202, the extension study of Study 201, which was conducted for 192 weeks, little past four years.

NS-065/NCNP-01　Phase 2 Extension Study

【TTSTAND CFB vs Natural History Controls】



*P<0.05; †P<0.01; ‡P≤0.001.
CFB, change from baseline; DNHS, Duchenne Natural History Study（DMD natural history control group）;
s, seconds; SE, standard error; TTSTAND, time to stand from supine; w, weeks.

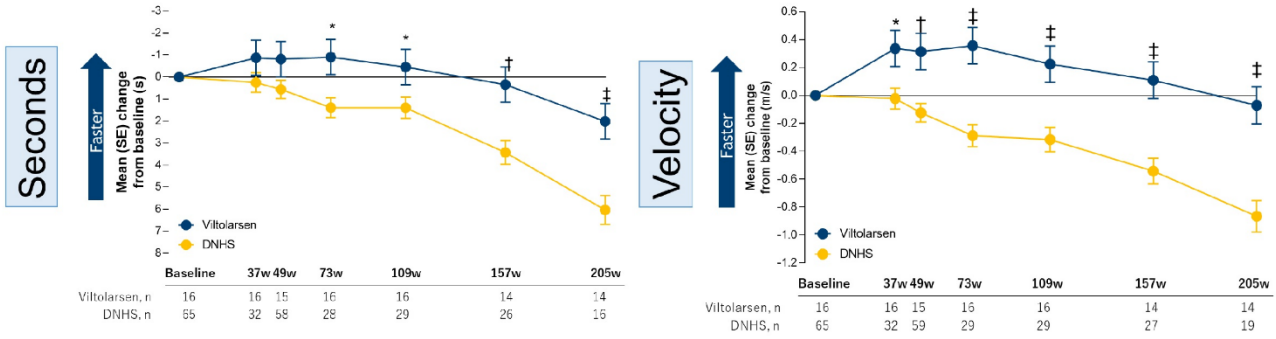
This slide shows the motor function results over the four-year period.

The blue line is for the group that received viltolarsen, and the yellow line represents natural history data of DMD patients. This is a test of time to stand from supine, with seconds on the left side and speed on the right side, showing the same data in seconds and speed.

As you can see, there was a slight improvement for about two years, and then coming up to the four-year point, a maintenance trend or a slight decline was observed, but, patients treated with viltolarsen showed a trend of maintenance compared to the natural history data.

NS-065/NCNP-01　Phase 2 Extension Study

【TTRW CFB vs Natural History Controls】



	Baseline	37w	49w	73w	109w	157w	205w
Viltolarsen, n	16	16	15	16	16	14	14
DNHS, n	65	32	58	28	29	26	16

	Baseline	37w	49w	73w	109w	157w	205w
Viltolarsen, n	16	16	15	16	16	14	14
DNHS, n	65	32	59	29	29	27	19

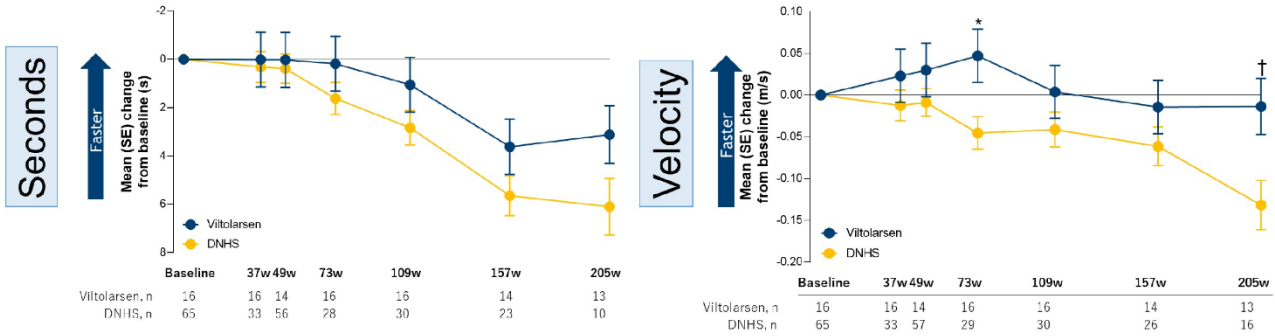
*P<0.05; †P<0.01; ‡P≤0.001.
CFB, change from baseline; DNHS, Duchenne Natural History Study（DMD natural history control group）;
s, seconds; SE, standard error; TTRW, time to run/walk 10 meters; w, weeks.

Next is a study for time to run/walk 10 meters.

The left side shows seconds, and the right side shows speed, which is still the same data described in a different way. The upper blue line is the viltolarsen group and the lower yellow line is the natural history data of DMD patients.

NS-065/NCNP-01　Phase 2 Extension Study

【TTCLIMB CFB vs Natural History Controls】



*P<0.05; †P<0.01; ‡P≤0.001.
CFB, change from baseline; DNHS, Duchenne Natural History Study（DMD natural history control group）;
s, seconds; SE, standard error; TTCLIMB, time to climb 4 stairs; w, weeks.

The next slide is data from a study of time to climb four stairs.

The left side shows seconds, and the right side shows velocity, both of which also showed improvement followed by maintenance in the viltolarsen group.

NS-065/NCNP-01　Phase 2 Extension Study

【 Safety Assessment / Common TEAEs (Preferred Term in ≥25% of Participants)】

	Viltolarsen participants		
Participants with:	40 mg/kg/wk (n = 8)	80 mg/kg/wk (n = 8)	Total (N = 16)
Any TEAE, n (%)	8 (100)	8 (100)	16 (100)
Any drug-related TEAE, n (%)	0	1 (13)	1 (6)
Any serious treatment-related AE, n (%)	0	0	0
Study drug discontinuation due to TEAE, n (%)	0	0	0
Death, n (%)	0	0	0
	Viltolarsen participants		
TEAEs (Preferred Term in ≥25% of Participants)	40 mg/kg/wk (n = 8)	80 mg/kg/wk (n = 8)	80 mg/kg/wk (n = 8)
Cough, n (%)	5 (63)	5 (63)	10 (63)
Nasopharyngitis, n (%)	4 (50)	5 (63)	9 (56)
Insect bite, n (%)	4 (50)	2 (25)	6 (38)
Rash, n (%)	2 (25)	4 (50)	6 (38)
Vomiting, n (%)	3 (38)	3 (38)	6 (38)
Fever, n (%)	2 (25)	3 (38)	5 (31)
Fall, n (%)	4 (50)	1 (13)	5 (31)
Headache, n (%)	3 (38)	2 (25)	5 (31)
Nasal congestion, n (%)	3 (38)	2 (25)	5 (31)
Influenza, n (%)	3 (38)	1 (13)	4 (25)

- The most frequently reported TEAEs (reported by ≥25% of participants) were cough and nasopharyngitis.

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These are adverse events of phase II extension study.

There have been eight cases reporting adverse events receiving the 40 mg/kg dose and eight cases on the 80 mg/kg dose. However, there was only one case reporting adverse events related to the drug receiving the 80 mg/kg dose.

In this one case, the adverse event was blood leakage from the blood vessel when the drug was administered. The most common adverse events in this study were cough and nasopharyngitis.

Conclusion

- Participants treated with viltolarsen for an additional 192 weeks (up to 216 weeks or 4 years) showed maintenance of function over the first 2 years and significantly delayed disease progression over the following 2 years in timed function tests compared with CINRG DNHS controls, which declined over this same time period.
- Viltolarsen was well tolerated over 192 weeks, with most reported TEAEs being mild or moderate; with no study drug discontinuations or deaths reported.
- Viltolarsen should be considered an important part of the treatment strategy for patients with DMD who are amenable to exon 53 skipping.

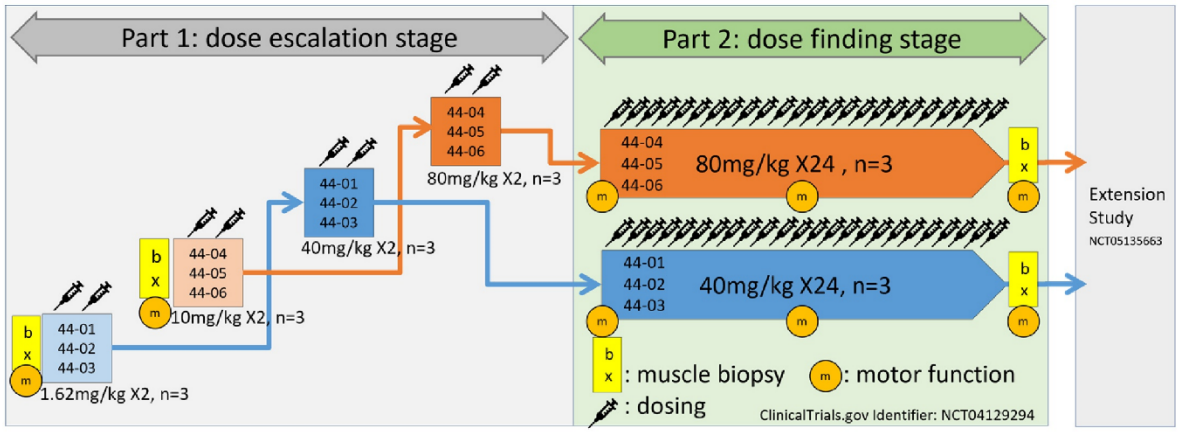
This is a summary of Phase II extension study.

When comparing patients receiving viltolarsen and natural history data of DMD patients, patients treated with viltolarsen showed maintenance of motor function over the first two years and showed a trend of delaying disease progression during the following two years.

Viltolarsen was well tolerated over 192 weeks, with most reported adverse events being mild or moderate; with no study drug discontinuations or death reported.

This study shows that viltolarsen should be considered as an important treatment for DMD patients amenable to exon 53 skipping.

NS-089/NCNP-02
Study design of Phase 1/2 Study （First-in-human, Open label study）



MDA, March 2022

Key inclusion Criteria
- Age : 4-17 years
- Ambulant
- Amenable to exon 44 skipping

Primary Objectives
- Safety and tolerability

Secondary Objectives
- Dystrophin protein expression
- Motor function assessments*
- Exon 44 skipping levels
- Pharmacokinetics
- Serum CK levels
- In vitro assays

＊Motor function assessments : NSAA (North Star Ambulatory Assessment), TTSTD (Time to stand from supine), TTRW (10-meter walk), 6MWT (6-minute walk), 2MWT (2-minute walk), TUG (Timed Up and Go), PUL (Performance of Upper Limb), Muscle strength assessment

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Next, I would like to talk about the results of the investigator-initiated clinical study for NS-089/NCNP-02.

This is an investigator-initiated clinical study conducted by the National Center of Neurology and Psychiatry, NCNP.

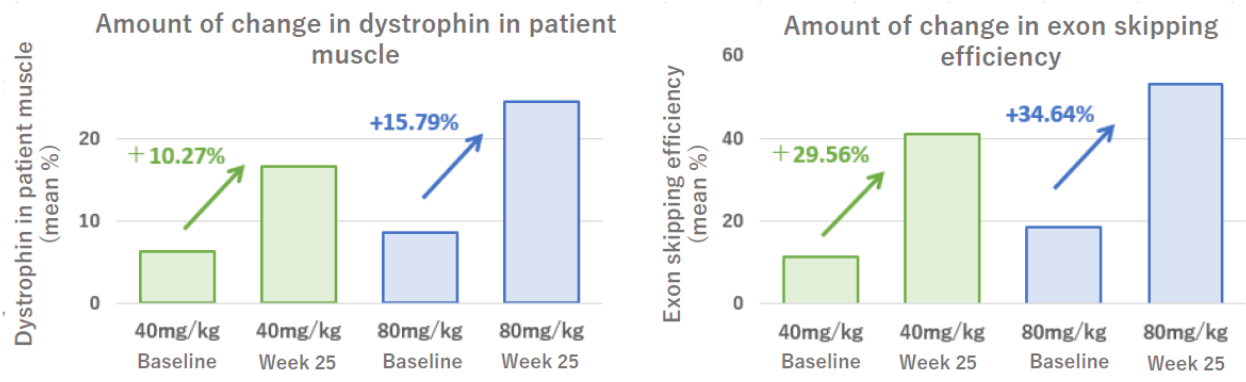
First, here is a design of the clinical study.

The left side is part one, the dose escalation part. The dose gradually increased from 1.62 mg/kg to 40 mg/kg or even 80 mg/kg.

In part two, the same dose, 40 mg/kg, or 80 mg/kg was administered.

After part two, we are currently conducting an extension study.

NS-089/NCNP-02
Study design of Phase 1/2 Study （First-in-human, Open label study)



MDA, March 2022

	Mean change from baseline in dystrophin expression %（SD)	Mean change from baseline in exon skipping efficiency %（SD)
40mg/kg(n=3)	10.27 (1.88)	29.56 (8.77)
80mg/kg(n=3)	15.79 (6.44)	34.64 (9.56)
Mean(%)	13.03 (5.21)	32.10 (8.71)

- After 24 weeks of 6 cases tested, a significant increase of dystrophin expression and exon skipping efficiency from baseline were observed. Also, NS-089/NCNP-02 was safe and well tolerated.
- Function assessment in the dose finding stage show a tendency of recovery and increase in motor function.
- The limitations of this study include the small number of participants and lack of placebo control arm, thus the observed effectiveness of NS-089/NCNP-02 in inducing endogenous dystrophin expression and stabilization of motor function needs further verification.

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These are the results of muscle biopsy after part two.

As for the mean change from baseline in dystrophin expression, a 10.27% increase of protein expression in the 40 mg/kg group and a 15.79% increase in the 80 mg/kg group were observed.

Patients amenable to exon 44 skipping had a rather high baseline, but even from there, we saw a large increase in protein expression. Since the average protein expression of viltolarsen was about 5%, NS-089 induces a considerably greater protein expression.

Next, the right side shows the mean change from baseline in exon skipping efficiency. An increase in exon skipping efficiency of 29.56% in the 40 mg/kg group and 34.64% in the 80 mg/kg group were observed.

This investigator-initiated clinical trial indicated a significant increase of dystrophin expression and exon skipping efficiency in six patients during the 24-week treatment period. In addition, NS-089/NCNP-02 was safe and well tolerated.

In part two, we have seen a trend of maintenance and improvement in motor function, albeit for a short period of time.

Since the number of cases in this study was only six, it was not a placebo-controlled study, and the duration for testing motor function was short, we believe that further investigation of efficacy of the drug is necessary.

Status of developing DMD pipelines

	Development stage	Contents
NS-065/ NCNP-01	Approved in Japan and US P3 study in progress	● P3 study, Study 502 (long-term follow-up study), and Study 211 (study in ambulant and non-ambulant boys with DMD) in progress.
NS-089/ NCNP-02	Preparation for P2 study in Japan and US	● Investigator-initiated clinical trial in Japan has been completed, and an extension study is ongoing. ● Throughout discussion with the FDA to begin P2 study in Japan and the United States, FDA commented on the result of nonclinical safety study and asked for a third-party expert meeting. During this year, a meeting with a third-party expert is expected to be completed and by the end of this fiscal year, we will renegotiate with the FDA.
NS-050/ NCNP-03	Preparation for P1/2 study in Japan and US	● Throughout discussion with the FDA to begin P1/2 study in Japan and the US, FDA requested an additional genotoxicity study to be conducted, which we are currently proceeding. We expect genotoxicity study to be completed during this fiscal year and submit results to the FDA.
NS-051/ NCNP-04	Preparation for P1/2 study in Japan and US	● We are currently discussing with PMDA, to initiate clinical study. We are also planning to have pre-IND meeting with the FDA, within this fiscal year.
Exon 45 skipping	Preclinical	● We have selected candidate sequeces and nonclinical studies are underway.
Exon 55 skipping	Preclinical	● We have selected candidate sequeces and nonclinical studies are underway.

Next, is the status of developing DMD pipelines.

NS-065 or viltolarsen is approved in Japan and the US and are now undergoing Phase III trials.

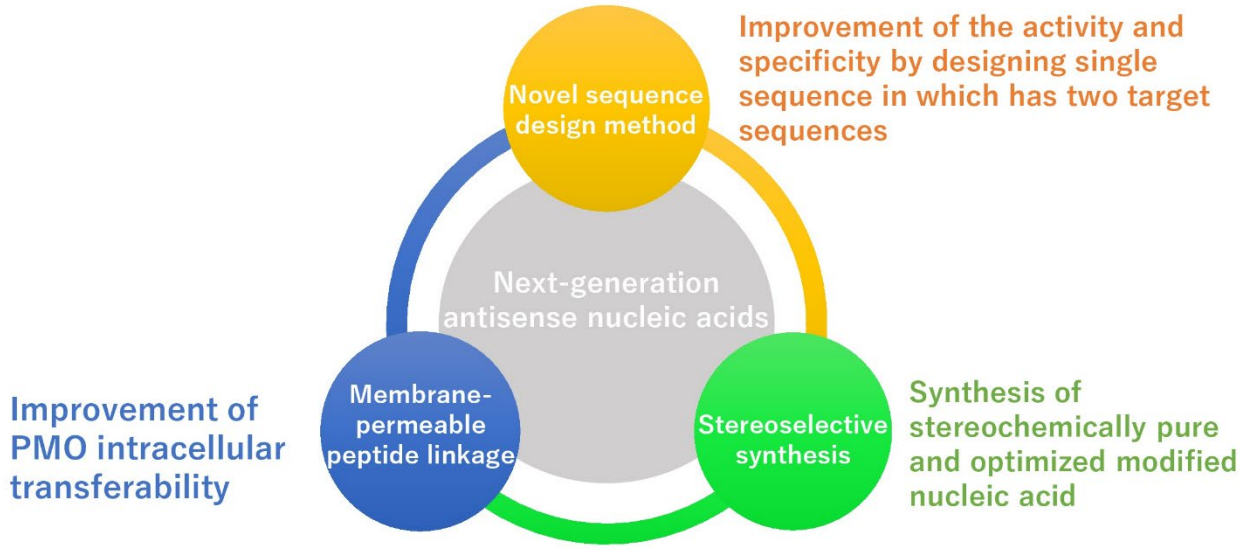
Regarding NS-089, investigator-initiated clinical trial in Japan have been completed and we are now conducting an extension study. Furthermore, we are now in discussion with the FDA to start Phase II trials in Japan and the US. The FDA has commented on the results of the non-clinical safety study and requested a meeting of third-party experts to be held. During this year, a meeting with a third-party expert is expected to be completed, and by the end of this fiscal year, we will renegotiate to reach agreement with the FDA to start clinical trials in beginning of the next fiscal year.

Next, regarding NS-050, we are now in discussion with the FDA with the intention of starting a phase I/II study in Japan and the US. Here, an additional genotoxicity study was requested to be conducted although we think there was no risk of genotoxicity according to the ICH guideline. However, the FDA requested that we conduct an additional study. The request was not in accordance with the ICH guideline. We are currently conducting this study and expect to have an agreement with the FDA by the end of this fiscal year and start clinical trials next fiscal year.

Regarding NS-051, negotiations are underway with the PMDA and the FDA for the initiation of clinical study. We plan to have pre-IND by the end of this fiscal year.

For exons 45 and 55 skipping, we have selected candidate sequences, and we are currently conducting non-clinical studies.

Development of next-generation antisense nucleic acids



Next generation antisense nucleic acids can improve distribution, efficacy (persistence and activity), safety, and physical properties compared to current antisense nucleic acids. This expands the application of nucleic acid drug to other diseases.

Next, I would like to talk about the next-generation technology.

As for next-generation antisense nucleic acids, we are promoting the three approaches shown here.

One is a novel sequence design method, in which a single sequence recognizes two target sequences to improve activity and specificity.

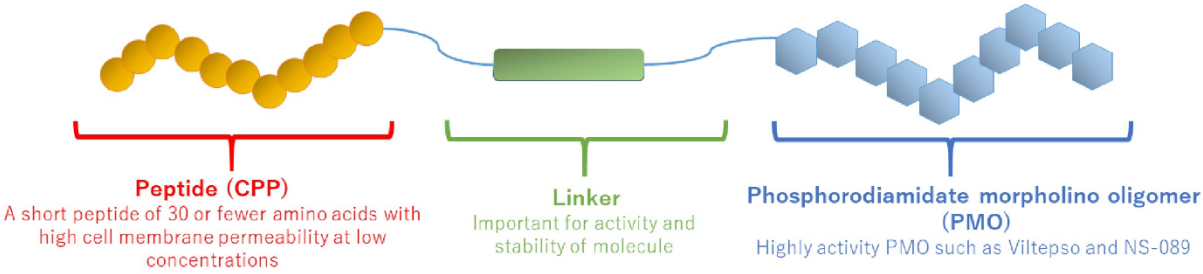
Next is stereoselective synthesis, which synthesizes stereochemically pure and optimized modified nucleic acids.

The third is a linkage of membrane-permeable peptides, called PPMO, which improves the intracellular translocation of PMO.

This approach can improve distribution, efficacy, persistence and activity, safety, and physical properties compared to current antisense nucleic acids. We believe that this will improve the current PMO characteristics, make the current application more effective, and not only that but also expand the application of nucleic acid medicine to other diseases.

Peptide-conjugated nucleic acid

PPMO（Peptide-conjugated phosphorodiamidate morpholino oligomer）



Peptide (CPP)
A short peptide of 30 or fewer amino acids with high cell membrane permeability at low concentrations

Linker
Important for activity and stability of molecule

Phosphorodiamidate morpholino oligomer (PMO)
Highly activity PMO such as Viltepso and NS-089

We are developing PPMO in which CPP is bound to morpholino nucleic acid as DDS technology to improve the pharmacokinetics of nucleic acid drugs by enhanced cell membrane permeability. As a result, we aim to improve the drug efficacy and reduce the frequency of administration using PPMO.

Selection of optimal peptide (Completed) → Optimize linker (Completed) → Highly active PMO sequence (Selected) → Selection of PPMO candidate (Completed) → Pre-clinical Studies (In progress)

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Firstly, I would like to start off with an explanation of peptide-conjugated nucleic acid.

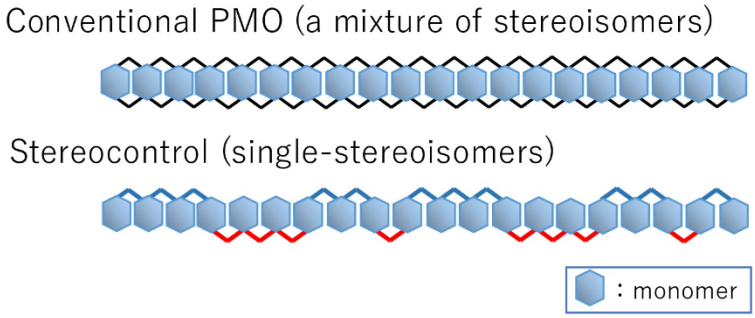
This is a membrane-permeable peptide, linked with a morpholino nucleic acid.

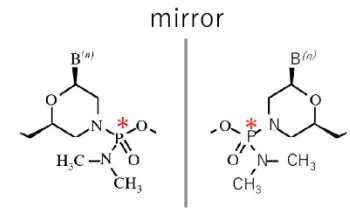
We are now realizing that the stability of PPMO is considerably influenced by not only the peptide and morpholino nucleic acid but also the linker written in the middle.

We have selected the optimal peptide, optimized the linker, and selected a highly active nucleic acid sequence. In this way, we have identified the PPMO candidate. We are currently conducting non-clinical studies and expect to be able to report back in due course.

As I mentioned earlier, we believe that the addition of membrane-permeable peptides will improve the permeability and pharmacokinetics of the drug, thereby increasing its efficacy and reducing the frequency of administration.

Stereoselective synthesis





Monomer has chirality and PMO is a mixture of stereoisomer.

Stereocontrolled synthesis of optimized modified nucleic acids create new added value (such as improvement of physical properties and activity)

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The next step is stereoselective synthesis.

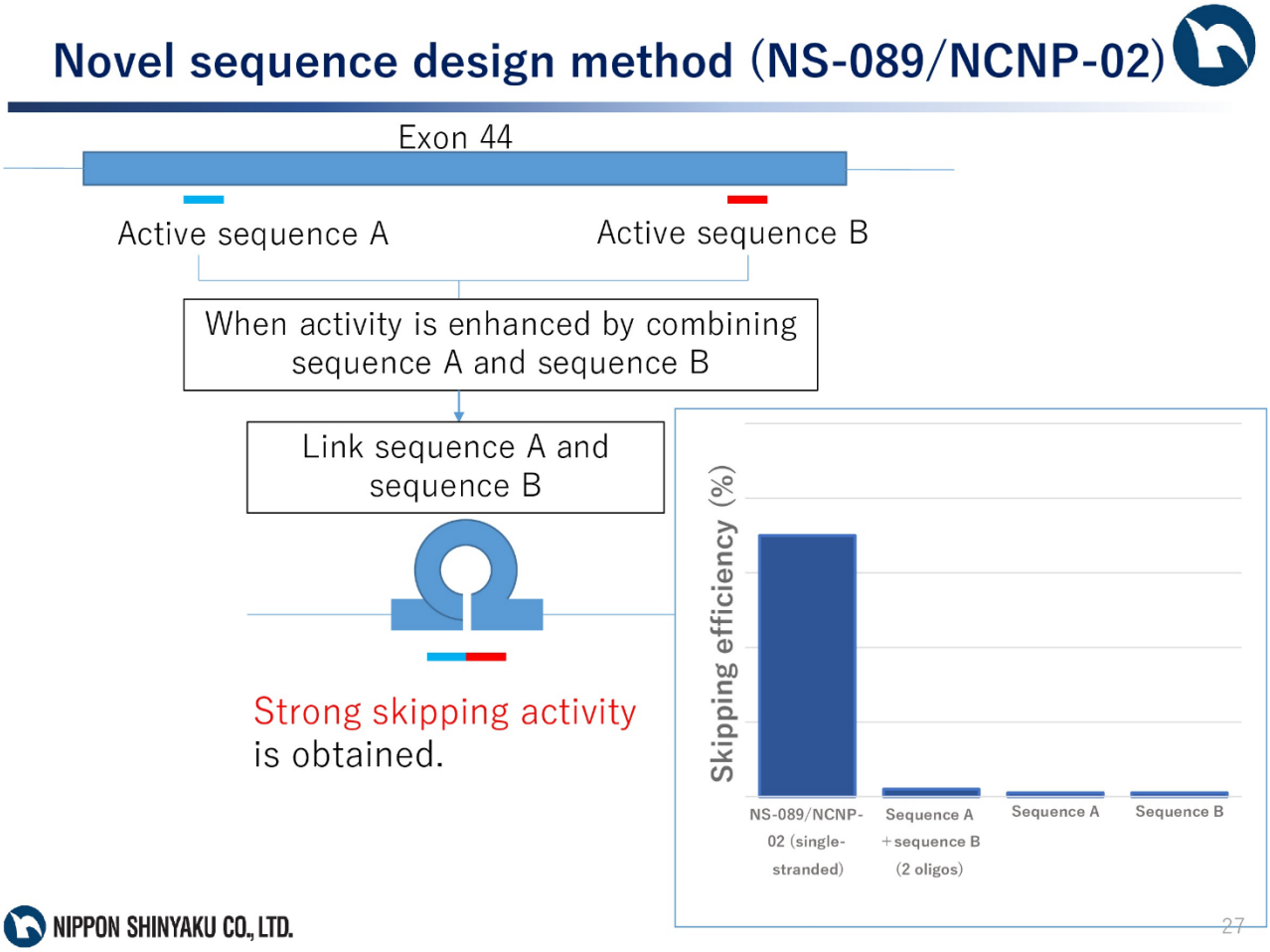
In this figure, “P”, the phosphorus with the red dot has a chiral center. It is just like a right-handed and left-handed relationship. However, the two molecules are different sterically.

In PMO, there are 20 linkages of the phosphate moiety for 21 monomers: it is an N-1 relationship. In the case of 21 monomers, there are 2 to the 20th power variations in the steric structure.

We believe that by separating these nucleic acids, it will be possible to create a single, chemically optimized nucleic acid that is a pure product, rather than a mixture of nucleic acids with disparate steric structures that have been produced in the past.

We believe that this will enable us to achieve new added value, improved physical properties, and increased activity.

The current progress, as noted below, is that we are now able to synthesize these stereoselective PMOs. We have conducted several studies and have confirmed improvement in physical properties and activity. Now that we have done this with one sequence, we are changing the sequence to another to check the reproducibility and regularity of the sequence. After this, we would like to decide a candidate for stereocontrolled PMO and proceed to non-clinical studies.



NS-089 is an example of our new sequence design method.

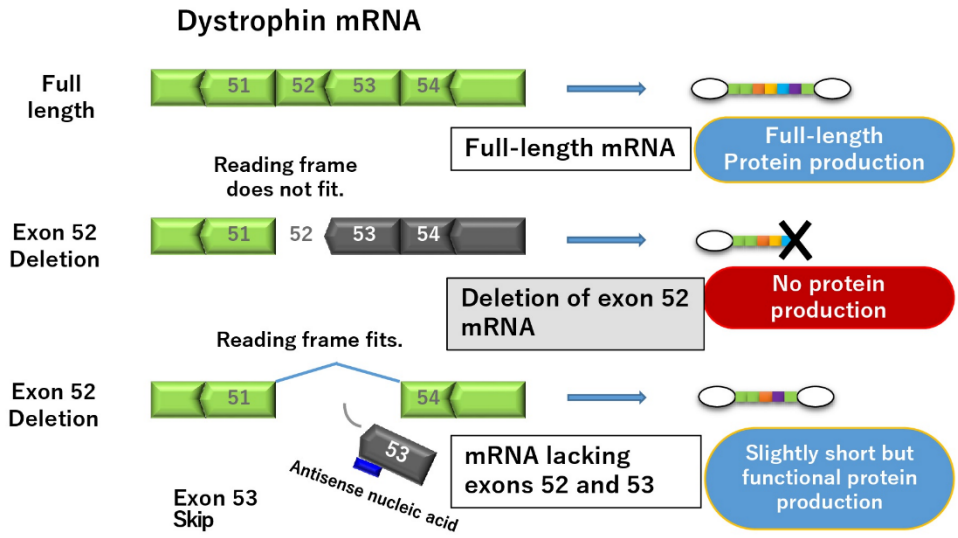
A single antisense oligo binding to a single target sequence in exon 44 is usually selected. In the case of NS-089, there were two target sequences or regions in exon 44 that caused activity, so we designed two antisense oligos for these target sequences and linked these oligos together.

As you all know, nucleic acids must be of a certain length to bind to each other, so if we design and combine sequences that bind to each of these target sites, as a result, the combined sequence becomes very long. We found that even if the active sequences A and B are shortened to the point that they are not active on their own, by combining these short sequences, we can obtain a strong activity that cannot be obtained with a single sequence.

This principle was used in NS-089. We have applied this design method to other compounds targeting exon 51.

The graph on the right side shows that sequences A and B are not active by themselves. Even a mixture of the two sequences has almost no activity. Though when bound together, they have strong activity.

Nucleic acid drug (exon skipping)



I will continue with a description of various approaches in DMD.

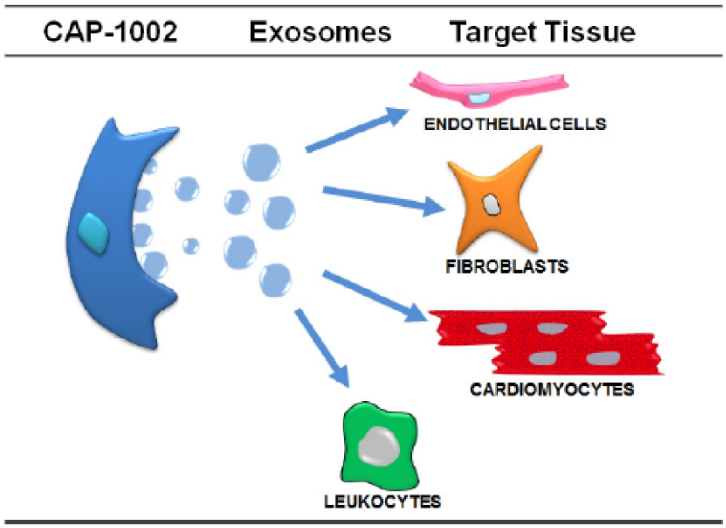
The first is exon skipping with nucleic acid medicine.

I am sure you all know this already, but the picture at the top shows production of full-length proteins. The second is an example of deletion of exon 52, in which the protein reading frame no longer fits, so protein production is no longer possible. The reading frame will be in-frame if it is a multiple of 3. If 53 is also deleted, it will be a multiple of 3, so the reading frames will be in-frame again, and a slightly shorter but still functional protein can be produced.

Treatment by exon 53 skipping is to skip exon 53 by introducing antisense nucleic acid.

Cell therapy CAP-1002

Cardiosphere-derived cell therapeutic.
Exosomes (extracellular vesicles) released from this drug are expected to reduce oxidative stress, inflammation, fibrosis, and increase cell energy and myocyte generation, resulting in reducing deterioration of motor and cardiac functions.

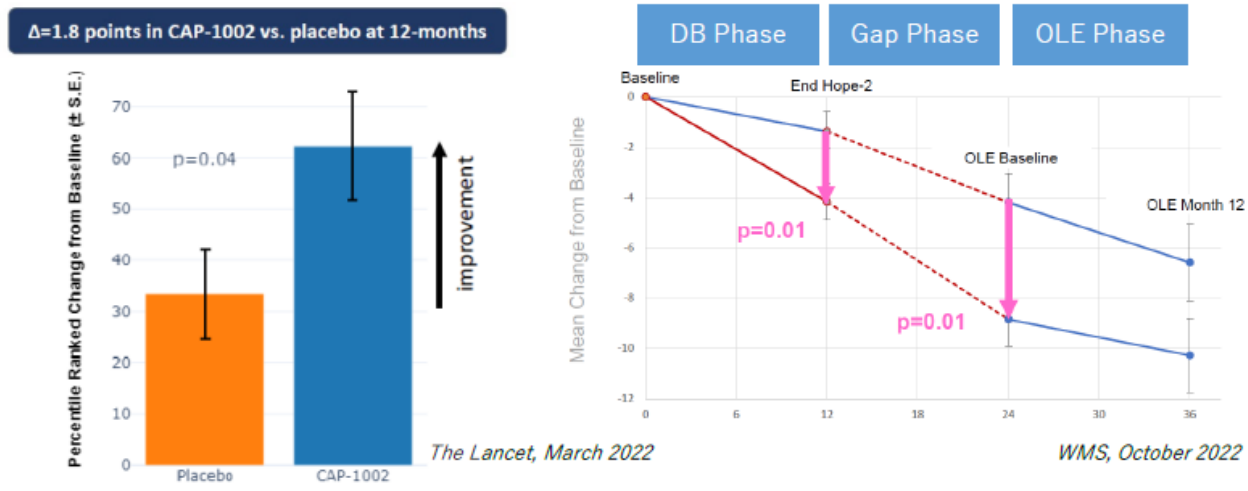


Next, here is an example of cell therapy CAP-1002.

This is a cardiosphere-derived cell therapy. Exosomes or extracellular vesicles released from CAP-1002 are expected to reduce oxidative stress, inflammation, fibrosis, and increase cell energy and myocyte generation, resulting in reducing deterioration of motor and cardiac function.

As you can see in the picture, we believe that exosomes are released and act on endothelial cells, fibroblasts, cardiomyocytes, leukocytes, and other cells to achieve an overall effect.

Cell therapy CAP-1002:HOPE-2 study + OLE study



HOPE-2 DB: PUL scoring

Key inclusion criteria

- **Age: 10 years or older**
- **Non-ambulant or late ambulant (10MWT>10S)**
- **PUL entry item score 2-5 (loss of full overhead reach but retained hand-to-mouth function)**

HOPE-2 DB+OLE: PUL scoring

Duration of treatment

- **DB Phase: CAP-1002 or placebo was given once every 3 months for 4 doses**
- **Gap Phase: Off treatment due to COVID-19 pandemic**
- **OLE Phase: CAP-1002 was given once every 3 months for 2 years**

As a result, CAP-1002 slowed decline of upper limb function for long period of time.

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This is some of the data from the HOPE-2 Phase II trial. Patients in this study were non-ambulant, so upper limb motor function are evaluated.

The left side bar is a result of placebo group, and the right side bar is a result of CAP-1002 group. A statically significant improvement in upper limb motor function compared to placebo group was observed.

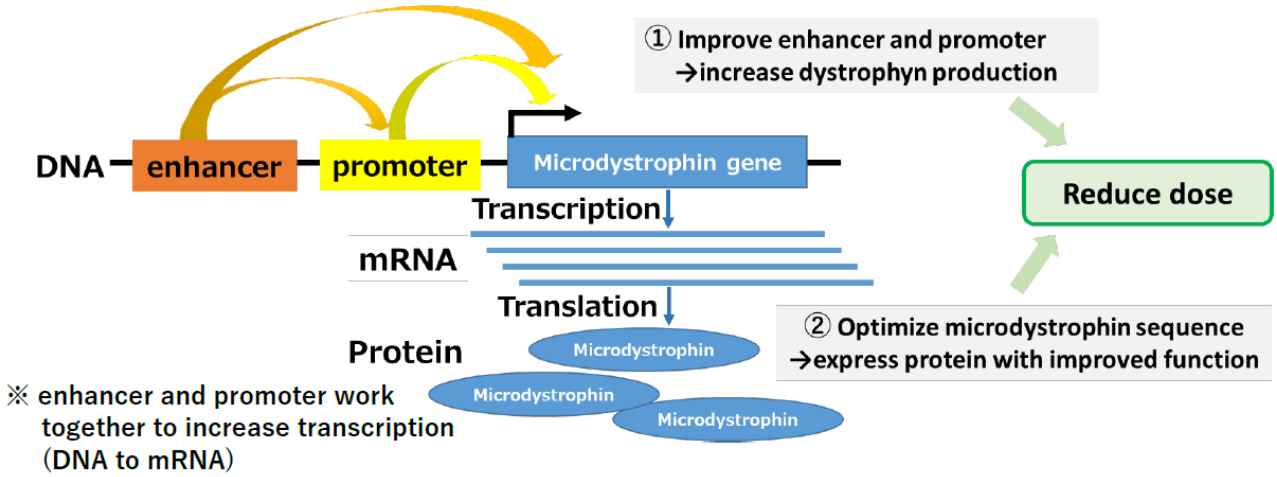
In the chart on the right, the upper blue line shows the CAP-1002 group, and the lower red line shows the placebo group. In the first DB period the dosing is started and a significant difference between CAP-1002 group and placebo group in slowing of disease progression was observed.

The gap period, was a time when the administration was not possible due to the COVID-19 pandemic. Even during this period, the difference between the two groups has not only been maintained but rather widened a bit. Then at the OLE period, the drug was administered to both groups, and in this case, the slope was almost the same, but the initial difference was maintained.

The results show that CAP-1002 delays the decline in upper limb function for a long period of time. A Phase III trial is currently underway.

Gene therapy (our activity)

Challenges of microdystrophin products: Serious adverse events associated with high-dose and systemic administration



Concept: Microdystrophin gene therapy with equivalent or higher efficacy and higher safety profile than developing drug.

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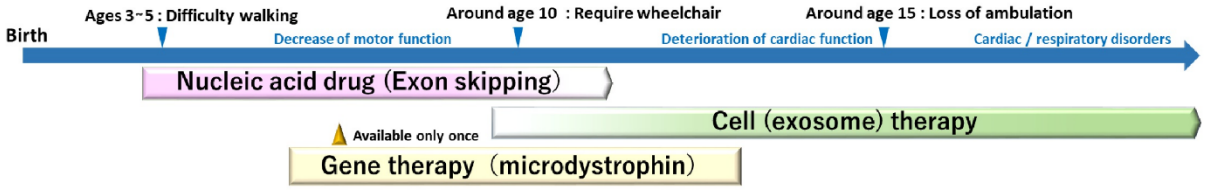
Next is gene therapy. I would like to introduce our company's approach.

We believe that the major issue with the current developing drug of microdystrophin for the treatment of DMD is that it is administered in very high doses and systemically. We consider this very problematic because of the potential for serious adverse safety events.

To remedy this, we will improve enhancer and promoter to increase the dystrophin expression level per vector to achieve a lower dose. Although microdystrophin needs to be shortend less than one-third of its full length of dystrophin, we will also optimize the design of the microdystrophin itself to create a protein with higher functionality, which will also contribute to lower dose. We are now working on a gene therapy that expresses microdystrophin with equivalent or higher efficacy and higher safety profile than the developing drug using both of these approaches.

Position within the three treatments

	Advantage	Disadvantage
Nucleic acid drug (Exon skipping)	・Multiple doses are possible ・Long-term safety and efficacy data are available	・Target patients are limited ・Therapeutic effects only towards skeletal muscle
Cell (exosome) therapy	・Potentially effective not only for skeletal muscle, but also for the heart ・Can improve upper limb function in patients who are non-ambulant	・Effect towards ambulant patients have not been examined. ・Difficulty in cell specification and distribution
Gene therapy (microdystrophin)	・Potentially effective not only for skeletal muscle but also for the heart ・May be available to DMD patient who is not amenable to exon skipping.	・High and systemic dose resulting to immunotoxicity ・Currently difficult to administer multiple doses. ・Not clear whether short-chain dystrophin adequately improves motor function



We believe that there is an optimal combination of treatments depending on the patient's genetic background, medical (health) condition and timing.

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Lastly, we have discussed the position of these three treatments.

Nucleic acid drug, cell (exosome) therapy, and gene therapy (microdystrophin) each have their own advantages and disadvantages, and we believe that the best treatment can be achieved by combining them.

In nucleic acid drug, multiple dosing is possible and required. Availability of long-term safety and efficacy data is an advantage, but one drug targeting a certain exon can only be administered to a certain type of patients. Furthermore, current nucleic acids are only effective toward skeletal muscle and are unlikely to go to cardiac muscle.

In the case of exosome therapy, it goes not only to skeletal muscle, but also to the heart and other organs, leading to unintentional affects in those areas. Data are emerging that upper limb muscle strength can be improved in patients who are non-ambulant. On the other hand, it remains to be seen if it will be effective for ambulatory patients. In addition, since we need to distribute cells, we consider setting specification and distribution of cells to be challenging.

Regarding gene therapy, it may be effective, not only for skeletal muscle but also for cardiac muscle. It is also not exon type-specific, so it has the potential for use in patients other than those amenable to exon skipping. Downsides include immunotoxicity due to high systemic doses and the difficulty in administering multiple doses. Since microdystrophin protein is shortened by less than one-third of dystrophin, we believe that it is unclear whether this type of treatment will adequately restore motor function.

The figure shown at the bottom is a diagram of what an expert in the US thought when we discussed this with him in September.

What he said was that for those who are not eligible for exon skipping, gene therapy is the only way to go for now. However, for patients who are eligible for exon-skipping therapy, initially, the patient has a lot of stem cells or satellite cells, so in that case, it would be a good idea to prevent the patient's muscle cells from being destroyed as much as possible using exon skipping. When those stem cells become scarce, gene therapy may be one option, and it may be a good idea to put microdystrophins in from the outside.

However, in the case of gene therapy, it is theoretically difficult to sustain the effect for a long period of time, so patients may return to exon skipping, or to move to exosome or cell therapy if the patient is no longer ambulatory when the effect of gene therapy wanes.

We believe that after each treatment method is approved, and clinical evidence is accumulated, the optimal treatment will be established based on the patient's genetic background, medical condition, and timing.

That is all.

Thank you very much.