English translation for reference purposes only
In case of any discrepancy, the Japanese version shall prevail

Second Quarter of 2025
Business and Financial report

(TSE：4883)

Modalis therapeutics Corporation

August 7, 2025

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MODALIS

About Modalis

MODALIS Value Highlights

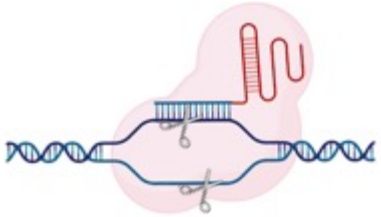
- Established the first robust **epigenetic platform** for activation and inhibition of endogenous genes using CRISPR-GNDM® platform
- Demonstrated sustained modulation of gene expression in multiple species (mouse, cyno) resulting in functional **efficacy without serious toxicities**
- Pipeline of preclinical assets in **muscular dystrophies**, additional programs in CNS, cardiovascular and unlimited therapeutic potential in other areas
- **Manufacturing process established** for challenging AAV capsids to enable tissue tropic delivery for lead programs
- **Experienced team** with deep knowledge of platform
- Strong **IP portfolio and strategy** that includes granted patents
- **Clear regulatory and clinical path** in place based on recent FDA guidance

Non-cleaving CRISPR = CRISPR-GNDM®

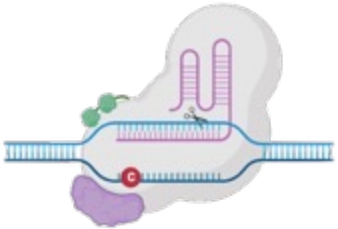
Enables treatment of genetic disorders by controlling epigenetic ON/OFF switch

GTx Technologies

Gene Editing | **Base/Prime Editing** | **siRNA / ASO**



Permanent Removal

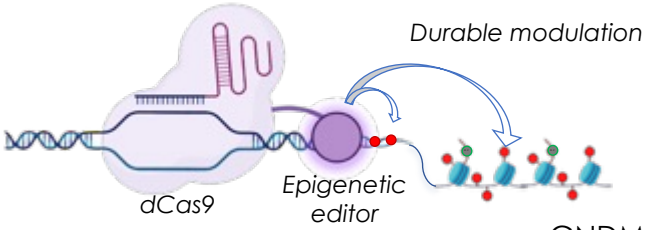


Permanent Replacement

Temporal silencing

Epigenome Editing(CRISPR-GNDM®)

Bind without cleaving
No DNA damage



GNDM=Guide Nucleotide Directed Modulation

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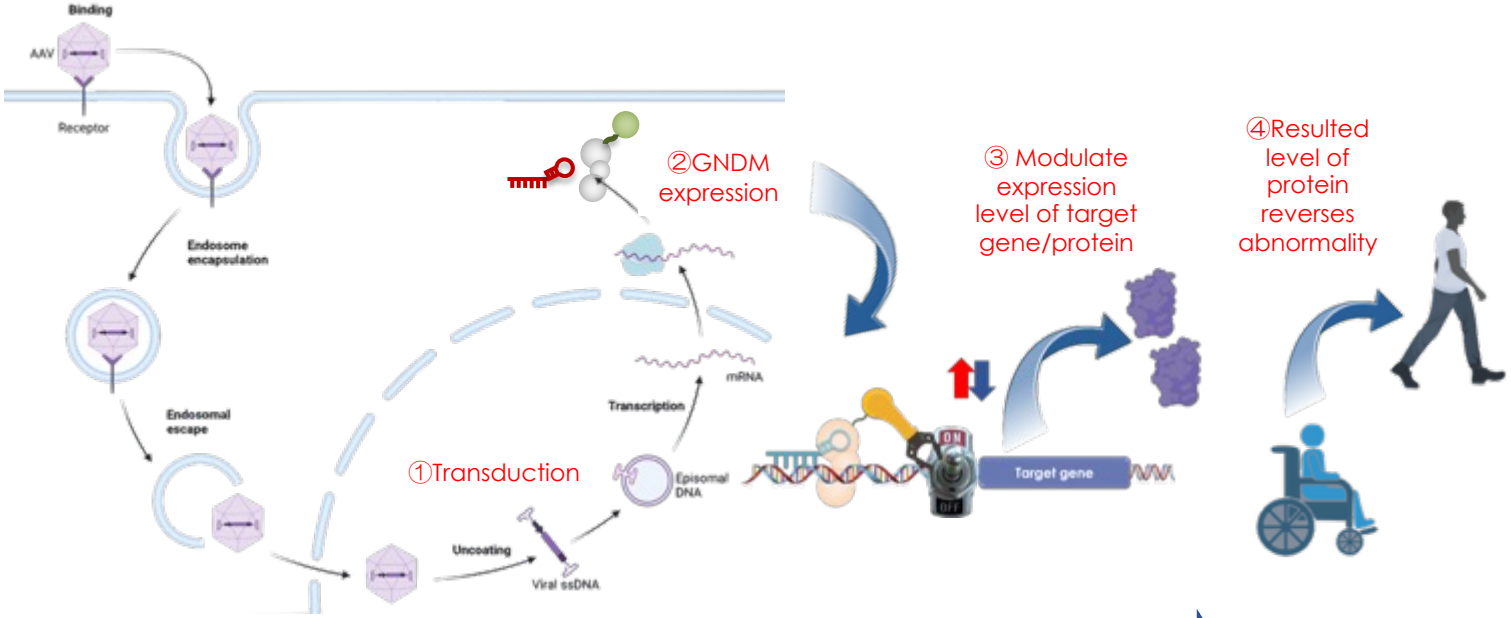
There are 3 steps for GNDM before providing efficacy

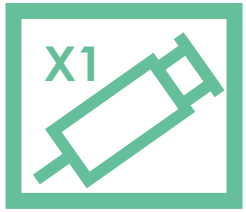
The GNDM is transduced, expressed and engages to the target to show efficacy



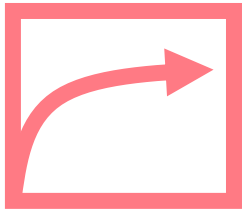
CRISPR-GNDM® is a promising new therapeutic modality

A single injection provides long term disease modifying effect

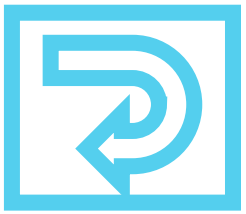
Potential benefits of CRISPR-GNDM® Technology



Single dose
Doesn't require
Repeated dosing



Long-lasting
Sustained effect
for years or decades



Disease Modifying
Not just to reduces
symptoms but
gives cure

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Epigenome editing competitive landscape

Momentum for epigenome editing remains strong

Company	Year Founded	Funding	Platform	Pipeline/Target indication	Stage of Development
MODALIS	2016	Public	CRISPR-GNDM x AAV	• MDL-101/LAMA2-CMD • MDL-201/DMD **Gene activation**	IND enabling
Tune Therapeutics	2020	Series B ($175M, 2025)	DNMT-KRAB fusion dCas9 x LNP	Une-401 for HBV **Gene suppression**	**CTA approval from NZ on HBV**
Chroma Medicine	2021	Merged into nChroma (Dec 2024)	DNMT-KRAB fusion dCas9 x LNP	CRMA-1001 for PCSK9 **Gene suppression**	Unclear
Epic Bio	2022	Series B ($68M, 2025)	Cas12f-fused with demethylation enzyme x AAVrh74	EPI-321/FSHD **Gene suppression**	IND clearance of EPI-321 from FDA

Table of contents

1. Key Points of the 2Q/2025

01	02	03	04	05
Timeline Revision	MYOAAV license w/ Broad	MDL-201 animal PoC data	XPRIZE and SolveFSHD	Finance and Others

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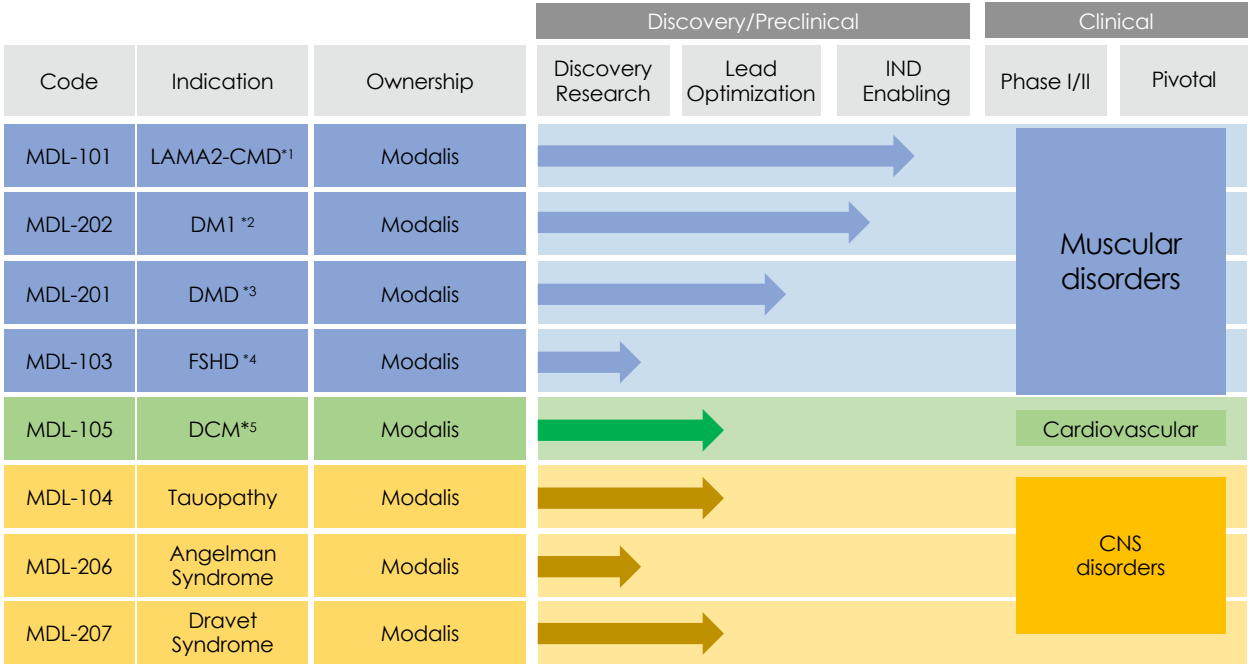
The current pipeline of MODALIS

Taking muscular disease-centered strategy with focus on MDL-101



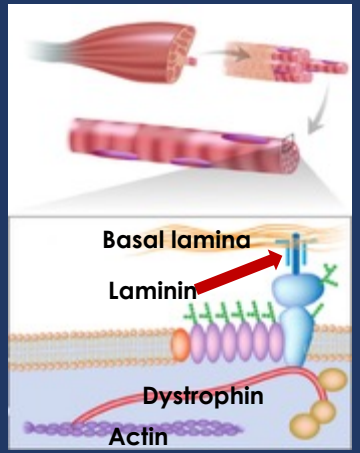
*1: LAMA2-related congenital muscular dystrophy
*2: Myotonic Dystrophy Type 1
*3: Duchene Muscular Dystrophy
*4: facioscapulohumeral muscular dystrophy
*5: Dilated Cardiomyopathy

LAMA2-CMD (aka CMD1a)

Severe muscular dystrophy caused by loss of function mutation in LAMA2 gene

MDL-101

Potential to be the first LAMA2-CMD gene activation therapy



Prevalence	**8.3 in 1 million*** 2,500 in US	
Disease Onset	Apparent at birth or within a few months after birth	
Disease Burden	Patients do not survive past adolescence	• Severe muscle weakness • Lack of muscle tone (hypotonia) • Little spontaneous movement • Joint deformities (contractures) • Heart problems and seizures
Disease Causing Gene	**LAMA2 mutation**	
Commercial opportunity	**$500M+**	

Source: *Estimating the Prevalence of LAMA2 Congenital Muscular Dystrophy using Population Genetic Databases (2023)

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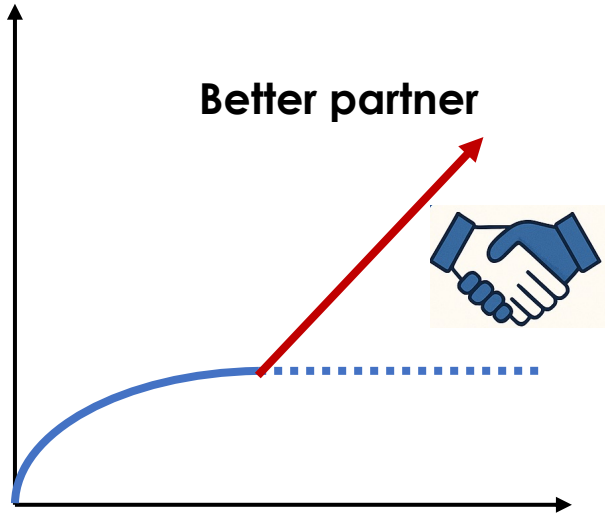
Timeline Revision

Rescheduling of MDL-101 IND target to 2026

- Causes
  - Time lag caused by restarting after last year's funding
  - Change in a major contractor
  - Delay in procurement of materials

  <u>But it is not due to technical issues</u>

- Revised timeline
  - IND in 2026 (The exact timing within 2026 will be reported after completion of the review)



Manufacturing

Established a manufacturing process for the engineered capsids and scale up achieved successfully

- Manufacturing process adapted to modified capsids
- Achieves reasonable production efficiency, yield, and quality
- Establishment of analytical methods also carried out in parallel
- Manufacturing plan for samples required for clinical use

GMP Manufacturing through strategic alliance with a CDMO

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Muscle Tropic Capsid
Acquired license for MYOAAV capsids from Broad Institute

- Modified capsid with excellent muscle selectivity
  - Achieves increased efficacy and/or reduced dosage (= improved safety)
- Manufacturing method established independently by our company
  - Practical yield and quality achieved
  - Scale-up completed
  - Manufacturing for GMP production underway at CDMO
- License terms within reasonable conditions
  - Modalis will pay license fees to the Broad Institute as progress is made

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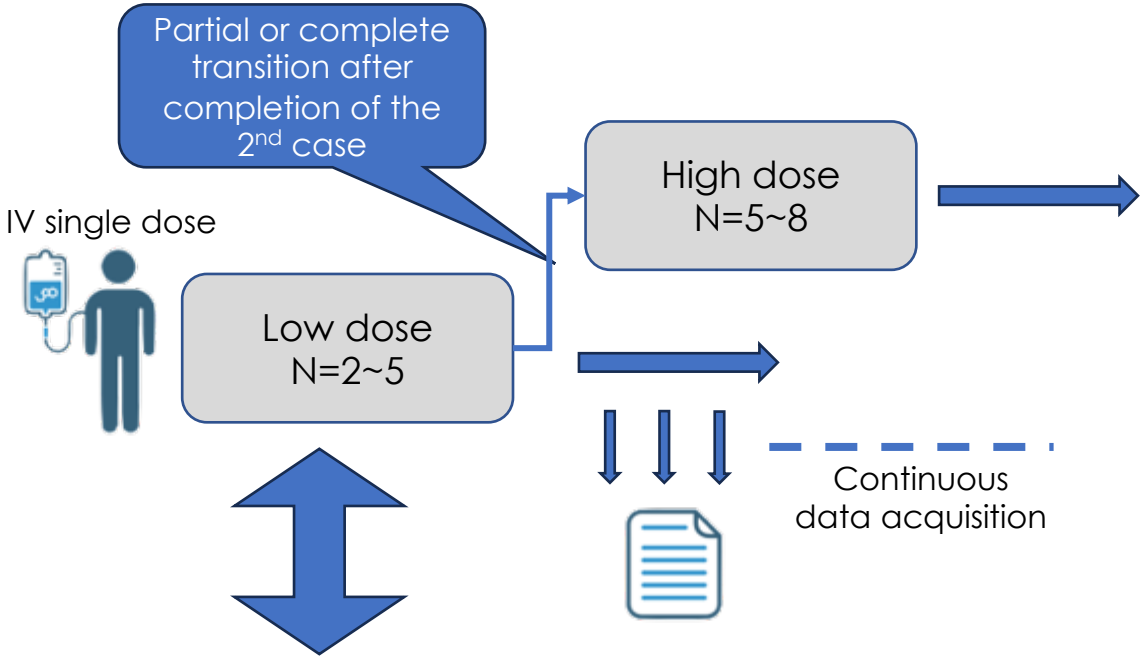
BROAD
INSTITUTE

MDL-101-001 Trial design

Open-label trial with two doses. Efficacy evaluated in comparison with natural history observation trial.

- Patients aged 36 months or younger (male or female)
- Clinical condition and/or significant reduction in LAMA2 protein levels in muscles associated with Lama2 gene mutations
- Stable condition during treatment
- Difficulty with independent walking or sitting

Phase1/2 Open-label dose escalating trial



Compare with Natural History Study
(NCT06354790, NCT04299321, NCT06132750)

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Updated

MDL-101

Towards clinical trials IND-enabling in progress

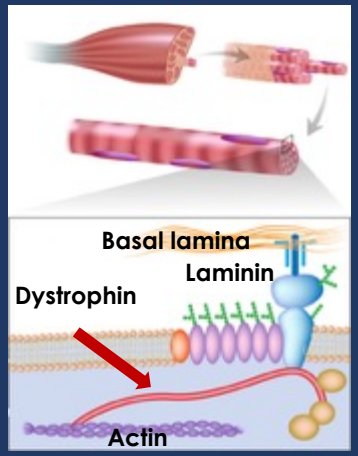
- Completed tech transfer to CDMO, scale up to 200L, and Pilot manufacturing. Progressing smoothly toward GMP manufacturing
- GLP Tox Study
  - Mouse IND enabling initiated
  - NHP GLP tox initiated
- Coordinating with patient groups for the clinical trial
- In addition to, or instead of the US, considering the possibility of conducting clinical trials in other countries.

Duchenne Muscular Dystrophy (DMD)

A type of muscular dystrophy caused by mutation in Dystrophin gene

MDL-201

Potentially best-in-class molecule by rebooting UTRN gene expression by GNDM



Prevalence	**1 in 3,500 to 5,000 male newborns**	Relatively high in genetic disorders
Disease onset	most commonly appears **between 3 and 6 years old**	
Disease Burden	Most severe clinical symptoms of all the muscular dystrophies including muscles weakness and atrophy	Motor development begins to slow in early childhood and muscle weakness progresses, followed by cardiomyopathy, scoliosis, and respiratory complications
Cause of disease	Disruption or mutation in Dystrophin gene	Loss of dystrophin and abnormal histological development of muscle necrosis and regeneration
Market size	**$1.1BM** 2022	Expected to grow at CAGR=42.5% with approval of new therapeutics

*Source: https://doi.org/10.1212/WNL.0000000000011425

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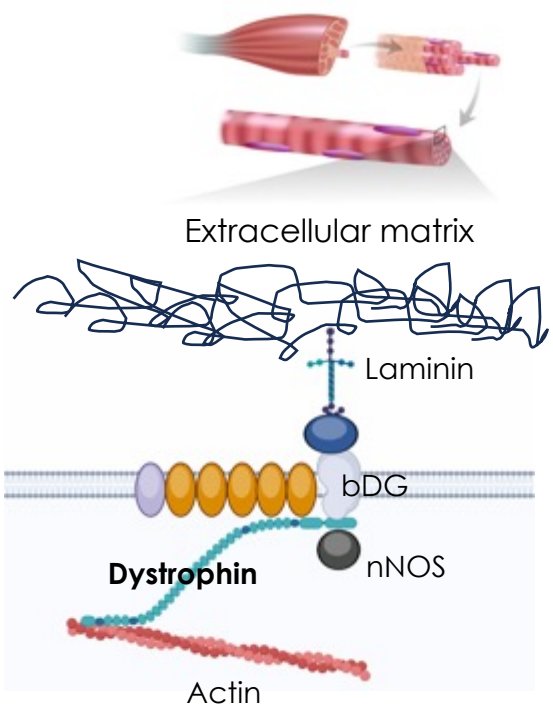
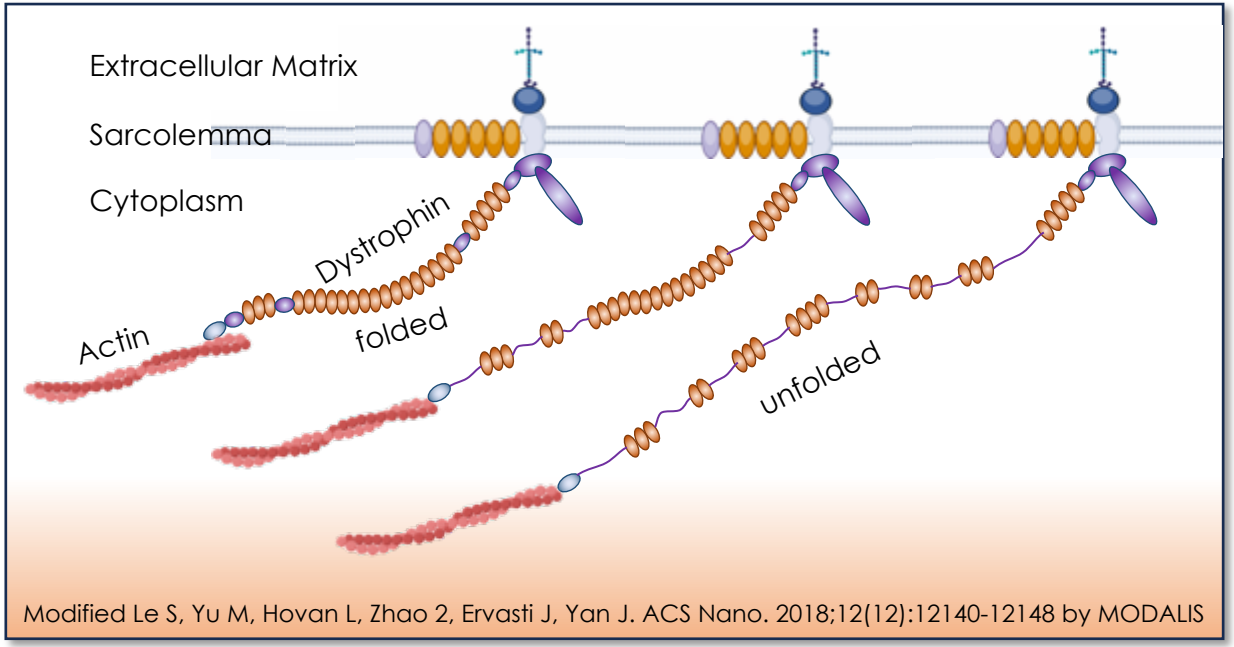
Dystrophin's function

Functions as a shock absorber and signal transmitting molecule in muscles

Dystrophin location



Dystrophin stretches and contracts to connect the cell membrane and actin



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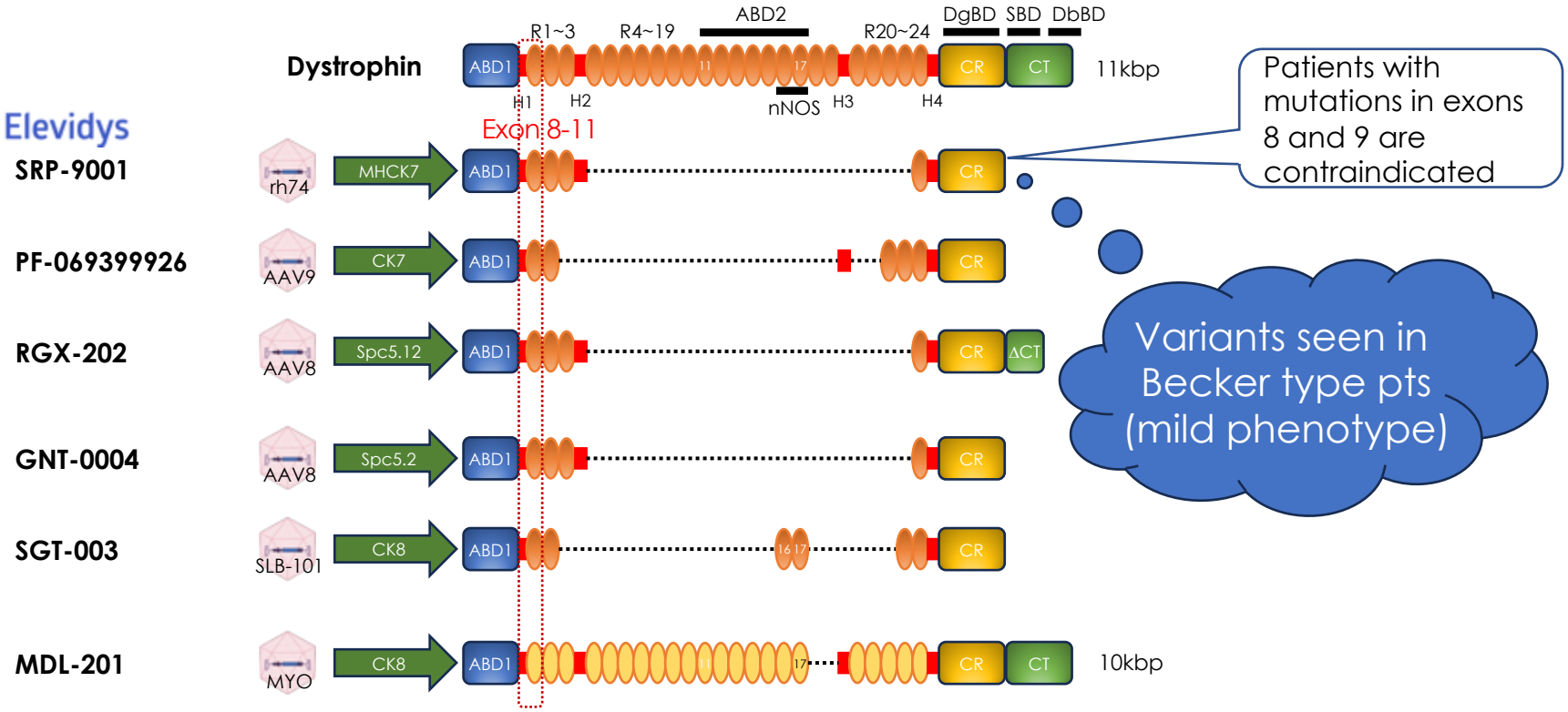
micro-Dystrophins payload comparison

Due to size constraints, small dystrophin derived from Becker patients is used for GTx

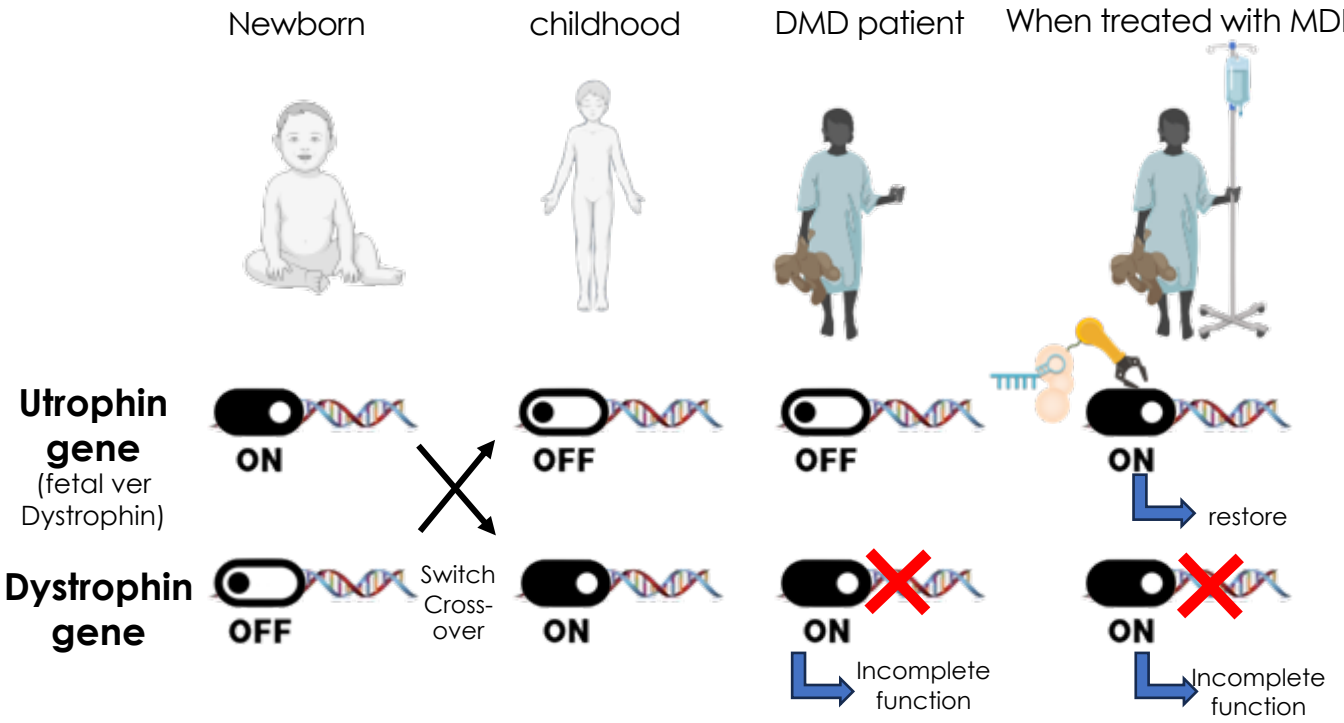
Dystrophin/Utrophin and mini-Dystrophin structure

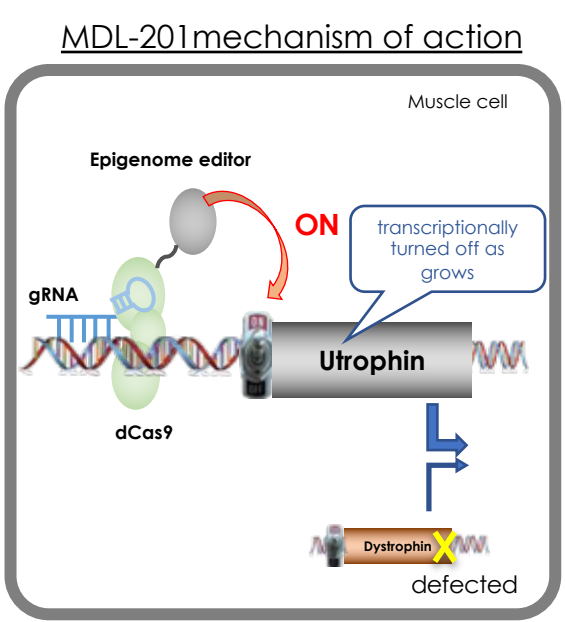


Modified from Crudele &Chamberlain, 2019

MDL-201 therapeutic concept

Reboot Utrophin genes , which is intact in patient, to compensate Dystrophin function





activating Utrophin using GNDM is expected to have a greater medicinal effect than mini-Dystrophin

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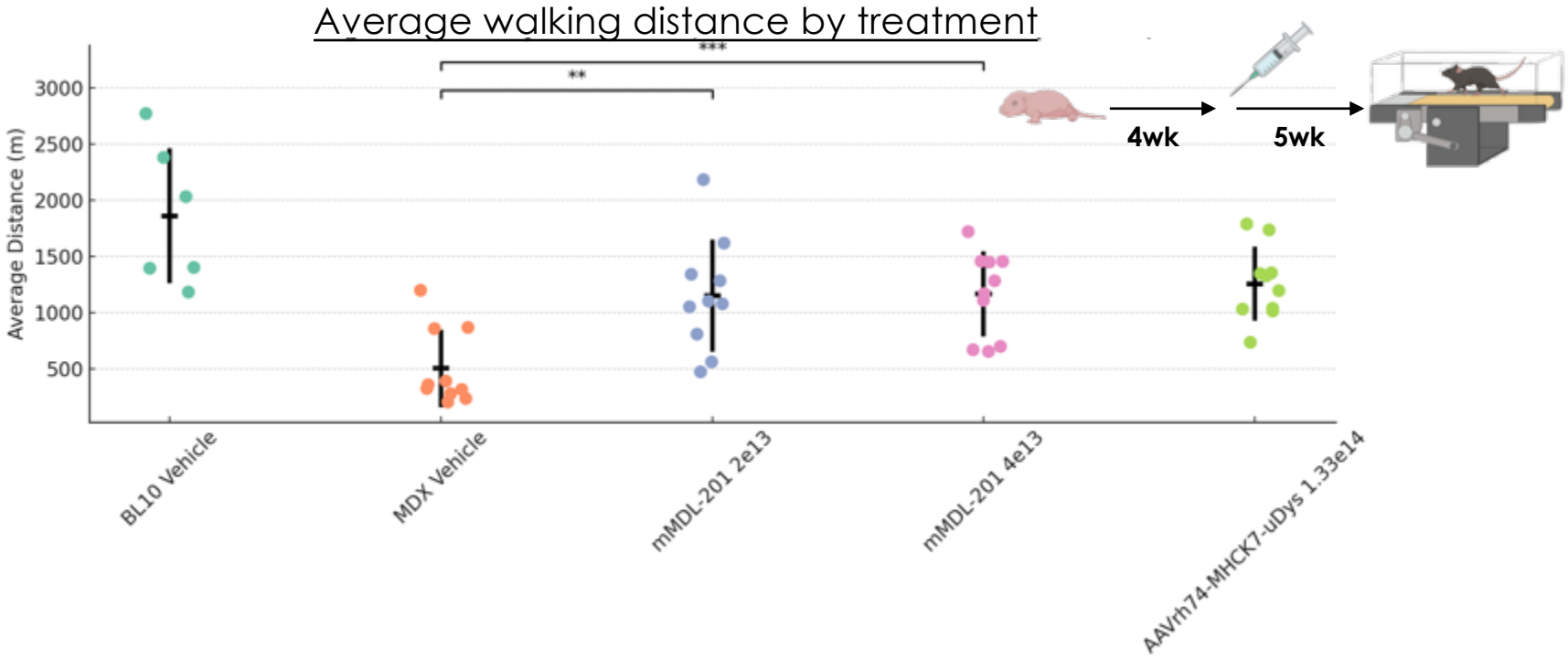
NEW

Functional improvement of DMD by MDL-201

achieves the same level of efficacy as the benchmark drug at a dose one order of magnitude lower



Data is presented as mean ± SEM. Normality was assessed using Shapiro-Wilk tests for all treatment groups. Post-normality test, unpaired t-tests were performed between the BL10 Vehicle and MDX Vehicle groups for both A and B (### p<0.001). Non-parametric ANOVAs (Kruskal-Wallis tests with Dunn's post-hoc test for multiple comparisons) were performed to compare all treatment groups against the MDX Vehicle (**p<0.01; ***p<0.001).

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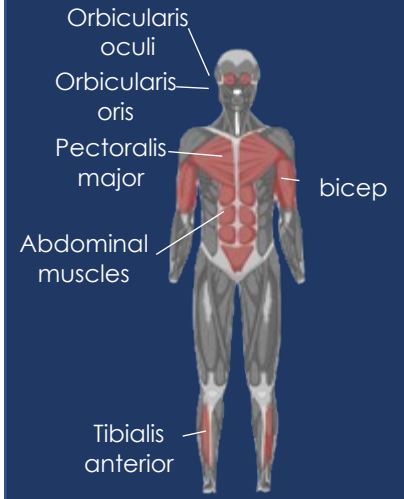
Facioscapulohumeral Muscular Dystrophy (FSHD)

A type of muscular dystrophy caused by impaired Dux4 gene expression

MDL-103

Potentially first-in-class treatment by silencing expression of toxic Dux4 gene product



Prevalence	**1 in 10,000-20,000**	Muscular dystrophy most frequent in adults
Disease Onset	Often not recognized until the 20s and tends to worsen during adolescence	Progression of disease to face, shoulders, and arms is generally slow
Disease Burden	weakness of the facial muscles, the stabilizers of the scapula, or the dorsiflexors of the foot	Symptoms of asymmetrical (unbalanced) muscle weakness Visual impairment, vascular abnormalities, hearing impairment, etc.
Disease Causing Gene	Over expression of Dux4 gene	DUX4 is originally expressed in germline cells but need to be suppressed in somatic cells
Commercial opportunity	**$500M+**	

Source: https://doi.org/10.1212/WNL.0000000000011425
Orphanet, Raymond A. Huml MD A concise guide

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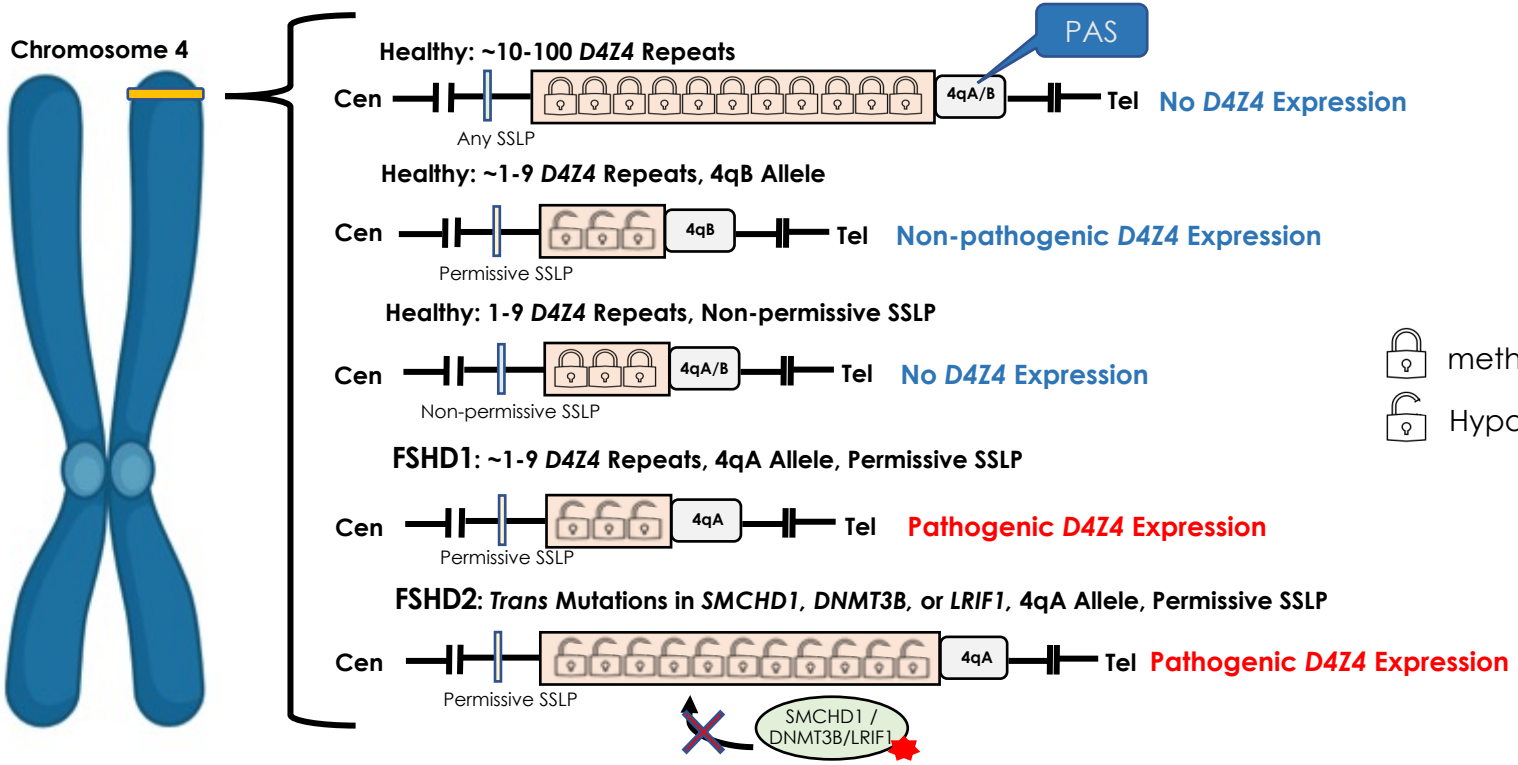
FSHD disease mechanism

Inappropriate expression of toxic Dux4 in skeletal muscles



DeSimone et al. 2020, *Dis Model Mech*

SSLP: Simple Sequence Length Polymorphism PAS: polyadenylation signal

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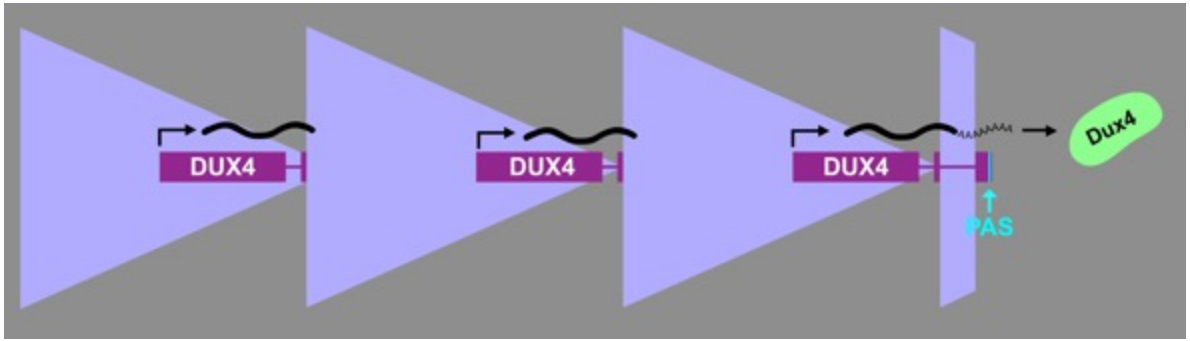
Why Epigenome editing makes sense for treating FSHD?

DUX4 Gene in the Last D4Z4 Repeat Codes for a Pathogenic Protein



- Each D4Z4 repeat contains a copy of the DUX4 gene, put the **polyadenylation signal(PAS=stabilizer)** is absent, so any transcribed RNA is unstable
- The DUX4 gene in the final repeat can read through the end of the array and incorporate a PAS(if the 4qA haplotype is present), resulting in synthesis of the pathogenic protein
- Dystrophy is presumably caused by the **cytotoxicity of the DUX4 protein**
- 1)The size of the array, 2)the presence of a nearly identical array on chromosome 10, and 3) the presence of individual D4Z4s spread across the genome makes traditional CRISPR-Cas9 gene replacement, base-editing, and indel approaches untenable
- Using a CRISPRi approach to inhibit expression of all D4Z4s is a more plausible approach

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Following the SOLVE FSHD–Sponsored XPRIZE Healthspan Bonus Prize, SOLVE FSHD itself has also decided to provide research and development grants

"I prefer not to sit in the stands, but to be on the court to solve this disease that is so very close to my heart."

Chip Wilson
Founder of SolveFSHD and Lululemon

- Selected lead gRNA and filed patent application
- Restarted MDL-103, a drug candidate for the treatment of FSHD
- Aiming to conduct clinical trials after verification using animal models in collaboration with universities and other research institutions

Source: Solve FSHD website

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Publication and conference presentations

Preclinical data for MDL-201 was and will be reported in coming conferences

Past presentation

2025 Scientific & Family Conference,
Congenital Muscular Dystrophy/Nemaline Myopathy/Titinopathy (2025 SciFam)

Title: Epigenetic Editing with CRISPR-GNDM®: MDL-101 is a Muscle -Tropic AAV Vectors for the Treatment of LAMA2-CMD
Date and Time : Aug 4th 9:00-110:00AM EST

Coming presentation

the 6th Genome Editing Therapeutics Summit

Title : Movement Toward the Clinic: Preclinical Development of Gene Activation programs with CRISPR-GNDM® platform

Date and Time : October 1st, 11:45 AM EST
Session: Optimizing CRISPR Technologies to Progress Epigenome Editors

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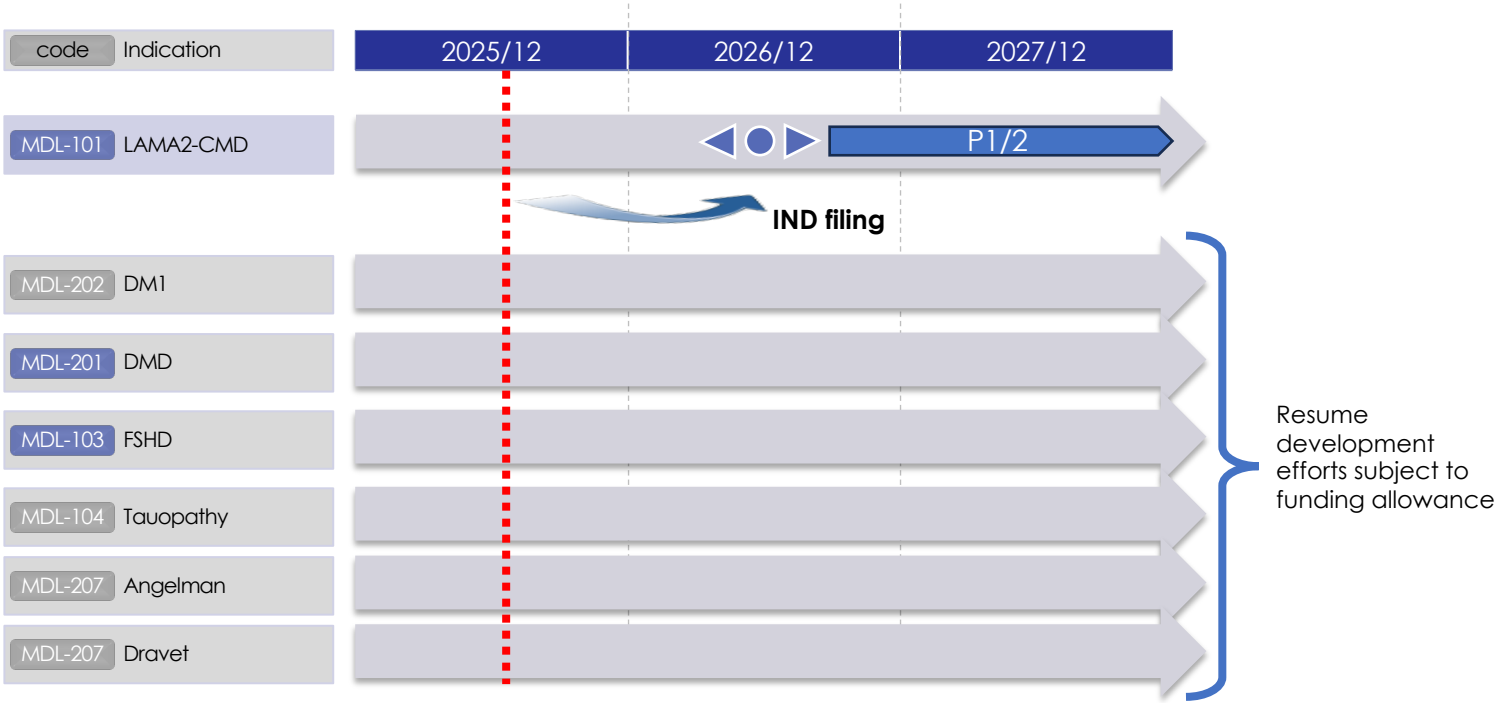
Updated

Pipeline status and coming milestones

Reset MDL-101 IND filing target to 2026

Pipeline status



- Scheduled milestone events are informational in the future and subject to change

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Updated

Achievements of the programs and coming milestones

	Achievement so far	Coming milestones
MDL-101 LAMA2-CMD	• Animal PoC • Target engagement in monkeys • Pre-IND response • Process Development and **Scale up** completed • ODD (Sep) and RPDD (Oct) received • Data presentation (**Most recently at SciFam (Aug)**)	• GLP-Tox • GMP manufacturing • IND (**2026**)

その他	• Established animal PoC
	  • MDL-201 (DMD): **Confirmation of superiority in functional improvement over the benchmark with disease models**
	  • MDL-202 (DM1)
	  • MDL-104 (Tauopathy)
	  • MDL-205 (Angelman syndrome)
	  • MDL-207 (Dravet syndrome)
	• MDL-103 (FSHD): **Received grant from xPrize and SolveFSHD**
	• MDL-105 (DCM)
	• Research collaboration with JCR in CNS
	• Collaboration with Ginkgo Bioworks, GenixCure
		• Additional readout of MDL-201
		• **Data presentation at (6th Next Generation Genome Editing Summit)**
		• Explore optimal capsid and route of administration for CNS program
		• Allocation of development funds through partnering and grants
		• Animal PoC
		• Continuing Research and Moving to Next Steps

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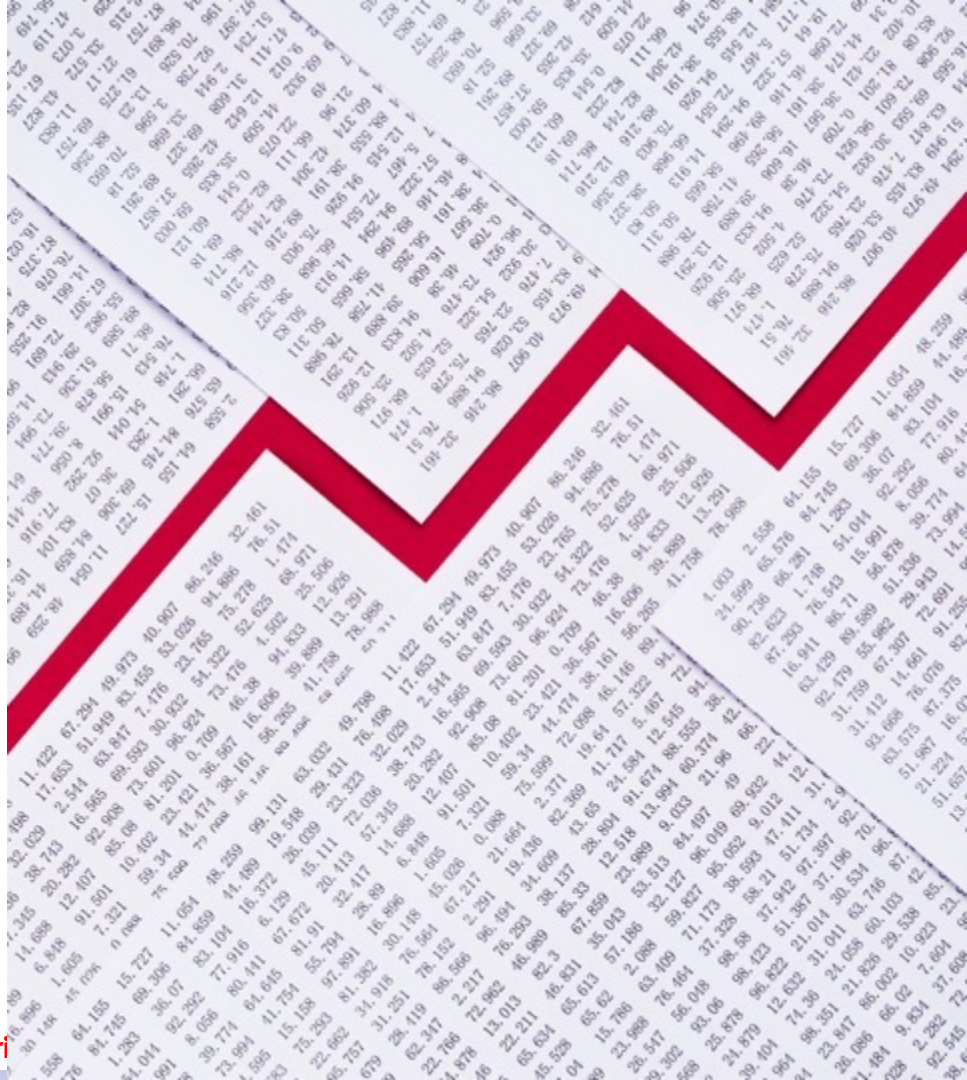
MDL-101 patent granted in US

- LAMA2-CMD patent granted in the US (July)
  - Treatment method for muscular dystrophy targeting LAMA1
  - Granted already in JPN (Jan)
  - US17/635,608

2. Financial reports



BS & Financial Position at the end of 2Q/2025

Maintain a certain level of cash and deposits needed for operations for ~12 months

(Million Yen)

	End of FY2024 (A)	End of 2Q FY2025 (B)	(B) – (A)
Current assets	3,617	3,348	△268
Cash & deposits	3,575	3,261	△313
Non-current assets	74	67	△7
Total assets	3,691	3,416	△275
Current liabilities	117	171	54
Non-current liabilities	26	56	30
Total liabilities	143	228	85
Total net assets	3,548	3,187	△360
Total liabilities and net assets	3,691	3,416	△275
Capital adequacy ratio	95.5%	92.5%	

Note

- Despite the exercise of stock acquisition rights, cash and deposits decreased and liabilities increased due to the increase in expenses described below.

Information purpose only

BS & Financial Position at the end of 2Q/2025

Maintain a certain level of cash and deposits needed for operations for ~12 months

(In thousand USD at @150yen/$)

	End of FY2024 (A)	End of 2Q FY2025 (B)	(B) – (A)
Current assets	24,113	22,320	-1,787
Cash & deposits	23,833	21,740	-2,087
Non-current assets	493	447	-47
Total assets	24,607	22,773	-1,833
Current liabilities	780	1,140	360
Non-current liabilities	173	373	200
Total liabilities	953	1,520	567
Total net assets	23,653	21,247	-2,400
Total liabilities and net assets	24,607	22,773	-1,833
Capital adequacy ratio	95.5%	92.5%	

Note

- Despite the exercise of stock acquisition rights, cash and deposits decreased and liabilities increased due to the increase in expenses described below.

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PL & Business Result at the end of 2Q/2025

1,031 million in operating expenses, mainly due to the cost of activities for clinical trials for the MDL-101 program

(Million Yen)

	2Q FY2024 (A)	2Q FY2025 (B)	(B)−(A)
Operating revenue	-	-	-
Operating expenses	838	1,031	192
R&D	716	906	189
SGA	122	125	△3
Operating income	△838	△1,031	△192
Ordinary income	△780	△1,019	△239
Current Profit	△780	△1,020	△239

Operating expenses

- Recorded non-operating income as an upfront payment of the funding provided under a strategic partnership with SOLVE FSHD and non-operating income from the grant money won at XPRIZE Healthspan.
- Expenses will increase due to progress in preclinical trials and investigational drug manufacturing for clinical trials of MDL-101.

PL & Business Result at the end of 2Q/2025

$6.9M in business expenses, mainly due to the cost of activities for clinical trials for the MDL-101 program

(In thousand USD at @150yen/$)

	2Q FY2024 (A)	2Q FY2025 (B)	(B)−(A)
Operating revenue	-	-	-
Operating expenses	5,587	6,873	1,280
R&D	4,773	6,040	1,260
SGA	813	833	20
Operating income	-5,587	-6,873	-1,280
Ordinary income	-5,200	-6,793	-1,593
Current Profit	-5,200	-6,800	-1,593

Operating expenses

- Recorded non-operating income as an upfront payment of the funding provided under a strategic partnership with SOLVE FSHD and non-operating income from the grant money won at XPRIZE Healthspan.
- Expenses will increase due to progress in preclinical trials and investigational drug manufacturing for clinical trials of MDL-101.

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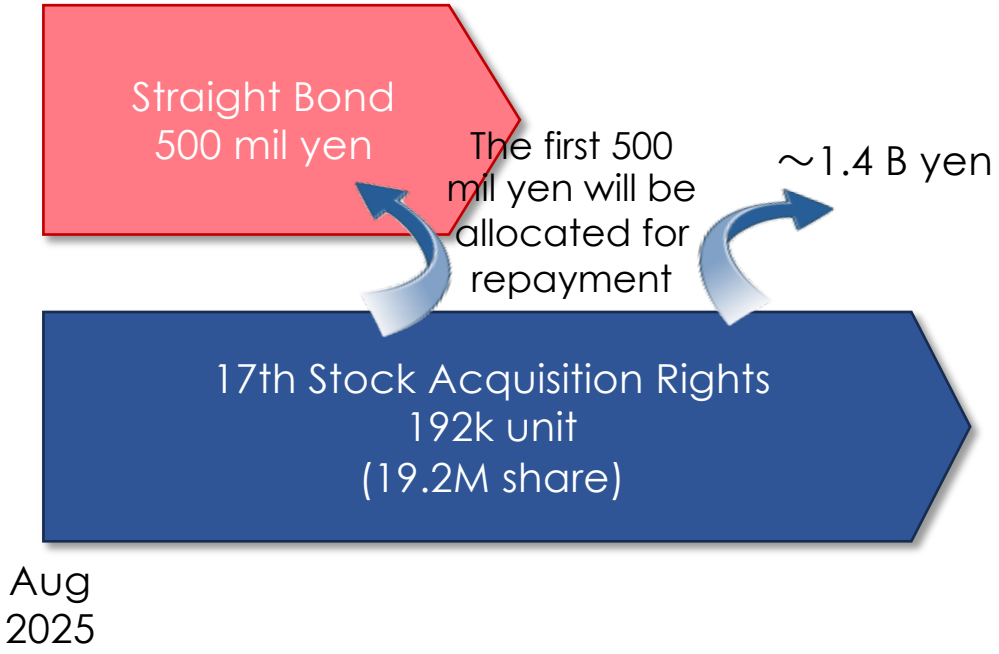
New funding scheme

Funding of approximately 1.4 billion yen, consisting of 500 million yen in SB and 192k MS warrant

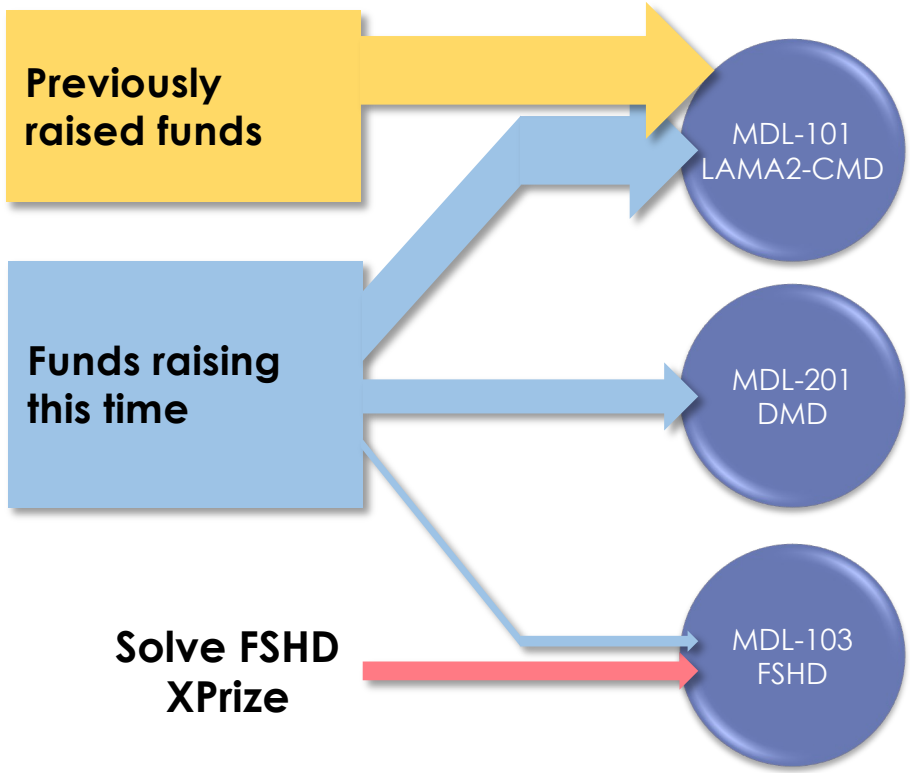


- Additional funding for MDL-101
- MDL-201 development costs
- R&D costs for MDL-103 and other subsequent pipeline products
- Administrative cost

Allocation of development funds

In addition to MDL-101, we will also deploy MDL-201 and 103 to promote development.

- Together with the funds raised in the previous round, the funds raised will be used, to finance preclinical and clinical proof-of-concept studies for MDL-101
- Also to be invested in the development of MDL-201, a candidate for a large-market pipeline.
- And be used to promote the development of MDL-103 in combination with external grants.



3. Growth Strategy

MODALIS

Diversified pipeline with their own missions

Pioneer the gene modulation With highly suitable indications

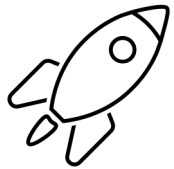
MDL-101

Expand technology opportunity with products for larger opportunity

MDL-201
MDL-202

Further approach to challenging applications

Other programs



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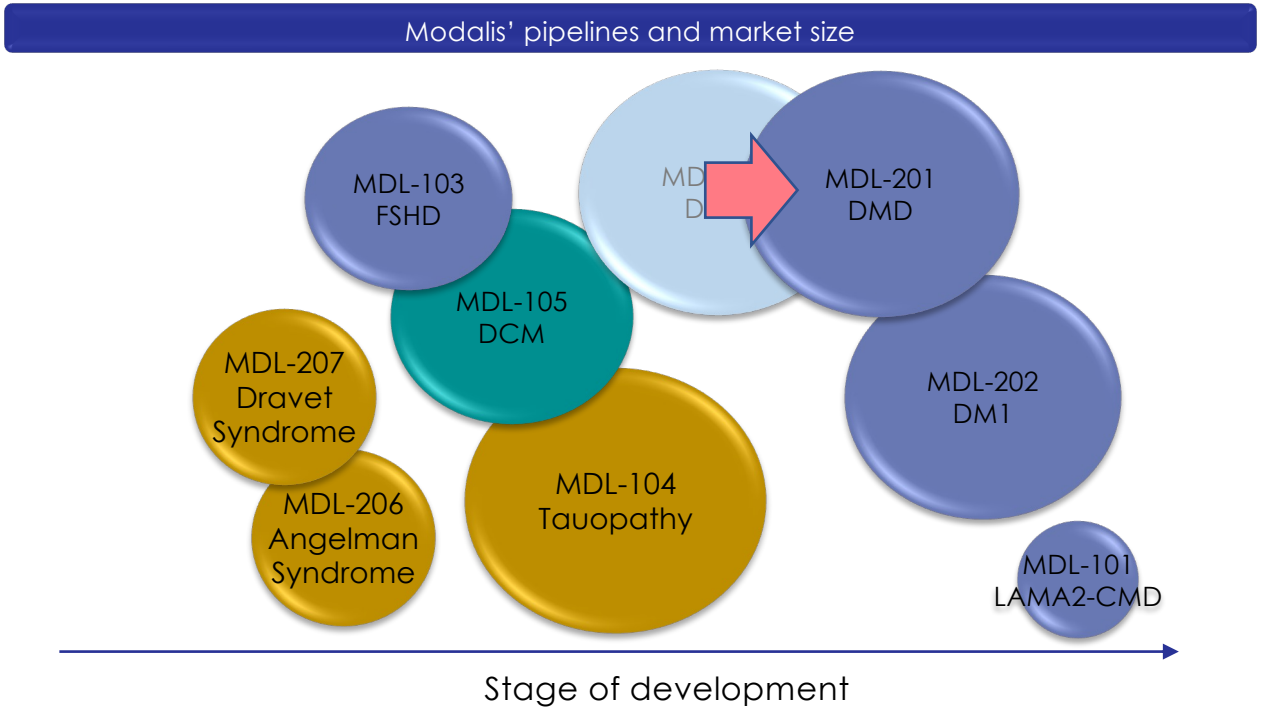
Modalis' pipelines and market size

Large indication programs follow MDL-101 which paves the clinical path

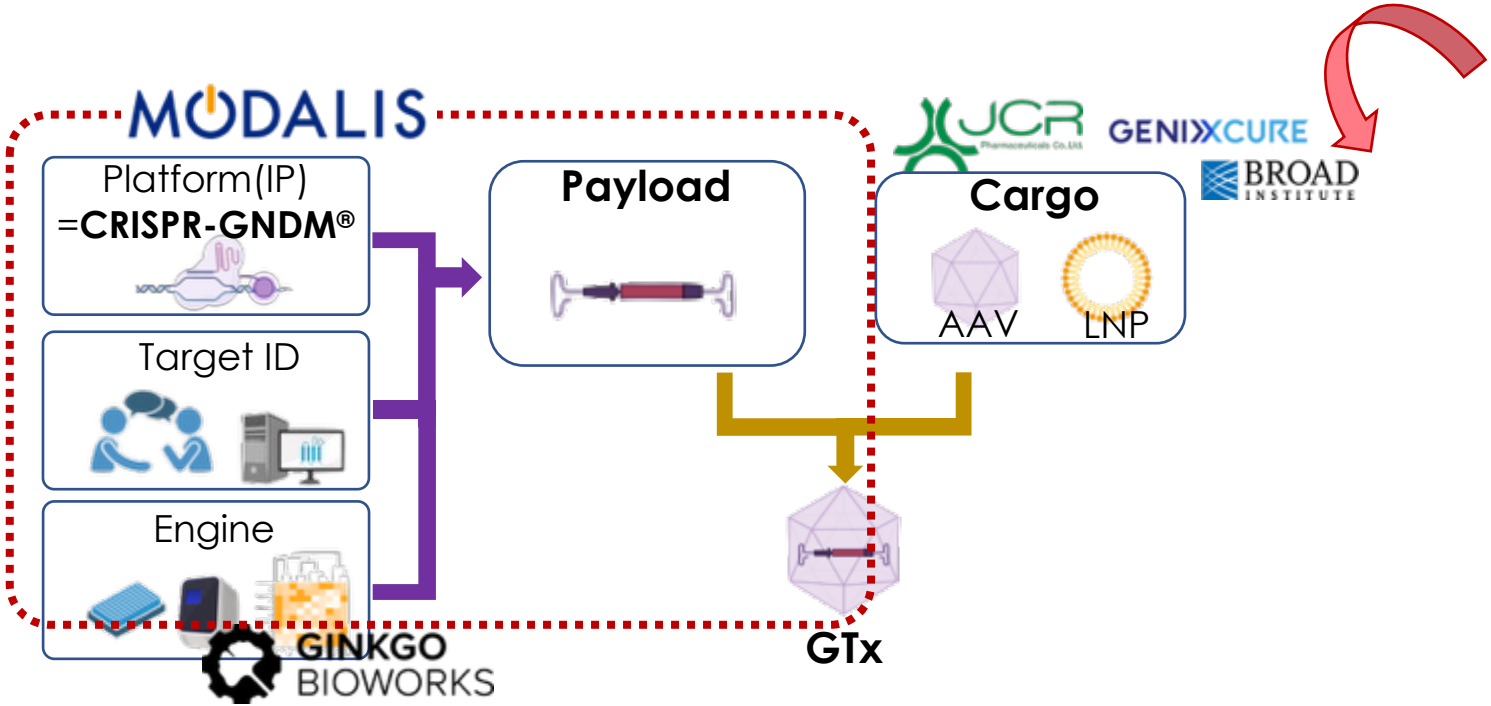


※ Size of circles represents an image of market size or patient number of each indication

Updated

MODALIS' core competence and collaboration

In the increasingly complex games, the necessary capabilities are accessed through partnership.



3. summary

Key Takeaway of 2025 2Q report

1. Revised IND Target for MDL-101 to 2026

2. License Agreement Signed with Broad Institute for Muscle-Tropic Capsid Technology

3. MDL-201, aimed for DMD Therapy, Confirms Efficacy Beyond Benchmark Drugs

4. MDL-103 for FSHD Research Receives Research Funding from Two Funding Programs

5. Additional funding to invest in growth opportunities created by MDL-201 and -103 in addition to MDL-101

Modalis Therapeutics

MODALIS

- Based in Greater Boston area
- Pioneering the first CRISPR-based gene modulation technology since 2016
- Leading company in CRISPR epigenetic modulation
- Develops novel precision medicines for genetic disorders that have no cure

4. Q&A

MODALIS

Q: Is there any impact from the recent toxicity issues of Elevidys?

- We understand that the reported toxicity issues with Elevidys suggest that there is a **growing need to avoid hepatotoxicity.**
- Considering the time when Elevidys was developed, around 2010, the technology and knowledge were state-of-the-art, but since then, the toxicity issues associated with systemic administration of viral vectors have been better understood, and at the same time, advanced technological developments have provided ways to avoid these issues. However, since then, we have made progress in understanding the toxicity issues associated with systemic administration of viral vectors, and at the same time, advanced technological developments have provided ways to avoid them.
- As reported in this report, we have addressed these issues by employing **the most advanced muscle-tropic viral vectors available**. Therefore, we believe that this issue provides **more room** for entry for second-generation DMD gene therapies, including our MDL-201, which employs novel technology.

Q: When in 2026 is MDL-101 expected to enter clinical trials?

- Details are still being worked out, but development is underway so that the drug can enter clinical trials as soon as possible within 2026.

- Fortunately, with regard to manufacturing, which generally tends to be a problem, we have already conducted manufacturing up to the scale of investigational drug production and have confirmed sufficient productivity, yield, and quality.

- In addition, we have already started animal studies for IND application in two animal species, which have been going well so far.

MODALIS

Q: What are the terms of the MYOAAV license?

- Although we cannot disclose details due to confidentiality agreements, the scheme is for us to make certain payments to the Broad Institute as we progress with development and sales.

Q: How much impact will the US policy and top management change have**?**

- Since the beginning of the year, various policy and management changes have been reported one after another. While we are doing our best to keep up with them, the changes are being reported too frequently and in ways that deviate from expectations, and some are even being withdrawn. As a result, we cannot say that we have fully captured all the changes.
- Even though, some policies that may have an impact include 1) exchange rates, 2) tariffs, and 3) pharmaceutical-related policies. For example, the positive impact of yen appreciation may offset the negative impact of tariffs, and some effects may cancel each other out internally, making it difficult to evaluate at this stage.
- On the other hand, regarding pharmaceuticals, if there are significant staff reductions at regulatory authorities leading to delays in reviews, or if the previously favorable stance toward advanced medical technologies is reversed, there is a possibility that this could have some impact on our business.