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In case of any discrepancy, the Japanese version shall prevail

First Quarter of 2025
Business and Financial report

(TSE：4883)

Modalis therapeutics Corporation

May 8, 2025

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About Modalis

MODALIS Value Highlights

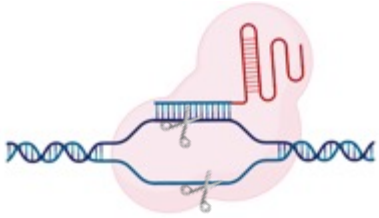
- Established the first robust **epigenetic platform** for activation and inhibition of endogenous genes using CRISPR-GNDM® platform
- Demonstrated sustained modulation of gene expression in multiple species (mouse, cyno) resulting in functional **efficacy without serious toxicities**
- Pipeline of preclinical 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®

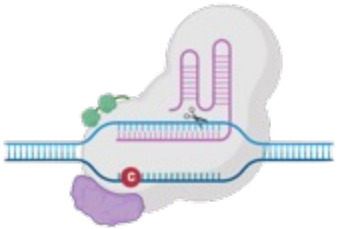
Enables treatment of genetic disorders by controlling epigenetic ON/OFF switch

GTx Technologies

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



Permanent Removal

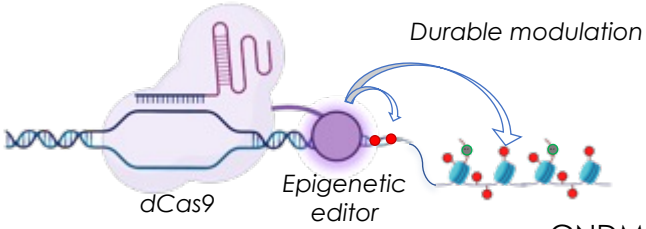


Permanent Replacement

Temporal silencing

Epigenome Editing(CRISPR-GNDM®)

Bind without cleaving
No DNA damage



GNDM=Guide Nucleotide Directed Modulation

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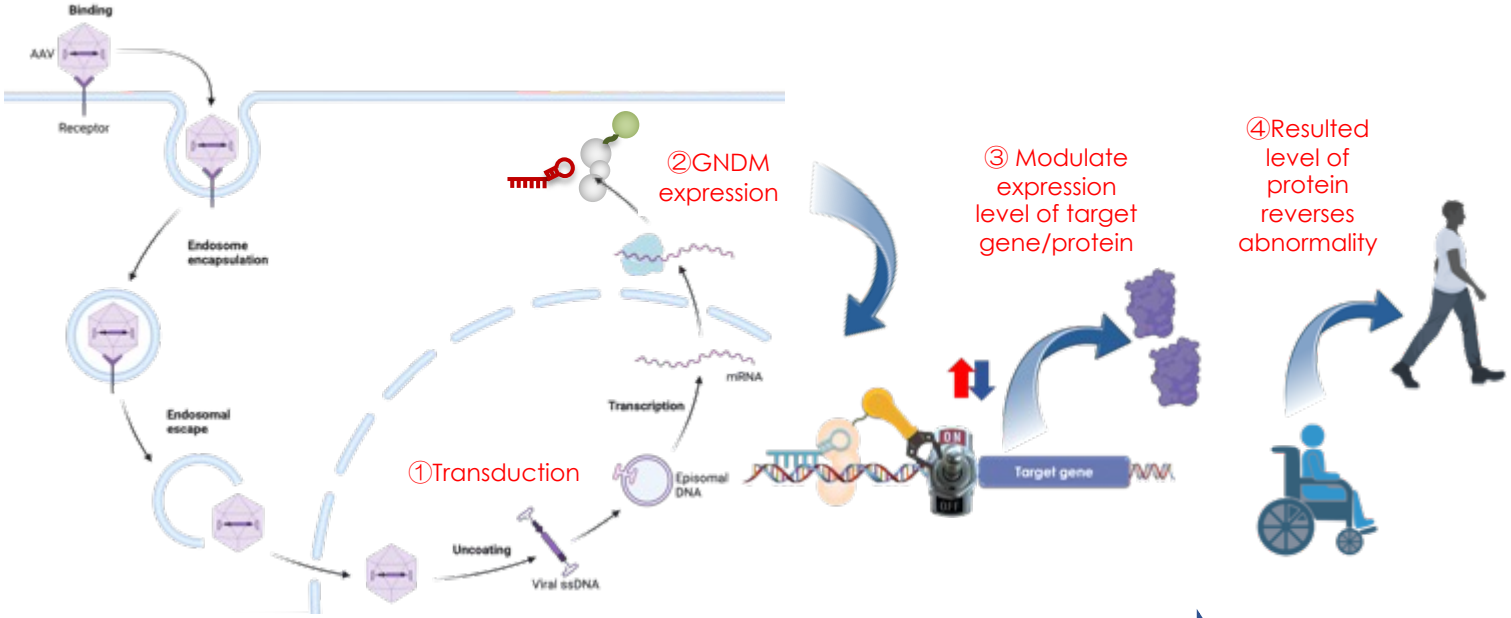
There are 3 steps for GNDM before providing efficacy

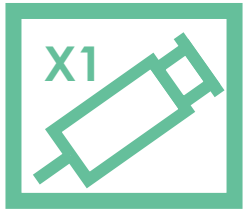
The GNDM is transduced, expressed and engages to the target to show efficacy



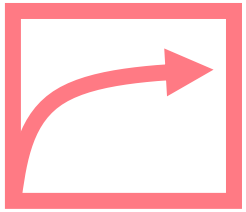
CRISPR-GNDM® is a promising new therapeutic modality

A single injection provides long term disease modifying effect

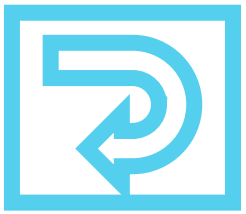
Potential benefits of CRISPR-GNDM® Technology



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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Updated

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**	PreIND completed 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**

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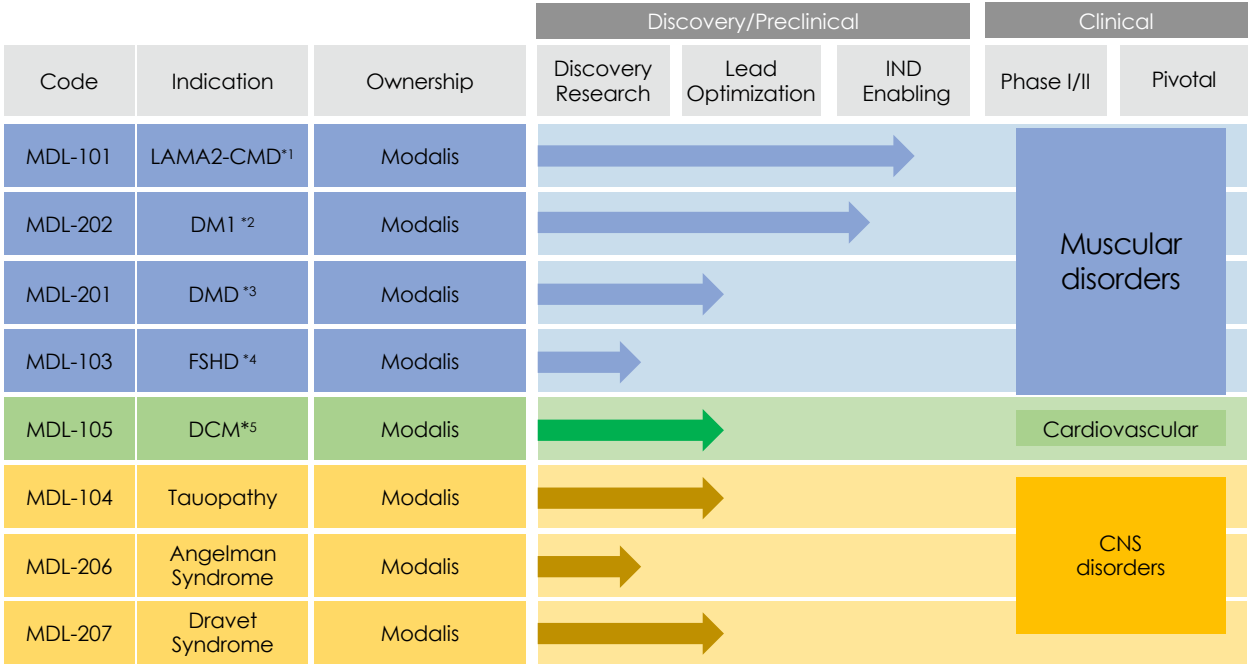
The current pipeline of MODALIS

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

1. Key Takeaway of the 1Q/2025

01

RPDD and ODD received from FDA

02

Paper and presentations

03

Advance in IP

04

Finance and Others

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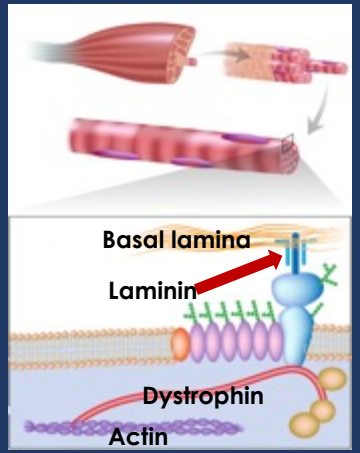
LAMA2-CMD (aka CMD1a)

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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MDL-101

Towards clinical trials IND-enabling in progress

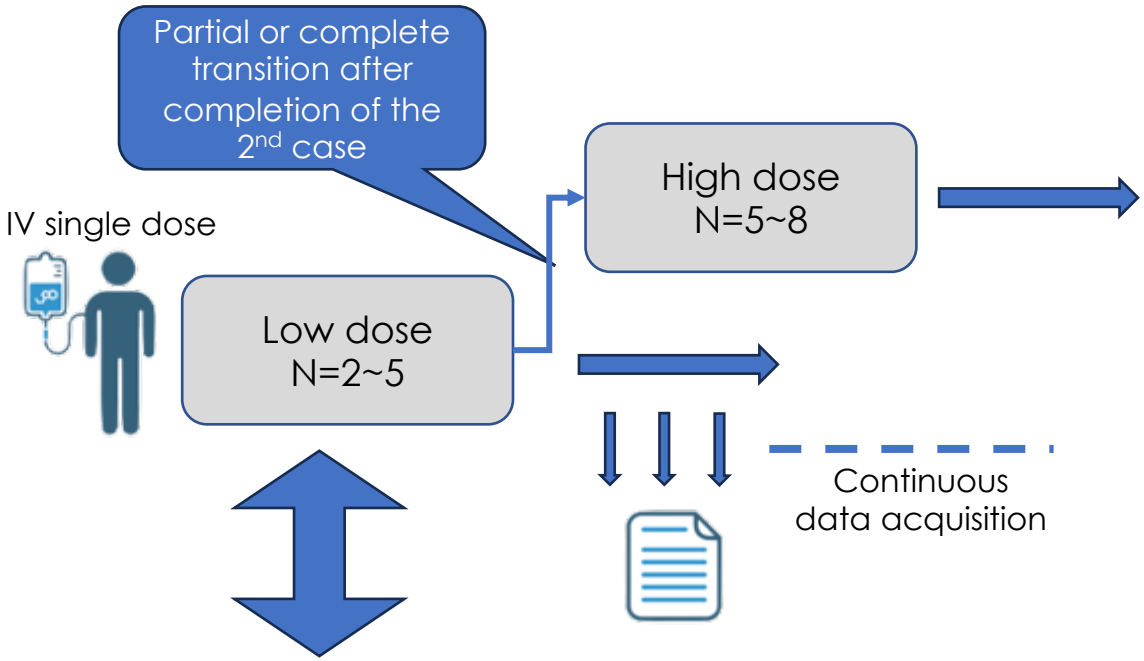
- Completed tech transfer to CDMO for GMP manufacturing. Pilot manufacturing is underway.
- GLP Tox Study
  - Mouse IND enabling
  - NHP GLP tox in prep
- Coordinating with patient groups for the clinical trial

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



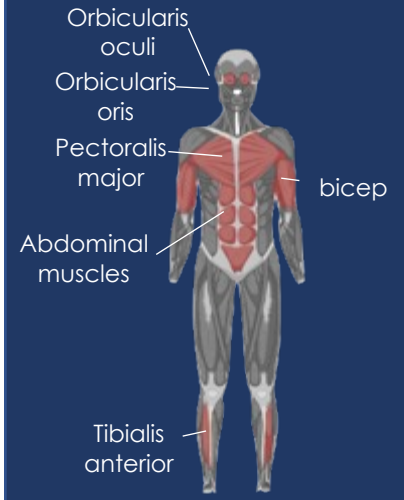
Compare with Natural History Study
(NCT06354790, NCT04299321, NCT06132750)

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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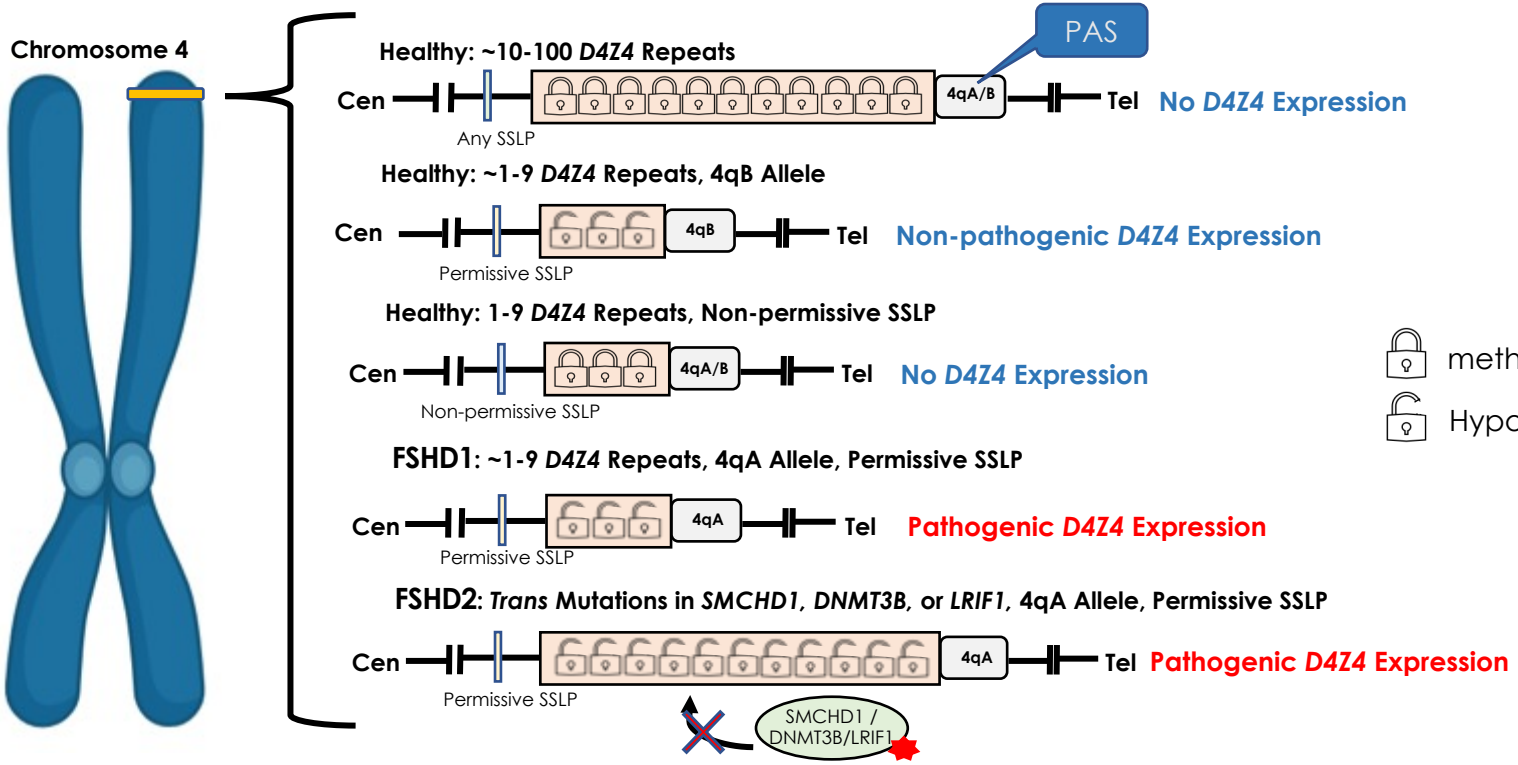
FSHD disease mechanism

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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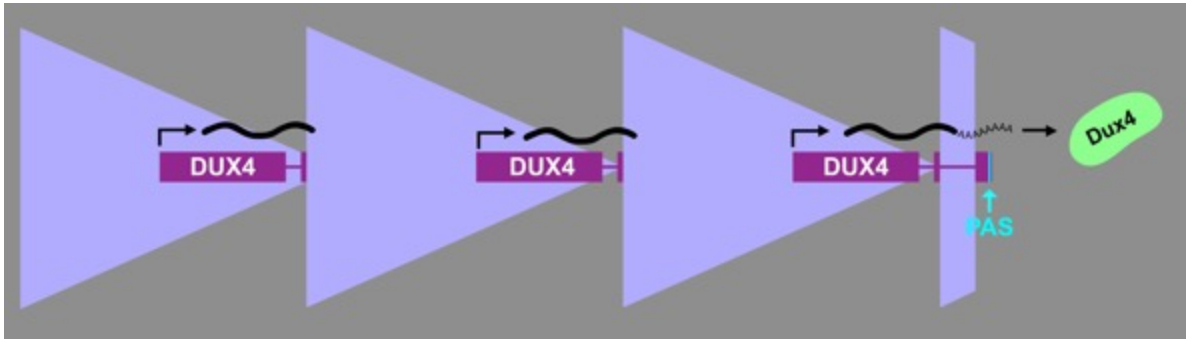
Why Epigenome editing makes sense for treating FSHD?

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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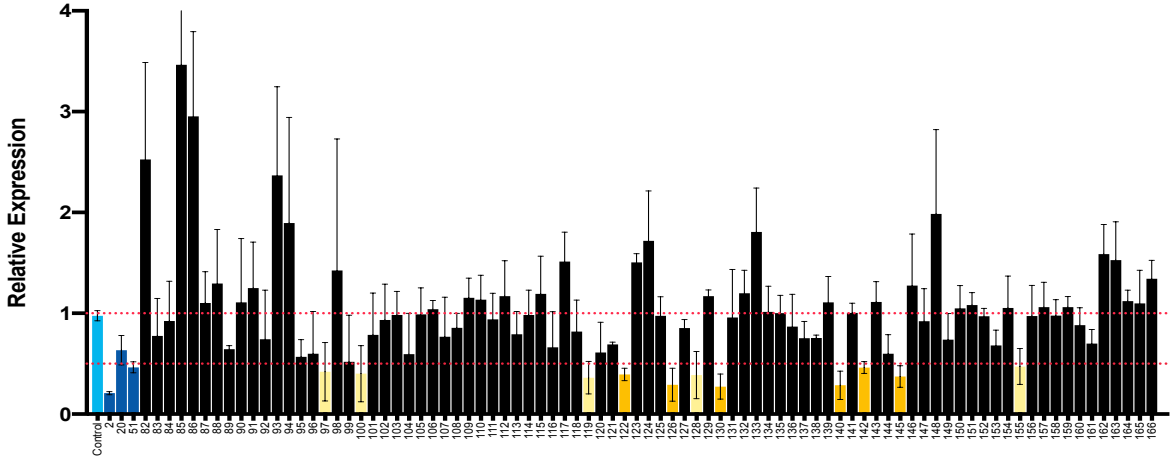
gRNA optimization

Modalis has screened over >100 gRNAs and identified candidates

sgRNAs covering the FSHD-associated D4Z4 repeat array (including the DUX4 gene), as well as nearby regulatory regions, were screened for their ability to inhibit DUX4 expression in patient-derived Cells

DUX4 Expression in GNDM-sgRNA Treated Cells Relative to Control



- Negative control guides
- Benchmark guides identified from initial screens
- Mean <50% expression, <60% expression 3x
- Mean <50% expression, <60% expression 2x

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Publication and conference presentations

Preclinical data for MDL-202 reported at multiple conferences

Past presentation

2025 Myotonic Dystrophy Foundation (MDF) Conference（URL；2025 MDF Conference | Myotonic Dystrophy Foundation）

Title : Myotonic dystrophy type 1 (DM1) treatment by CRISPR-GNDM® mediated suppression of DMPK mRNA
Date and Time: May 1st 2:30-5:45PM EST & May 3rd 2:30-5:45PM EST
Session : Pharma Day & Industry Updates

Coming presentation

The 28th American Society of Gene & Cell Therapy （ASGCT） Annual Meeting

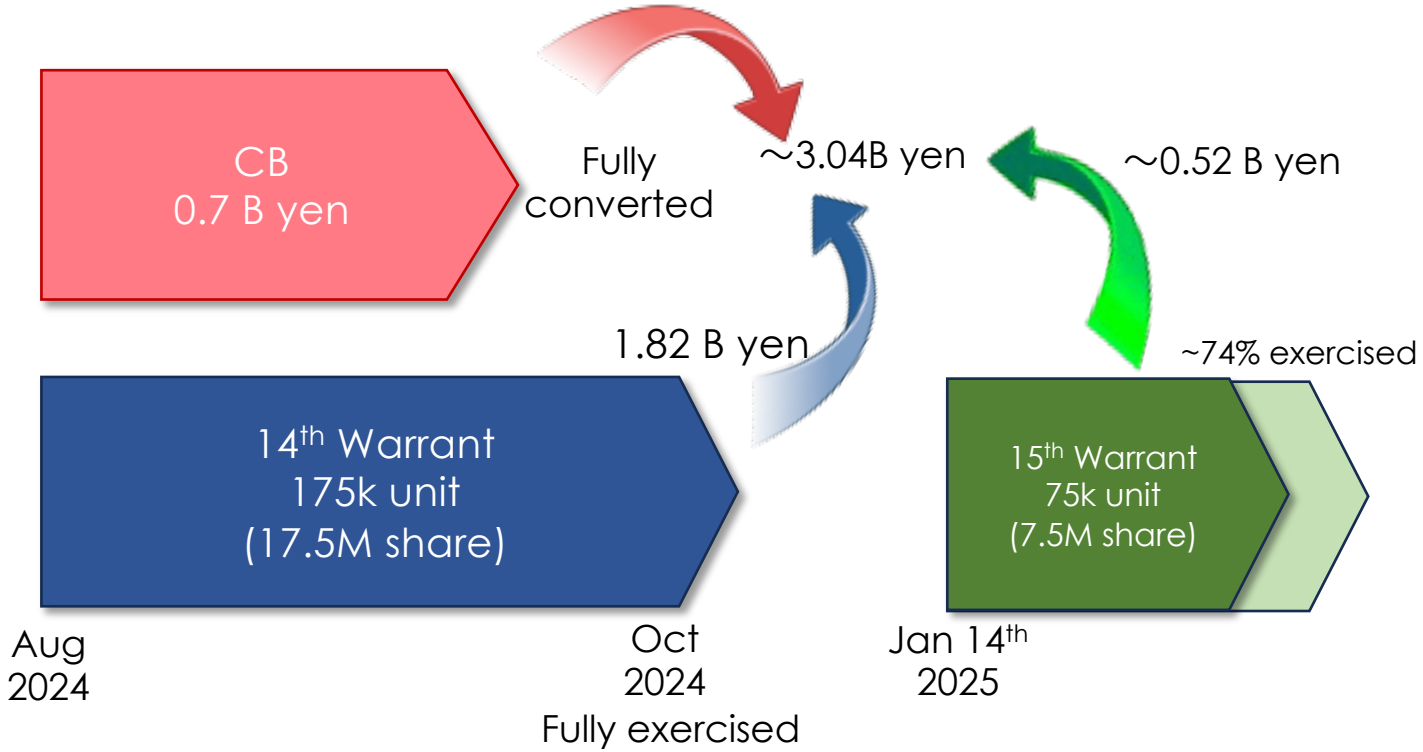
Title: Treatment of Myotonic Dystrophy Type 1 (DM1) by GNDM-mediated Suppression of the DMPK Gene
Date and Time : May 17th 10:45-11:00AM CST
Session : Gene Therapy for Muscle Diseases(Oral presentation)

Title : Nanopore Sequencing and Screening of AAV Genomes for Optimal Production and Function
Date and Time : May 13th 6:00-7:00PM CST
Session: Poster

Updated

Status of CB/warrant finance

The 15th series of SO initiated ahead of schedule. >70% had been exercised by the end of April



As of the end of April 2025. As reported in the monthly exercise status.

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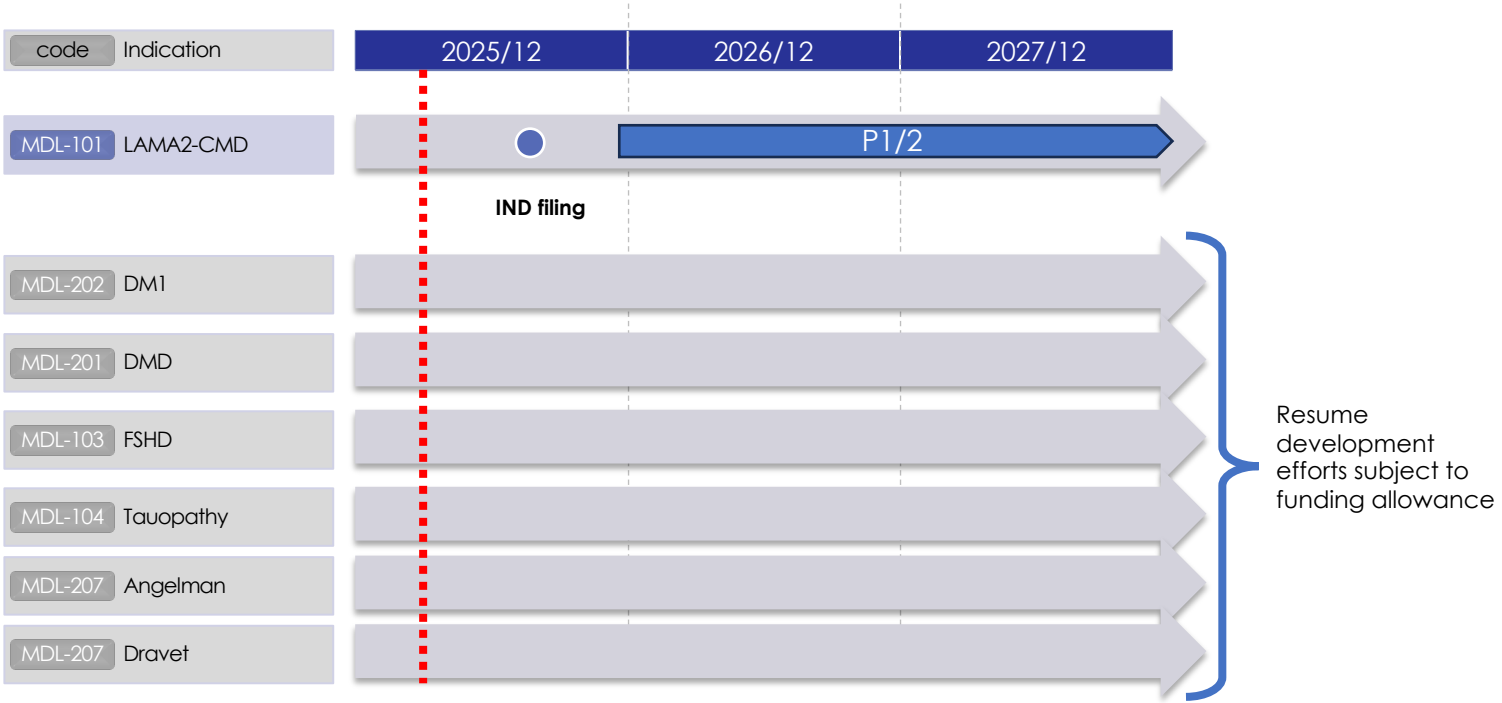
Updated

Pipeline status and coming milestones

Development continues with the aim of entering clinical trials for MDL-101 in 2025.

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 • Establishment of manufacturing process • ODD (Sep) and RPDD (Oct) received • Data presentation (July, Aug, Sep and Dec)	• GLP-Tox • GMP manufacturing • IND (2025)

その他	• Established animal PoC
	  • MDL-201 (DMD)
	  • MDL-202 (DM1)
	  • MDL-104 (Tauopathy)
	  • MDL-205 (Angelman syndrome)
	  • MDL-207 (Dravet syndrome)
	• MDL-103 (FSHD)
	• MDL-105 (DCM)
	• Research collaboration with JCR moved to the 2nd phase.
	• Collaboration with Ginkgo Bioworks, GenixCure
		• Benchmark study with new version capsid(201)
		• **Data presentation at (MDF conference and ASGCT : MDL-202)**
		• 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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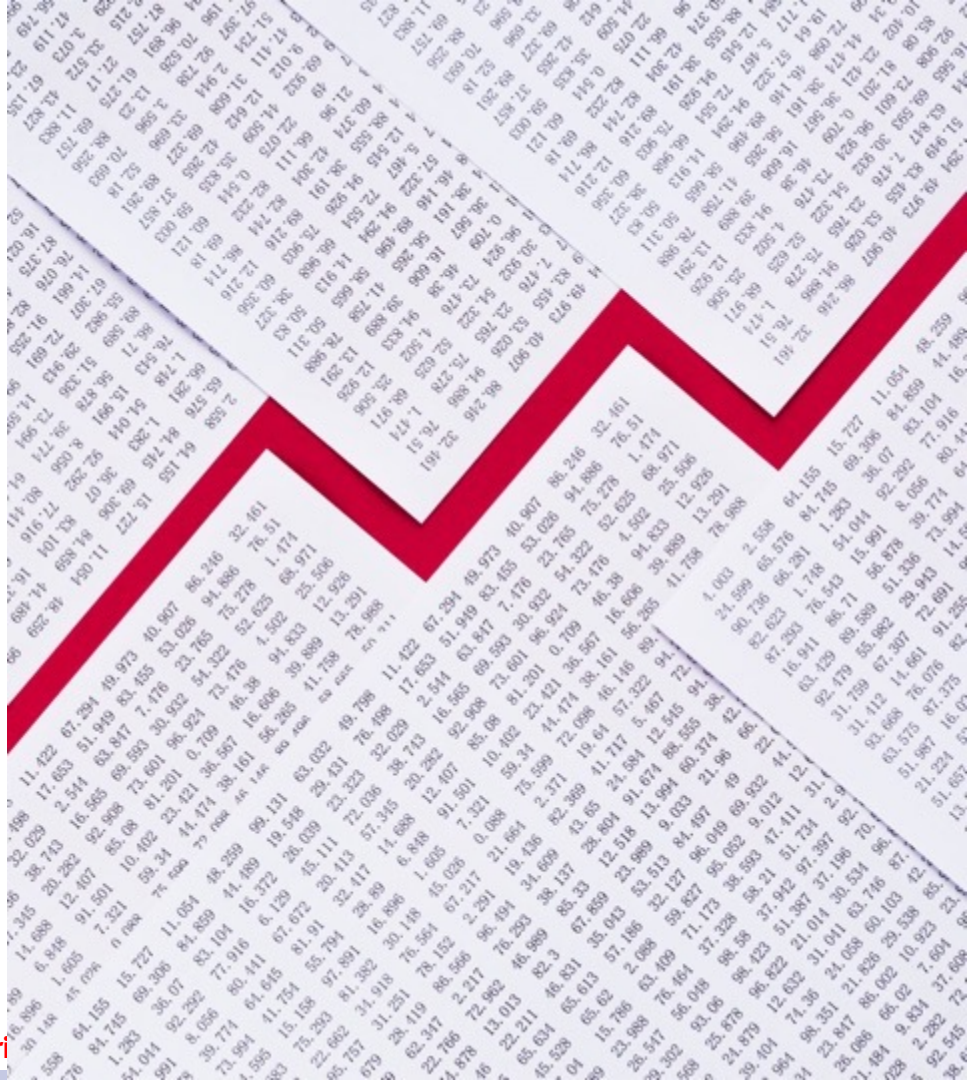
2. Financial reports



BS & Financial Position at the end of 1Q/2025

(Million Yen)

	End of FY2024 (A)	1Q FY2025 (B)	(B) – (A)
Current assets	3,617	3,606	△10
Cash & deposits	3,575	3,559	△15
Non-current assets	74	69	△4
Total assets	3,691	3,676	△14
Current liabilities	117	342	225
Non-current liabilities	26	21	△4
Total liabilities	143	364	220
Total net assets	3,548	3,312	△235
Total liabilities and net assets	3,691	3,676	△14
Capital adequacy ratio	95.5%	89.5%	

Note

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

PL & Business Result at the end of 1Q/2025

(Million Yen)

	1Q FY2024 (A)	1Q FY2025 (B)	(B)−(A)
Operating revenue	-	-	-
Operating expenses	490	632	142
R&D	422	571	149
SGA	67	61	△6
Operating income	△490	△632	△142
Ordinary income	△457	△651	△194
Current Profit	△457	△652	△194

Operating expenses

- Expenses will increase due to progress in preclinical trials and investigational drug manufacturing for clinical trials of MDL-101.

3. Growth Strategy

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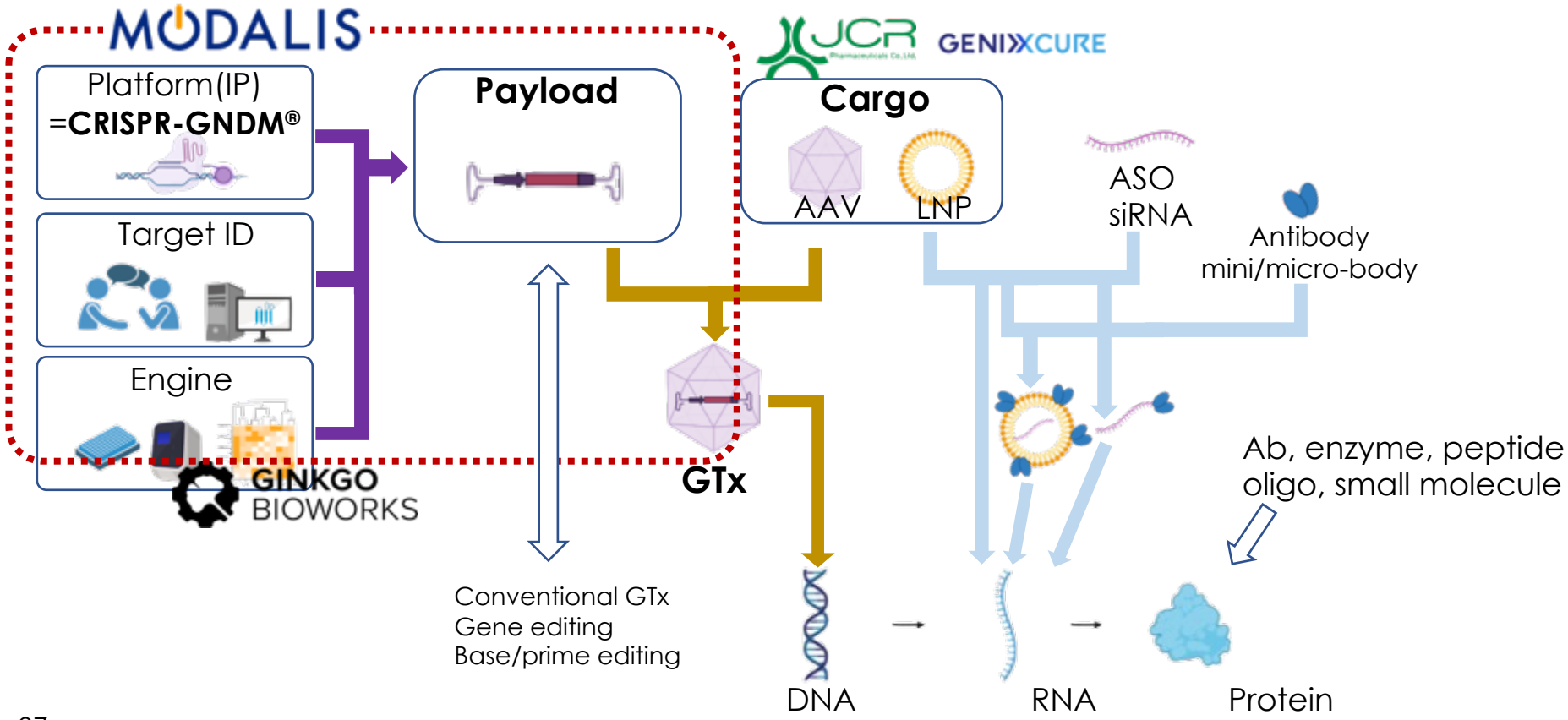
New

MODALIS' core competence and collaboration

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



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Diversified pipeline with their own missions

Pioneer the gene modulation With highly suitable indications

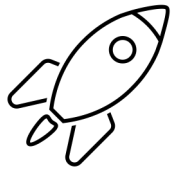
MDL-101

Expand technology opportunity with products for larger opportunity

MDL-201
MDL-202

Further approach to challenging applications

Other programs



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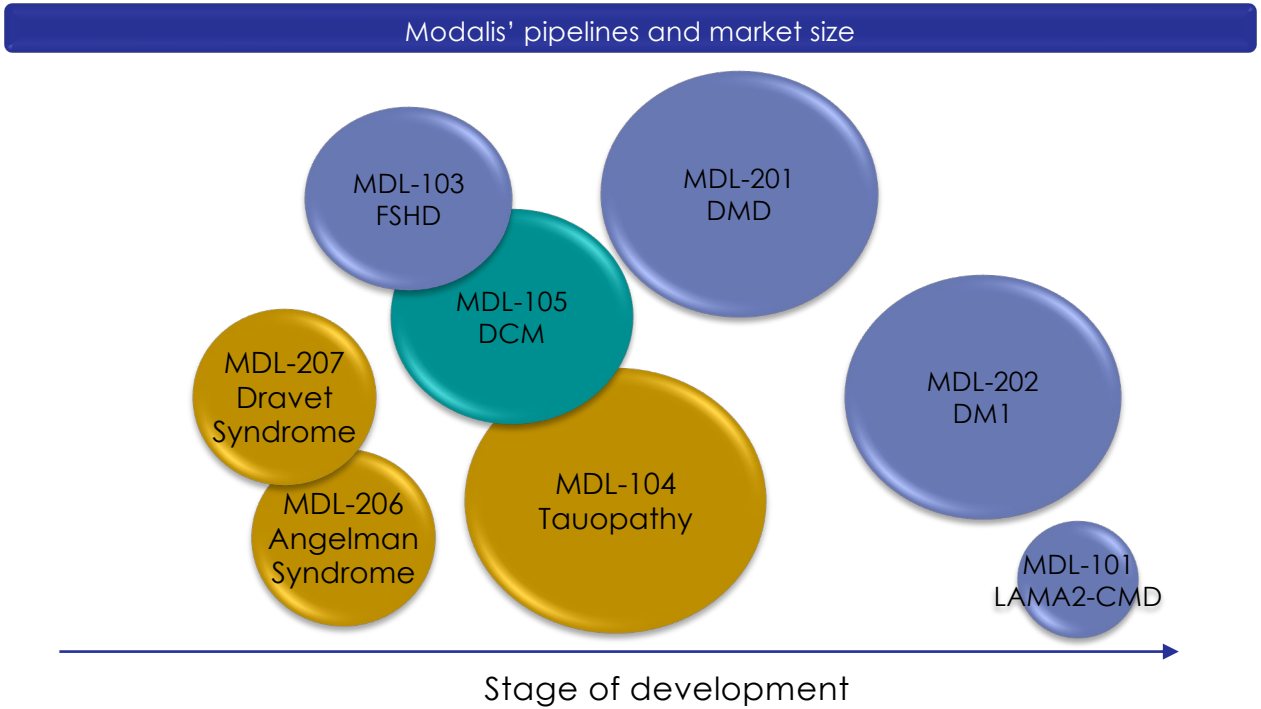
Modalis' pipelines and market size

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

3. summary

Key Takeaway of 2025 1Q report

1. Development of lead program MDL-101 continues with IND targeted for 2025
   - Received **ODD and RPDD** designations (ODD at the end of October)
   - IND enabling studies and GMP manufacturing are underway.

2. Development of DMD treatment MDL-201, which has the same mechanism to MDL-101, has resumed. Overcame the challenge of previous version, potentially becoming a **best-in-class** DMD product

3. Joint research with JCR is progressing. Moving to **Step 2**

Modalis Therapeutics

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- 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

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Q1: How much impact will the US policy change have?

- Since the beginning of the year, various policy 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.