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In case of any discrepancy, the Japanese version shall prevail

The fiscal year end of 2025
Business and Financial report



(TSE：4883)

Modalis therapeutics Corporation

February 12th, 2026

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MODALIS



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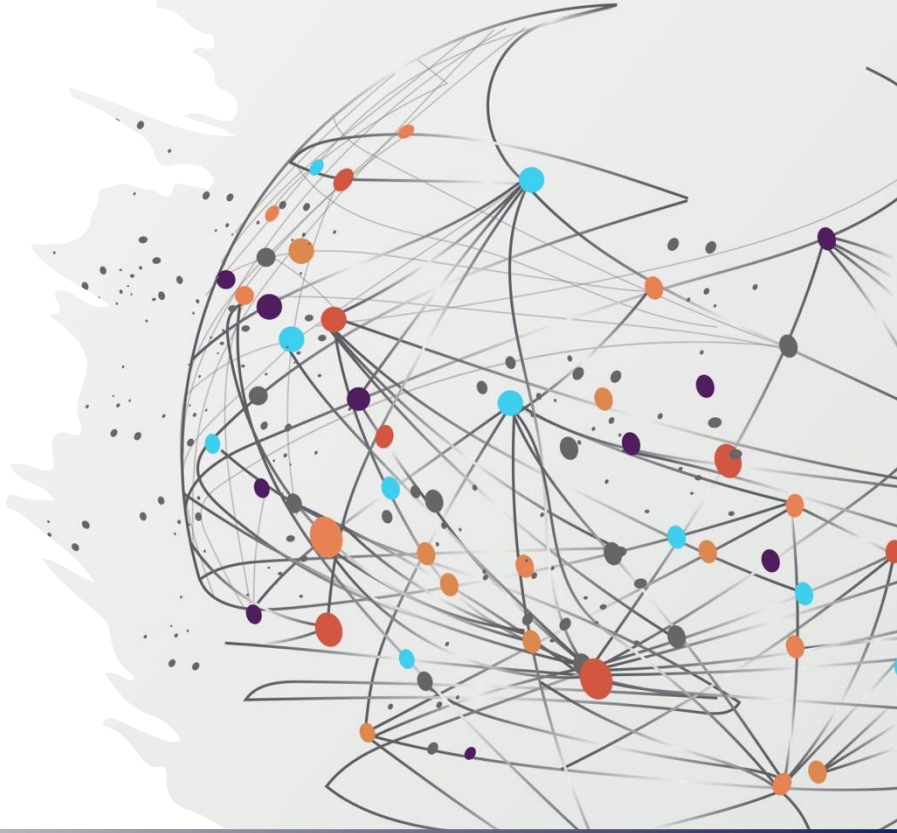
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About Modalis



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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 across species resulting in functional **efficacy without serious toxicities**

Pipelines 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 programs

Experienced team with deep knowledge of platform

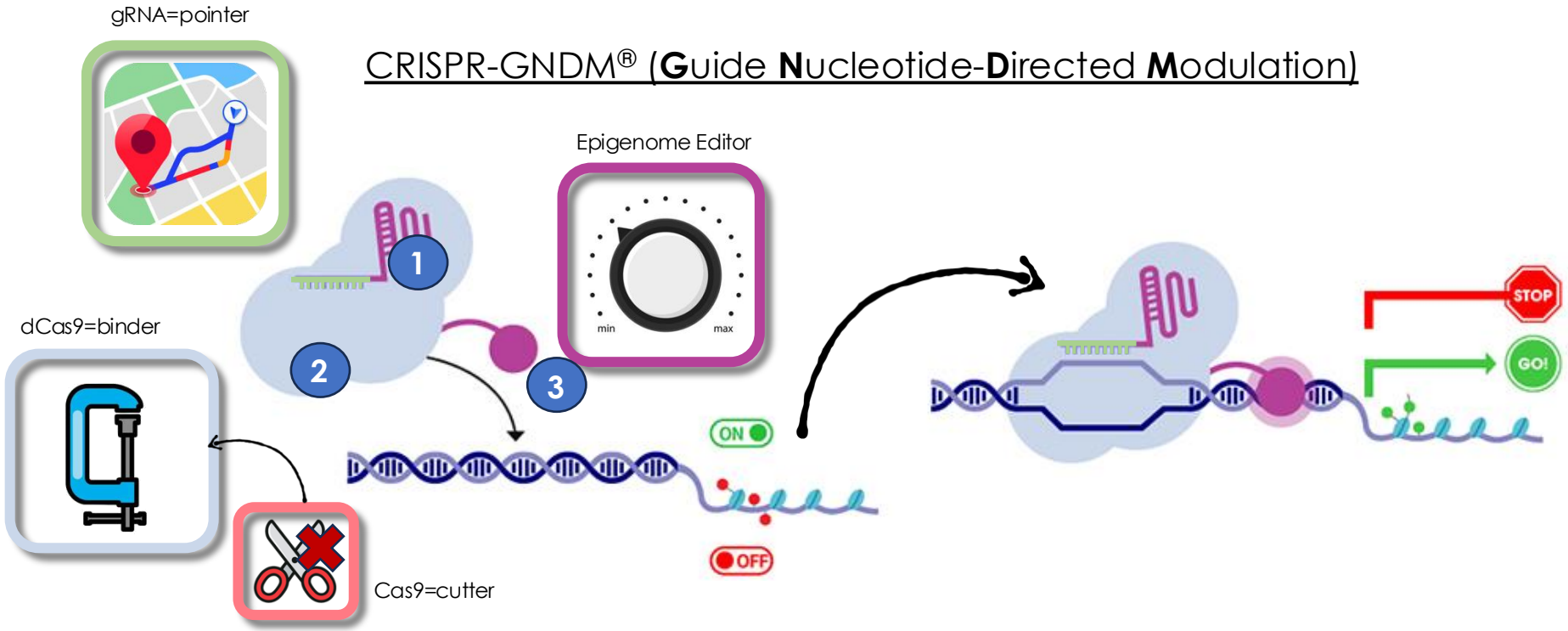
Strong **IP portfolio and strategy** that includes granted and licensed patents

Clear regulatory and clinical path in place based on recent FDA guidance and commnnuications

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CRISPR-GNDM®

GNDM controls the expression of target proteins through epigenetic regulation

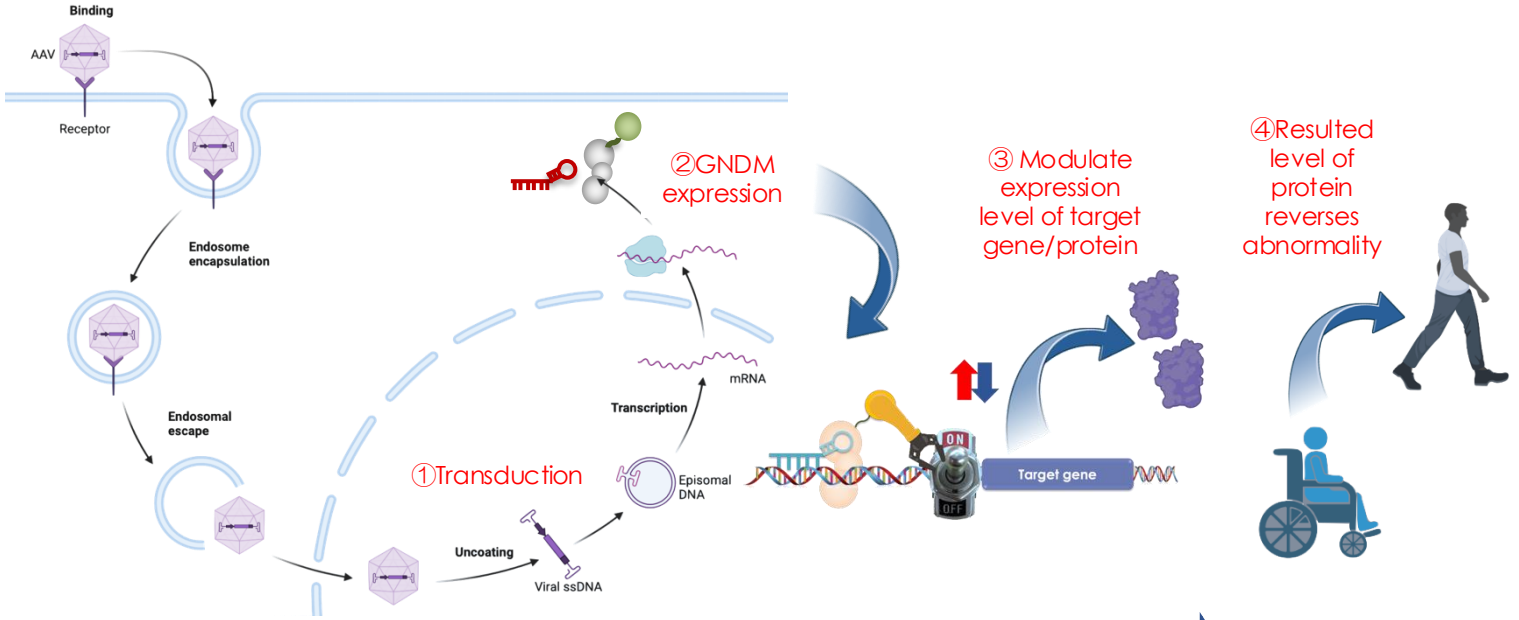


CRISPR-GNDM® consists of: ① a "guide RNA (gRNA)" for positioning, ② 'dCas9' as the binding device to DNA, ③ an "editor" for editing the epigenome, enabling precise control over gene expression on and off.

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Delivery of GNDM to the target

Packed in a vector, GNDM is delivered to target cells and selectively controls the expression of the target gene

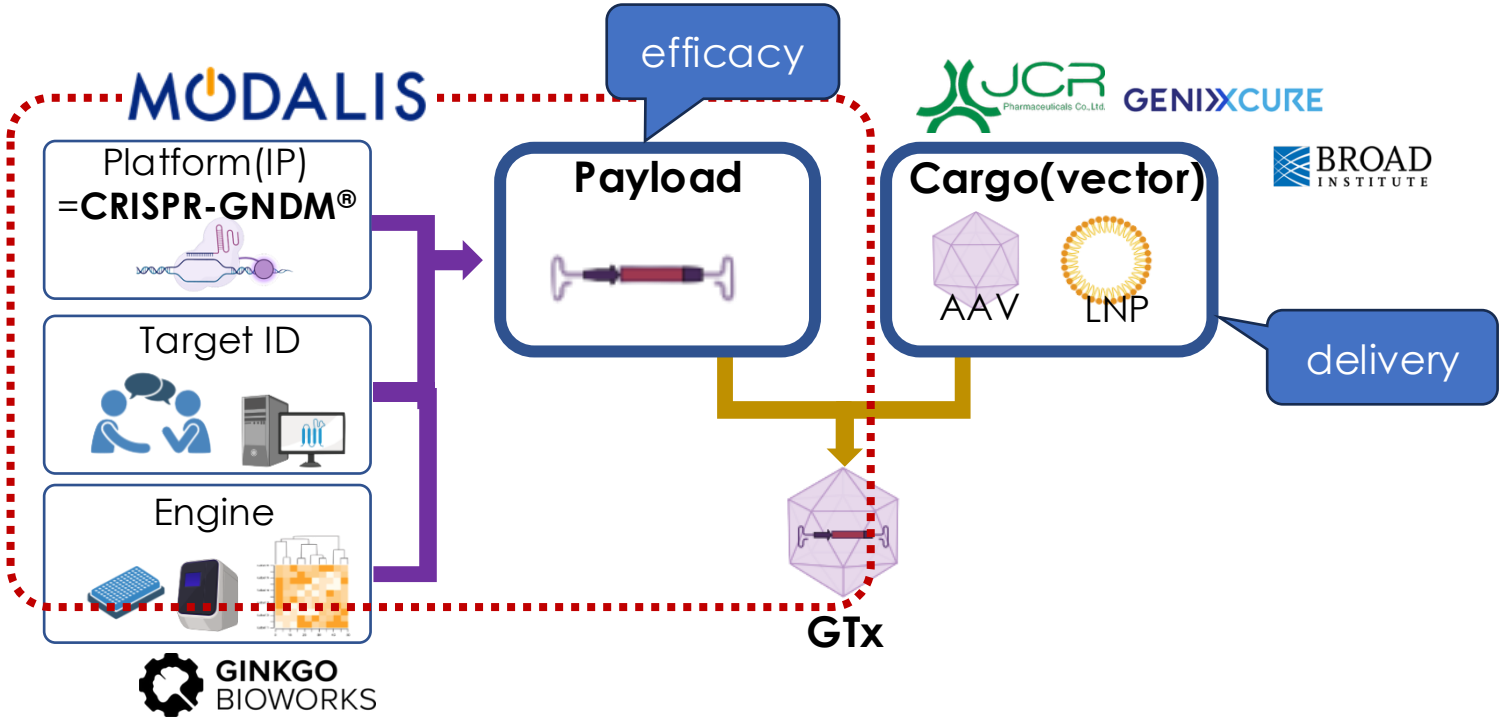


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Updated

MODALIS' core competence and collaboration

For GTx, the payload—the active component—and the cargo (vector) that delivers it to the target tissue are crucial

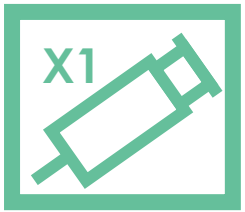


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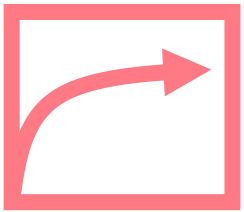
CRISPR-GNDM®'s advantages

A single injection provides long term disease modifying effect

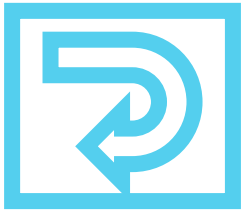
Potential benefits of CRISPR-GNDM® Technology



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

The field is gaining more traction and MODALIS is uniquely differentiated from the other epigenome companies

Company	Year Founded	Funding	Platform	Pipeline/Target indication	Stage of Development
MODALIS	2016	Public	CRISPR-GNDM x AAV	MDL-101 for LAMA2-CMD **Gene activation**	IND enabling
Tune	2020	Series B ($175M, 2025)	DNMT-KRAB fusion dCas9 x LNP	Une-401 for HBV **Gene suppression**	**CTA approval from Hongkong, NZ and Moldova on HBV**
nChroma	2021	Merged into nChroma (Dec 2024)	DNMT-KRAB fusion dCas9 x LNP	CRMA-1001 for PCSK9 **Gene suppression**	**P1/2**
Epicrispr	2022	Series B ($68M, 2025)	Cas12f-fused with demethylation enzyme x AAVrh74	EPI-321/FSHD **Gene suppression**	P1/2
Epigenic	2022	Series B ($60M, 2025)	dCas+editor x LNP	EPI-001 PCSK9 for hypercholesteremia Gene suppression	Chinese IIT
Scribe	2018	**SerC? ($75M, 2025)**	dCas+repressor x LNP	**STX1150** PCSK9 for hypercholesteremia **Gene suppression**	**IND enabling**
Mammoth	2017	**Corp.Minority ($2024, $95M)**	miniCas x editor x LNP	**MB-111** APOC3 for Triglycemia **Gene suppression**	**IND enabling**

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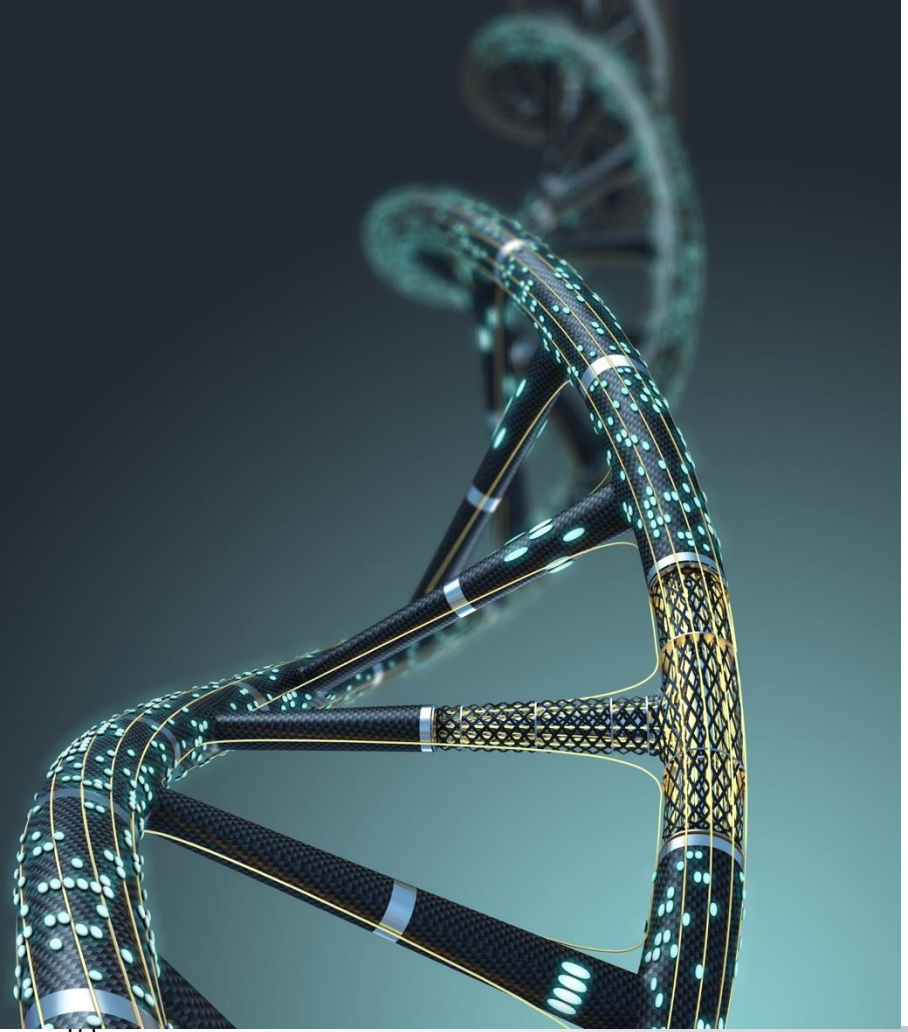


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1. Business Highlights of the 4Q/2025

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Progress in MDL-103(FSHD)

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Progress in IPs

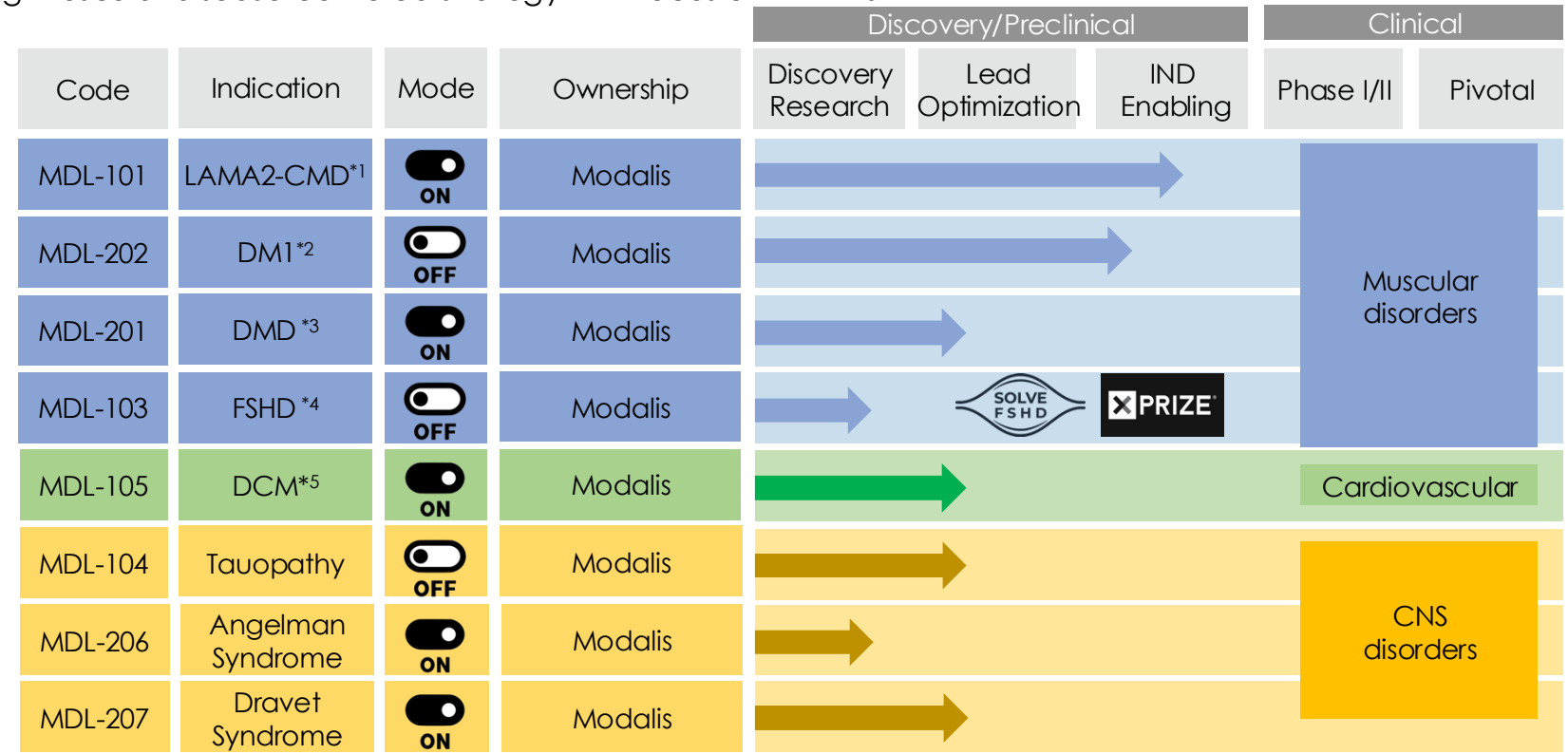
04

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

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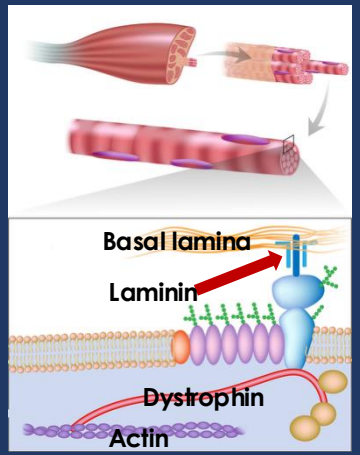
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LAMA2-CMD (aka CMD1a)

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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Progress towards the FIH trial

Development update of MDL-101

- GLP Toxicity Study
  - The in-life phase has passed the 3-month mark and is awaiting 6 months of data.
- Mouse IND Enabling
  - Study progressing smoothly. Interim analysis demonstrated significant survival and functional recovery effects compared to the control group in the disease model, with no issues expected for completion.
- Manufacturing
  - Investigational drug AAV manufacturing (GMP) is underway.
- Clinical Trial Preparation
  - Interviews with US trial candidate sites/PI completed. Selection in progress.
  - For clinical trials outside the United States, a memorandum of understanding has been signed with the pharmaceutical company in the relevant country regarding the conduct of the trial and future sales within the region.
  - Preparing for various evaluation studies.









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Key Points for Plan Revision

Confirm biological validity and promote optimization for clinical transition

1. Biological foundation maintained and strengthened

- Clear survival time extension compared to control group confirmed in IND enabling studies using disease model mice
- Mechanism of action and pharmacological efficacy consistently supported
- No new safety concerns identified at this time
- No change to the treatment concept itself

2. Refinement of Development for Clinical Transition

- Conduct additional analyses to enhance certainty of transition to clinical phase
- Strengthen translational reproducibility through refinement of development parameters
- Maximize success probability through data-driven decision-making

3. Clear Next Steps

- Complete additional analysis and optimize development plan
- Ensure alignment with regulatory authorities
- Reviewing IND filing timing to ensure optimal clinical readiness
- Conduct site preparation in parallel

By prioritizing the optimization of biological and clinical readiness, we aim to maximize the probability of long-term clinical succes

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Publication

Preclinical trial data for our MDL-101 published in *Human Gene Therapy*

Efficient LAMA1 Gene Activation by Epigenome Editing as a Therapeutic Approach for LAMA2-CMD

Yuanbo Qin, Talha Akbulut, Rajakumar Mandraju, Keith Connolly, John Bechill, Farzaneh Assadian, Claudia Foster, Alison Shottek, Seth Levy, Jamie Benoit, and Tetsuya Yamagata

Modalis Therapeutics, Inc., Waltham, Massachusetts, USA.

Epigenome editing technology holds great promise for treating diverse genetic disorders. In this study, we demonstrate epigenetic activation of the *LAMA1* gene for the treatment of *LAMA2*-CMD, a severe congenital muscle dystrophy (CMD) caused by biallelic mutations in the *LAMA2* gene. *LAMA1* is a sister homolog that is known to compensate for the function of *LAMA2*. However, supplementing *LAMA1* or *LAMA2* gene via viral platform is not feasible due to the large size of their coding sequences. Through a single administration of our adeno-associated virus (AAV) vector encoding all the necessary elements for epigenetic activation, we observed significant *LAMA1* gene upregulation and phenotype improvements in mouse disease models. The muscle-tropic AAV capsid exhibited desired vector biodistribution and promising pharmacodynamics with good safety profiles in 2-year-old juvenile nonhuman primates (NHPs). Moreover, administration to 8-month-old infant NHPs demonstrated superior pharmacodynamics compared with 2-year-old juveniles, even at half the dose. Our approach holds broad applicability for a range of loss-of-function genetic disorders and could offer a therapeutic breakthrough where active epigenome offers clinical benefit.

Keywords: gene therapy, epigenetic editing, CRISPR, LAMA1, LAMA2-CMD, MDC1A, AAV

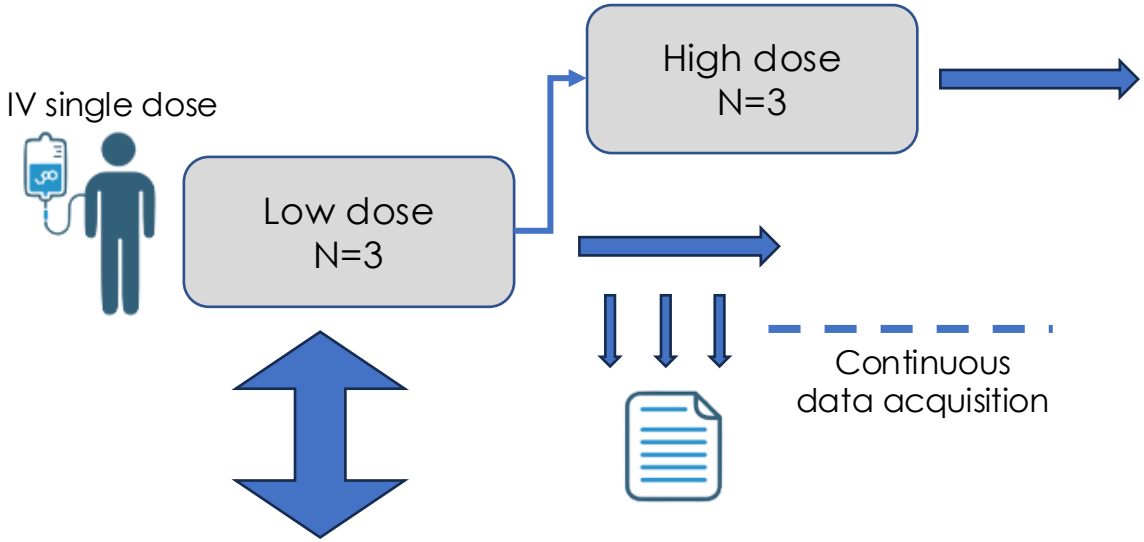
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MDL-101-001 Trial design

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)

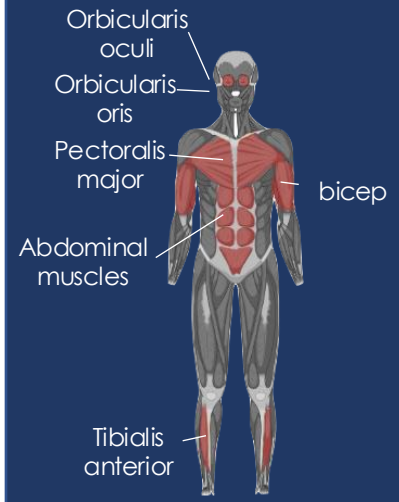
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Facioscapulohumeral Muscular Dystrophy (FSHD)

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+**	

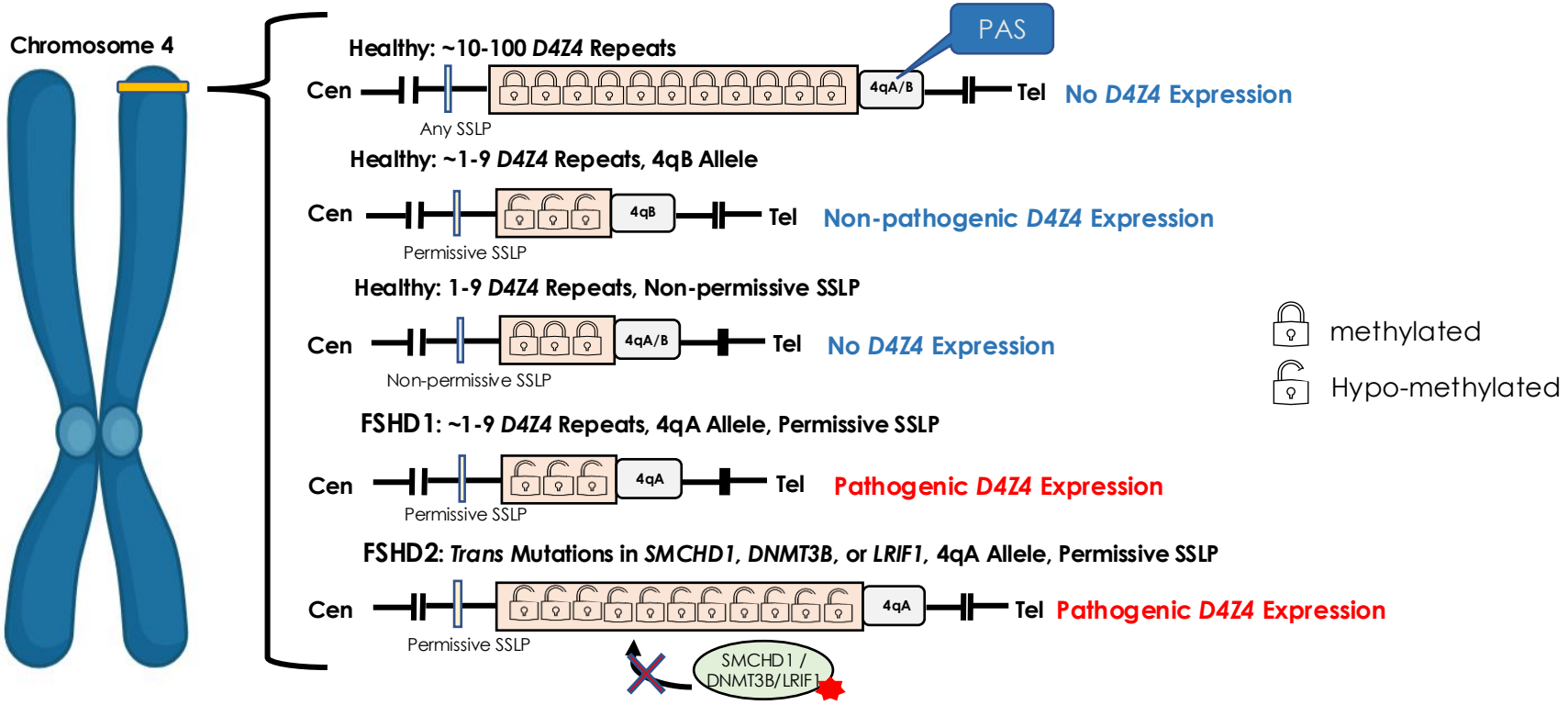
Source: https://doi.org/10.1212/WNL.0000000000011425
Orphanet, Raymond A. Huml MD A concise guide

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FSHD disease mechanism

Inappropriate expression of toxic Dux4 in skeletal muscles



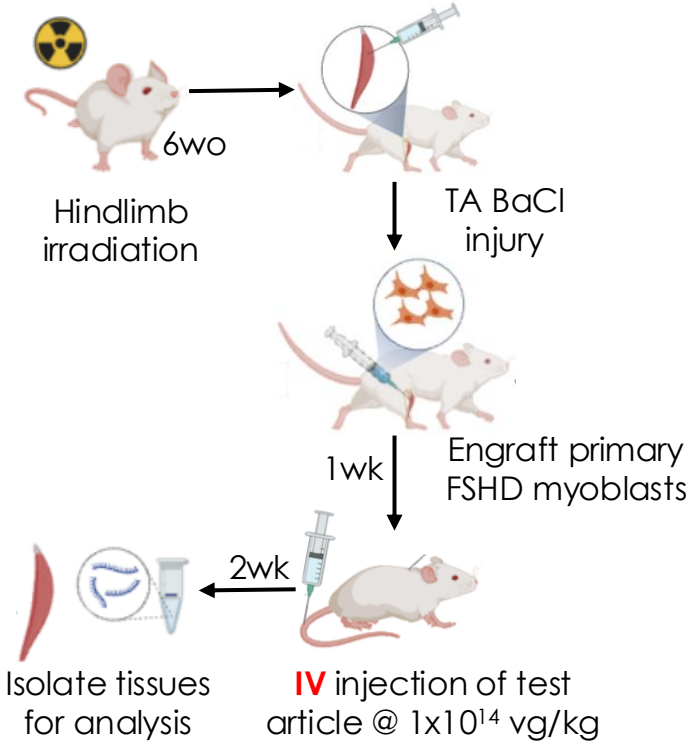
DeSimone et al. 2020, *Dis Model Mech*

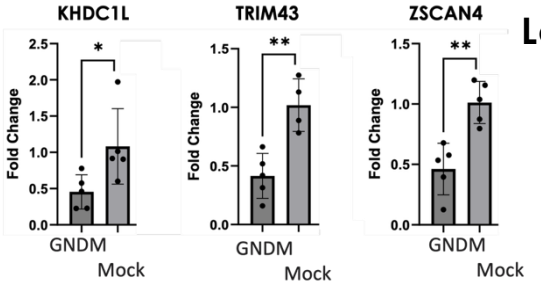
SSLP: Simple Sequence Length Polymorphism PAS: polyadenylation signal

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The DUX4 downstream gene was even strongly suppressed by systemic administration

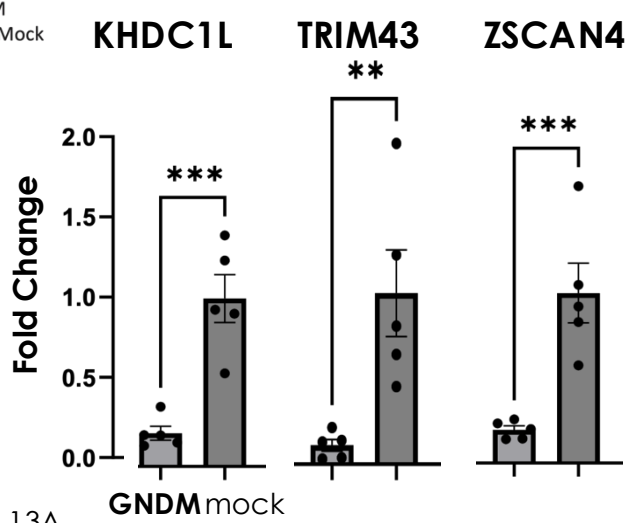
Expression of DUX4-Target Genes In Xenografted human muscle





Local(*i.m.*) injection

Systemic(i.v.) injection



- N=5 Normalized to hRPL13A
- Statistical significance by 1-way ANOVA with Dunnett's test

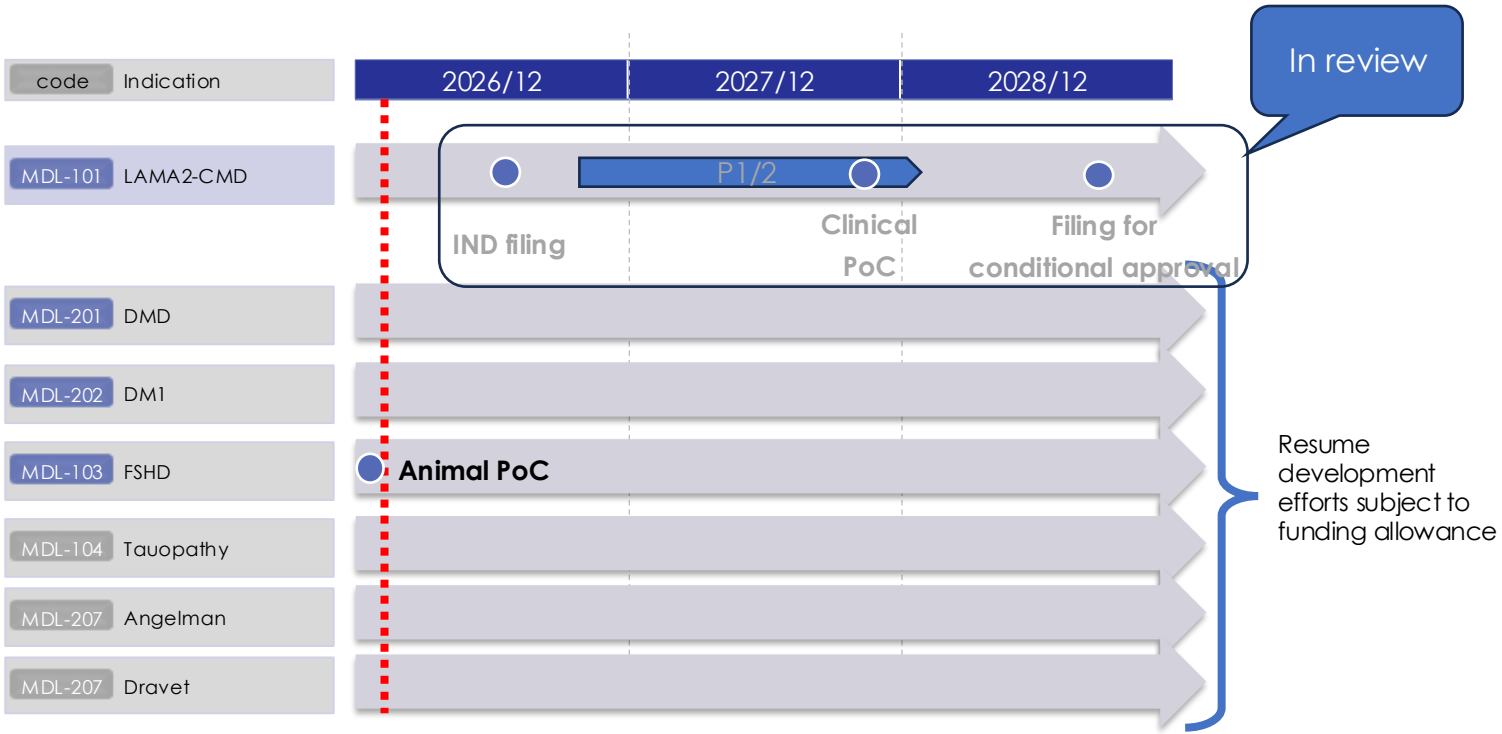
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Updated

Pipeline status and coming milestones

Target filing for conditional approval in later 2028

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 NHP ✓ Pre-IND ✓ GMP manufacturing (Plasmid) ✓ ODD and RPDD designation ✓ **Publication on HGT (Dec)**	☐ Completion of GLP-Tox (1H) ☐ Completion of Mice IND enabling(1H) ☐ Completion GMP manufacturing(1H) ☐ IND (mid 2026) ☐ FPFD (late 2026) ☐ **Clinical PoC (2027~2028)** ☐ **Filing for conditional approval(2028)**

その他	• Established animal PoC
	  • MDL-201 (DMD)
	  • MDL-202 (DM1)
	  • **MDL-103 (FSHD)**
	  • MDL-104 (Tauopathy)
	  • MDL-205 (Angelman syndrome)
	  • MDL-207 (Dravet syndrome)
	• Research collaboration with JCR in CNS
	• Collaboration with Ginkgo Bioworks, GenixCure
		• 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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Progress on IP

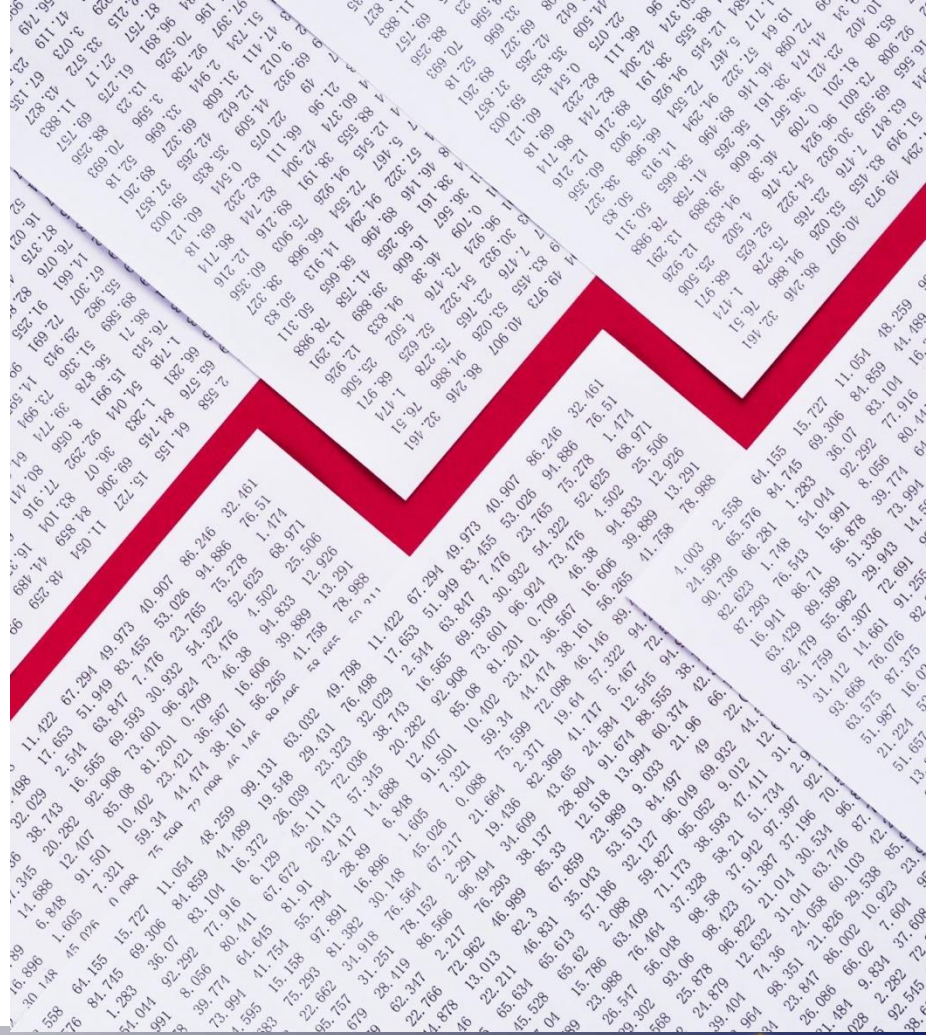
Three patents were granted in Japan in 2025

- Patent “Method for Treating Muscular Dystrophy Targeting the LAMA1 Gene” related to **MDL-101,** the lead program drug for LAMA2-CMD, registered in Japan (Patent No. 7641644) (March)
- Patent related to **MDL-103**, targeting the DUX4 gene for the treatment of facioscapulohumeral muscular dystrophy (FSHD), registered in Japan (Patent 7736329) (September)
- Patent related to **MDL-104**, a therapeutic agent for tauopathies including Alzheimer's disease, “Therapeutic method for Alzheimer's disease targeting the MAPT gene” (Patent 7749244) registered in Japan (October)



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2. Financial updates at the end of FY2025



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BS & Financial Position at the end of 2025

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

(Million Yen)

	End of FY2024 (A)	End of FY2025 (B)	(B) – (A)
Current assets	3,617	2,892	△724
Cash & deposits	3,575	2,812	△762
Non-current assets	74	71	△2
Total assets	3,691	2,964	△727
Current liabilities	117	134	17
Non-current liabilities	26	36	9
Total liabilities	143	170	27
Total net assets	3,548	2,793	△773
Total liabilities and net assets	3,691	2,964	△727
Capital adequacy ratio	95.5%	93.0%	

Note

- Despite the exercise of stock acquisition rights, cash and deposits decreased due to the increase in expense.

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BS & Financial Position at the end of 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 3Q FY2025 (B)	(B) – (A)
Current assets	24,113	19,281	-4,832
Cash & deposits	23,835	18,749	-5,086
Non-current assets	496	479	-16
Total assets	24,610	19,761	-4,848
Current liabilities	782	898	116
Non-current liabilities	174	240	66
Total liabilities	956	1,139	183
Total net assets	23,653	18,270	-5,156
Total liabilities and net assets	24,610	19,761	-4,848
Capital adequacy ratio	95.5%	93.0%	

Note

- Despite the exercise of stock acquisition rights, cash and deposits decreased due to the increase in expense.

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PL & Business Result at the end of 2025

2,211 million in operating expenses, mainly due to the cost of related to MDL-101 program

(Million Yen)

	FY2024 (A)	FY2025 (B)	(B)−(A)
Operating revenue	-	-	-
Operating expenses	1,337	2,211	874
R&D	1,092	1,979	887
SGA	245	231	△13
Operating income	△1,337	△2,211	△874
Ordinary income	△1,303	△2,148	△845
Current Profit	△1,317	△2,152	△834

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

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PL & Business Result at the end of 2025

$14.7M in business expenses, mainly due to the cost of related to MDL-101 program

(In thousand USD at @150yen/$)

	3Q FY2024 (A)	3Q FY2025 (B)	(B)−(A)
Operating revenue	-	-	-
Operating expenses	8,917	14,745	5,827
R&D	7,281	13,200	5,918
SGA	1,636	1,545	-91
Operating income	-8,917	-14,745	-5,827
Ordinary income	-8,687	-14,324	-5,636
Current Profit	-8,786	-14,351	-5,565

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

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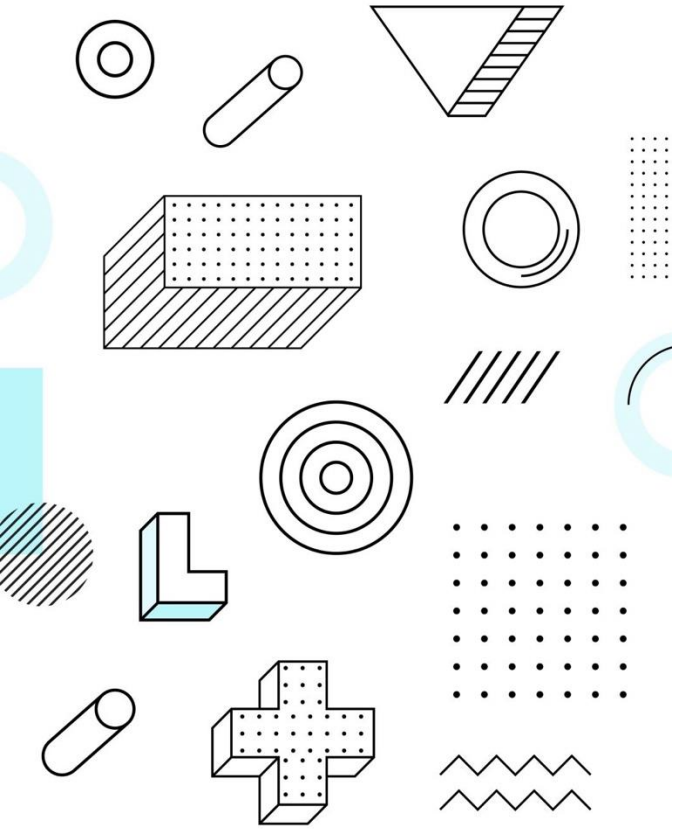


3. Growth Strategy

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Three-phase Growth Strategy

Diversified pipeline with their own missions



Pioneer the gene modulation
With highly suitable indications

MDL-101

Expand technology opportunity with products for larger opportunity

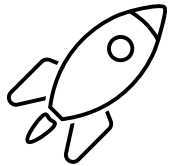
MDL-201
MDL-202

Further approach to challenging applications

Other programs





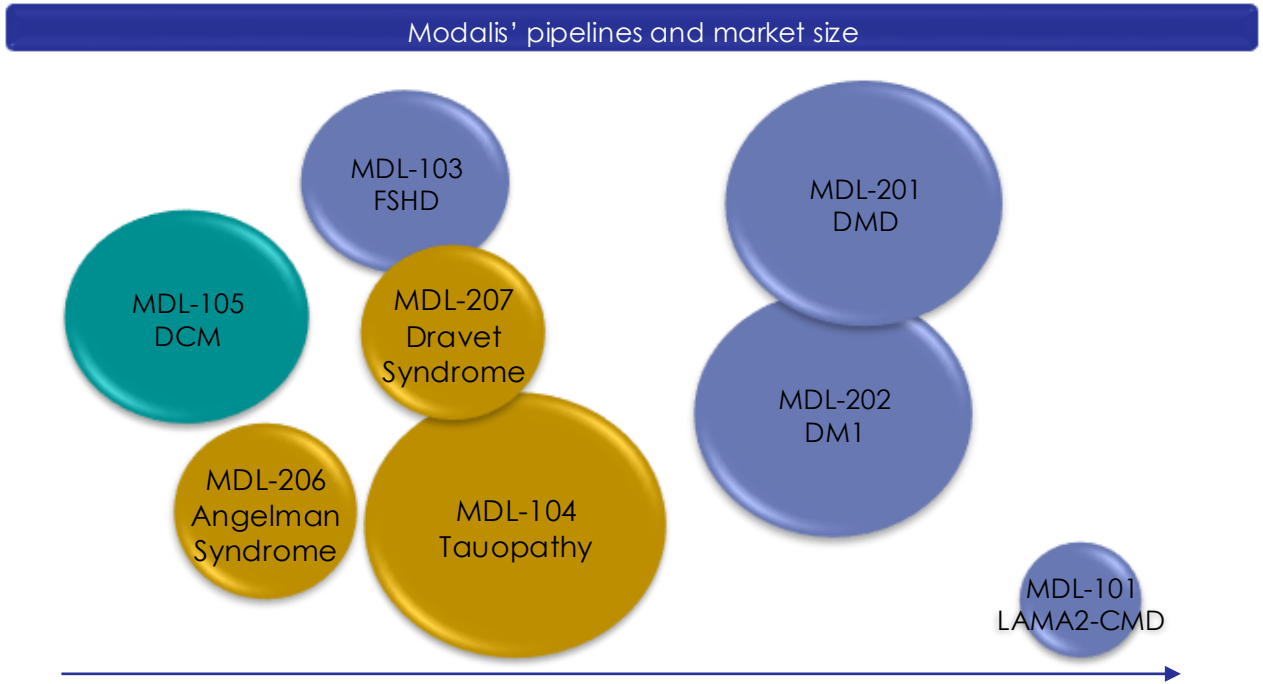


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Updated

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

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4. summary

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Key Takeaway of 2025 full year report

1. Preparations for the MDL-101 clinical trial application are in their final stages. Work is progressing smoothly toward the mid-year application target

2. Reported outlook for clinical trial plans. Set targets of Clinical Proof of Concept in 2027-28 and conditional approval application in 2028.

3. MDL-103 demonstrated robust efficacy in a disease model, establishing proof-of-concept in animals.

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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



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5. Q&A

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Q1. Is there a problem with the treatment concept of MDL-101 or GNDM itself?

- **A:** In IND-enabling studies using disease model mice, a clear survival extension effect has been confirmed compared to the control group, and the mechanism of action and pharmacological efficacy have been consistently supported. We recognize that this matter pertains to development optimization for clinical transition, not the therapeutic concept itself.

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Q2. Are there any safety concerns?

- **A**: At this time, no new safety concerns have been identified. Current efforts are primarily aimed at enhancing development certainty.

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Q3. Why is it necessary to review the timeline now?

- **A**: We prioritize biological and clinical readiness at the transition point to the clinical phase over adherence to a fixed schedule. We believe it is crucial to maximize the probability of long-term success through data-driven decision-making.

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Q4. What impact will this have on other pipelines and platforms?

- **A**: What impact will this have on other pipelines and platforms?

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Q5. What are the next specific milestones?

- **A:** Following the completion of additional analyses, confirmation of regulatory alignment, and finalization of the optimized development plan, we will proceed with preparations for the IND application.

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Q6. Does this not suggest an essential challenge regarding translation into human language?

- **A:** The data obtained to date consistently support the mechanism of action and pharmacological activity, including a clear survival extension effect in disease model mice. The current initiative aims not at biological validity itself, but at optimizing development parameters and enhancing translational reproducibility at the transition point to the clinical phase. Our company maintains its recognition of the therapeutic concept's viability.

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