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

2024 Fiscal Year End
Business and Financial report



(TSE：4883)

Modalis therapeutics Corporation

February 13, 2025

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About Modalis



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MODALIS Value Highlights

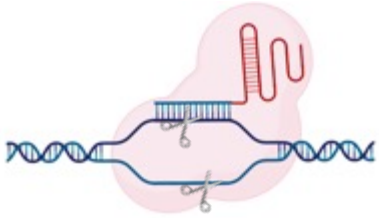
- Established the first robust **epigenetic platform** for activation and inhibition of endogenous genes using CRISPR-GNDM® platform
- Demonstrated sustained modulation of gene expression in multiple species (mouse, cyno) resulting in functional **efficacy without serious toxicities**
- Pipeline of preclinical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

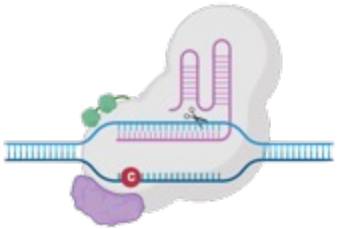
Enables treatment of genetic disorders by controlling epigenetic ON/OFF switch

GTx Technologies

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



Permanent Removal



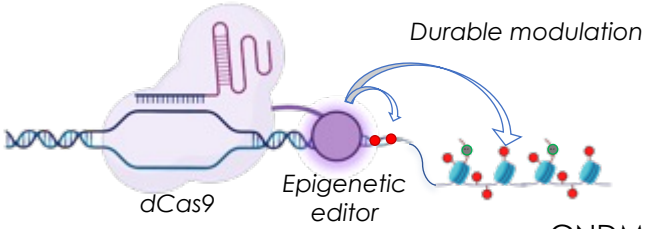
Permanent Replacement



Temporal silencing

Epigenome Editing(CRISPR-GNDM®)

Bind without cleaving
No DNA damage



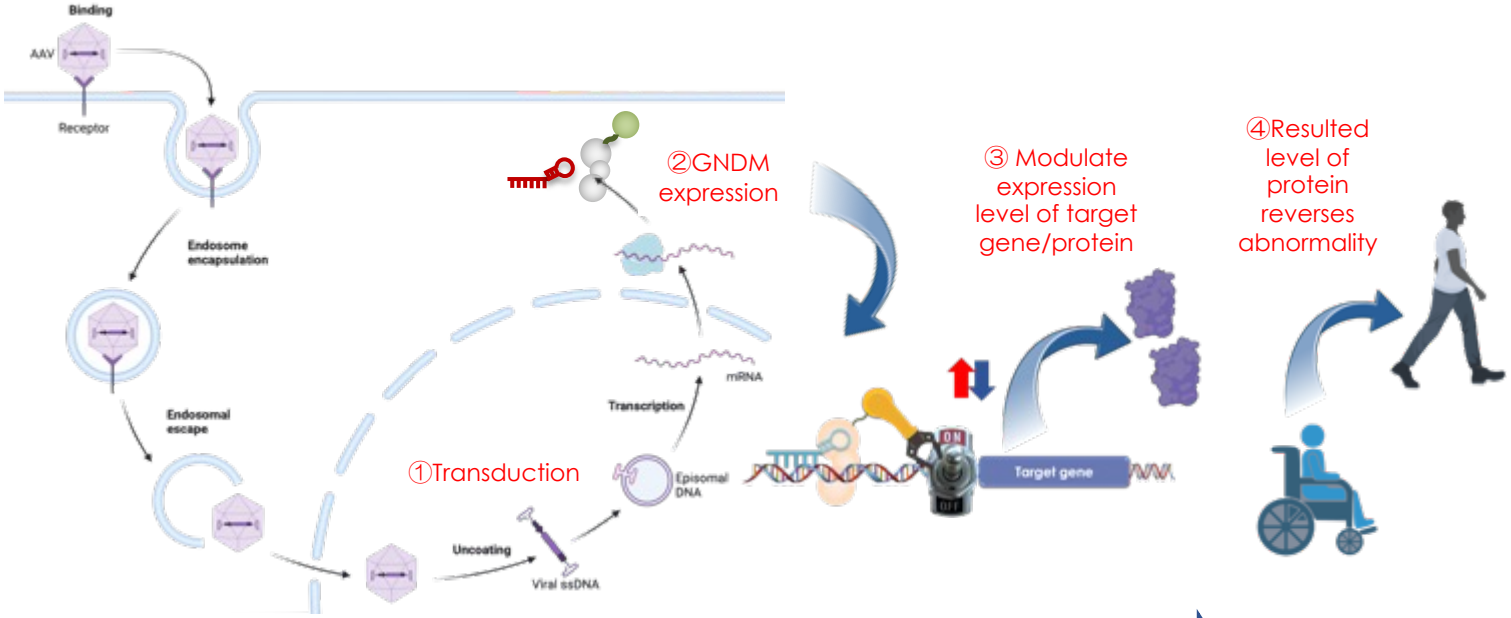
GNDM=Guide Nucleotide Directed Modulation

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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

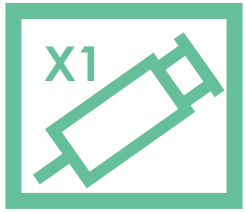


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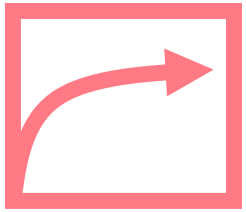
CRISPR-GNDM® is a promising new therapeutic modality

A single injection provides long term disease modifying effect

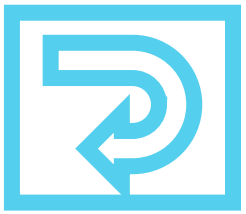
Potential benefits of CRISPR-GNDM® Technology



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

There was movement in the year-end to new year, and the survival of the fittest became clear

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 A ($55M Jul 2022)	Cas12f-fused with demethylation enzyme x AAVrh74	EPI-321/FSHD **Gene suppression**	IND enabling

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Table of contents

1. Topics of the 4Q and FY2024
2. Financial update
3. Growth strategy
4. Q&A

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1. Key Takeaway of the 3Q/2024 outcome

01

RPDD and ODD received from FDA

02

Paper and presentations

03

Advance in IP

04

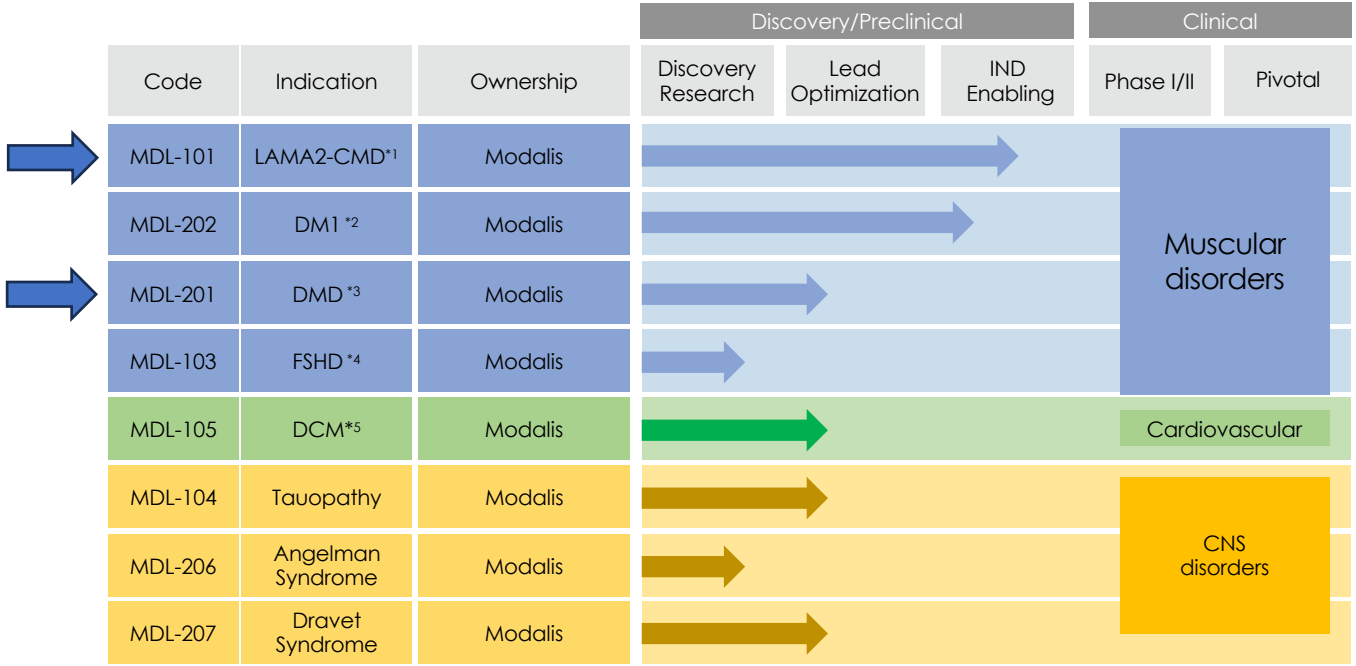
Finance and Others

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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

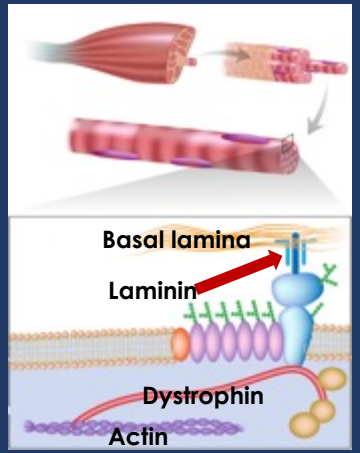
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LAMA2-CMD (aka CMD1a)

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)

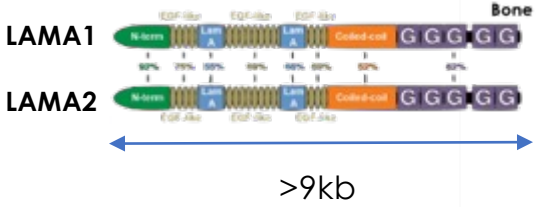
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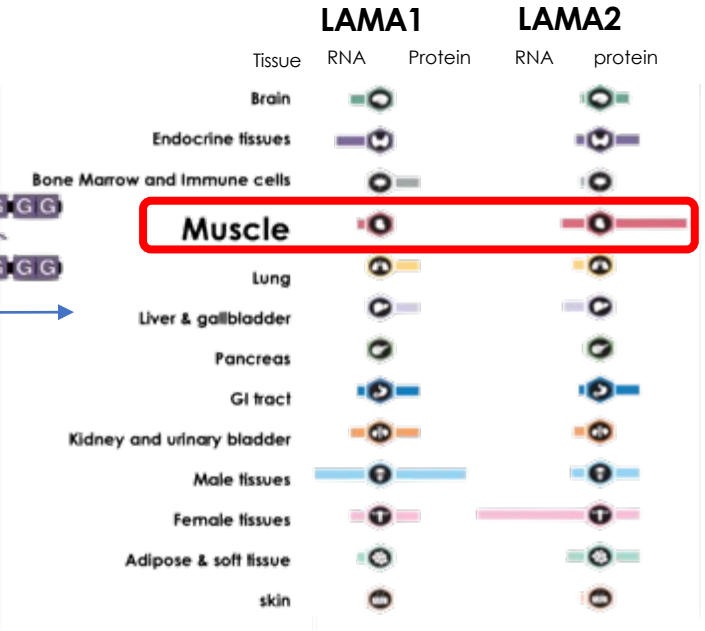
CRISPR-GNDM®'s mechanism of action on LAMA2-CMD

Turning on the sister gene LAMA1 for mutated LAMA2 to restore muscle function

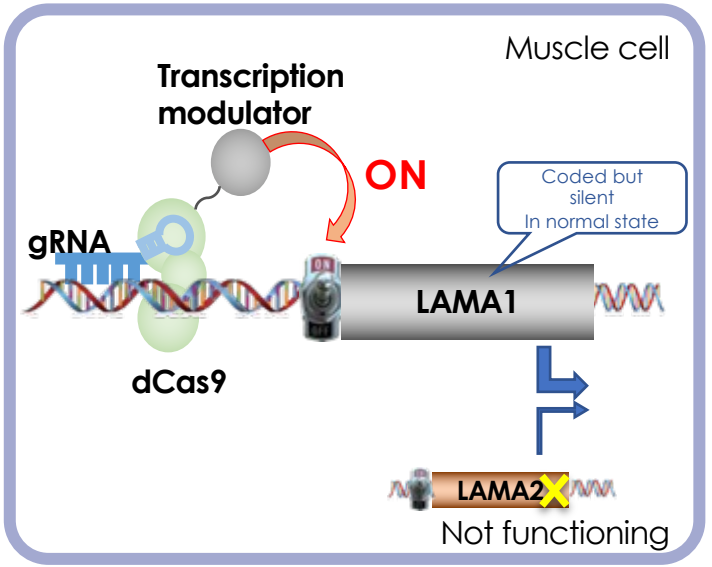
Protein structure of LAMA1 and 2



Exspression pattern of LAMA1and 2 by tissues



CRISPR-GNDM® targeting LAMA1



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MDL-101 is moving toward to IND

- Tech transfer to CDMO for coming GMP
- GLP Tox Study
  - Mouse IND enabling
  - NHP GLP tox in prep
- Coordinating with patient groups for the clinical trial

Regulatory Update

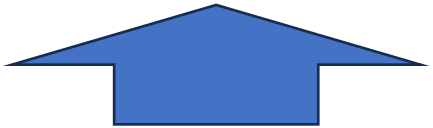
ODD and RPDD have been granted from US FDA

- **Orphan Drug Designation**
  - Tax deduction for clinical trial expenses
  - Exemption from application fees, etc.
  - Exclusive status for 7 years after market launch

→ Granted in Oct

- **Rare Pediatric Disease Designation and Priority Review Voucher Programs**
  - Granting priority review voucher after application for approval (The voucher program will end soon)

→ Granted in Sep



Reviewed by the rarity and medical relevance of the target disease, etc.

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Publication and conference presentations

Starting with the publication of MDL-101 papers, we will continue to disseminate information as a leader in the field of epigenome editing at conferences.

bioRxiv
THE PREPRINT SERVER FOR BIOLOGY

Efficient and durable gene activation by Cas9-mediated epigenome editing in vivo

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

doi: https://doi.org/10.1101/2024.05.03.592438

By 2024/3Q

CELL & GENE THERAPY SUMMIT-2024

18TH ANNUAL BIOPROCESSING SUMMIT
SOLVING TODAY'S CHALLENGES, LEADING TO TOMORROW'S ADVANCES

Gene Therapy Immunogenicity Summit

Nanopore Community Meeting Boston

2024/4Q

9th Annual Genome Editing Therapeutics Summit
Shaping the Future of Therapeutic Gene Editing
FORMERLY KNOWN AS CRISPR 2.0



Oral presentation:
Title: **Epigenome editing with CRIPSR-GNDM® as a treatment platform for unmet medical conditions**
Date: Dec 5, 2024
Session title: Progressing Epigenome Editors into the Clinic

Reported
The progress of our MDL-101 development and future strategy

The industry's attention was drawn to our achievements in leading the world in epigenome editing

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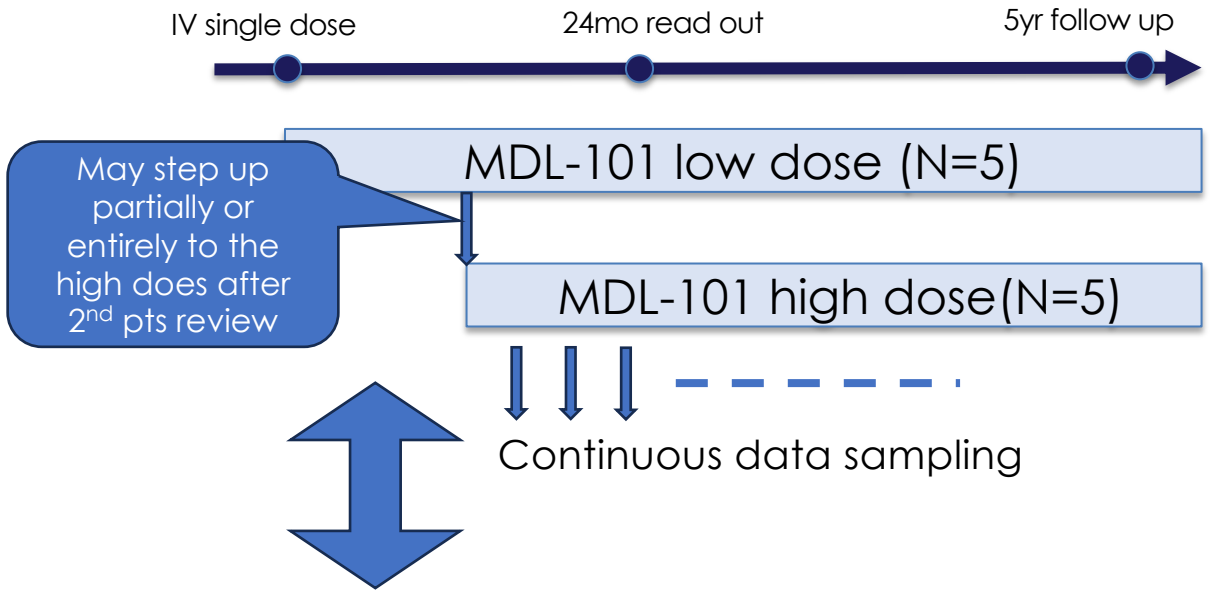
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Design of the FIH trial

Phase 1/2, open-label, dose-escalation study

Summary of MDL-101-001 phase 1/2 Open-Label Dose-Escalation Study

- Male or female LAMA2-CMD patients **36 months** of age and younger
- Clinical phenotype and Lama2 gene mutations and/or decreased LAMA2 staining in muscle consistent with LAMA2-CMD
- Stable background medications
- No independent ambulation or sitting



Comparison with Natural History Study in the US, France, and Netherland (NCT06354790, NCT04299321, NCT06132750)

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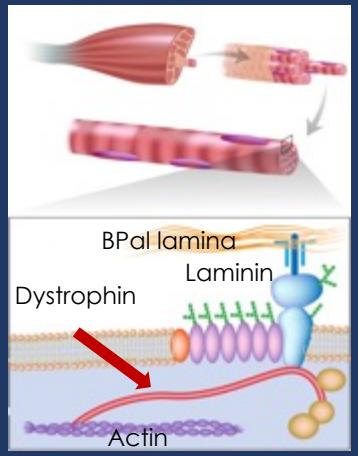
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Duchenne Muscular Dystrophy (DMD)

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

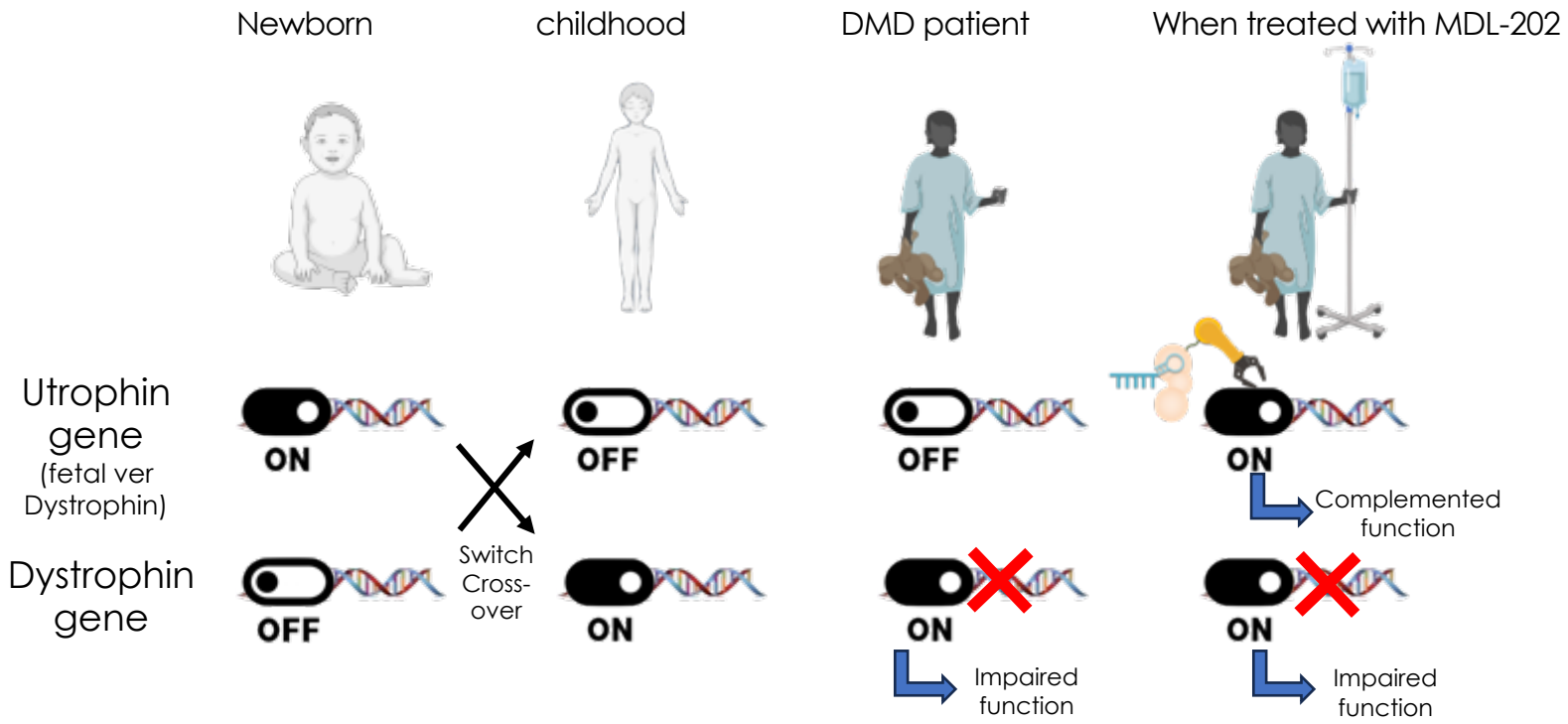
*Source: https://doi.org/10.1212/WNL.0000000000011425

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MDL-201 therapeutic concept

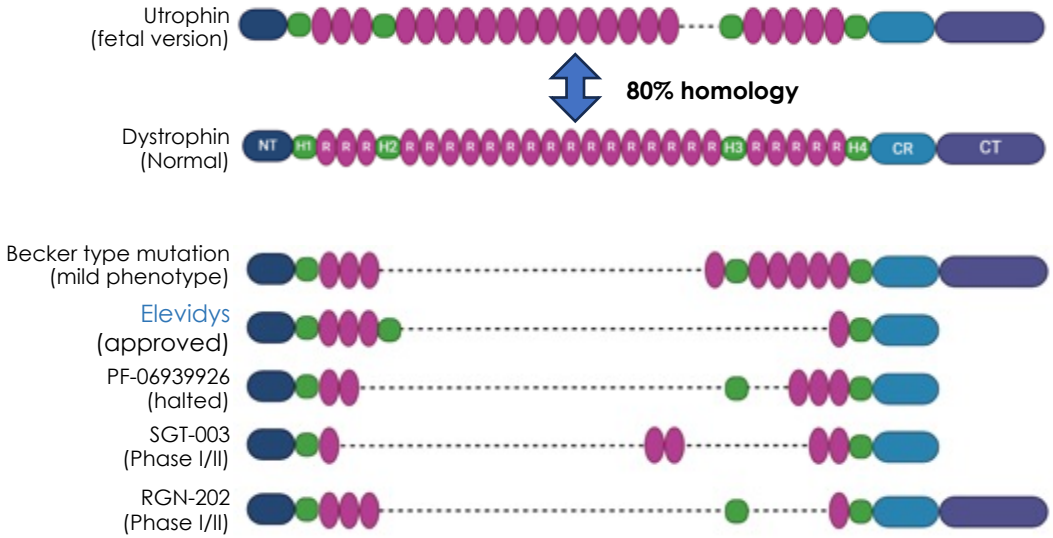
Reboot Utrophin genes , which is intact in patient, to compensate Dystrophin function



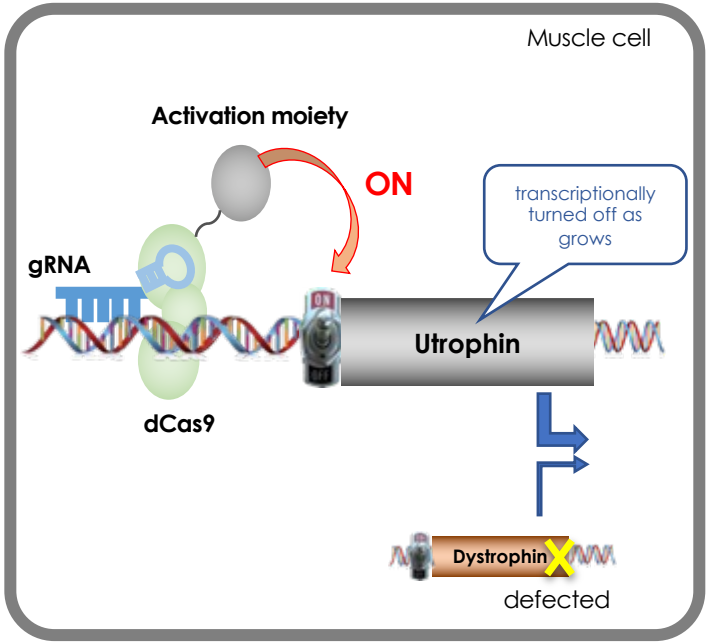
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Challenge of existing molecules and MoA of MDL-201

mini/micro-Dystrophin is missing many functional domains that exist in the full-length protein, but Utrophin retains most of them



MDL-201mechanism of action



Neuropathol Appl Neurobiol. 2021 Oct;47(6):711-723.

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

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Background to the development of MDL-201

- Although exon-skipping drugs and gene therapy drugs have been marketed for DMD, **unmet medical needs remain significant** due to their limited efficacy.
- Because of the limitations on the payload size that can be loaded onto AAV, **current gene therapy drugs are unable to load the full-length dystrophin gene,** and instead use the shorter dystrophin genes (mini-/micro-dystrophin) derived from Becker muscular dystrophy, a milder form of dystrophy, patients.
- Because mini-/micro-Dystrophin lacks some of the functional regions, its **efficacy is inherently limited**.
- Our MDL-201 is an innovative DMD therapeutic that aims to improve muscle function by **reactivating the Utrophin gene, a fetal version homolog of the dystrophin gene** with a normal sequence in most patients, through epigenome editing.
- MDL-201 has been shown to have advantages over the marketed drug's approach by **mini-Dystrophin in terms of behavioral evaluation data** in disease model mice.
- The current prototype is based on conventional AAV, but data from our other programs has shown that it is possible to achieve a several-fold to approximately 50-fold increase in efficacy by **replacing the AAV capsid with a muscle-tropic AAV capsid**.
- If we can verify this in mice and then in monkeys, we have the potential to catch up with our competitors and provide **best-in-class DMD gene therapy** by applying the manufacturing, safety, and pharmaceutical know-how we have accumulated through our leading programs, MDL-101.

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MDL-201 and 202-related patent granted in Japan

- DMPK patent granted in Japan (September)
  - Treatment method for muscular dystrophy targeting DMPK gene
  - Patent application JP2022-518586

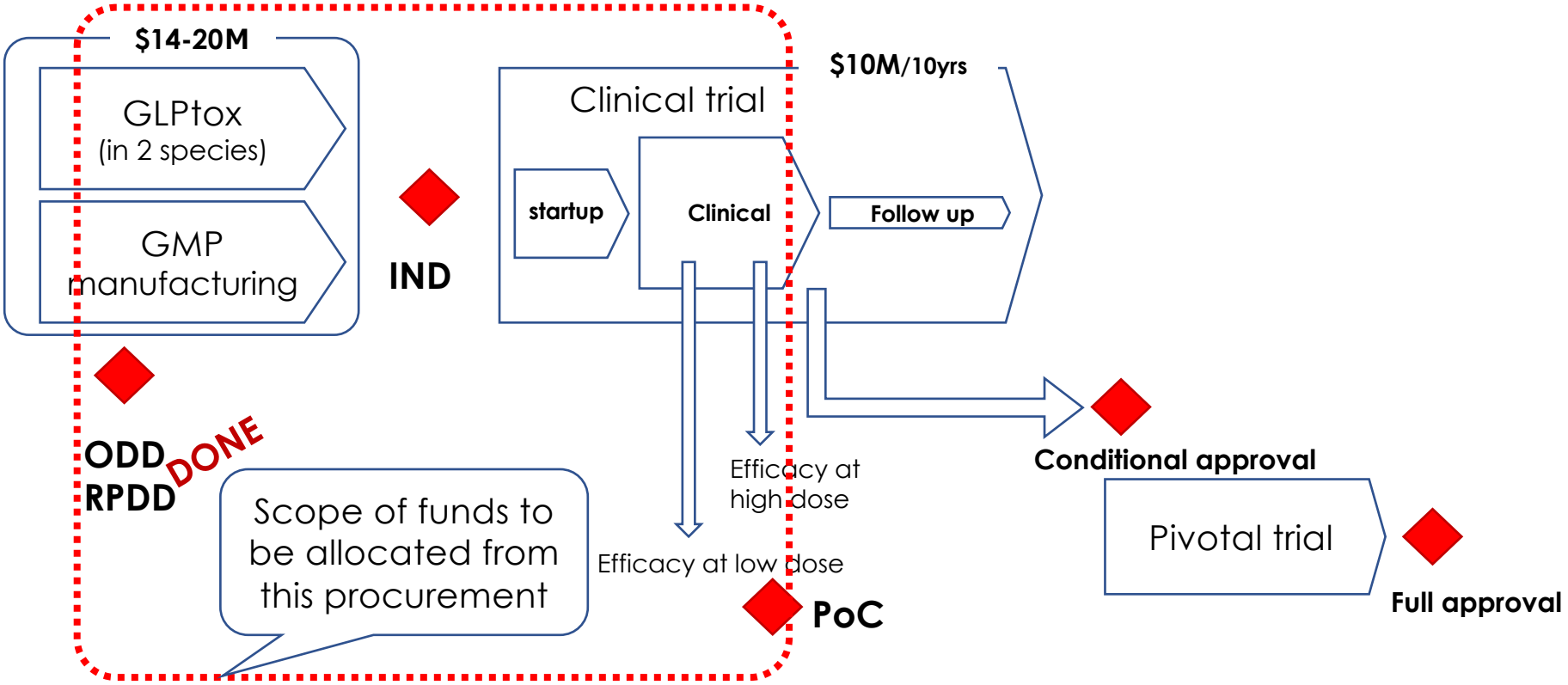
- LAMA2-CMD patent granted in Japan (Jan)
  - Treatment method for muscular dystrophy targeting LAMA1
  - Patent application JP2022-509664



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Use of funds procured through 2nd CB and 14th/15th warrant finance

MDL-101 *Value Inflection Points and* Funds Needed to Reach Them

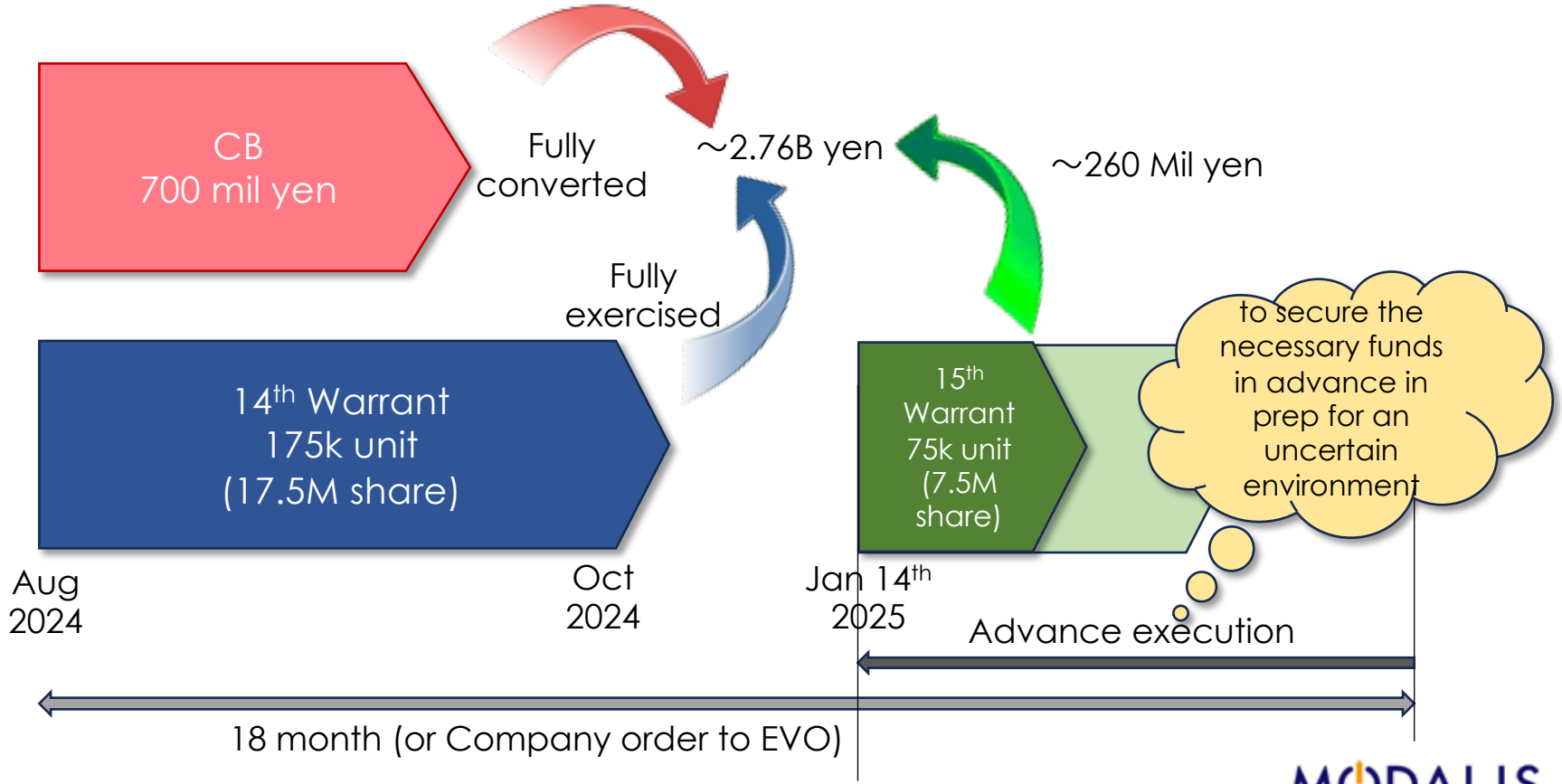


Note) The demand for funds is stated in U.S. dollars because it is primarily generated in U.S. dollars, and the Japanese yen equivalent may fluctuate depending on exchange rates.

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Status of CB/warrant finance

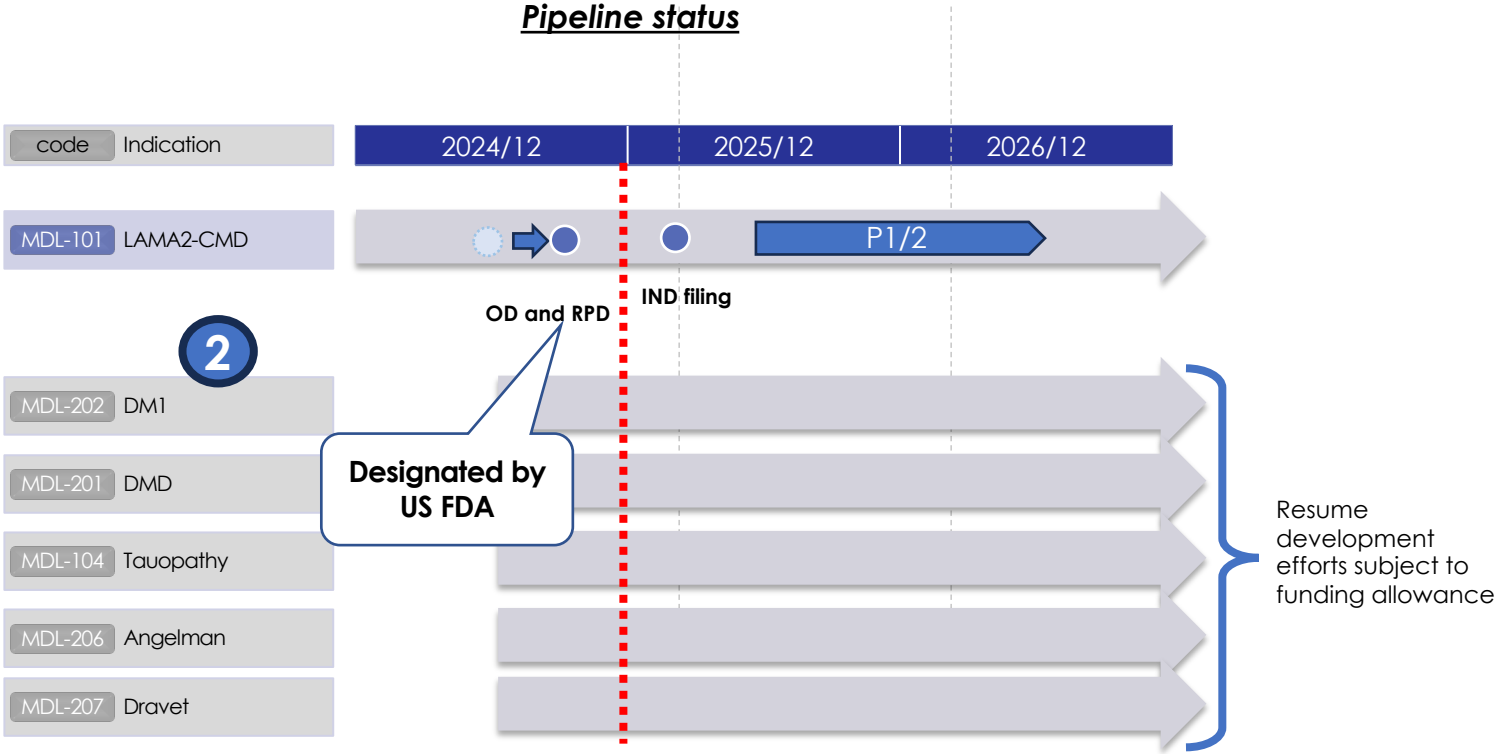
The 15th series of SO initiated ahead of schedule. 43.9% had been exercised by the end of January



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ODD and RPDD received

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



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

#: ODD: Orphan Disease designation, RPDD: Rare Pediatric disease designation

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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-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
	• Entered MOU with GenixCure
		• Transition to a New Capsid Version (MDL-201) and validation in animals
		• Explore optimal capsid and route of administration for CNS program
		• Allocation of development funds through partnering
		• Animal PoC
		• Continuing Research and Moving to Next Steps

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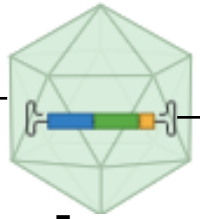
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Joint Research with JCR moves forward.

Aiming to develop an innovative therapeutic drug that is minimally invasive and efficiently reaches a wide area of the brain through intravenous injection

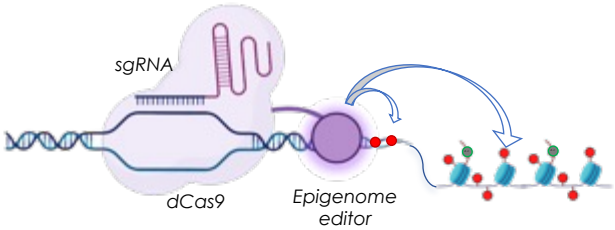
JCR Pharmaceuticals

BBB penetrating AAV Capsid
JBC（J-Brain Cargo®）-AAV



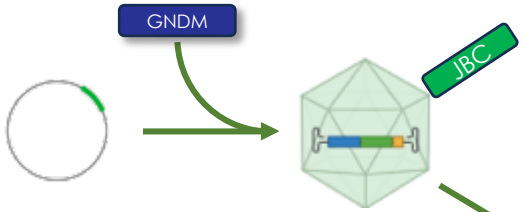
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Payload
CRISPR-GNDM®



For an undisclosed CNS target

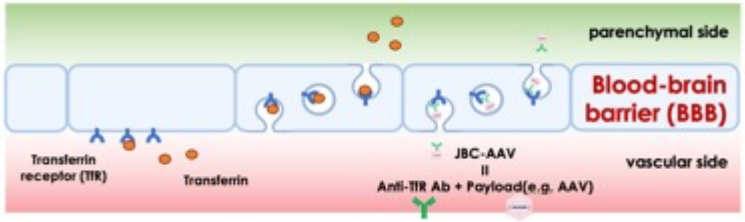




AAVCapsid + JBC fusion protein Coding gene

JBC-AAV

JBC-AAV exerts effects within parenchyma

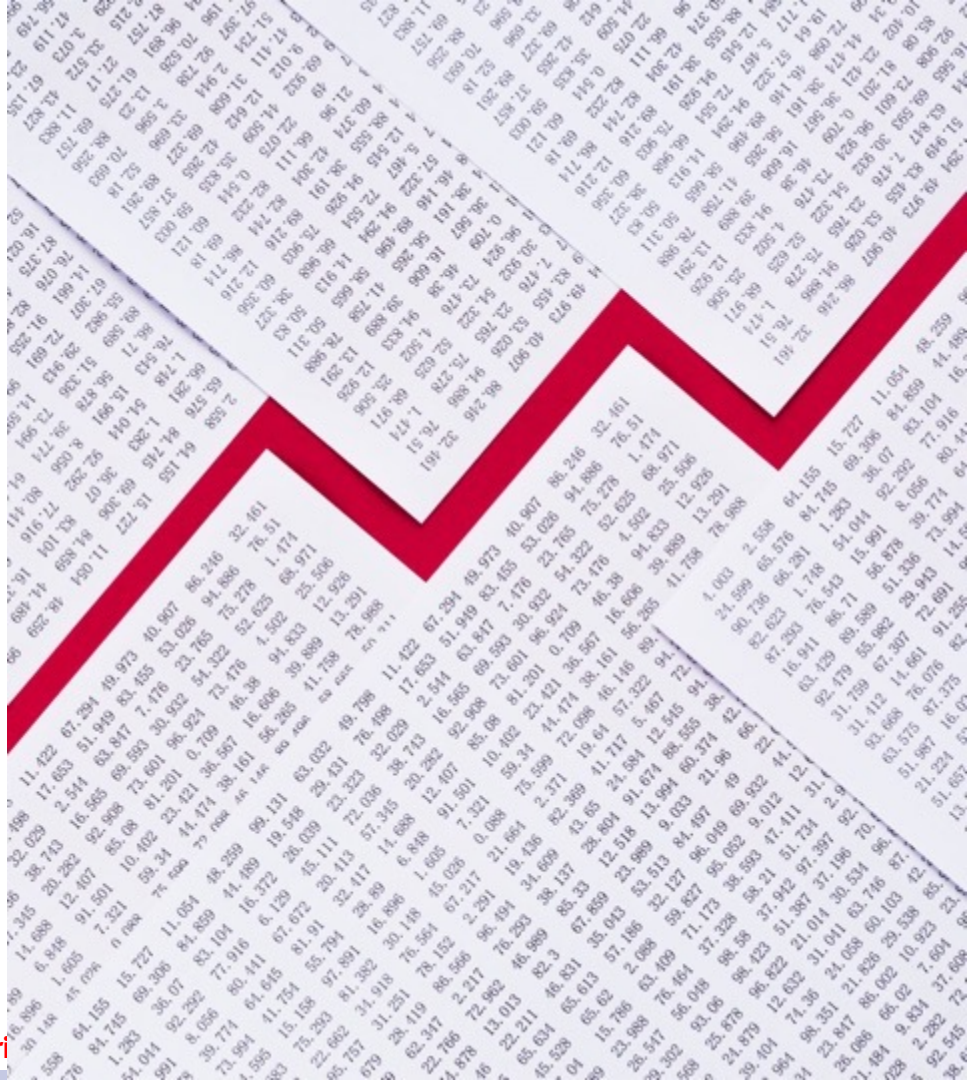


Source: Modalis therapeutics based on JCR Pharma's R&D meeting dated Nov 20, 2024

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2. Financial reports



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BS & Financial Position

(Million Yen)

	End of FY2023 (A)	End of FY2024 (B)	(B) – (A)
Current assets	1,956	3,617	1,660
Cash & deposits	1,883	3,575	1,691
Non-current assets	69	74	4
Total assets	2,025	3,691	1,665
Current liabilities	198	117	△80
Non-current liabilities	447	26	△421
Total liabilities	645	143	△502
Total net assets	1,380	3,548	2,167
Total liabilities and net assets	2,025	3,691	1,665
Capital adequacy ratio	66.8%	95.5%	

Note

- Cash and deposits increased due to the exercise of stock acquisition rights
- Fixed liabilities decreased due to the conversion of convertible bonds with stock acquisition rights. The equity ratio increased.

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PL & Business Result

(Million Yen)

	FY2023 (A)	FY2024 (B)	(B)−(A)
Operating revenue	-	-	-
Operating expenses	2,370	1,337	△1,033
R&D	2,102	1,092	△1,010
SGA	267	245	△22
Operating income	△2,370	△1,337	1,033
Ordinary income	△2,351	△1,303	1,048
Current Profit	△2,391	△1,317	1,073

Operating expenses

- Pre-clinical trials and manufacturing costs for investigational new drugs for MDL-101 clinical trials
- R&D costs for in-house model pipelines, including MDL-101 (mainly personnel costs, research material costs such as reagents, and rent)

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3. Growth Strategy

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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

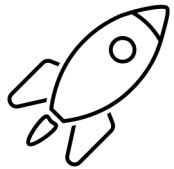
MDL-201
MDL-202

Further approach to challenging applications

Other programs





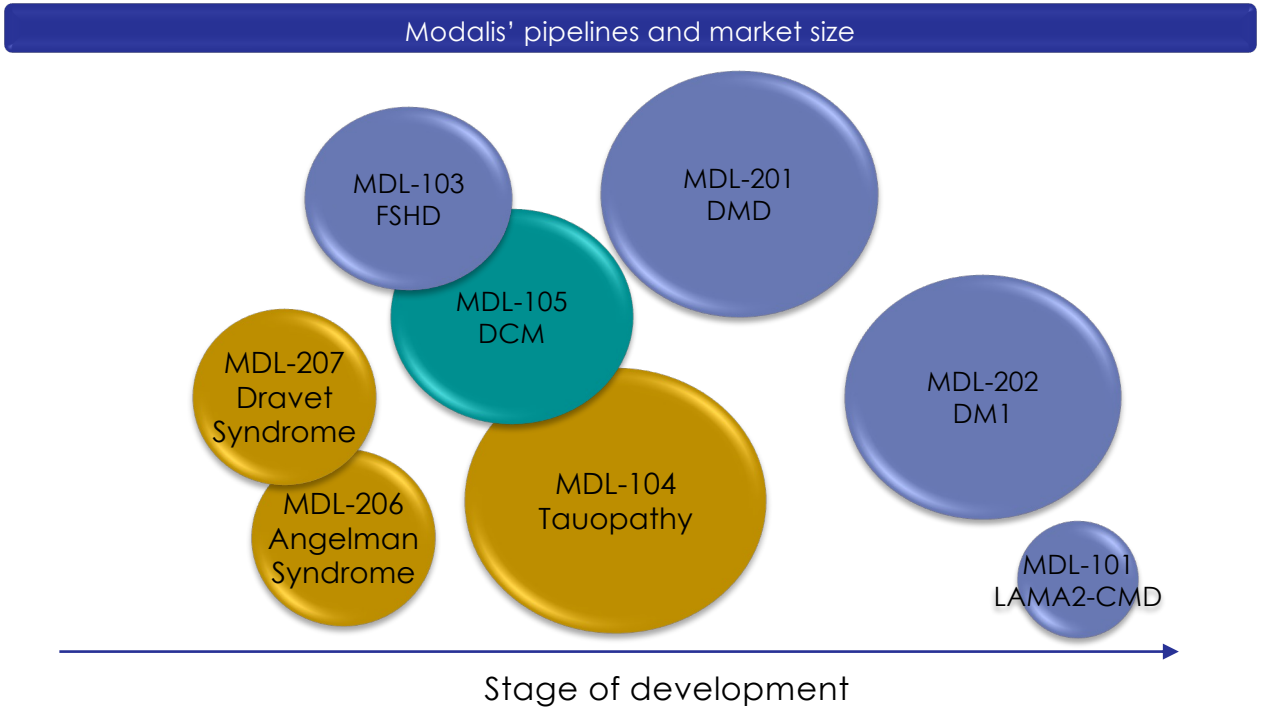


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Modalis' pipelines and market size

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

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3. summary

Key Takeaway of 2024 4Q 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.

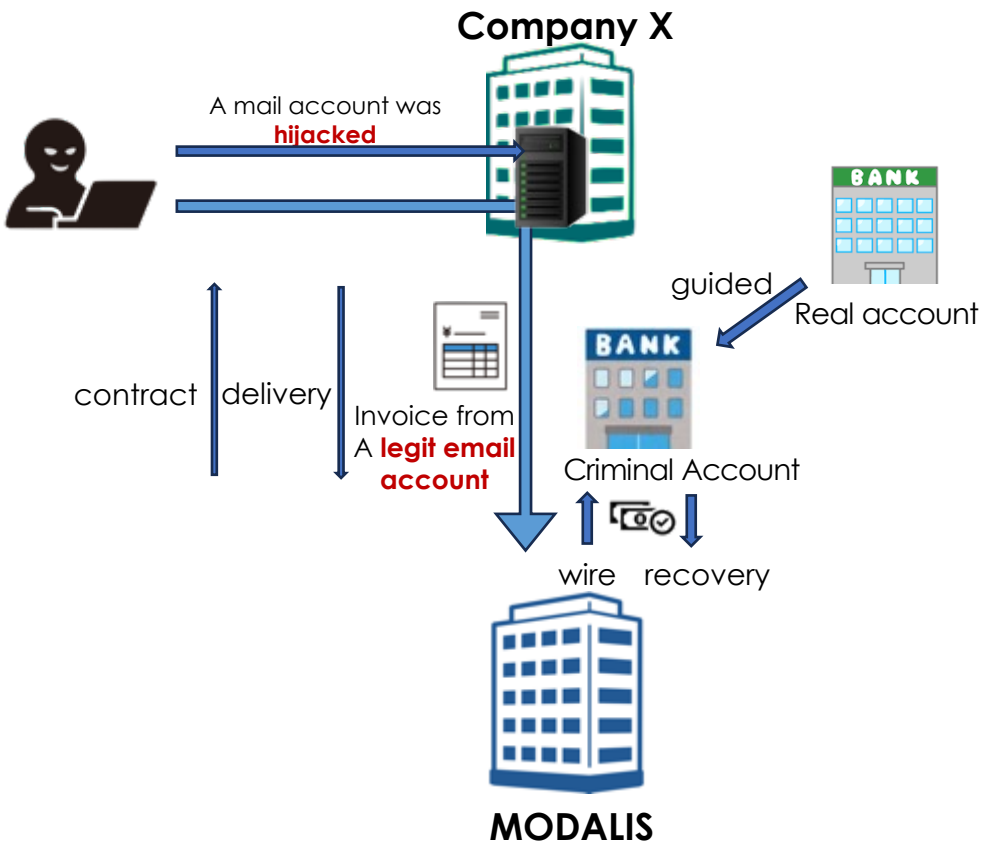
2. Development of DMD treatment MDL-201, which has the same mechanism to MDL-101, has resumed. Overcame the challenge of previous version, potentially becoming a **best-in-class** DMD product

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

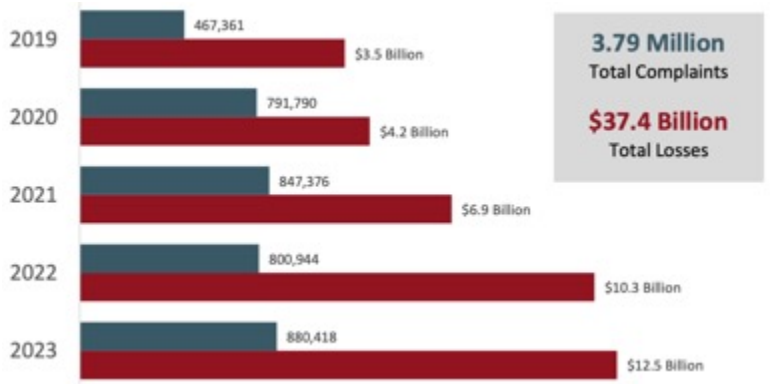
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Overview of Business Email Compromise (BEC) issue

Our prompt response, in conjunction with the efforts of the IC3 RAT, has enabled us to freeze the criminal's account and recover the majority of the transferred funds



Complaints and Losses over the Last Five Years



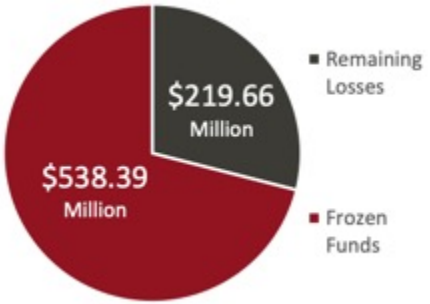
Success to Date

71% Success Rate

3,008 Incidents

$758.05 Million Losses

$538.39 Million Frozen



Source: www.ic3.gov

RAT: RECOVERY ASSET TEAM

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4. Q&A

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Q1: What is the background of advance execution of 15th series of warrant

- Although the raised approx. 2.5 billion yen funds through the issuance of its second unsecured convertible bond and 14th series of stock acquisition rights fulfils near term expenses, there was still a gap, and in light of the fact that the business funds described in the August 7, 2024 release and on page 24 of this document had not been raised, as well as the uncertainty of the current market environment, the company decided to make advance execution.
- As announced on February 3rd, approximately 43.9% of the stock options had been exercised by the end of January, but we believe that the remaining options are being exercised in a way that has little impact on supply and demand, in accordance with the agreements with the Optionee.

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Q2: How much is the gross damage from the BEC?

- In accordance with an agreement with Company A, which was also affected by the disaster, we are unable to disclose any further details beyond those already reported.

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