English translation for reference purposes only

FY2023 4Q
Financial Results

Modalis therapeutics Corporation

(TSE：4883)

Feb 20, 2024

In case of any discrepancy, the Japanese version shall prevail

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MODALIS Value Highlights

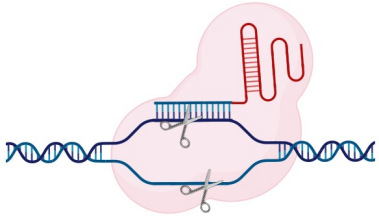
- Established the first robust **epigenetic editing platform** for activation and inhibition of endogenous genes using CRISPR-GNDM® platform
- Demonstrated **sustained modulation** of gene expression in multiple species (mouse, cyno) resulting in **functional efficacy without toxicities**
- Pipeline of preclinical assets in **neuromuscular diseases**, 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
- **Regulatory and clinical path** in place based on recent FDA guidance

Non-cleaving CRISPR = CRISPR-GNDM®

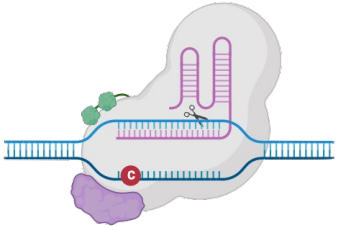
Enables treatment of genetic disorders by controlling epigenetic ON/OFF switch

GTx Technologies

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



Permanent Removal

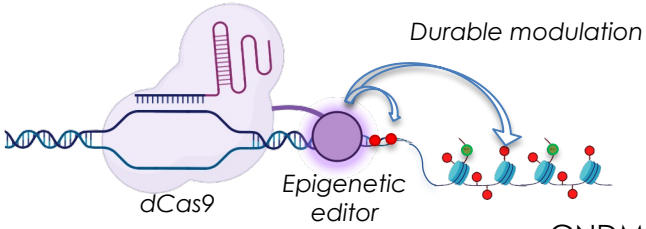


Permanent Replacement

Temporal silencing

Epigenome Editing(CRISPR-GNDM®)

Bind without cleaving
No DNA damage



GNDM=Guide Nucleotide Directed Modulation

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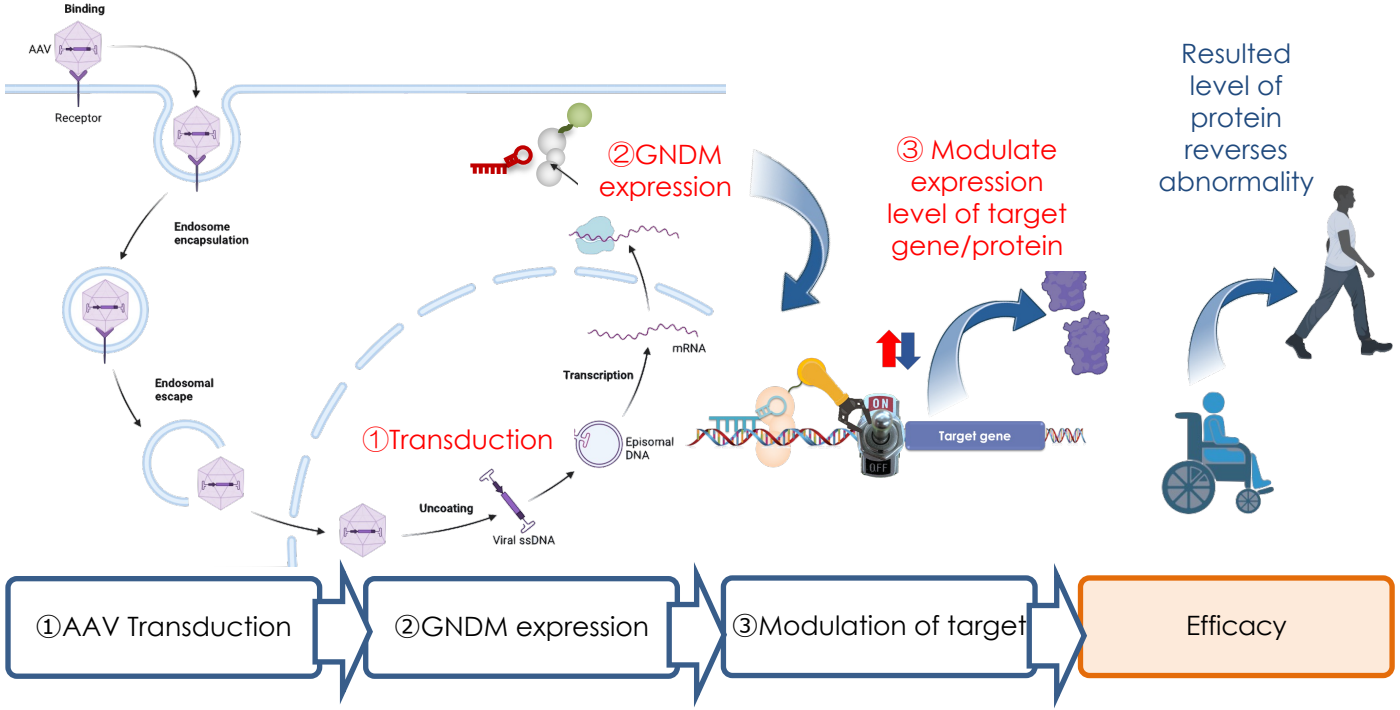
GNDM-CRISPR is a three-step process that leads to effectiveness.



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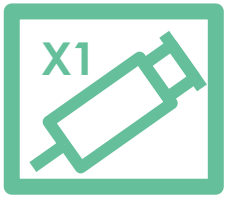
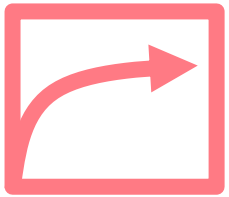
CRISPR-GNDM® is a promising therapeutic modality that controls the epigenome to modulate expression

A single injection reverts pathogenical condition with durability

Potential benefits of CRISPR-GNDM® Technology



Single dose
Does not require
Repeated dosing



Long-lasting
Sustained effect
for years or decades

Disease Modifying
Not just reduction
of symptoms but
potential to cure

CRISPR-GNDM® does not alter DNA sequence

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With the initial success, gene therapy has begun to expand targets from local to systemic administration

Gene therapies approved by US FDA

Trade Name	Year of Approval	cost	Indication	Manufacturer	Patient Population	WW market size* (mil USD)
Lxturna	2017	$850k	RPE65	Spark/Roche	2 per 100,000	$65M[#3]
Zolgensma	2018	$2.1M	SMA	Novartis (Avexis)	1 in 10,000 live births (Approx. 10,000 to 25,000 in US)	$1.3B[#3]
HEMGENIX	2022	$3.5M	Hemophilia B	uniQure CSL Behring	1 in 30,000 male	$88M[#3]
Vyjuvek	2023	$631k per patient per year	DEB[*2]	Krystal	3.5–20.4 in 1 million	~$200M[#2]
ELEVIDYS		$3.2M	DMD	Sarepta	1 in 3,500 male birth	$4.1B[#4]
Roctavian		$2.9M	Hemophilia A	BioMarin	1 in 5,000 male	$262M[#4]
Casgevy		$2.2M	SCD	CRISPR Tx/Vertex	100,000 in America	>$2B[#5]

Source: National Organization for Rare Disorder、#2 Fierce Biotech #3 Corporate website #4Grand view research #5 Fortune Business Insight
*1: Spinal muscular atrophy *2: dystrophic epidermolysis bullosa *3: Duchenne muscular dystrophy

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CRISPR-GNDM® targets genes that cannot be addressed by other modalities

	Conventional Gene therapy	Gene Editing	ASO siRNA	CRISPR-GNDM
Precise targeting	Yes	Yes	Delivered to off-target tissues	**Yes**
Durability	Years	Permanent	Require repeated injection	**Years**
Applications	LoF ONLY	Mostly GoF	GoF only	**LoF and GoF**
Target gene limitation	Limited to small size genes	Limited to a specific point of mutation	Causative tissue is limited (e.g. liver)	**Size agnostic**
Effect on DNA	none	Causes double-stranded breaks	none	**None**

LoF=Loss of function, GoF=gain of function

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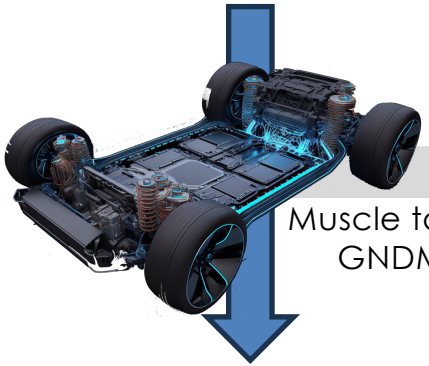
Programs share the same platform as MDL-101

Well-verified in terms of medicinal efficacy, safety, and manufacturability



Muscle targeting AAV
GNDM platform

MDL-101

MDL-202

MDL-201

MDL-103

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Epigenome editing competitive landscape
Modalis is in the lead

Company	Year Founded	Funding	Platform	Pipeline/Target indication	Stage of Development
Modalis Therapeutics	2016	Public	CRISPR-GNDM x AAV	• MDL-101/LAMA2-CMD • MDL-202/Myotonic Dystrophy Type 1(DM1)	IND enabling PreIND completed
Tune Therapeutics	2020	Series A ($40M, Dec 2021)	DNMT-KRAB fusion dCas9 x LNP	PCSK9 for hypercholesterolemia? HBV	NHP study reported at ASGCT2023
Chroma Medicine	2021	Series B ($135M, Mar 2023)	DNMT-KRAB fusion dCas9 x LNP	PCSK9 for cardiovascular disease	Mice study reported at ASGCT2023
Epic Bio	2022	Series A ($55M Jul 2022)	Cas12f-fused with demethylation enzyme x AAVrh74	EPI-321/FSHD	Mice study reported at ASGCT2023
Moonwalk Bioscience	2023	Series A ($57M 2023)	Not known	Not known	Not known

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1. Key Topics in 4Q

Key topics

1. **MDL-101 marching towards IND filing**
   - Process Development has been completed
     - Got ready to transfer the process to CDMO for GMP
     - Manufacturing initiated for GLP tox study
   - GLP tox study design completed
     - Based on PreIND and follow-up responses, the design has adopted.

2. **Pilot NHP study analysis ongoing for MDL-202**
   - In-life part of 8-wk study completed
   - GNDM expression comparable to that of MDL-101 is confirmed

3. **Added MDL-207 targeting Dravet syndrome as an internal program**
   - A unique approach to upregulate SCN1a protein to treat the disorder

4. **Established and kicked off a collaboration with JCR for CNS**
   - A research collaboration in a CNS disorder using JBC-AAV and CRISPR-GNDM

5. **Multiple GNDM element patents have been granted**
   - miniCas9 technology patent in issued Japan
   - PAM-flex SpCas9 patent granted in China
   - miniVR (small transcription activator) patent granted in Russia

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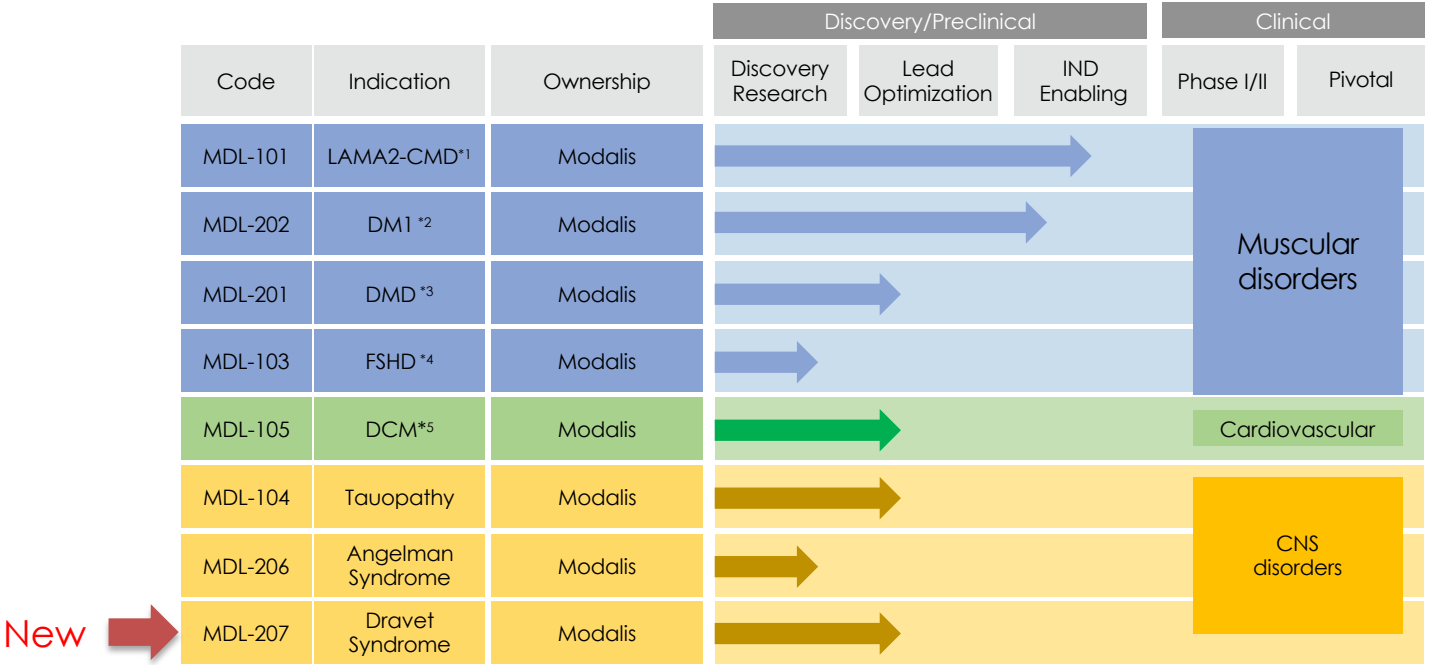
Pipeline Status
Focusing on 101 and 202



*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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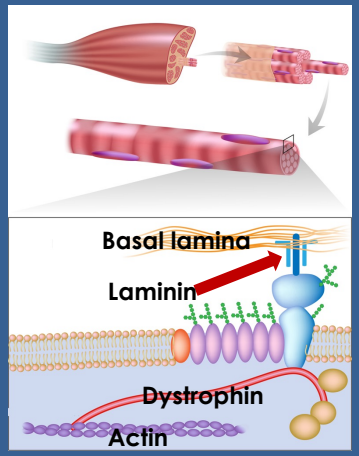
LAMA2-CMD (aka CMD1a)

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*** 2500 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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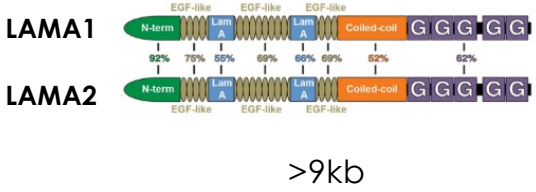
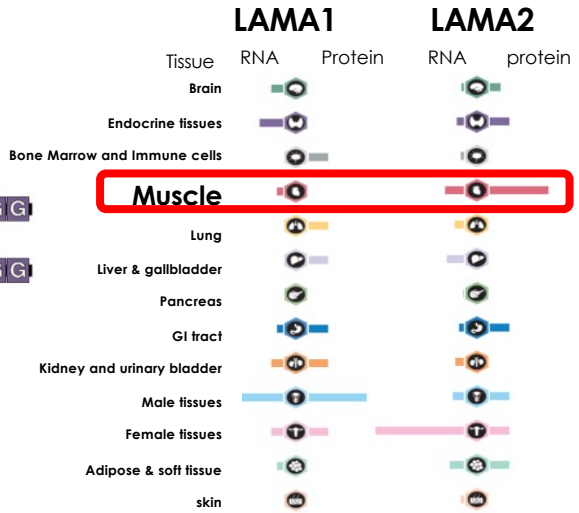
MDL-101 activates LAMA-1 and compensates for the missing function of LAMA2, which is too large for classical gene therapy approach

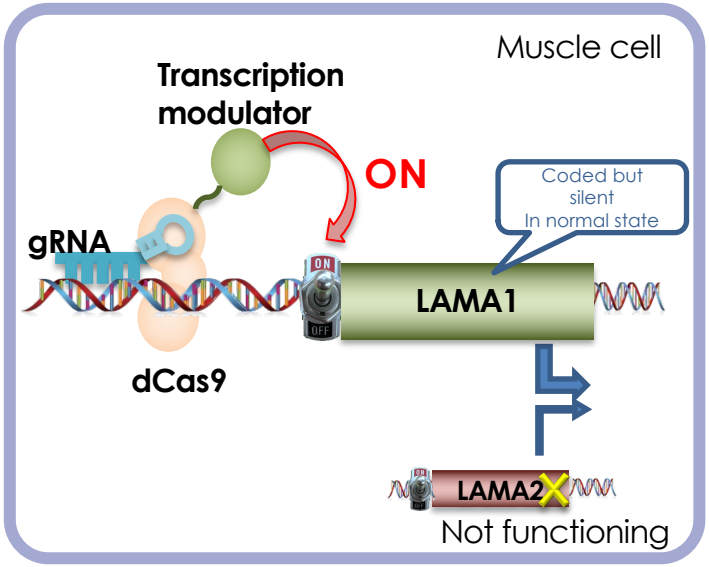
Protein structure of LAMA1 and 2



Exspression pattern of LAMA1and 2 by tissues



CRISPR-GNDM® targeting LAMA1



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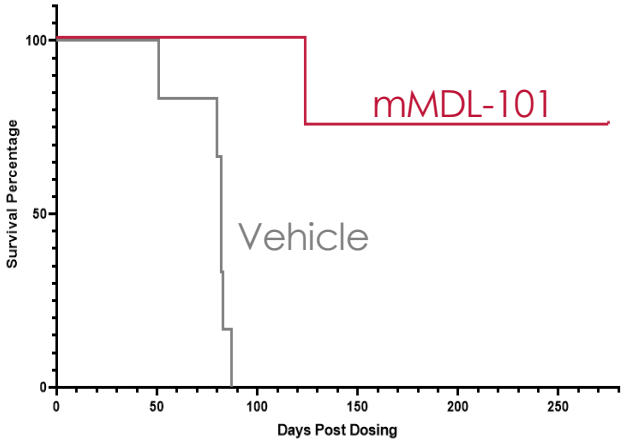
mMDL-101 is efficacious in severe MDC1a model

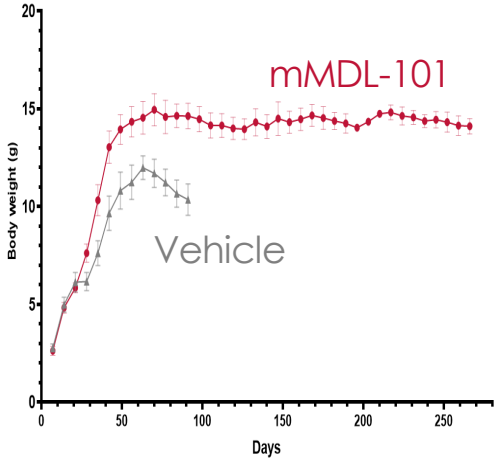
Increased lifespan, body weight and grip strength of dy^{W} mice

Extended lifespan
(% Survival)



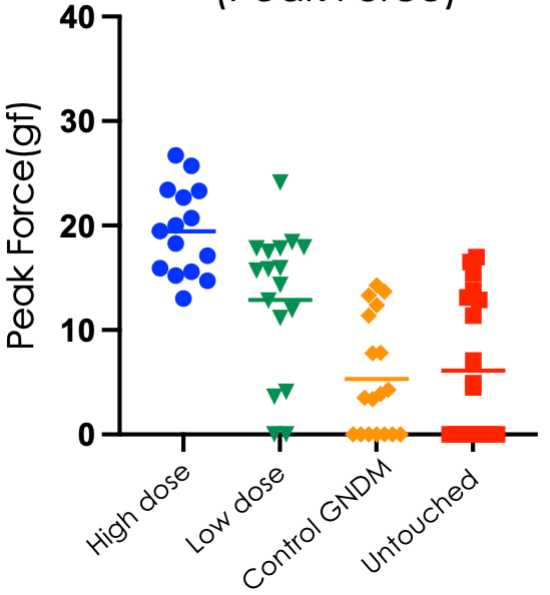
p<0.005, log rank test

Improved growth
(Weight)



p<0.0001, Mann-Whitney test

Forepaw Grip Strength
(Peak Force)



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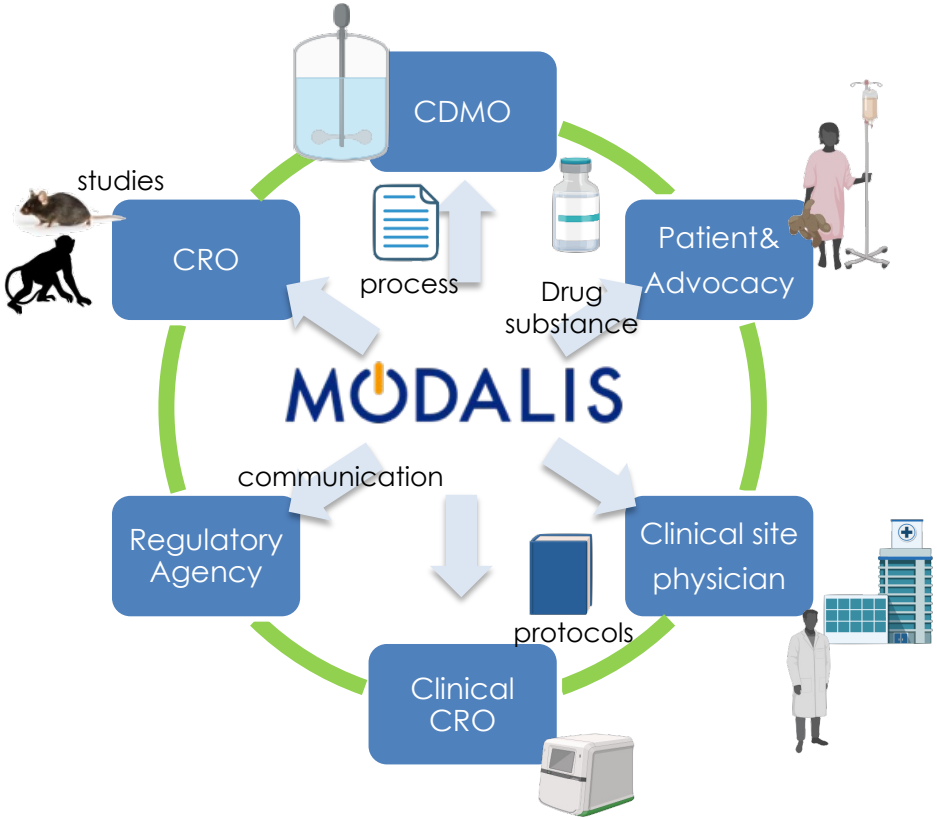
Modalis has set up the network for the clinical trial and is working with them



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Summary of MDL-101 for LAMA2-CMD

Major technical challenges have been resolved. GLP-tox and GMP are the remaining

- Reported by 3Q/2023
  - Confirmed efficacy in mice disease model and target engagement in NHP with the **muscle tropic capsid version MDL-101**
  - Confirmed **long-term expression of GNDM and LAMA1** in disease model mice
  - Completed **a juvenile NHP study** that confirmed comparable or better LAMA1 expression than adult NHP study
  - KOL meetings and drafting **clinical synopsis and protocol**
  - Presented development updates of MDL-101 as a late-breaking abstract at **ASGCT**
  - Received positive **Pre-IND response** from FDA (June)
  - Established a feasible **manufacturing process** with reasonable yield and quality
- Progress after that
  - ✓ Initiating GLP tox study
  - ✓ Received follow-up question to the preIND response
- Next steps:
  - Continue IND enabling GLP tox and PK/PD
  - Pilot productions and GMP campaign

MDL-101 summary

CRISPR-GNDM efficiently targets and **upregulates LAMA1** gene

Strong Animal PoC confirmed in mice *in vivo* including functional improvement

The **process to manufacture** the molecule with muscle-specific vector has been established with feasible productivity, yield and quality

The injection of 101 **did not cause detrimental safety issues** in mice and NHPs

Myotonic dystrophy type 1(DM1)

extension of CTG repeat in 3' UTR of DMPK gene

MDL-202

Potential to be the first-in-class and the first DM1 treatment

Prevalence	**1-4.8 in 10,000** (1 in 2,300*)	DM is the most common muscular dystrophy among adults of European ancestry
Disease onset	DM1 can occur from birth to old age	Age at onset is between 20 and 70 years (typically onset occurs after age 40)
Disease Burden	muscle weakness and wasting (atrophy), myotonia	DM causes weakness of the voluntary muscles, although the degree of weakness and the muscles most affected vary greatly according to the type of DM and the age of the person with the disorder
Cause of disease	Microsatellite expansion in 3' UTR of DMPK gene	Extended CTG repeat capture MBNL1 protein which is essential for normal splicing
Market size	**$2.2B #** By 2032	$80M market as of 2022 without any treatment but is expected grow

*Source: Myotonic Disease Foundation # DelveInsight (including both DM1 and DM2)

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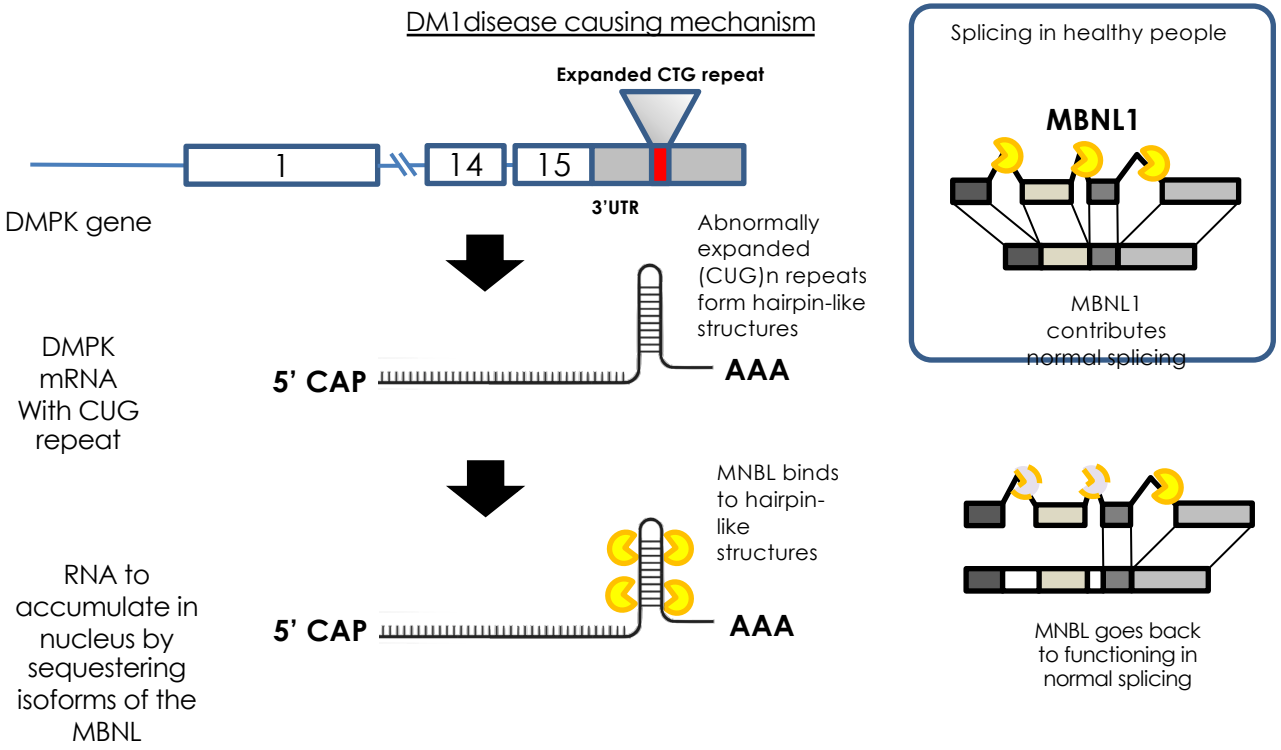
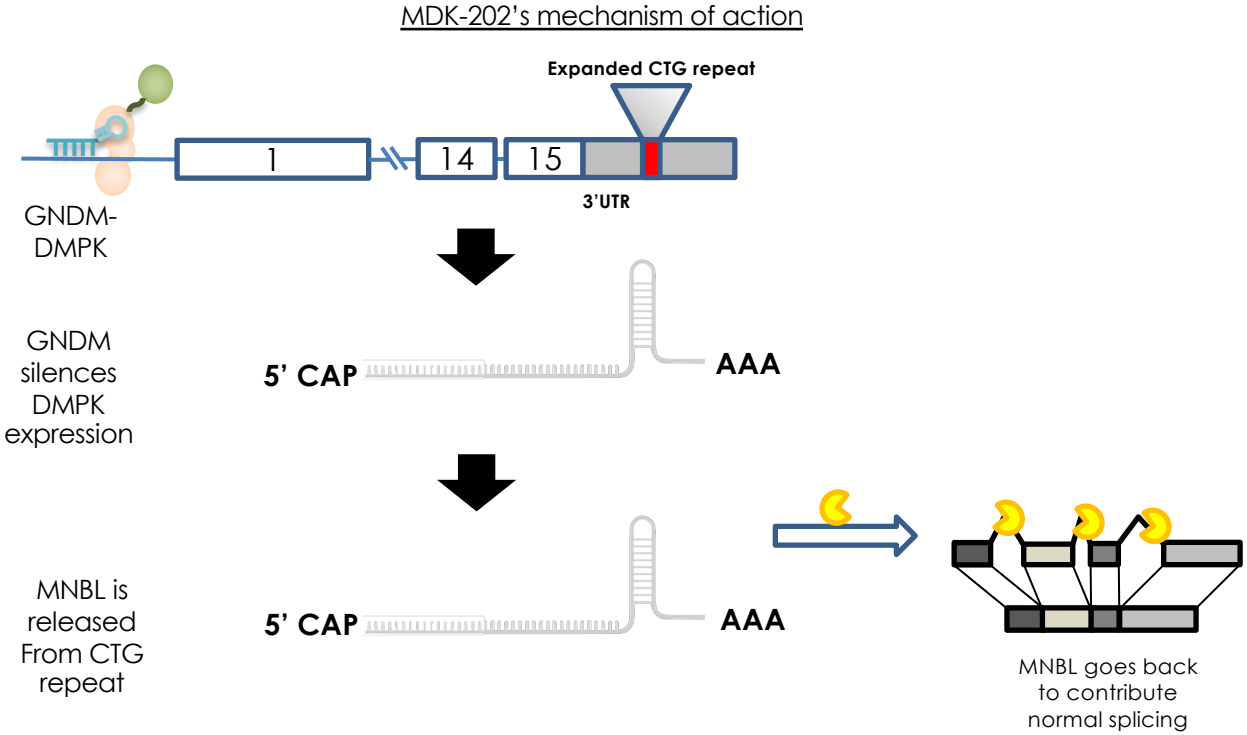
DM1 is caused by abnormal splicing rooted from CTG extension in 3'UTR of DMPK gene



MDL-202 silences DMPK expression and release splicing protein MNBL to function properly in muscle cells



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Development Summary of MDL-202 for DM1

transferring GNDM to the muscle capsid system, which is validated in 101

- Reported by 3Q
  - ✓ **Regained rights** of MDL-202
  - ✓ Completed transition to the **muscle tropic capsid**
    - ✓ Designed multiple candidate constructs
    - ✓ Pilot production of the candidate constructs
    - ✓ Initiated mouse and NHP target engagement studies
- Progress thereafter
  - ✓ In-life part of pilot **NHP study** completed
    - ✓ Demonstrated comparable GNDM expression seen in MDL-101
  - ✓ mice study initiated
    - ✓ GNDM expression confirmed in WT mice
    - ✓ Disease model mice (DMSXL) study initiated
- Next step
  - Readout of NHP target engagement study
  - Pharmacology studies with mice disease model

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MDL-202 offers a feasible and fast path to the clinic

Modalis has candidate Myo tropic AAV-based molecules confirmed in NHP

Modalis has established a manufacturing process available for large-scale production

Modalis had done INTERACT and PreIND meetings for MDL-101 which shared the same platform

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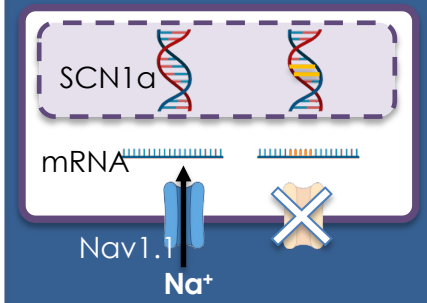
Dravet Syndrome

A type of epilepsy caused by haploinsufficiency mutation in SCN1A gene

MDL-207

Potential to be the best-in-class and first precision medicine for Dravet Syndrome



Prevalence	**1 in 20,000-40,000*** ~10,000 in US	
Disease Onset	Seizure starts between **1 and 5 yo**	
Disease Burden	**10-20%** of DS patients pass away before reaching adulthood	• SUDEP (sudden unexpected death in epilepsy patients) • status epilepticus (SE). • Autism-like spectrum (ASD) • Attention deficit hyperactivity disorder (ADHD)
Disease Causing Gene	**SCN1A**	• Haploinsufficiency of SCN1A
Commercial opportunity	**$500M+**	• Currently with no curable drugs • The market is estimated to grow at CAGR of 9.6% # driven by new therapeutics

Source: *Epilepsy foundation #Technavio

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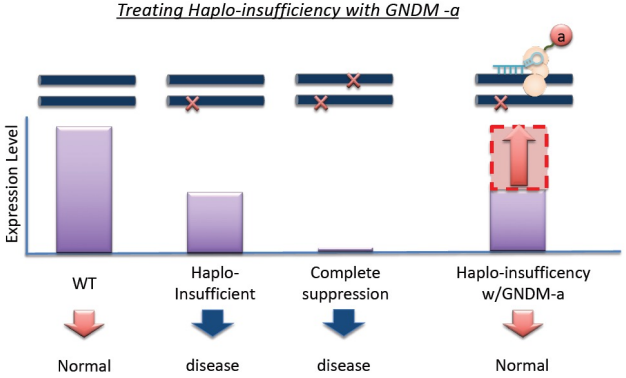
A simple solution is to double-up SCN1a protein expression



Company	Modality	MOA	Route	Stage	IND
Enoded Therapeutics	AAV-ETN (regulatory element)	• Overexpress regulatory element for Scn1a • Upregulate endogenous Scn1a expression specifically in GABAergic inhibitory neurons	ICV	IND cleared	2021
E-Rare	Adenovirus-Scn1a	• Restore Scn1a mRNA and Nav1.1 protein levels	ICV	Preclinical	TBD
UCL	Lentivirus-Scn1a	• Restore Scn1a mRNA and Nav1.1 protein levels	ICV(?)	Preclinical	TBD
OPKO	AntagoNAT	• Binds to the DNA and removes an endogenous repressor of SCN1A • Restore Scn1a mRNA and Nav1.1 protein levels	IT	Preclinical	TBD
PTC therapeutics	Small molecule (nonsense reading through)	• Read through premature nonsense stop signals on mRNA and allow the cell to produce a full-length, functional protein (not specific to Scn1a)	Oral	Phase 2 (pending?)	N/A
Stoke Therapeutics	ASO (TANGO)	• Reduce non-productive mRNA and increase productive Scn1a mRNA via modulation of splicing • Increase in the levels of mature mRNA and Nav1.1 protein	i.c.v.	Preclinical	2020

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What has been achieved and coming next

	What has been achieved	What's coming next
MDL-101 LAMA2-CMD	• Animal PoC in disease model mice • Target engagement in NHP • Pre-IND with FDA (June 2023) • Presentation at ASGCT 2023	• GLP-Tox • GMP manufacturing • IND (2H 2024)
MDL-202 DM1	• Animal PoC in disease model mice • Regain rights from Astellas • Transition to muscle tropic capsid • Mice study (WT and disease model) • NHP target engagement study (in-life)	• Readout of NHP target engagement study (1Q/2024) • Readout of mouse disease model study (2Q/2024) • Partnering
Other	Muscle program • MDL-201 (DMD) • MDL-103 (FSHD) • MDL-105 (DCM) CNS programs • MDL-104 (Tauopathy) • MDL-206 (Angelman) • MDL-207 (Dravet)	• Transplantation to muscle tropic capsid • Animal PoC (FSHD, DCM) • Partnering • Continuing research • Explorer neurology capsids and LNPs • Partnering

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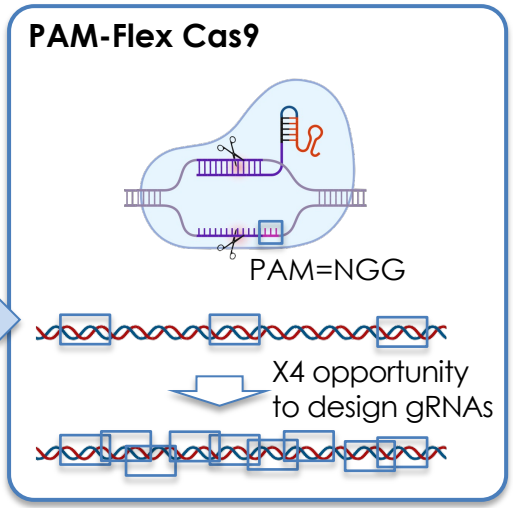
Other updates on business

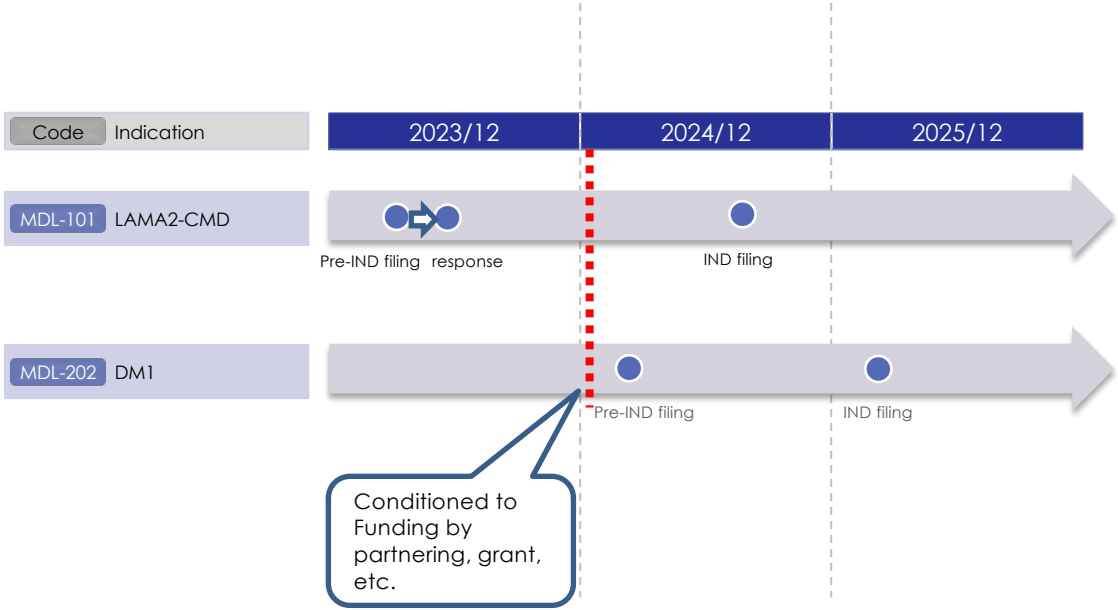
- Progress on intellectual property
  - **miniCas9** technology issued in Japan (Patent #7412001 (JP2020-523211)
  - **PAM-flex SpCas9** granted in China (CN201880050453.1)
  - **miniVR** (transcription activator) patent issued in Russia (RUS 2800921)

- Progress on partnering
  - **JCR** collaboration established and initiated
    - Research collaboration to develop a molecule for an undisclosed CNS target with JCR's JBC-AAV technology and Moldais' CRISPR-GNDM technology
  - Partnering discussion ongoing with pharma/biotech companies for MDL-101 which potentially be the first CRISPR-based epigenetic editing therapeutics
  - Partnering discussions ongoing for MDL-202.
  - Research collaboration: In discussion with pharma/biotech companies on new targets



Status of the focused pipeline

Reorganized pipelines and put higher priority on muscle disorder programs



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

2. Financial Highlights

PL & Business Result

(Million Yen)

	FY2022 (A)	FY2023 (B)	(B)−(A)
Operating revenue	40	-	(40)
Operating expenses	2,103	2,370	267
R&D	1,861	2,102	241
SGA	242	268	26
Operating income	(2,063)	(2,370)	(307)
Ordinary income	(1,995)	(2,351)	(355)
Current Profit	(2,702)	(2,392)	310

Operating expenses

- Advancement in the effort of MDL-101 development (process development, manufacturing costs, etc.)
- Increase in R&D expenses due to increase in pipeline including MDL-202 and depreciation of the yen against the U.S. dollar (mainly personnel expenses, material cost, and rent)

Extraordinary loss

- In net income, the increase was mainly due to a decrease in impairment loss on fixed assets.

SGA: Selling and Generally Administrative Expenses

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BS & Financial Position

(Million Yen)

	FY2022 (A)	FY2023 (B)	(B) – (A)
Current assets	3,061	1,956	(1,104)
Cash & deposits	2,933	1,883	(1,049)
Non-current assets	68	69	1
Total assets	3,129	2,025	(1,104)
Current liabilities	141	198	56
Non-current liabilities	47	447	400
Total liabilities	188	645	456
Total net assets	2,941	1,380	(1,560)
Total liabilities and net assets	3,129	2,025	(1,104)
Capital adequacy ratio	93.4%	66.8%	

Note

- Long-term liabilities increased (412 million yen) due to issuance of convertible bonds with rights to acquire stocks.
- Decrease in net assets due to a decrease in retained earnings

3. Growth Strategy

MODALIS GNDM platform provides a diversified pipeline

Pioneering gene modulation applied to high unmet need indication

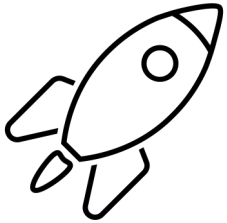
MDL-101

Apply technology to products with larger opportunities

MDL-202

Expand approach to challenging applications

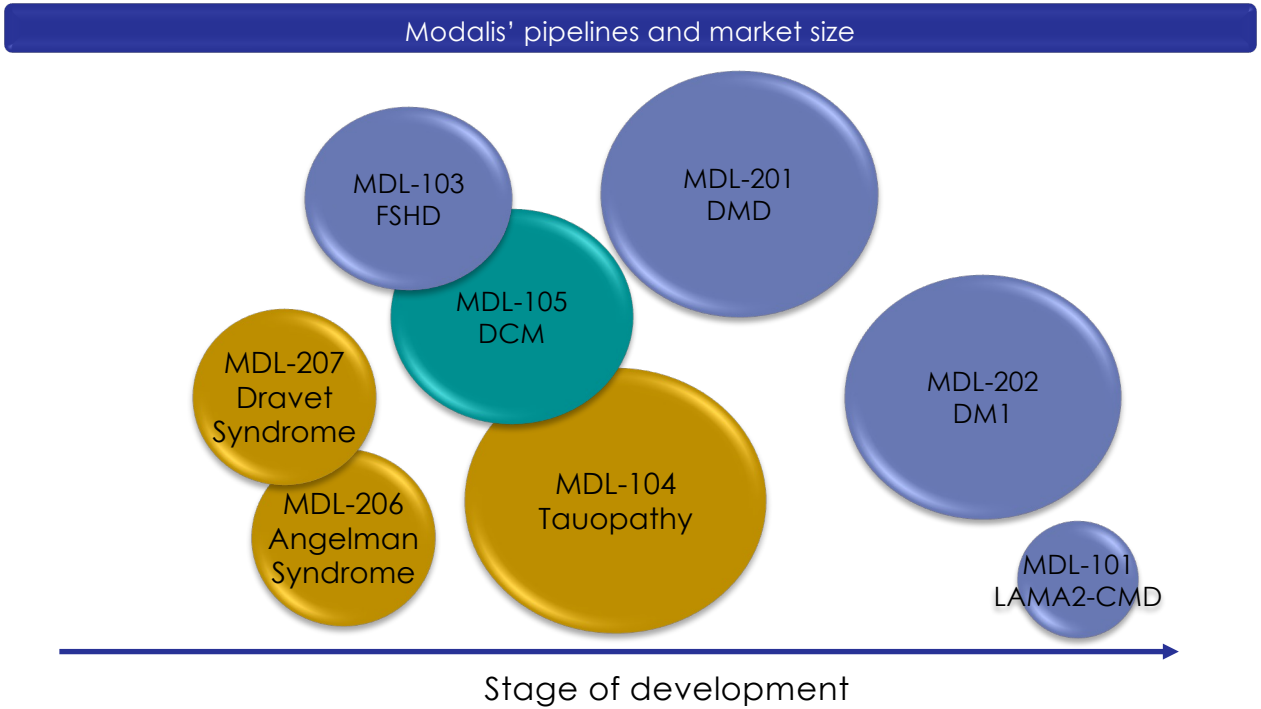
CNS, CV and other programs



MODALIS

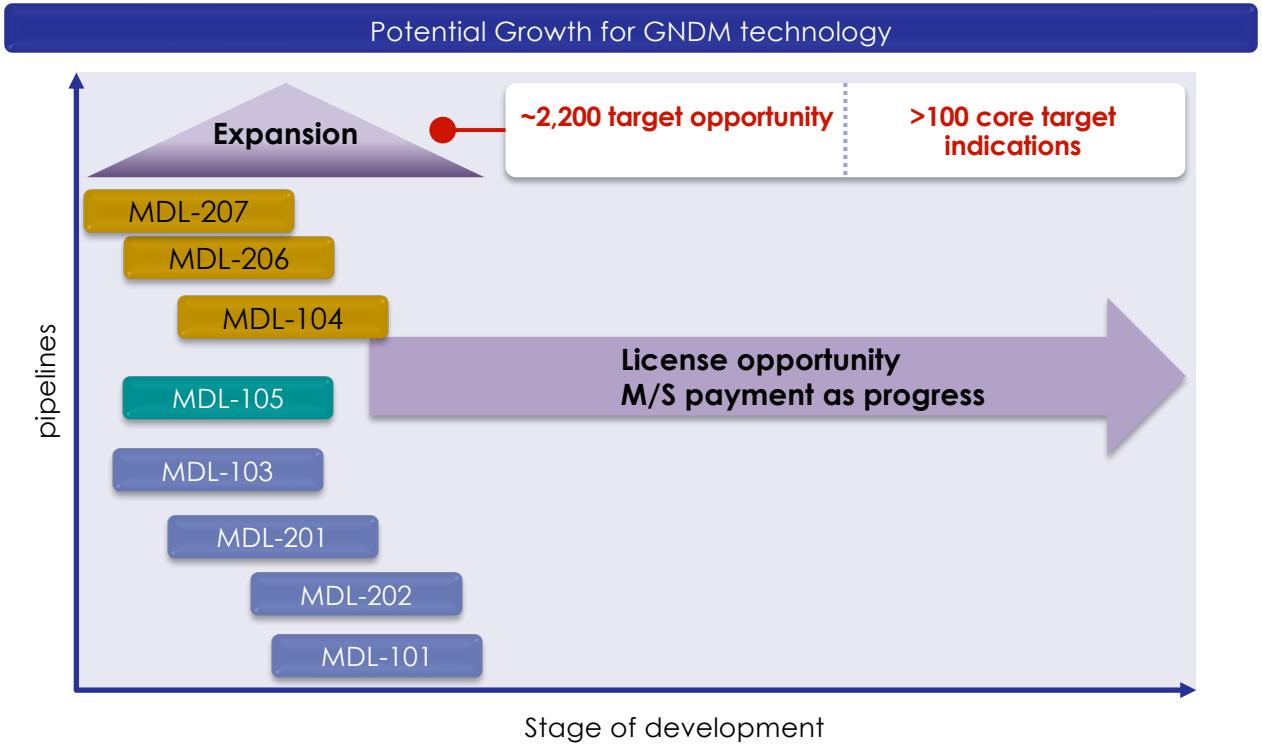
Modalis' pipelines and market size

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



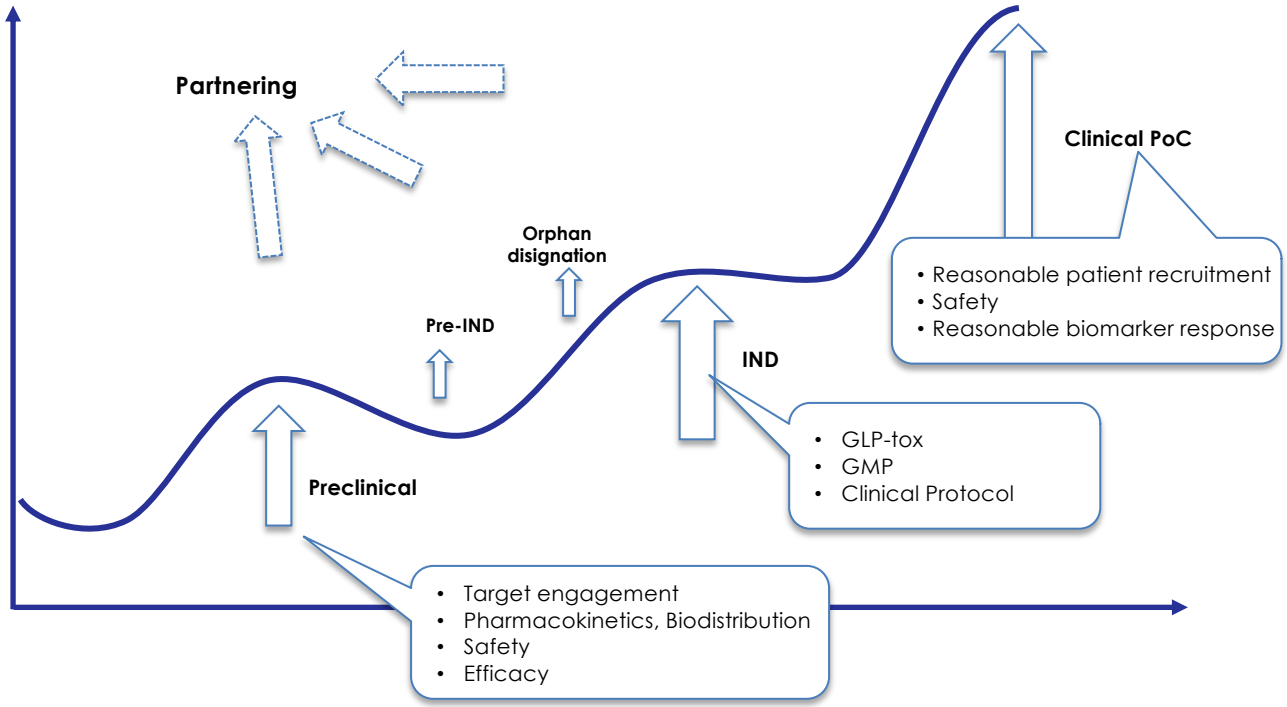
※ Size of circles represents an image of market size or patient number of each indication

Growth Strategy
opportunity expands two dimensionally



Future pre-clinical and clinical trials are expected to increase the value of the company

Expected milestone events and impact on corporate value



MODALIS

Our disclosure policy

In light of fair disclosure, Modalis thinks that it is appropriate to respond to inquiries regarding IR, etc. by enriching information disclosure on our website and making it widely and equally known to the public, rather than responding to individual inquiries by direct contact.

Inquiries are accepted on the "Contact Us" page of the Company's website.
https://www.modalistx.com/en/contact/
We will be answering questions that we think it's appropriate on FAQ page of our website or in future disclosures.

Please be advised that we will not be able to accept inquiries by phone or connect them to a person in charge.

We will continue to make every effort to disclose information fairly to our shareholders and investors, and we appreciate your understanding.