

FY2023 Financial Results



The switch is the Key

Modalis therapeutics Corporation
(TSE : 4883)
Feb 14, 2023

In case of any discrepancy,
the Japanese version shall
prevail

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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 toxicities



Pipeline of preclinical assets in muscular dystrophies, additional programs in CNS, cardiovascular and unlimited therapeutic potential in other areas



Manufacturing 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®

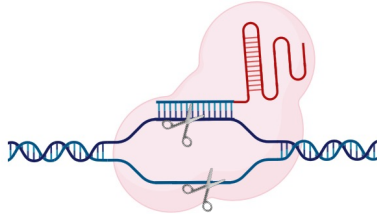
Enables treatment of genetic disorders by controlling epigenetic ON/OFF switch

GTx Technologies

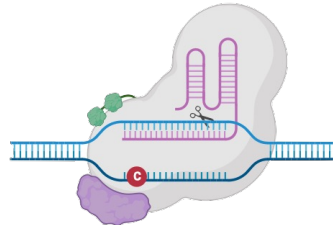
Gene Editing

Base/Prime Editing

siRNA / ASO



Permanent Removal



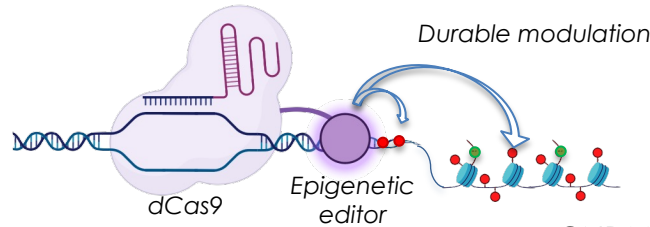
Permanent Replacement



Temporal silencing

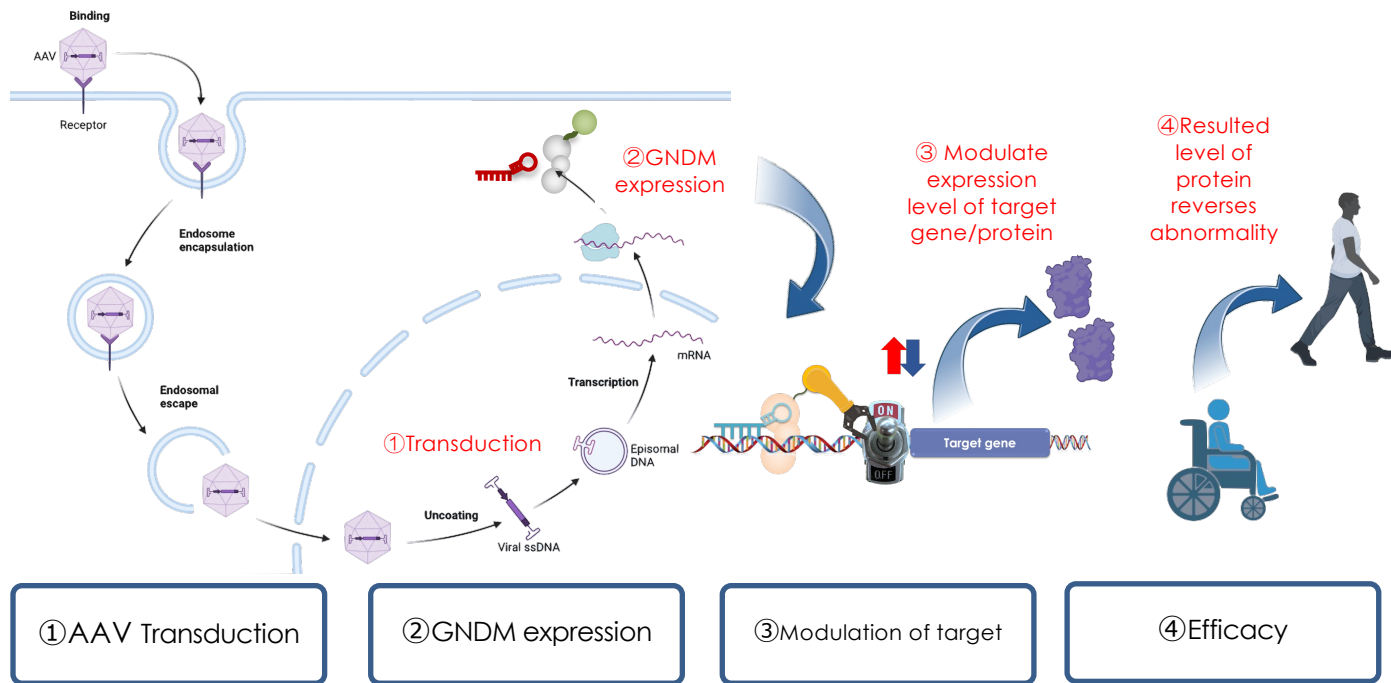
Epigenome Editing(CRISPR-GNDM®)

Bind without cleaving
No DNA damage

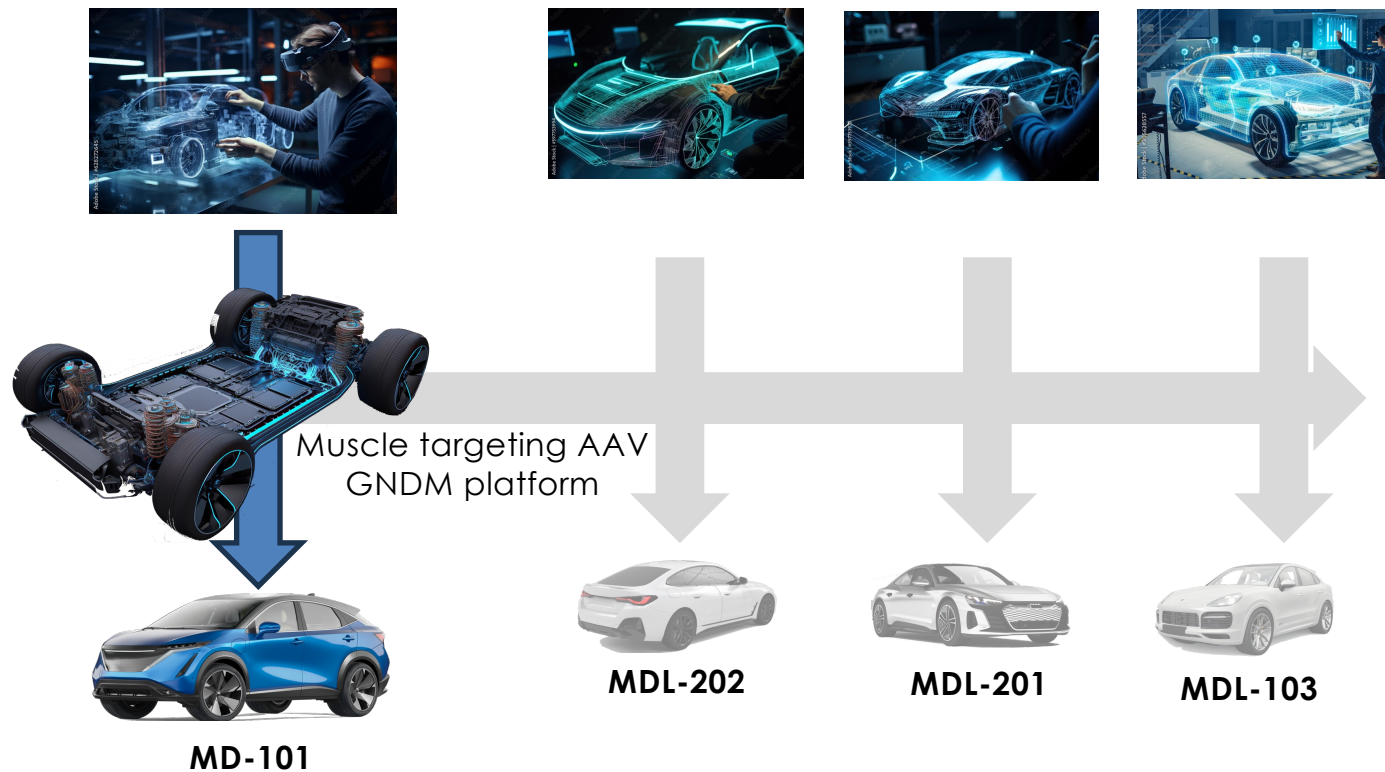


GNDM=Guide Nucleotide Directed Modulation

GNDM-CRISPR is validated - MDL-101 efficacy in mouse disease models and target engagement in monkey



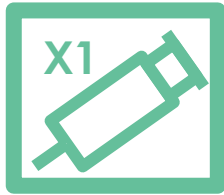
All muscle programs share the same platform as MDL-101



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

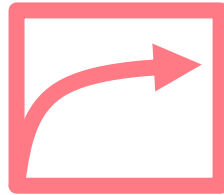
A single injection reverts pathological condition with durability

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

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

	Conventional Gene therapy	Gene Editing	ASO siRNA	
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

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	<ul style="list-style-type: none"> 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

Pipeline Status

Focusing on 101 and 202

Code	Indication	Ownership	Discovery/Preclinical			Clinical	
			Discovery Research	Lead Optimization	IND Enabling	Phase I/II	Pivotal
MDL-101	LAMA2-CMD*1	Modalis	→			Muscular disorders	
MDL-202	DM1 *2	Modalis	→				
MDL-201	DMD *3	Modalis	→				
MDL-103	FSHD *4	Modalis	→				
MDL-105	DCM*5	Modalis	→			Cardiovascular	
MDL-104	Tauopathy	Modalis	→			CNS disorders	
MDL-206	Angelman Syndrome	Modalis	→				
New → MDL-207	Dravet Syndrome	Modalis	→				

*1: LAMA2-related congenital muscular dystrophy

*2: Myotonic Dystrophy Type 1

*3: Duchene Muscular Dystrophy

*4: facioscapulohumeral muscular dystrophy

*5: Dilated Cardiomyopathy

Key topics

1. MDL-101 marching towards IND filing

- Process Development has been almost completed
 - Got ready to be transferred 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 been revised

2. Pilot NHP study analysis ongoing

- 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 CNS

- A research collaboration in a CNS disorder using JBC-AAV and CRISPR-GNDM

5. Multiple GNDM element patents have been granted

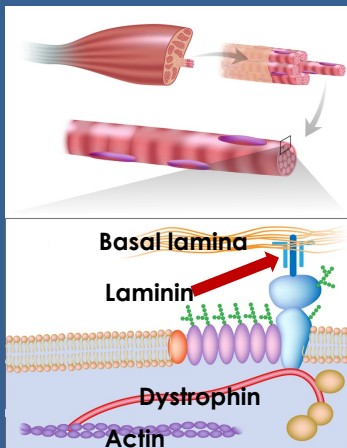
- miniCas9 technology patent in issued Japan
- PAM-flex SpCas9 patent granted in China
- miniVR (small transcription activator) patent granted in Russia

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

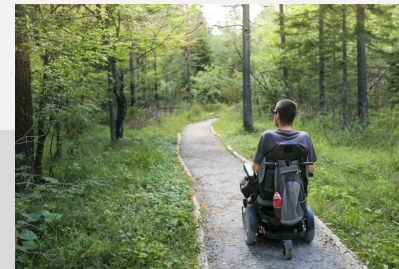
- Severe muscle weakness
- Lack of muscle tone (hypotonia)
- Little spontaneous movement
- Joint deformities (contractures)
- Heart problems and seizures

Disease Causing Gene

LAMA2 mutation

Commercial opportunity

\$500M+



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

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

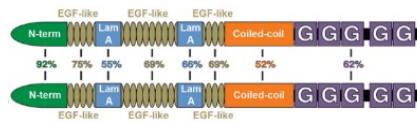
Protein structure of LAMA1 and 2

Expression pattern of LAMA1 and 2 by tissues

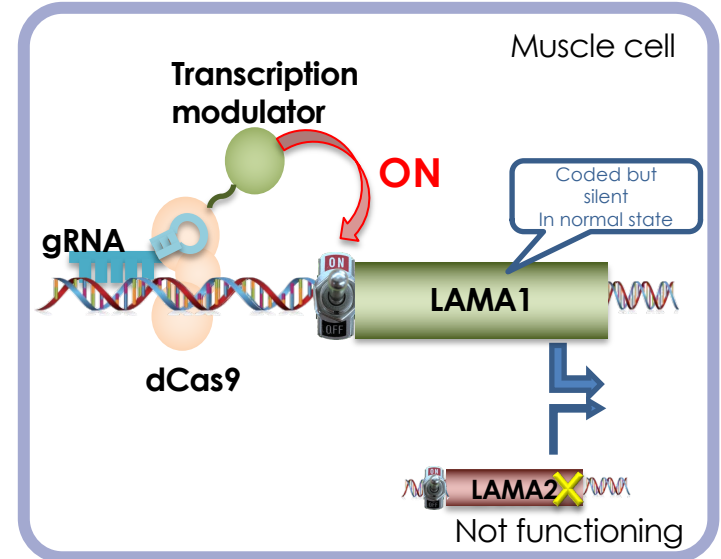
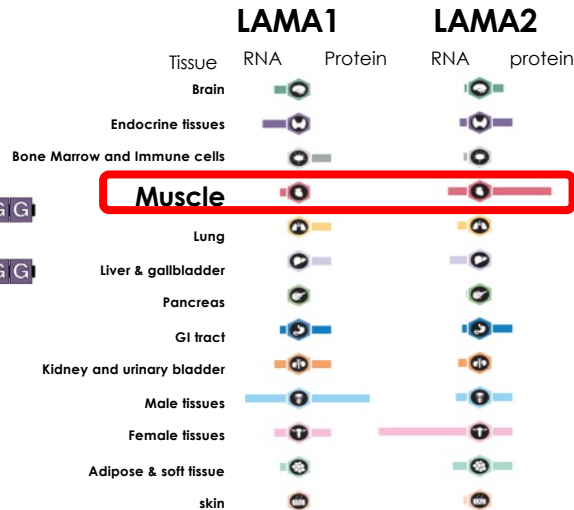
CRISPR-GNDM® targeting LAMA1

LAMA1

LAMA2



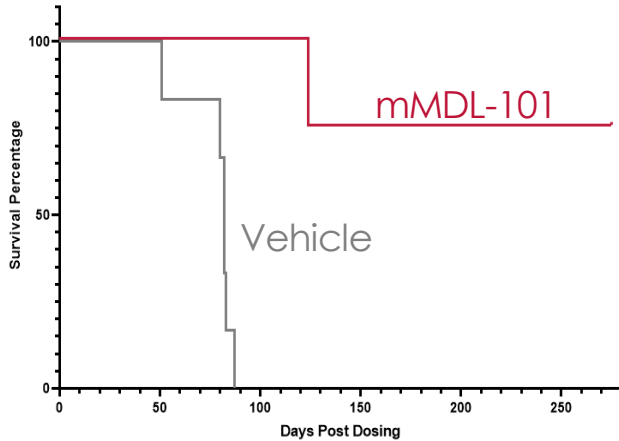
>9kb



mMDL-101 is efficacious in severe MDC1a model

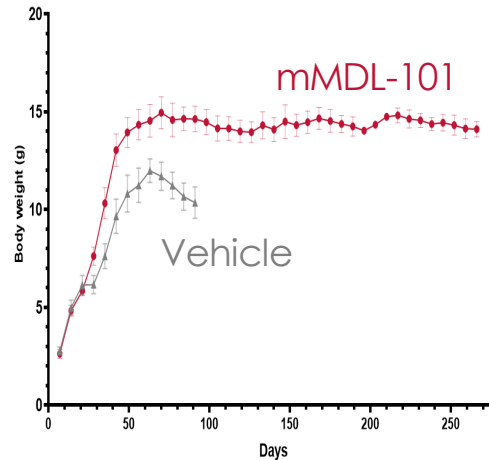
Increased lifespan, body weight and grip strength of dy^W mice

Extended lifespan
(% Survival)



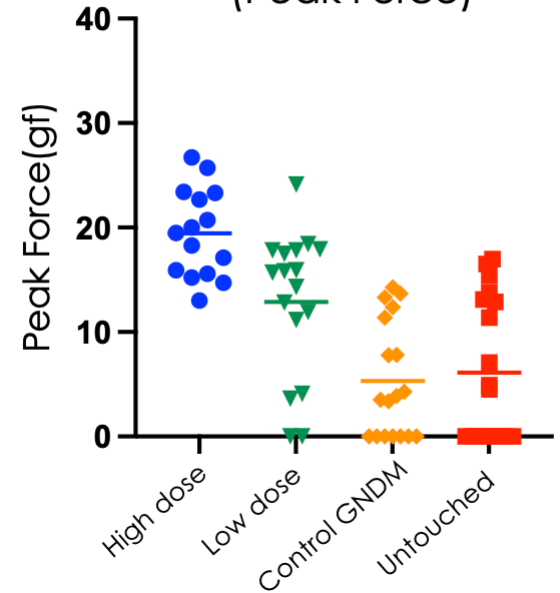
$p < 0.005$, log rank test

Improved growth
(Weight)



$p < 0.0001$, Mann-Whitney test

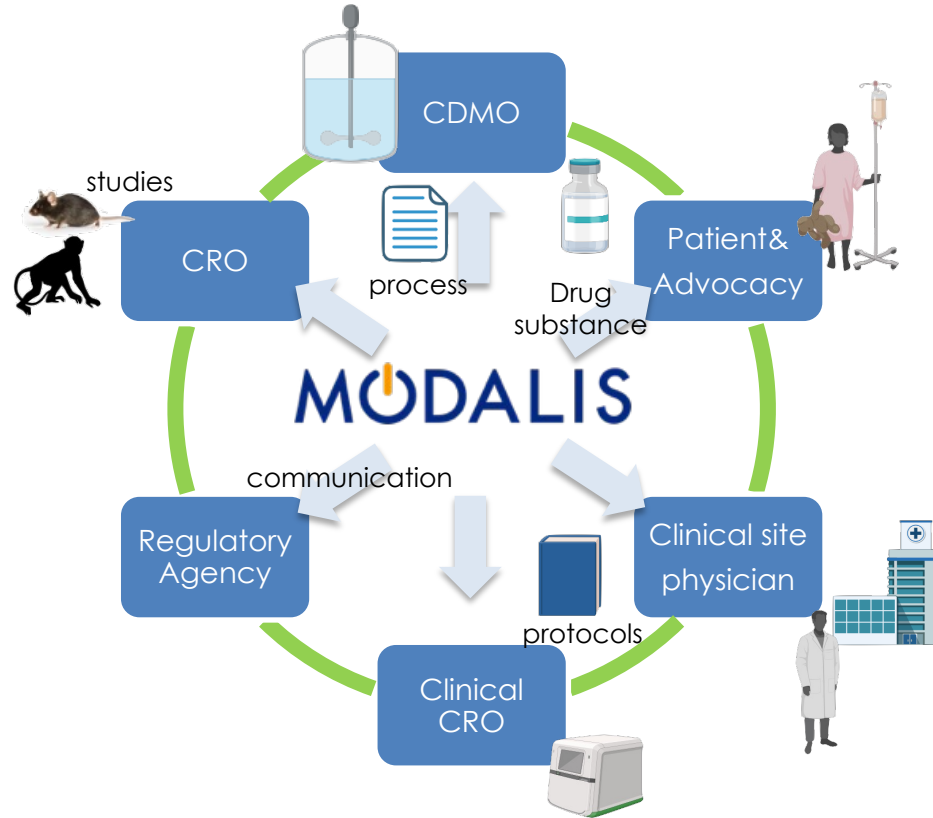
Forepaw Grip Strength
(Peak Force)



Summary of MDL-101 for LAMA2-CMD

- Reported by 3Q/2023
 - Confirmed efficacy in mice disease model and target engagement in NHP with the muscle tropic capsid version MDL-101
 - Completed a juvenile NHP study that confirmed comparable or better LAMA1 expression than adult NHP study
 - Confirmed long term expression of GNDM and LAMA1 in disease model mice
 - KOL meetings and drafting clinical synopsis and protocol
 - Presented development updates of MDL-101 as a late-breaking abstract at ASGCT
 - Received Pre-IND response from FDA (June)
 - Established a feasible manufacturing process with reasonable yield and quality
- Progress thereafter
 - ✓ 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

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



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 the product 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

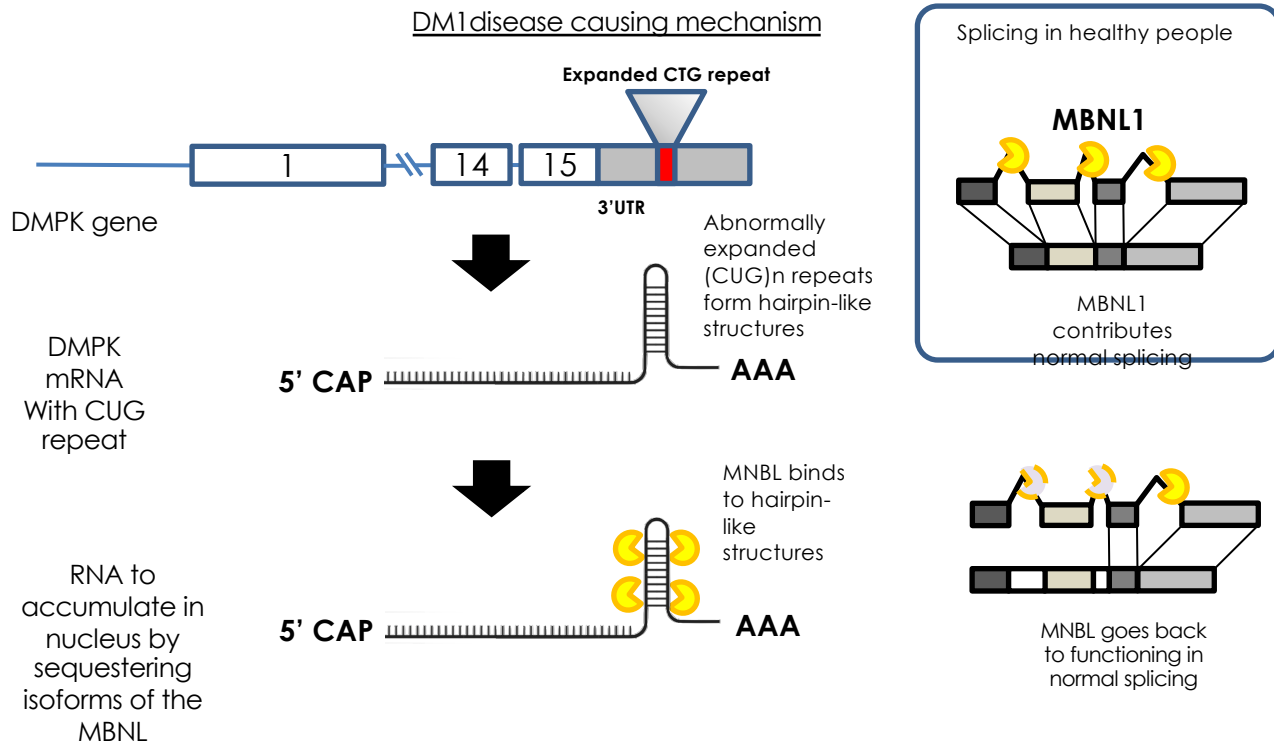
MDL-202

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

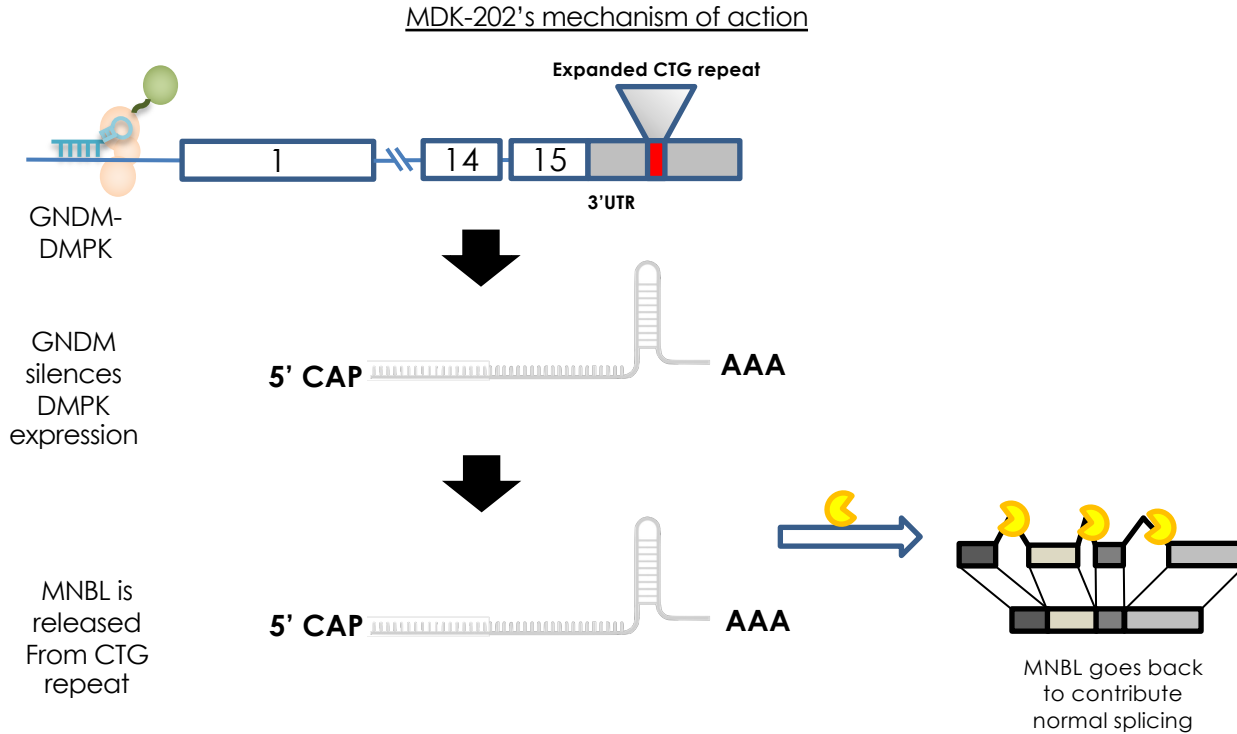
Prevalence	1-4.8 in 10,000 (1 in 2,300*)	DM is the most common muscular dystrophy among adults of European ancestry
Disease onset	DM1 can occur from birth to old age	Age at onset is between 20 and 70 years (typically onset occurs after age 40)
Disease Burden	muscle weakness and wasting (atrophy), myotonia	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)

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



Development Summary of MDL-202 for DM1

- Reported by 3Q
 - ✓ Regained rights of MDL-202
 - ✓ Signing the agreement (Aug)
 - ✓ Asset transfer completed
 - ✓ 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
- Next step
 - Readout of NHP target engagement study
 - Pharmacology studies with mice disease model

MDL-202 offers a feasible and fastest 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



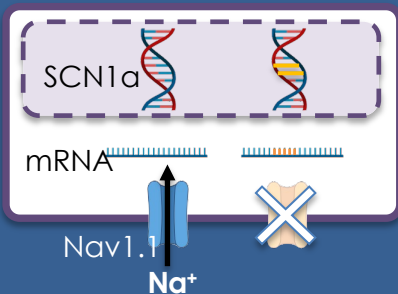
Modalis had INTERACT and PreIND meetings and knows what is required for IND

Dravet Syndrome

A type of epilepsy caused by haploinsufficiency mutation in SCN1A gene

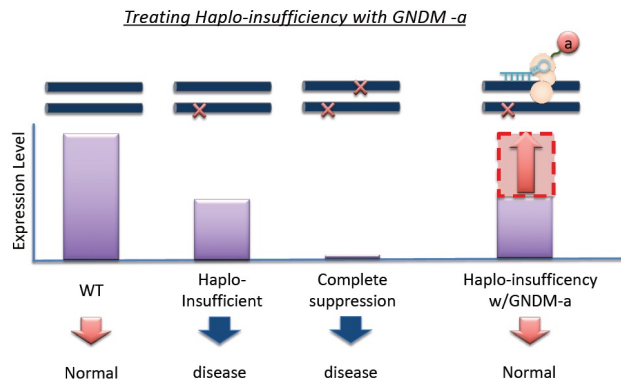
MDL-207

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	<ul style="list-style-type: none">• SUDEP (sudden unexpected death in epilepsy patients)• status epilepticus (SE).• Autism-like spectrum (ASD)• Attention deficit hyperactivity disorder (ADHD)
Disease Causing Gene	SCN1A	<ul style="list-style-type: none">• Haploinsufficiency of SCN1A
Commercial opportunity	\$500M+	<ul style="list-style-type: none">• Currently with no curable drugs• The market is estimated to grow at CAGR of 9.6% # driven by new therapeutics

A simple solution is to double-up SCN1a protein expression



Company	Modality	MOA	Route	Stage	IND
Enoded Therapeutics	AAV-ETN (regulatory element)	<ul style="list-style-type: none"> Overexpress regulatory element for Scn1a Upregulate endogenous Scn1a expression specifically in GABAergic inhibitory neurons 	ICV	IND cleared	2021
E-Rare	Adenovirus-Scn1a	<ul style="list-style-type: none"> Restore Scn1a mRNA and Nav1.1 protein levels 	unknown	Preclinical	TBD
UCL	Lentivirus-Scn1a	<ul style="list-style-type: none"> Restore Scn1a mRNA and Nav1.1 protein levels 	Direct injection	Preclinical	TBD
OPKO	AntagoNAT	<ul style="list-style-type: none"> 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)	<ul style="list-style-type: none"> 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)	<ul style="list-style-type: none"> 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

What has been achieved and coming next

	What has been achieved	What's coming next
MDL-101 LAMA2-CMD	<ul style="list-style-type: none"> • Animal PoC in disease model mice • Target engagement in NHP • Pre-IND with FDA (June 2023) • Presentation at ASGCT 2023 	<ul style="list-style-type: none"> • GLP-Tox • GMP manufacturing • IND (2H 2024)
MDL-202 DM1	<ul style="list-style-type: none"> • 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) 	<ul style="list-style-type: none"> • Readout of NHP target engagement study (1Q/2024) • Readout of mouse disease model study (2Q/2024) • Partnering
Other	<p>Muscle program</p> <ul style="list-style-type: none"> • MDL-201 (DMD) • MDL-103 (FSHD) • MDL-105 (DCM) <p>CNS programs</p> <ul style="list-style-type: none"> • MDL-104 (Tauopathy) • MDL-206 (Angelman) • MDL-207 (Dravet) 	<ul style="list-style-type: none"> • Transplantation to muscle tropic capsid • Animal PoC (FSHD, DCM) • Partnering <ul style="list-style-type: none"> • Continuing research • Explorer neurology capsids and LNPs • Partnering

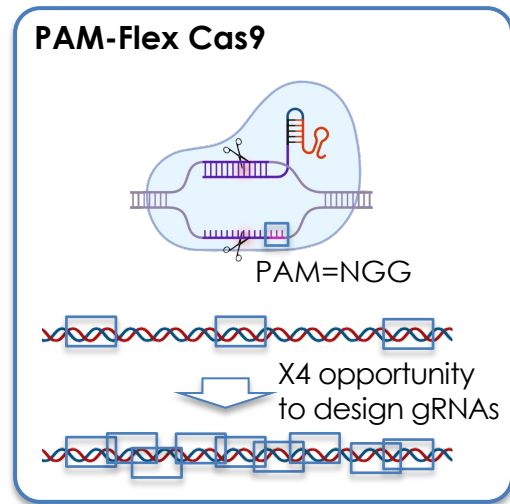
Other updates on business

➤ 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)

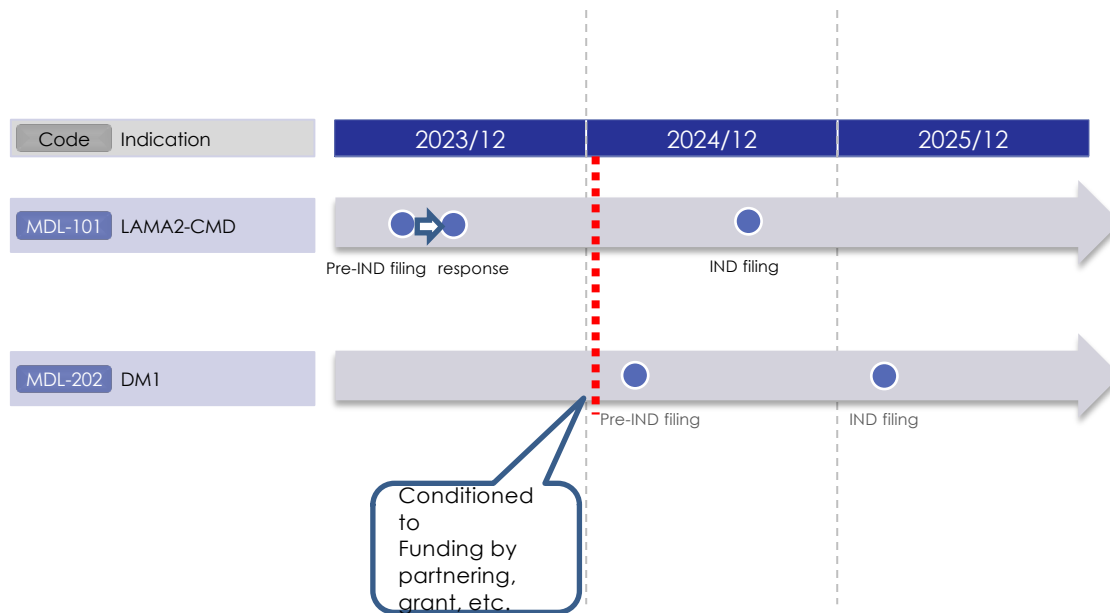
➤ Partnering

- 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

As regained rights of MDL-201 and 202, 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

BS & Financial Position

(Million Yen)

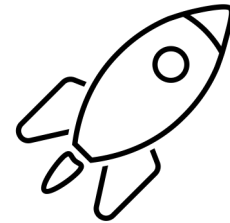
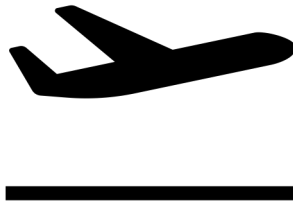
	FY2022 (A)	FY2023 (B)	(B) – (A)
Current assets	3,061	1,956	(1,104)
Cash & deposits	2,933	1,883	(1,049)
Non-current assets	68	69	1
Total assets	3,129	2,025	(1,104)
Current liabilities	141	198	56
Non-current liabilities	47	447	400
Total liabilities	188	645	456
Total net assets	2,941	1,380	(1,560)
Total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

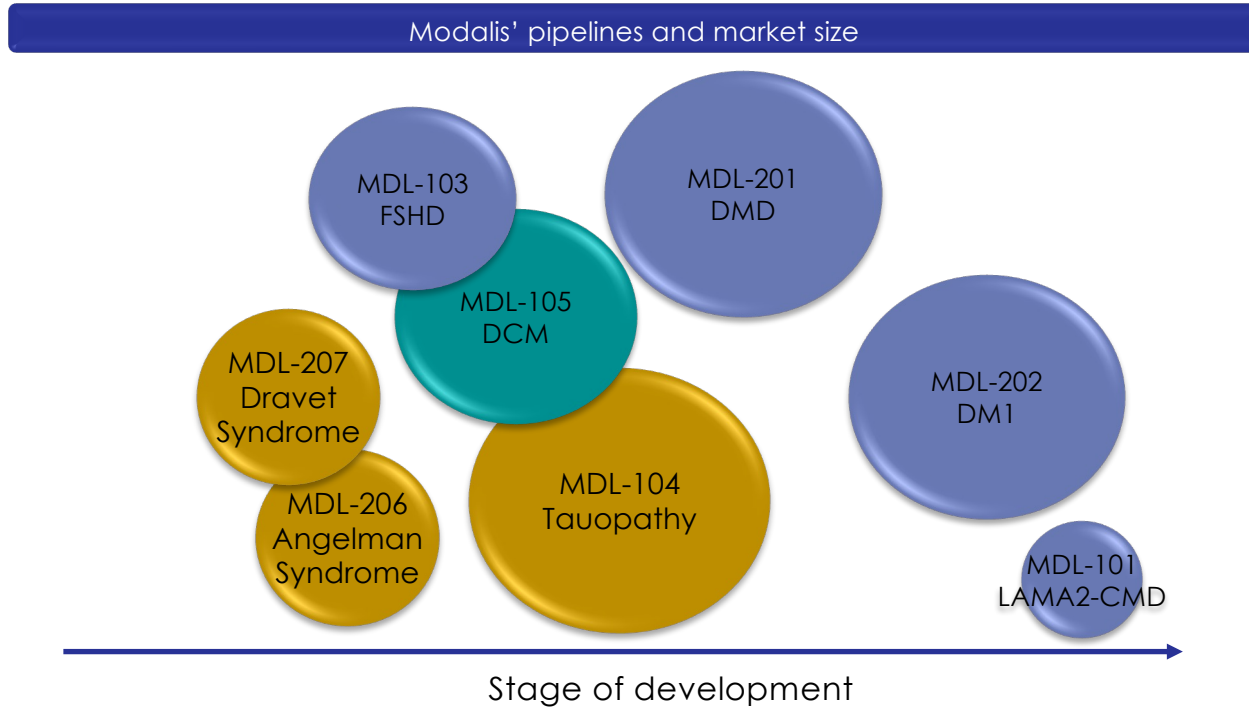
3. Growth Strategy

MODALIS GNDM platform provides a diversified pipeline



Modalis' pipelines and market size

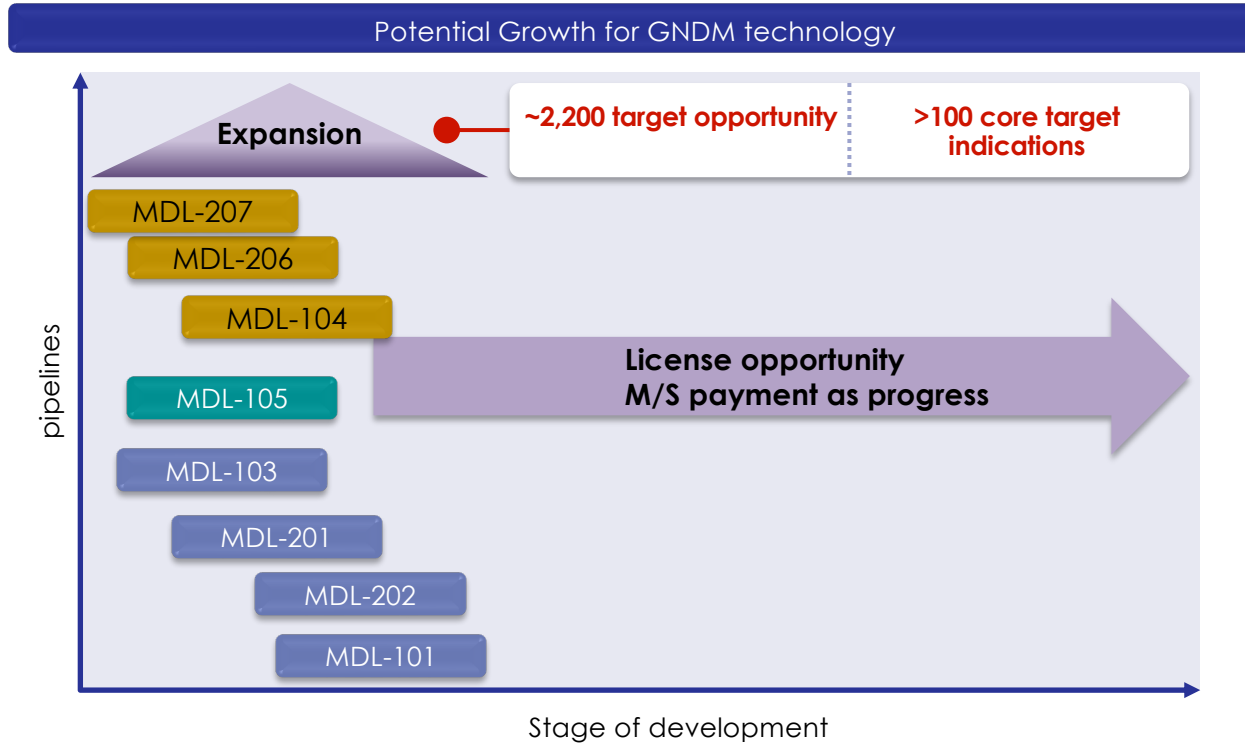
Large indication programs follow MDL-101 which paves the clinical path



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

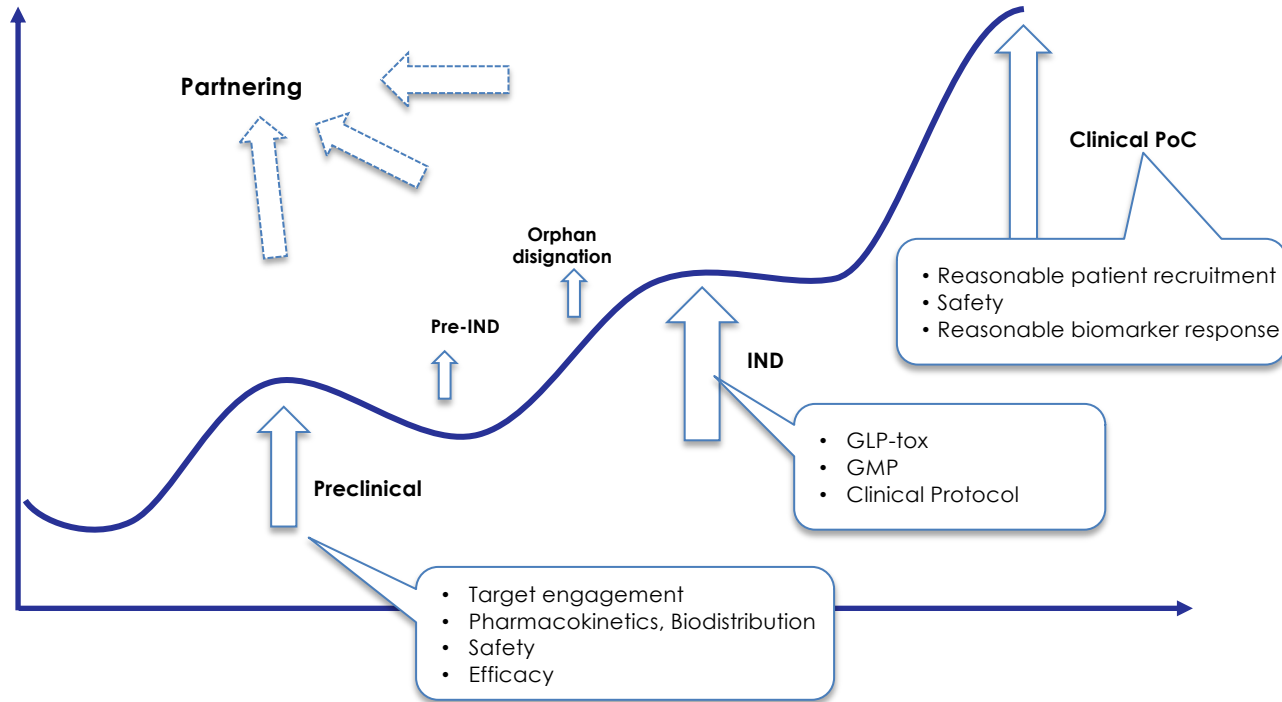
Growth Strategy

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



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<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.