English translation for reference purposes only

FY2023 3Q
Financial Results



In case of any discrepancy,
the Japanese version shall prevail

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Modalis therapeutics Corporation
(TSE：4883)
November 7, 2023

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MODALIS Value Highlights

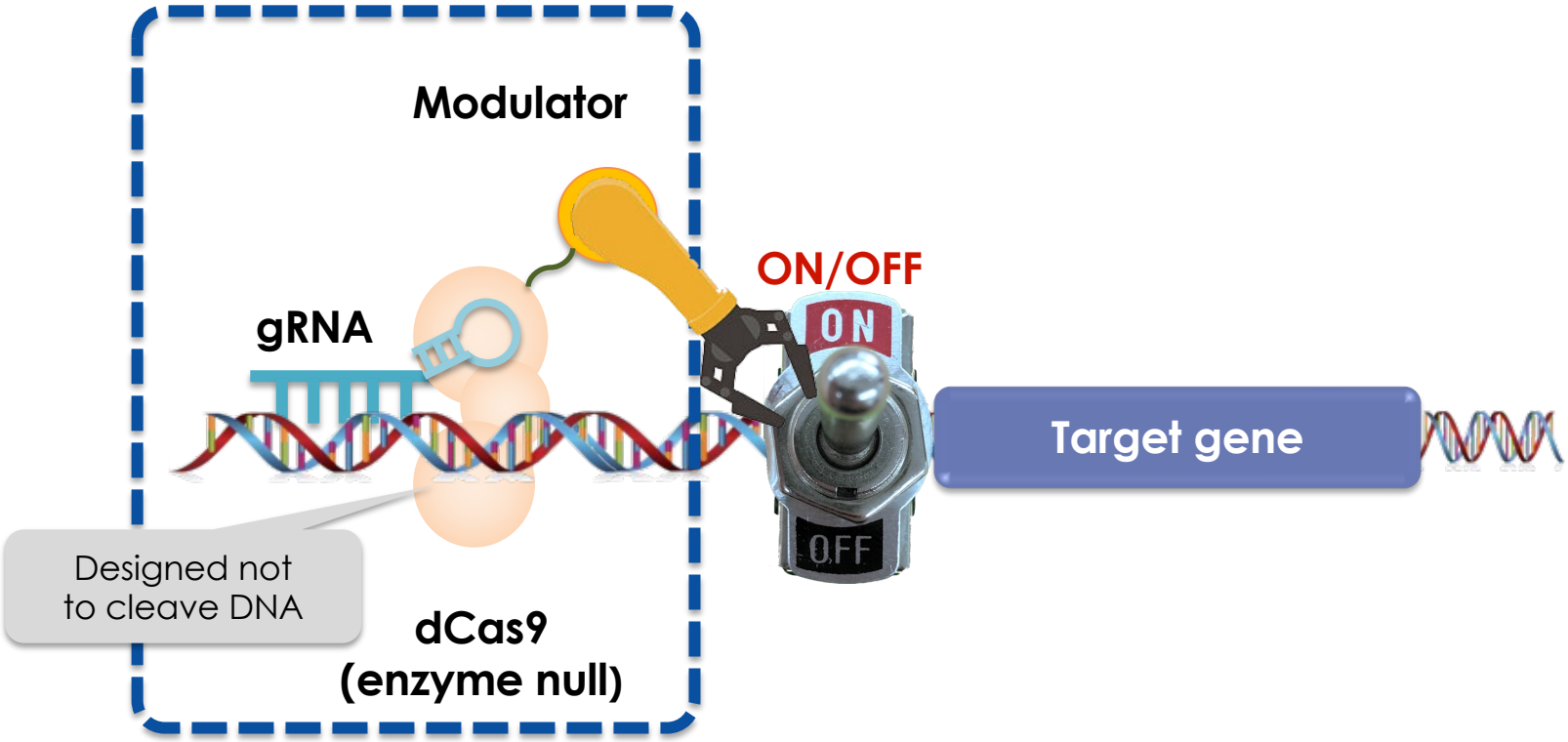
- Established the first robust epigenetic platform for activation and inhibition of endogenous genes using CRISPR-GNDM® platform
- Demonstrated sustained modulation of gene expression in multiple species (mouse, cyno) resulting in functional efficacy without toxicities
- Pipeline of preclinical assets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

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Non-cleaving CRISPR = CRISPR-GNDM®

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

CRISPR-GNDM® (Guide Nucleotide-Directed Modulation) platform

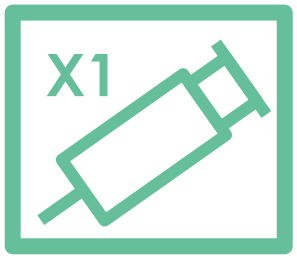


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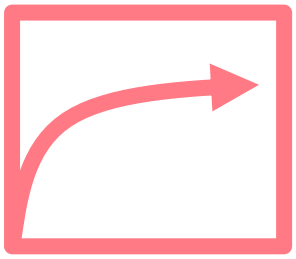
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CRISPR-GNDM® is a promising therapeutic modality that controls the epigenome to modulate expression

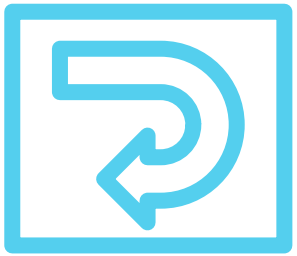
Potential benefits of CRISPR-GNDM® Technology



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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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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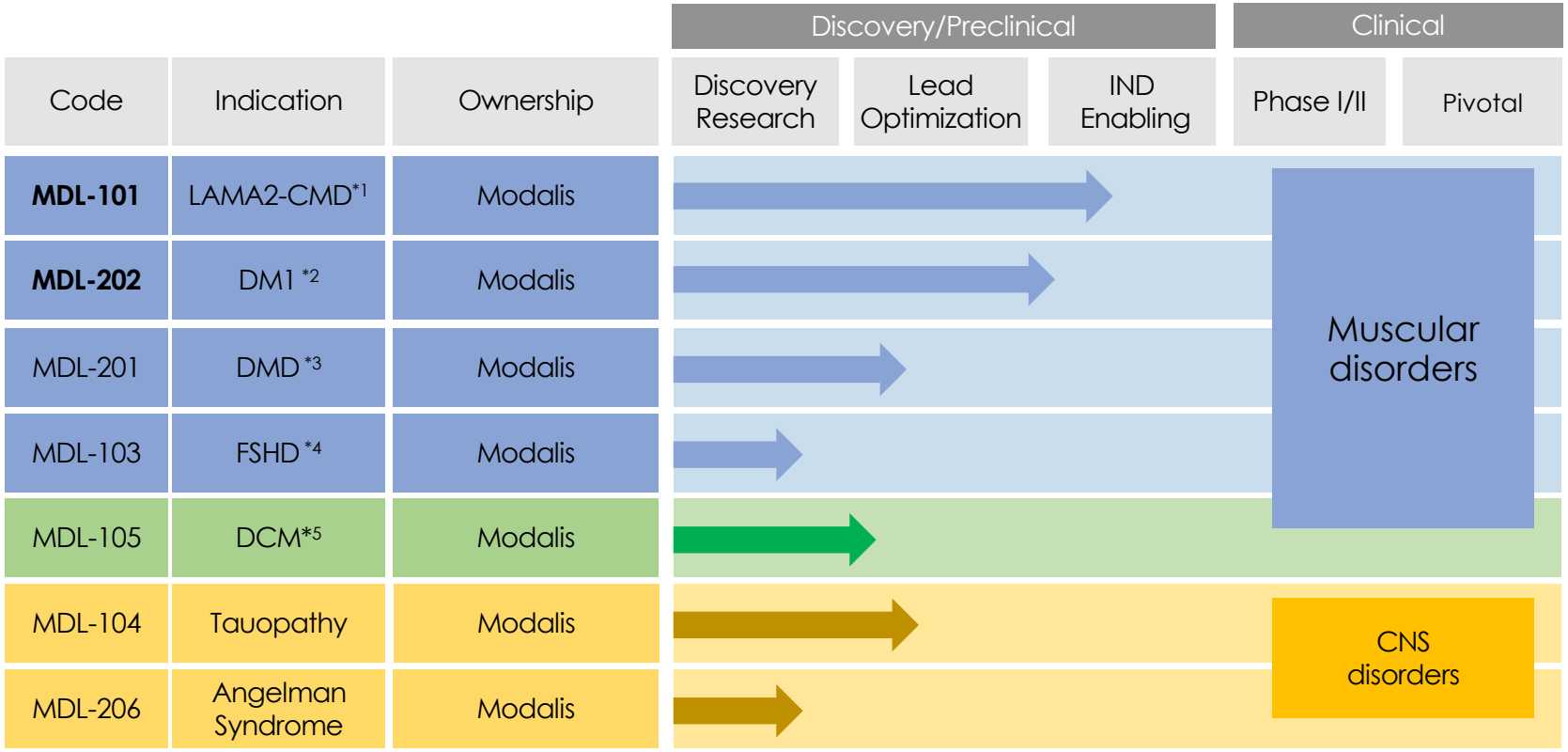
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1. Key Topics in 3Q

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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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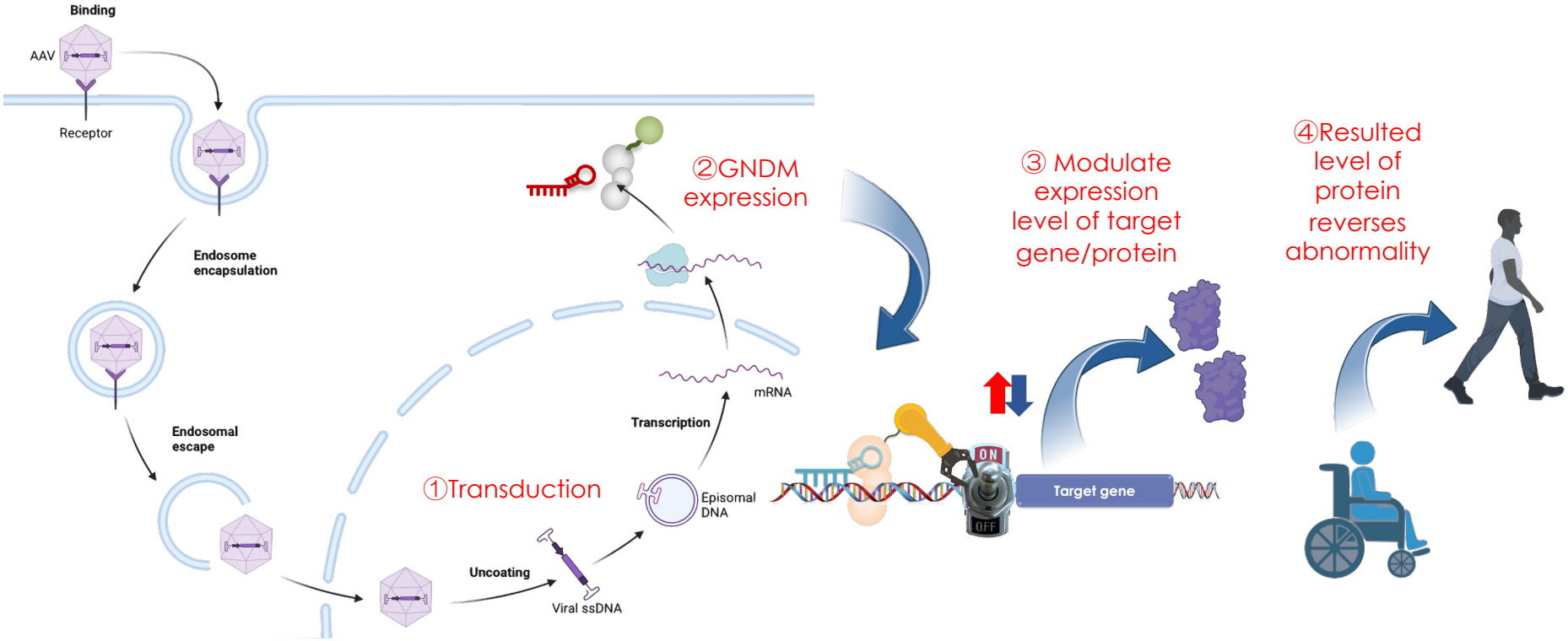
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Key topics in 3Q

- Completed conversion of MDL-202 to muscle-specific capsid
  - Mouse and NHP study initiated
    - Readout is expected 1Q/2024 or later
- Pursuing the IND enabling strategy revised after preIND
  - Completion of juvenile NHP study
  - Established manufacturing process
  - Revision of study design for GLP-tox studies (NHP, mice)
- Going around the CB+WR finance to fund R&D including IND enabling of MDL-101

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



①AAV Transduction | ②GNDM expression | ③Modulation of target | ④Efficacy

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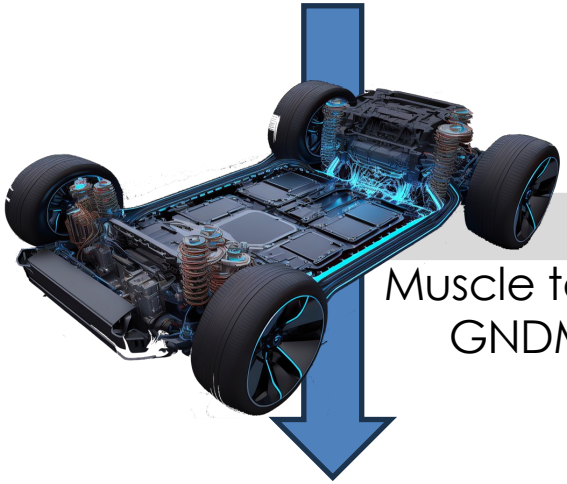
All muscle programs share the same platform as MDL-101











Muscle targeting AAV
GNDM platform



MD-101



MDL-202



MDL-201



MDL-103

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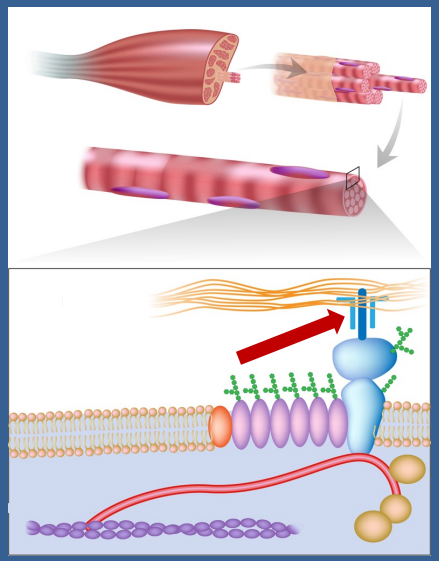
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LAMA2-CMD (aka CMD1a)

Severe muscular dystrophy caused by loss of function mutation in LAMA2 gene

MDL-101

Potential to be the first LAMA2-CMD treatment



Prevalence	**1 in 40,000*** 8,000 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+**	

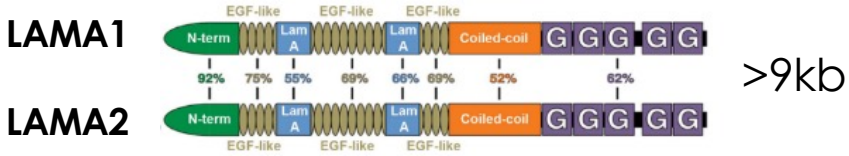
Source: *Ophanet #*Modalis assumption based on prevalence and potential*

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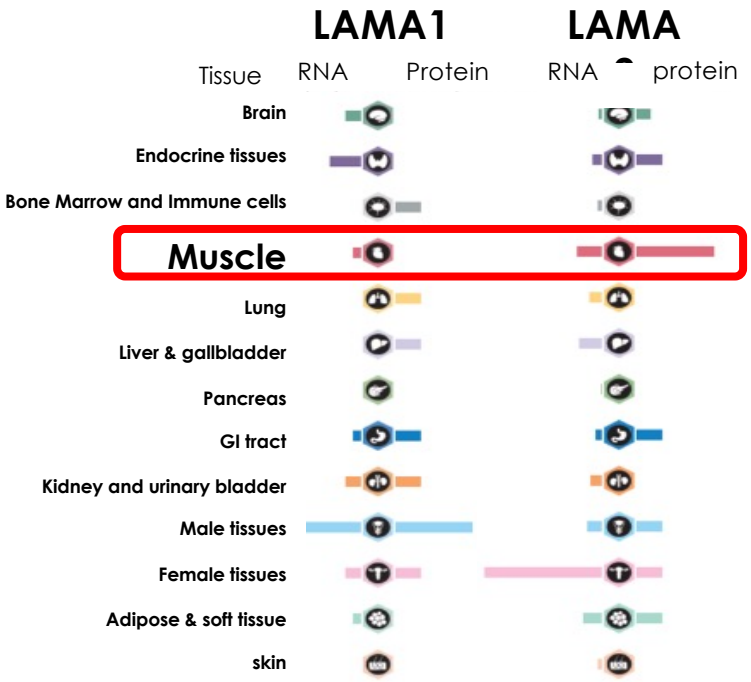
MDL-101 activates LAMA-1, compensates for the missing function of LAMA2, which is too large for classical gene therapy approach

Protein structure of LAMA1 and 2

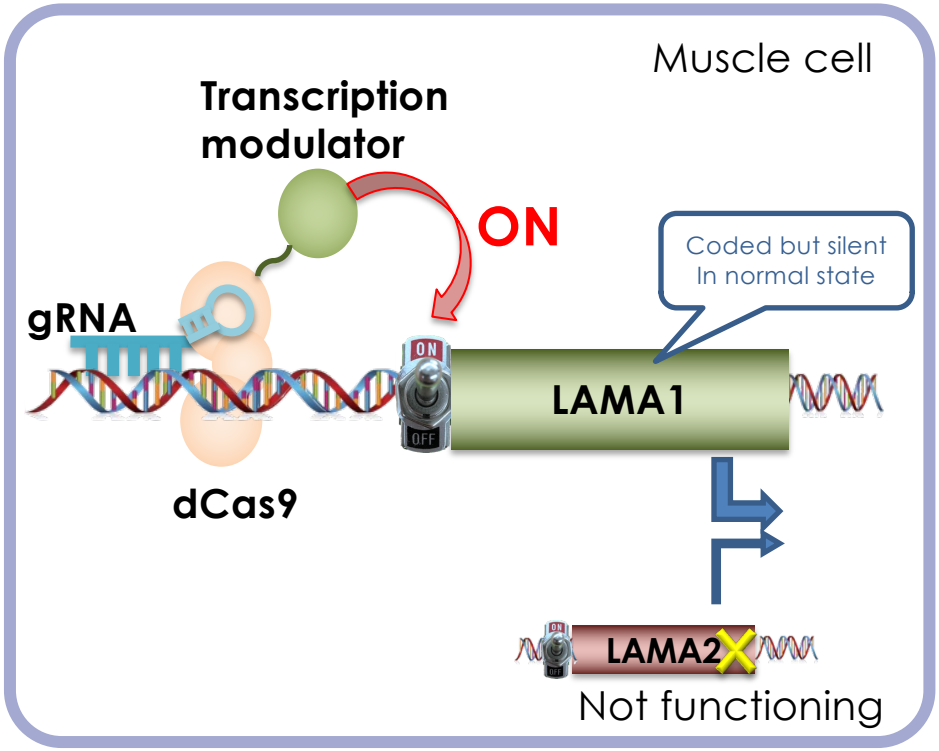


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Exspression pattern of LAMA1and LAMA2 by tissues



CRISPR-GNDM® targeting LAMA1



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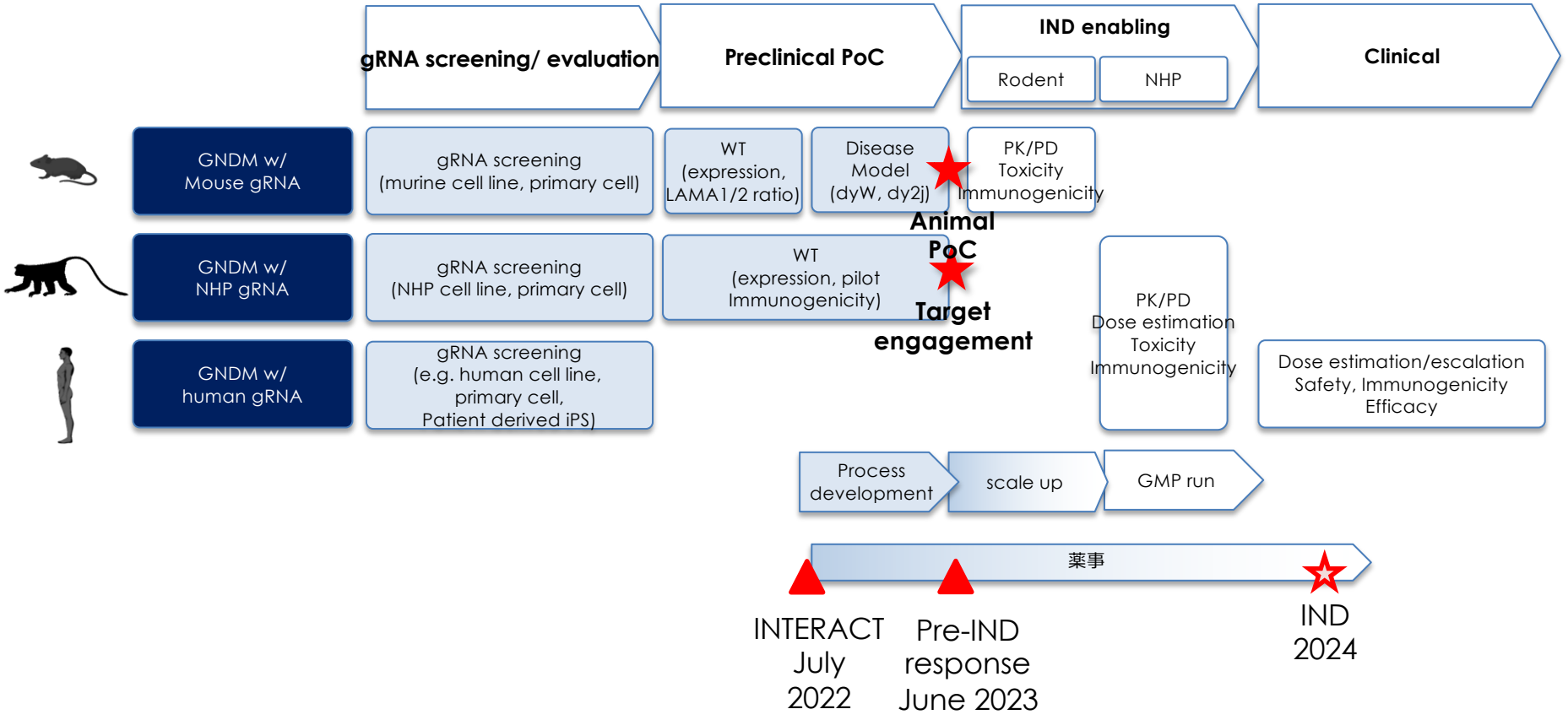
Summary of MDL-101 for LAMA2-CMD

- Reported by 2Q/2023
  - Confirmed efficacy in mice disease model and target engagement in NHP with the muscle tropic capsid version MDL-101
  - 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)
- Progress thereafter
  - ✓ Confirmed long term expression of GNDM and LAMA1 in disease model mice
  - ✓ Juvenile monkey study completed
    - ✓ Well tolerated without any toxicity symptom
    - ✓ Comparable or even better transduction efficiency and LAMA1 expression to adult
  - ✓ Established a feasible manufacturing process with reasonable yield and quality
- Next steps:
  - Continue IND enabling GLP tox and PK/PD
  - Continue process development and pilot productions for GMP campaign

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Conducting IND enabling studies as well as process development

Current status of MDL-101 and road map to clinic



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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

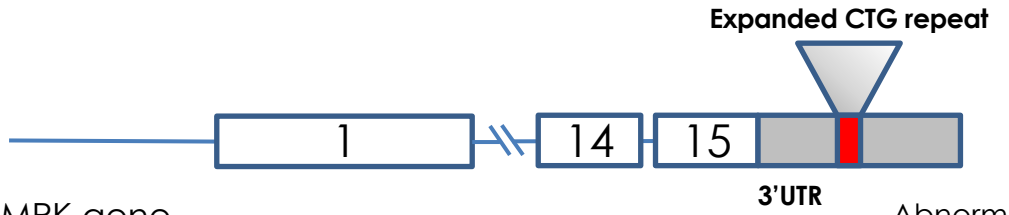
*Source: Myotonic Disease Foundation # DelveInsight (including both DM1 and DM2)

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

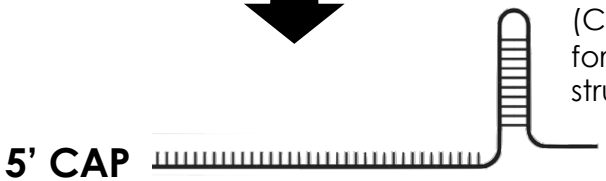
DM1disease causing mechanism



DMPK gene

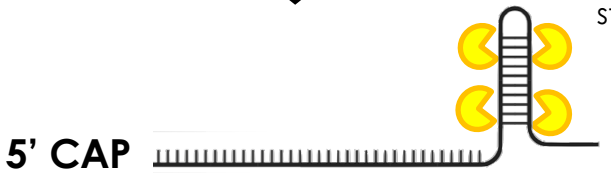
Abnormally expanded (CUG)n repeats form hairpin-like structures

DMPK mRNA With CUG repeat

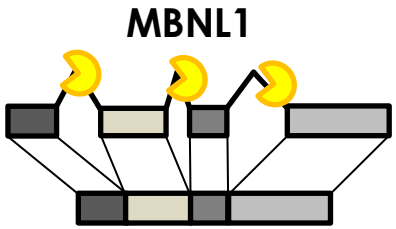


MNBL binds to hairpin-like structures

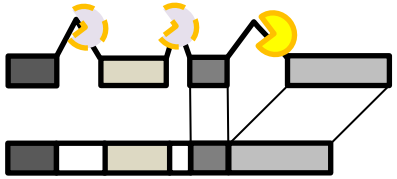
RNA to accumulate in nucleus by sequestering isoforms of the MBNL



Splicing in healthy people



MBNL1 contributes normal splicing



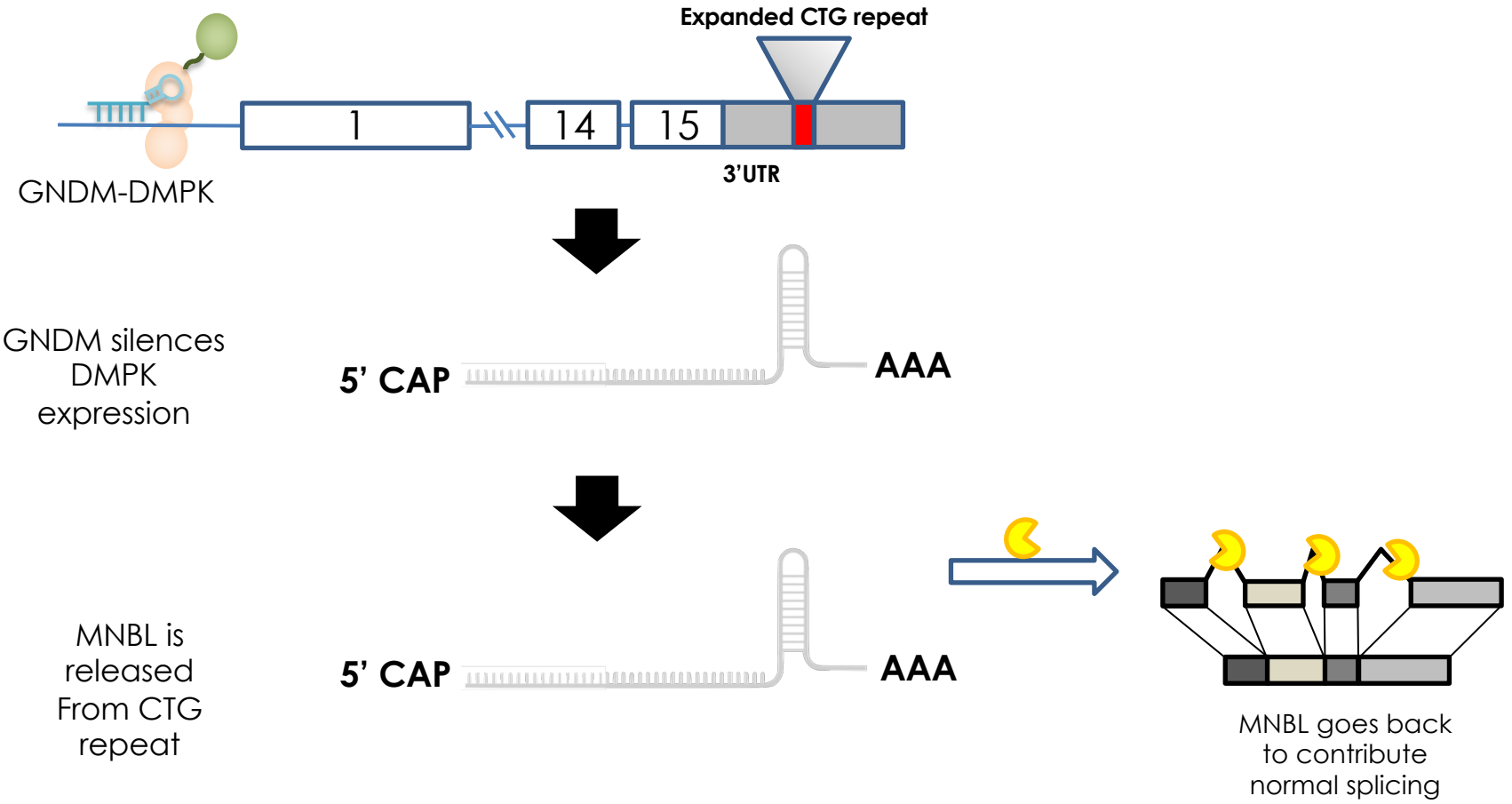
MNBL goes back to functioning in normal splicing

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

MDK-202's mechanism of action



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Development Summary of MDL-202 for DM1

- ✓ Regained rights of MDL-202 from Astellas
  - ✓ Signing the agreement (Aug)
  - ✓ Asset transfer completed
- ✓ Completed transition to the muscle tropic capsid
  - ✓ Designed multiple candidate constructs
    - ✓ Based on the experience in the MDL-101 development
    - ✓ The decision will be made after the NHP study
  - ✓ Pilot production of the candidate constructs
  - ✓ Initiated mouse and NHP target engagement studies

- ➢ Next step
  - ■ Pharmacology studies with mice disease model
  - ■ The animal study data will be reported in ASGCT2024

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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 • Initiation of mice and NHP target engagement study	• Mouse disease model • Readout of NHP target engagement study (1Q/2024) • Partnering
Other	• MDL-201 (DMD) • MDL-103 (FSHD) • MDL-105 (DCM) • CNS programs	• 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
  - Transfer of patent rights to MDL-201 and MDL-202 upon reacquisition of the rights to MDL-201 and MDL-202

- Progress on partnering
  - Partnering discussion ongoing with pharma/biotech companies with the new MDL-101 data
  - Started partnering discussions as MDL-202 development resumes.
  - Research collaboration: In discussion with pharma/biotech companies on new targets

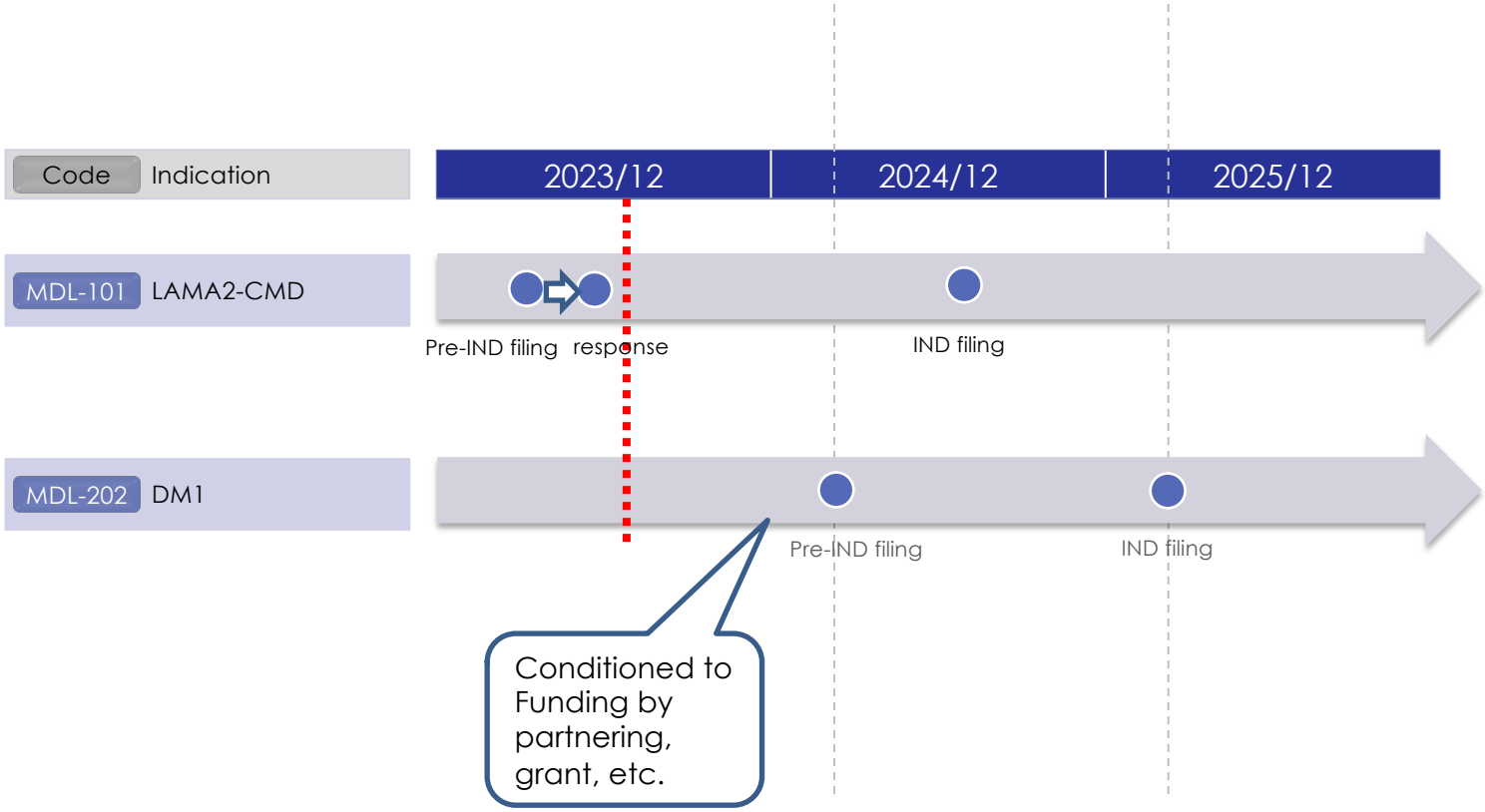
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2. Financial Highlights

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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

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PL & Business Result

(Million Yen)

	FY2022 3Q (A)	FY2023 3Q (B)	(B) – (A)
Operating revenue	40	-	(40)
Operating expenses	1,478	1,609	131
R&D	1,290	1,401	111
SGA	187	207	20
Operating income	(1,438)	(1,609)	(171)
Ordinary income	(1,314)	(1,542)	(228)
Current Profit	(1,309)	(1,581)	(272)

Operating expenses

- R&D increased year on year as business progressed(primarily in personnel expenses, research material expenses, rent fee, expenses for conducting clinical trials of MDL-101 and yen depreciation against US dollar)

Extraordinary loss

- Impairment loss on fixed assets

SGA: Selling and Generally Administrative Expenses

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BS & Financial Position

(Million Yen)

	FY2022 (A)	FY2023 3Q (B)	(B) – (A)
Current assets	3,061	2,105	(956)
Cash & deposits	2,933	1,897	(1,036)
Non-current assets	68	74	5
Total assets	3,129	2,179	(950)
Current liabilities	141	160	18
Non-current liabilities	47	40	(6)
Total liabilities	188	200	12
Total net assets	2,941	1,978	(962)
Total liabilities and net assets	3,129	2,179	(950)
Capital adequacy ratio	93.4%	90.0%	

Note

- High Equity ratio
  Initiated finance to secure higher financial stability (refer to p35)
- Fixed assets decreased from the end of FY2022 due to impairment losses and B/S became slimmer

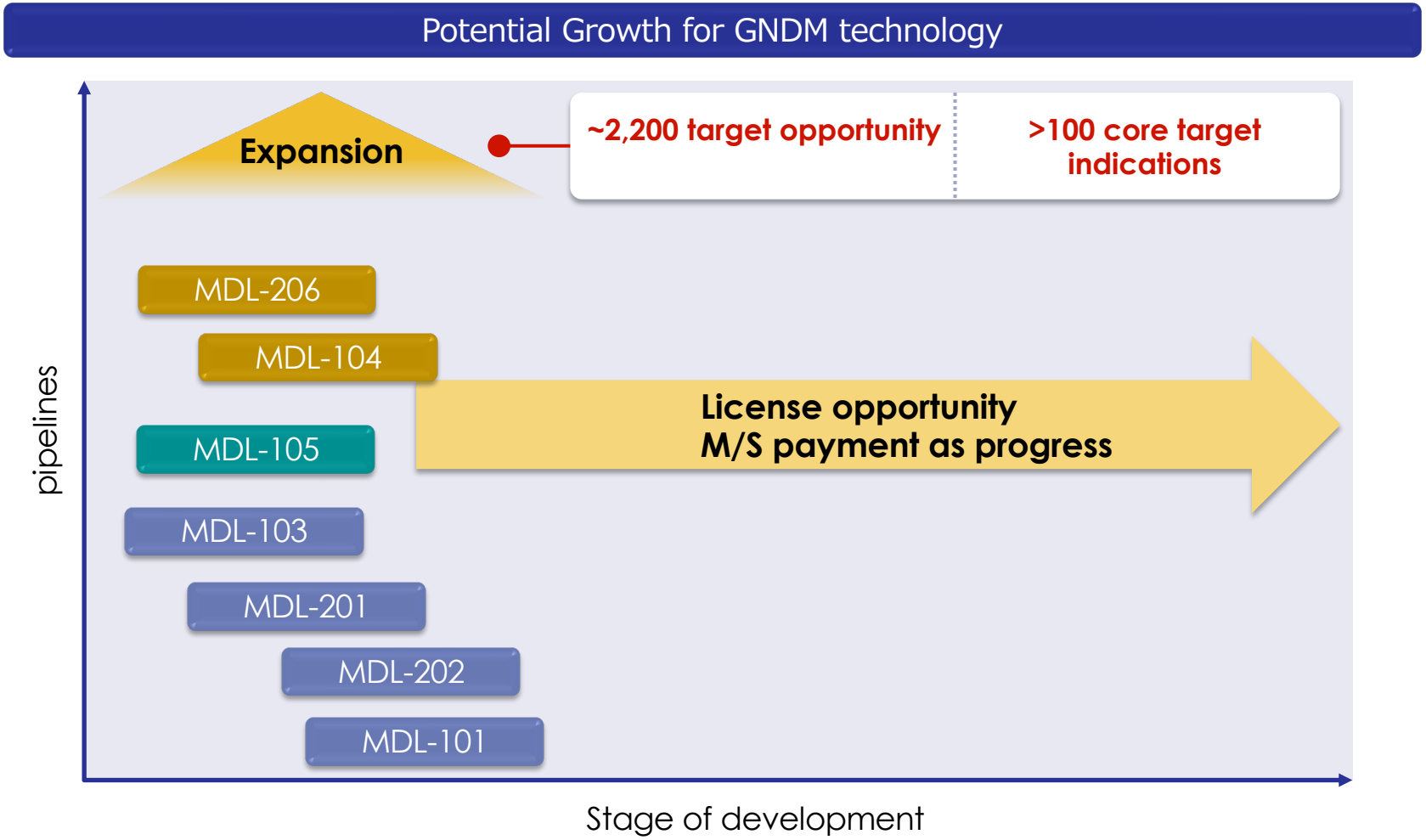
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3. Growth Strategy

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Growth Strategy

opportunity expands two dimensionally



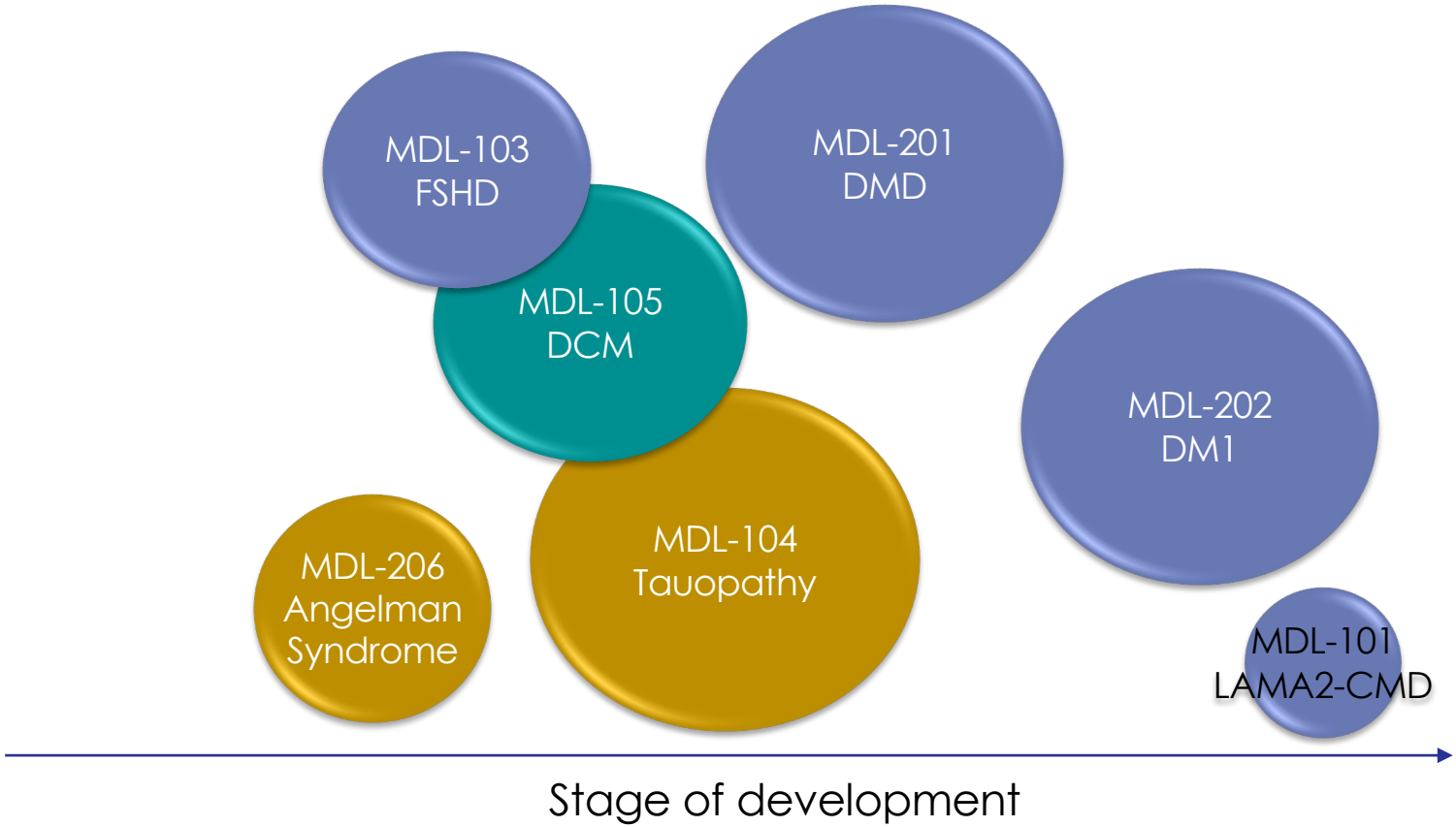
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Modalis' pipelines and market size

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

Modalis' pipelines and market size



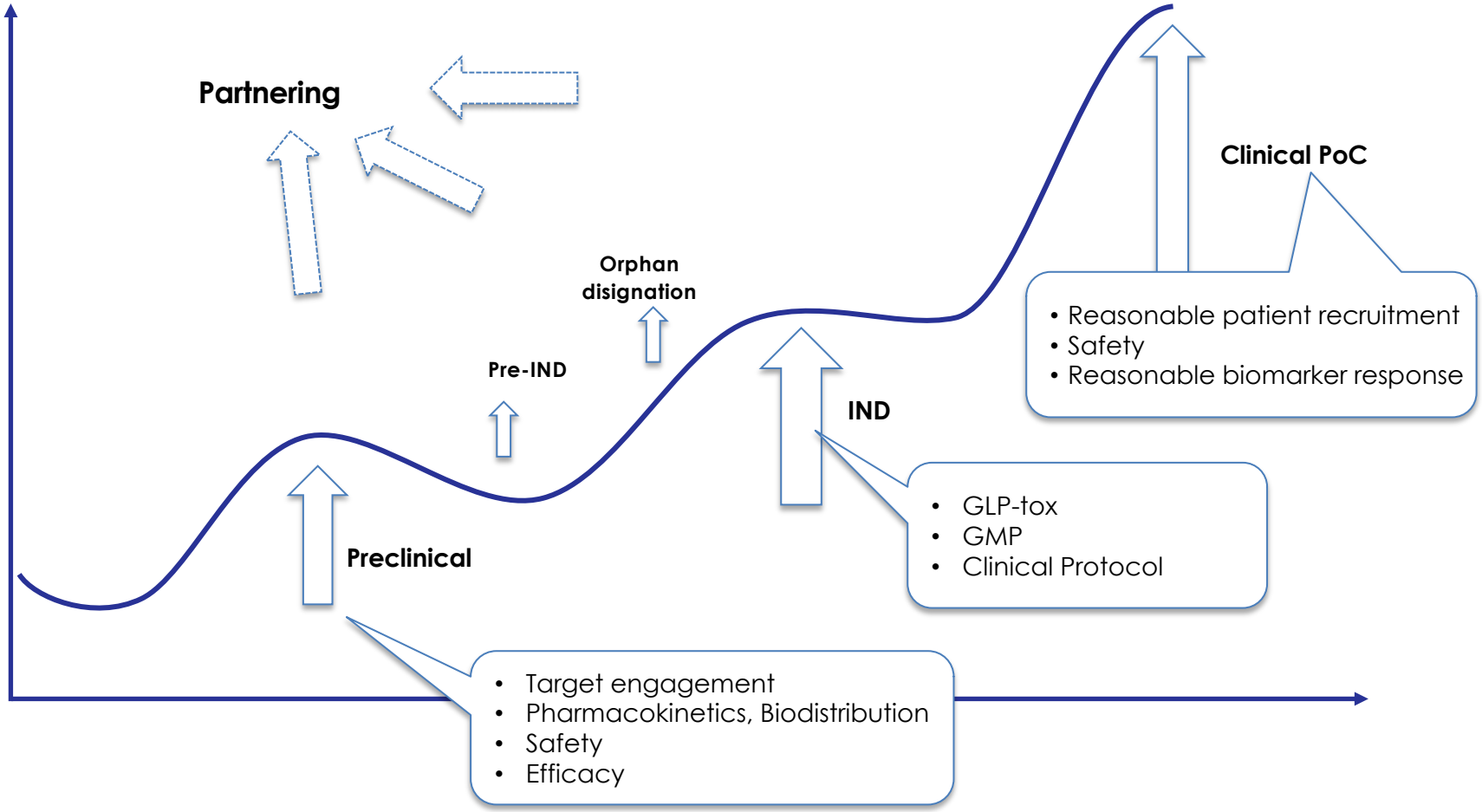
※ Size of circles represents an image of market size or patient number of each indication

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

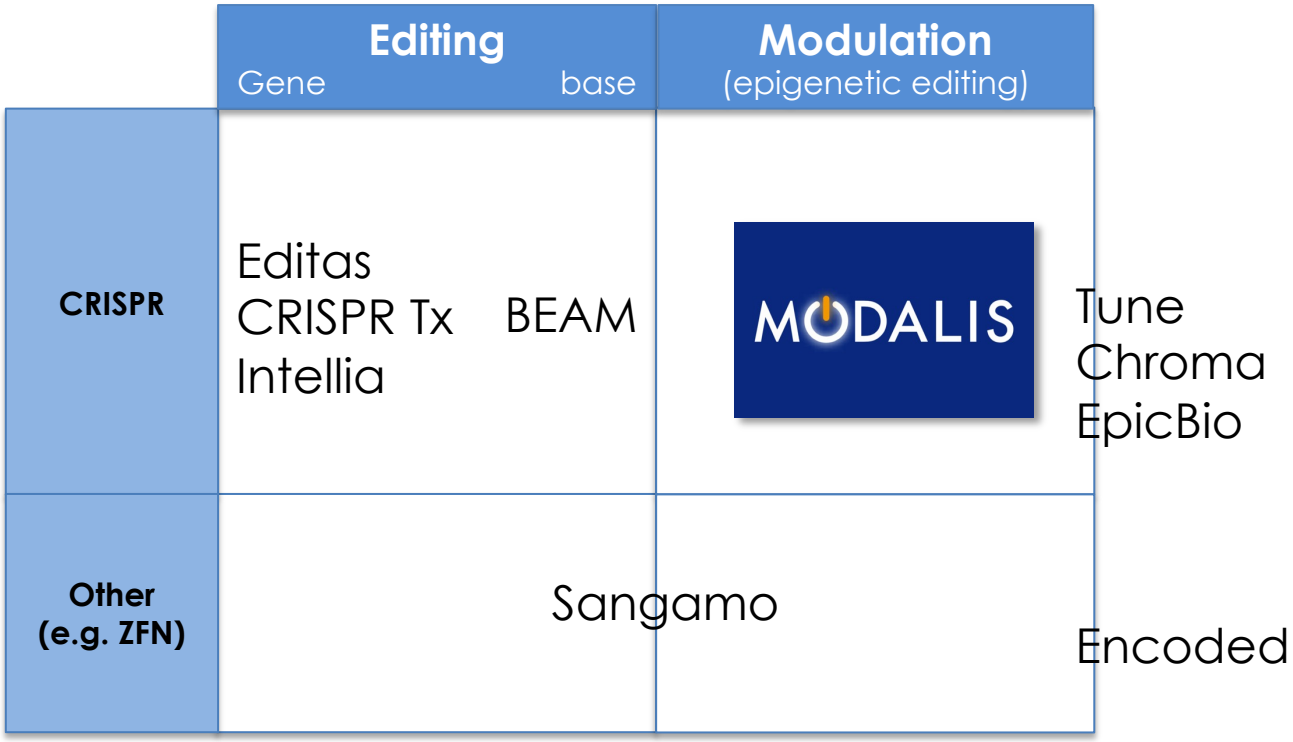
Expected milestone events and impact on corporate value



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Modalis is uniquely positioned within the CRISPR field



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