English translation for reference purposes only

FY2021 3Q Financial Results



In case of any discrepancy,
the Japanese version shall prevail

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Modalis therapeutics Corporation

(TSE : 4883)

November 5 , 2021

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1. Financial Highlights

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PL & Business Result

(Million Yen)

	FY2020 3Q（A）	FY2021 3Q（B）	(B)－(A)
Operating revenue	340	1	(339)
Operating expenses	508	678	170
R&D	349	493	144
SGA	159	185	26
Operating income	(168)	(677)	(509)
Ordinary income	(209)	(661)	(452)
Profit	(214)	(181)	33

Operating expenses

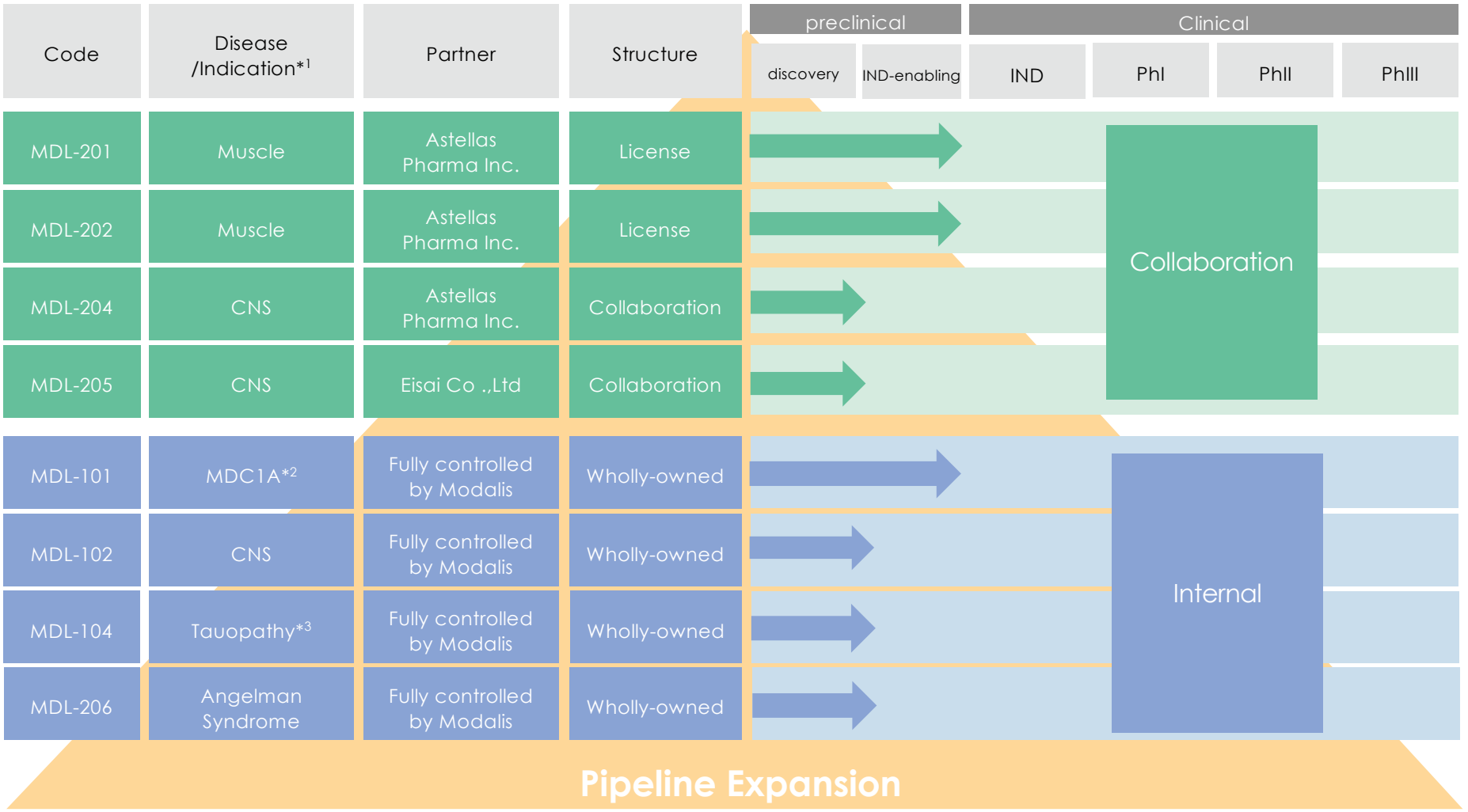
・R&D increased year on year as business progressed(primarily in personnel expenses, research material expenses)

Extraordinary income

・ Income of compensation　485 Million Yen (the Infringement of the Lock-Up System)

SGA: Selling and Generally Administrative Expenses
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Pipeline



*1: We have adopted a strategy of withholding specific indications until the patent application is published for competitive reasons.
*2: MDC1A=Merosin-deficient congenital muscular dystrophy type 1A
*3: Tauopathy belongs to a class of neurodegenerative diseases involving the aggregation of tau protein. Correlation with Alzheimer's disease has been suggested.

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BS & Financial Position

（ Million Yen ）

	FY2020 (A)	FY2021 3 Q (B)	(B) – (A)
Current assets	5,448	5,622	174
Cash & deposits	5,421	5,463	42
Non-current assets	828	876	48
Right to use patent	767	720	(47)
Total assets	6,277	6,498	221
Current liabilities	58	86	28
Non-current liabilities	11	318	307
Total liabilities	70	405	335
Total net assets	6,206	6,093	(113)
Total liabilities and net assets	6,277	6,498	221
Capital adequacy ratio	98.9%	93.8%	

- Stable financial base, High Equity ratio
- Recorded access to CRISPR/Cas9 foundational IPs from Editas Medicine, Inc
- A portion of the licensing fees were received from the out-licensing party as a Non-current liability

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2. Key Topics

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Summary in R&D

- MDL-101
  - IND enabling study initiated and on-going
  - Initiated preparation for FDA meetings
  - Entered strategic alliance with a CDMO* for GMP manufacturing of MDL-101
    - Modalis to get access to the CDMO's vector system and production capabilities
    - As a result of detailed analysis and planning, revised the IND plan to mid 2023.
  - Discussion concurrently on-going with multiple potential partners
- Other programs
  - Steady progress in all programs
  - Further downsized GNDM cassette to improve AAV productivity

CDMO*: Contract Development and Manufacturing Organization

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Other business topic

- Relocated US operation as of Oct 20*
  - To Waltham MA, which is adjacent to Cambridge
  - Substantially upgraded and expanded from the Company's prior facility to have 13,000sqf (1,200 ㎡)size that accommodates process development function as well as expanded discovery group.
  - Can accommodate up to 40~50 people level.

*As reported on Oct 20

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Conference room
@old space

MDL-101

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MDC1A

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

- Frequency: **1 in 30,000***
- Inheritance Pattern: **Autosomal Recessive**
- Early onset: apparent at birth or within the **first few months of life**
- Symptoms:
  Severe muscle weakness;
  Lack of muscle tone (hypotonia);
  Little spontaneous movement;
  Joint deformities (contractures);
  Heart problems and seizures.
- Life expectancy:
  Because of the serious health problems that occur in this form of the disorder, many affected individuals **do not survive past adolescence**.
- Genetic cause: **LAMA2** mutation

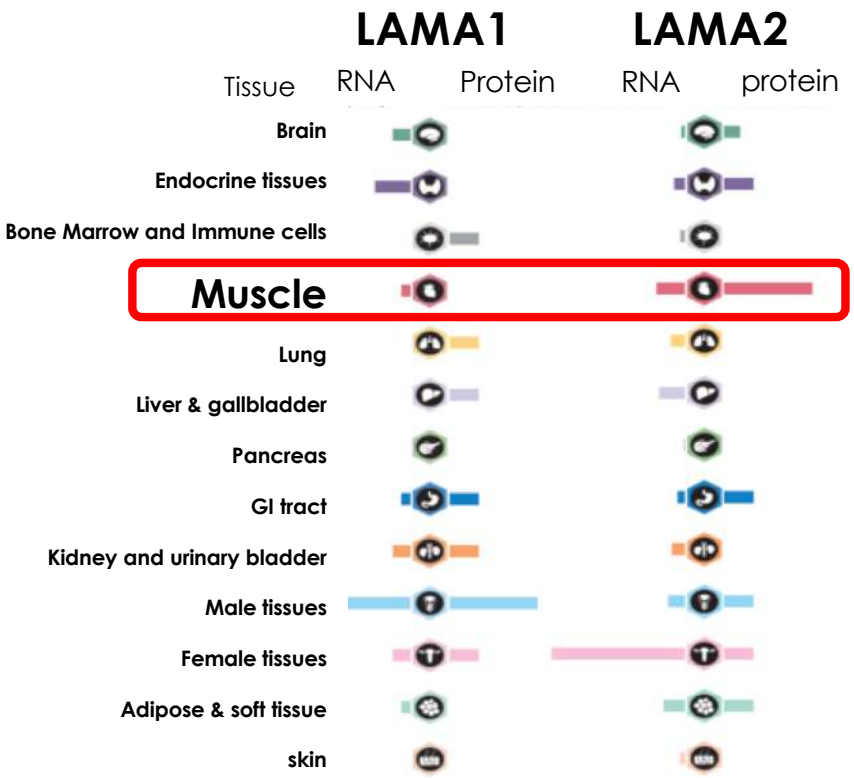
MDC1A: merosin- deficient congenital muscular dystrophy type 1A
*Orphanet

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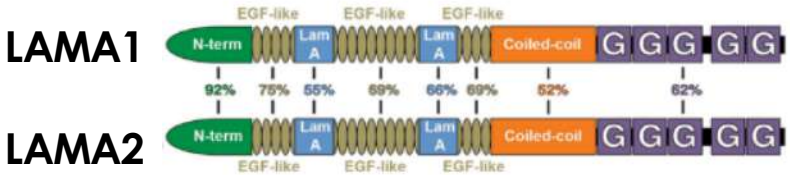
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By activating the sister gene, LAMA1, GNDM compensates missing function of LAMA2

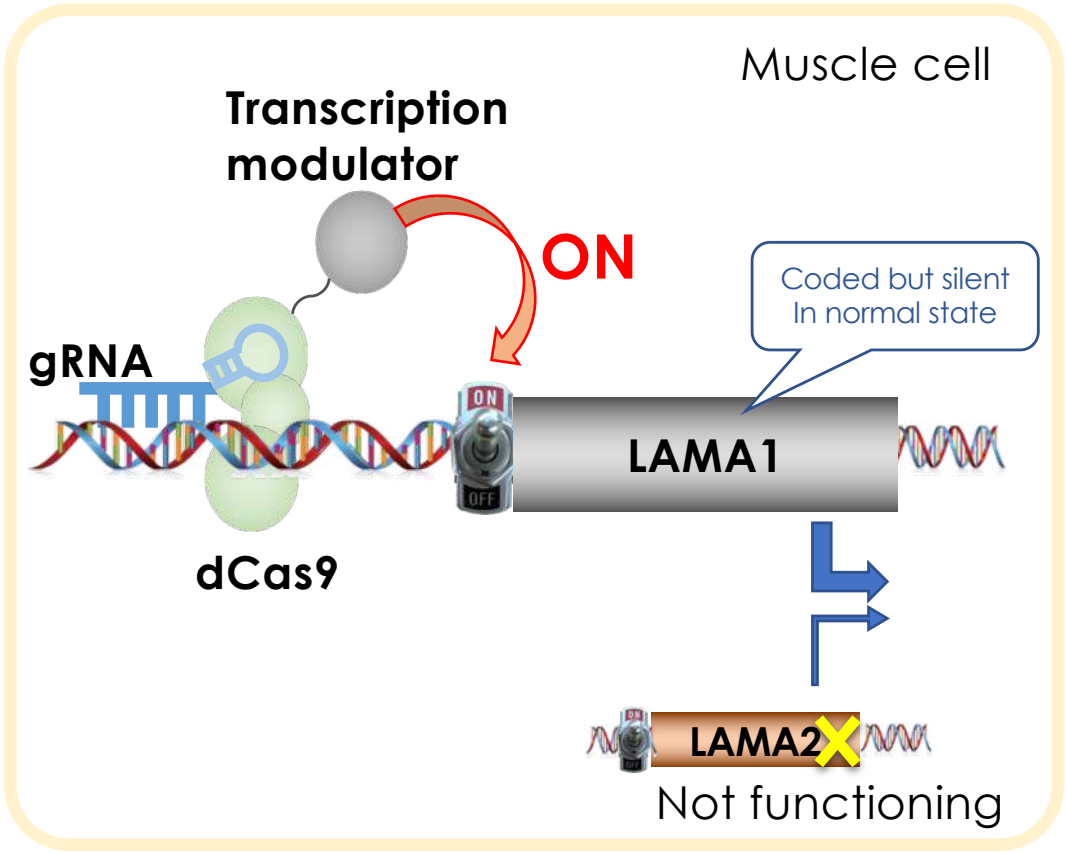
Exspression pattern of LAMA1and LAMA2 by tissues



Protein structure of LAMA1 and 2



CRISPR-GNDM® targeting LAMA1

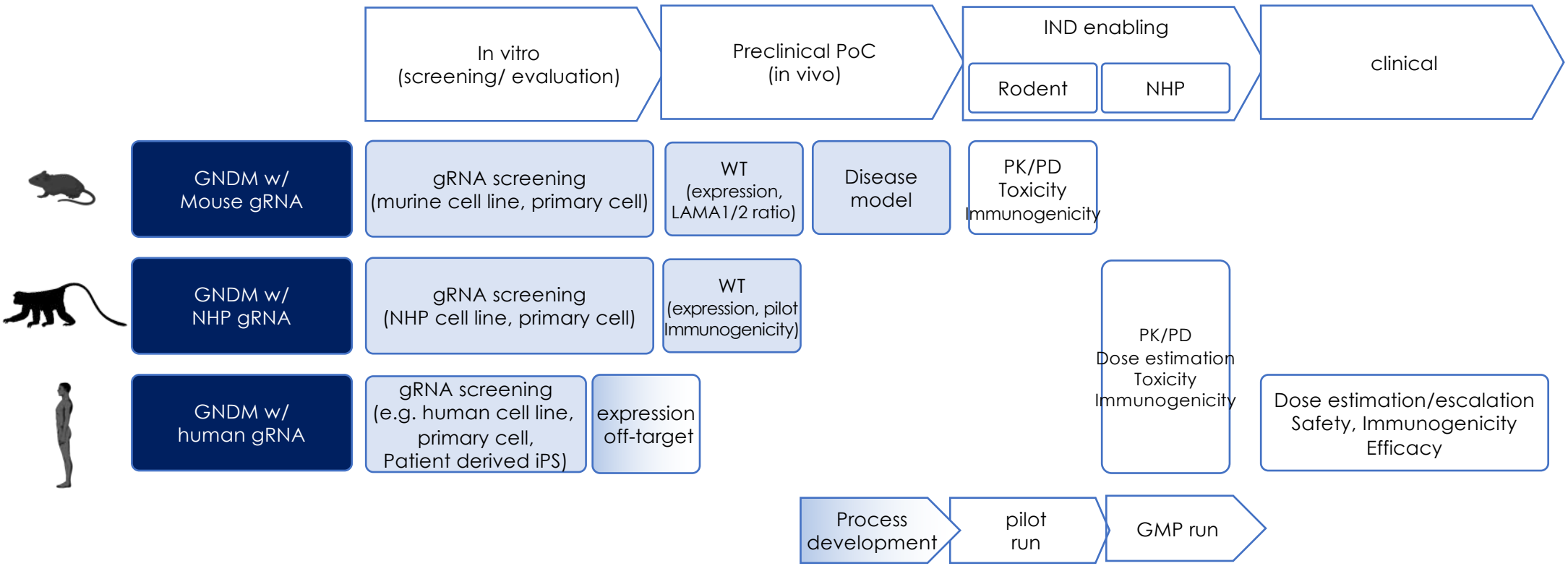


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Having convincing animal data both in 2 species, moving forward to IND enabling studies with establishing manufacturing process

Path to clinic for CRISPR-GNDM®



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In vivo study Summary

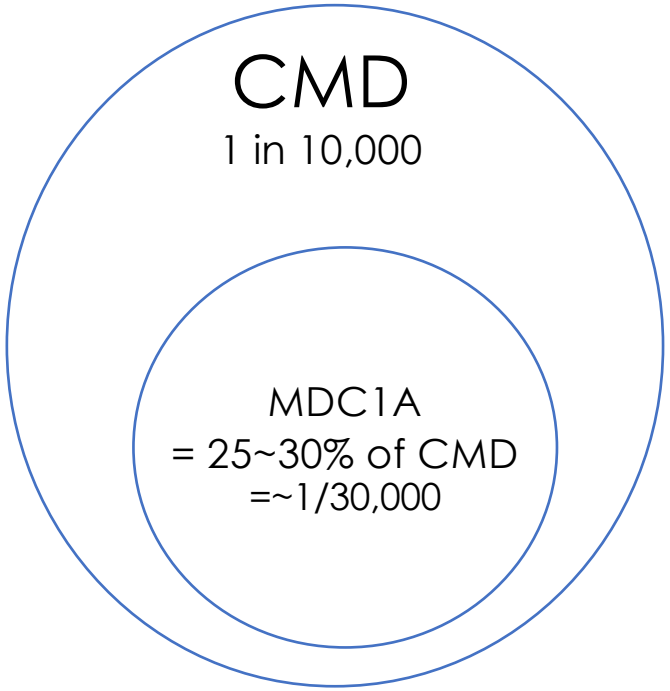
- Mouse
  - in vivo upregulation of LAMA-1 in skeletal and cardiac muscles using a Lama-1 specific gRNA
  - Efficacy study in MDC1a disease models completed
  - **Long term GNDM expression observed up to 2yrs**
- Cyno
  - NHP studies with AAV-cyMDL-101
    - Mild anti-Cas9 immune reaction elicited in AAV injected animals
    - No obvious lymphocytes infiltration nor tissue destruction observed in muscle tissues
    - Persistent GNDM expression detected in muscle tissues in high dose group up to the end the study(20wks)
- Manufacturing
  - **Finalizing vector system for manufacturing**
  - **Improved GNDM cassette including further downsizing**

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Prevalence of MDC1a

- Exact prevalence of MDC1A is still unknown but…
  - The prevalence of congenital muscular dystrophies (CMD) has been estimated between
    - 1-9/100,000
  - MDC1A is about ~30% of CMD:
    - **~1/30,000** with regional variation



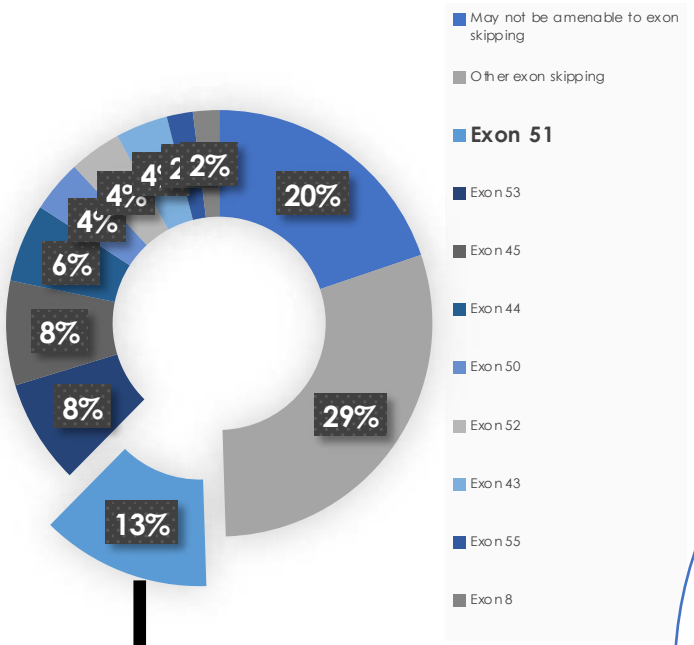
CMD: congenital muscular dystrophy

Source: orpha.net

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MDC1A is about the same size to DMD caused by Exon 51 mutation



DMD
=1 in 3,500#

exon51
=~13% of DMD*
=~1/27,000

CMD
1 in 10,000

MDC1A
= ~30% of CMD
=~1/30,000#
=10,000 in US

DMD: Duchenne muscular dystrophy
*https://www.cureduchenne.org/cure/exon-skipping/
#Source: www.orpha.net

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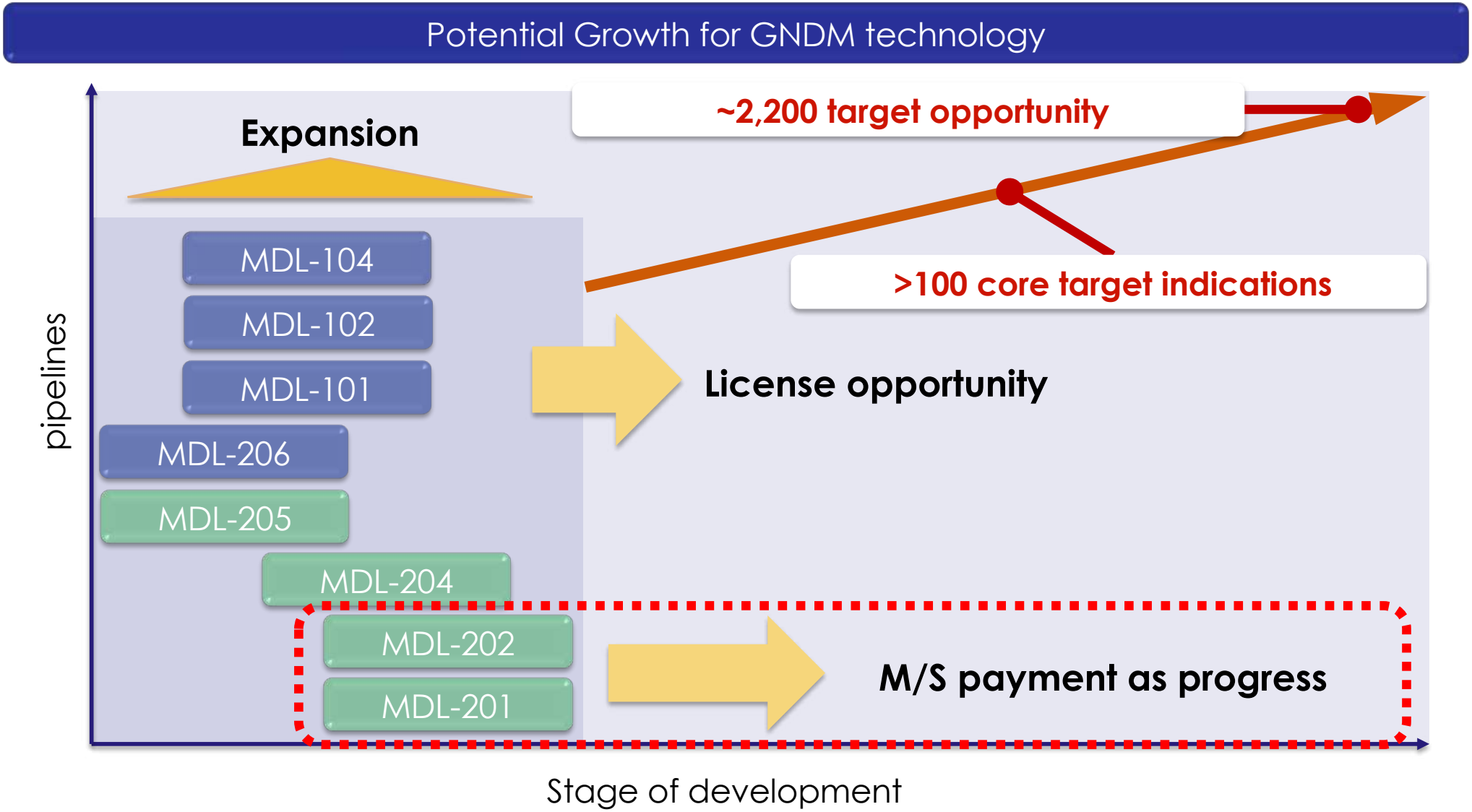
3. Growth Strategy

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Growth Strategy

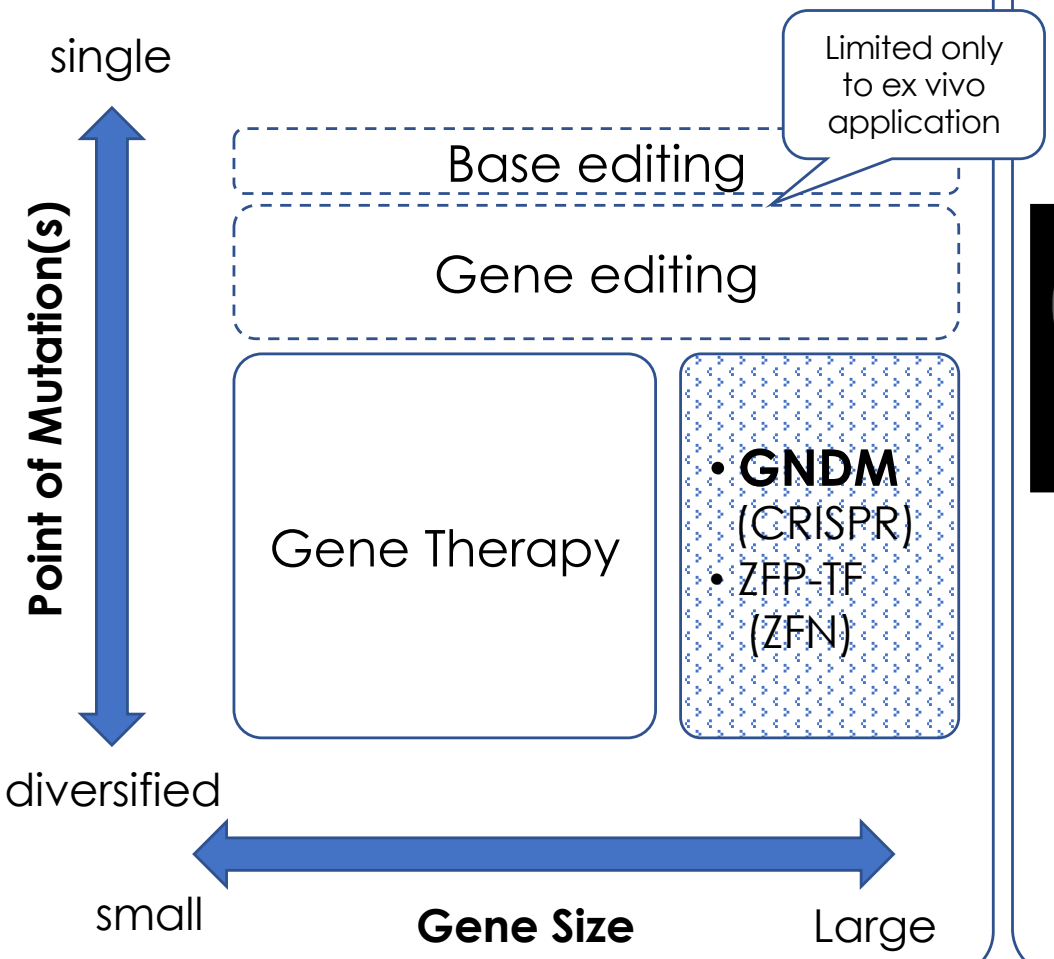
opportunity expands two dimensionally



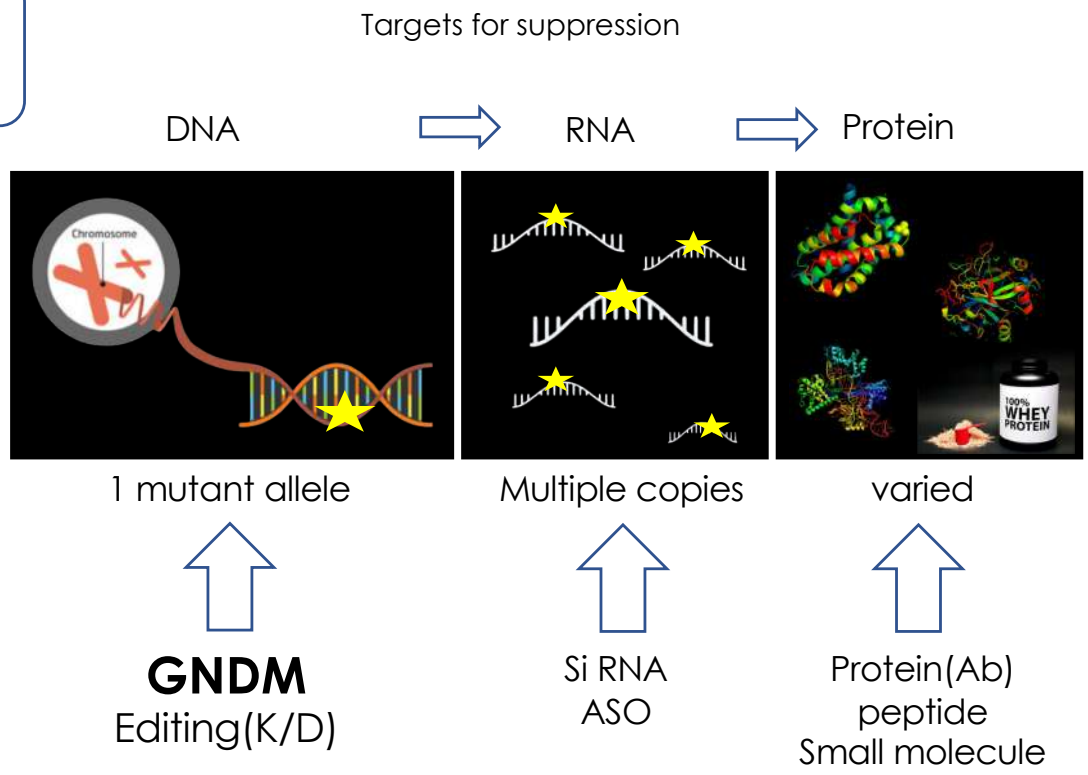
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GNDM is efficient approach both for LoF and GoF mutation

In LoF disorders



In GoF disorders

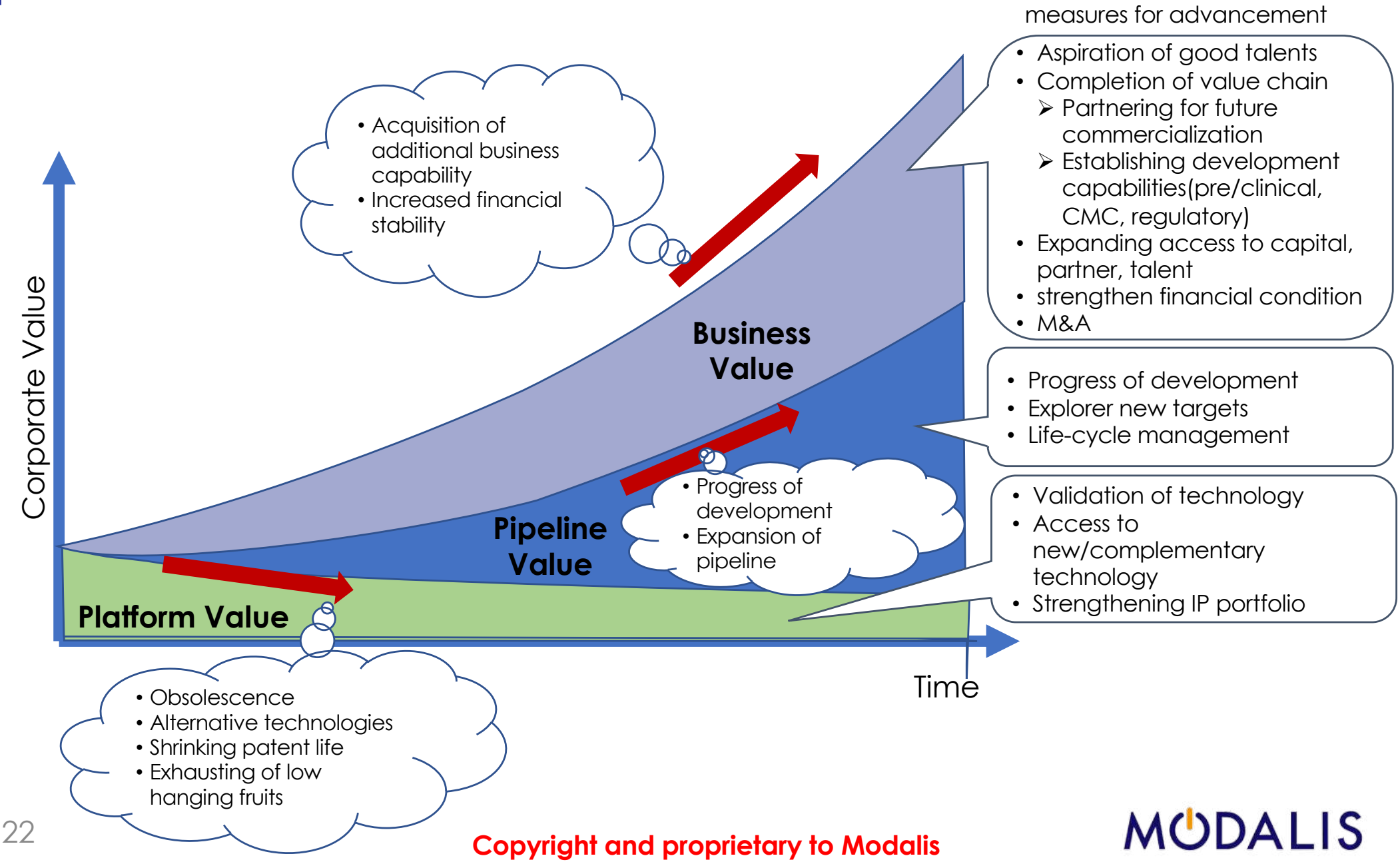


LoF: Loss of function
GoF: Gain of (mal)function

K/D: Knock-down

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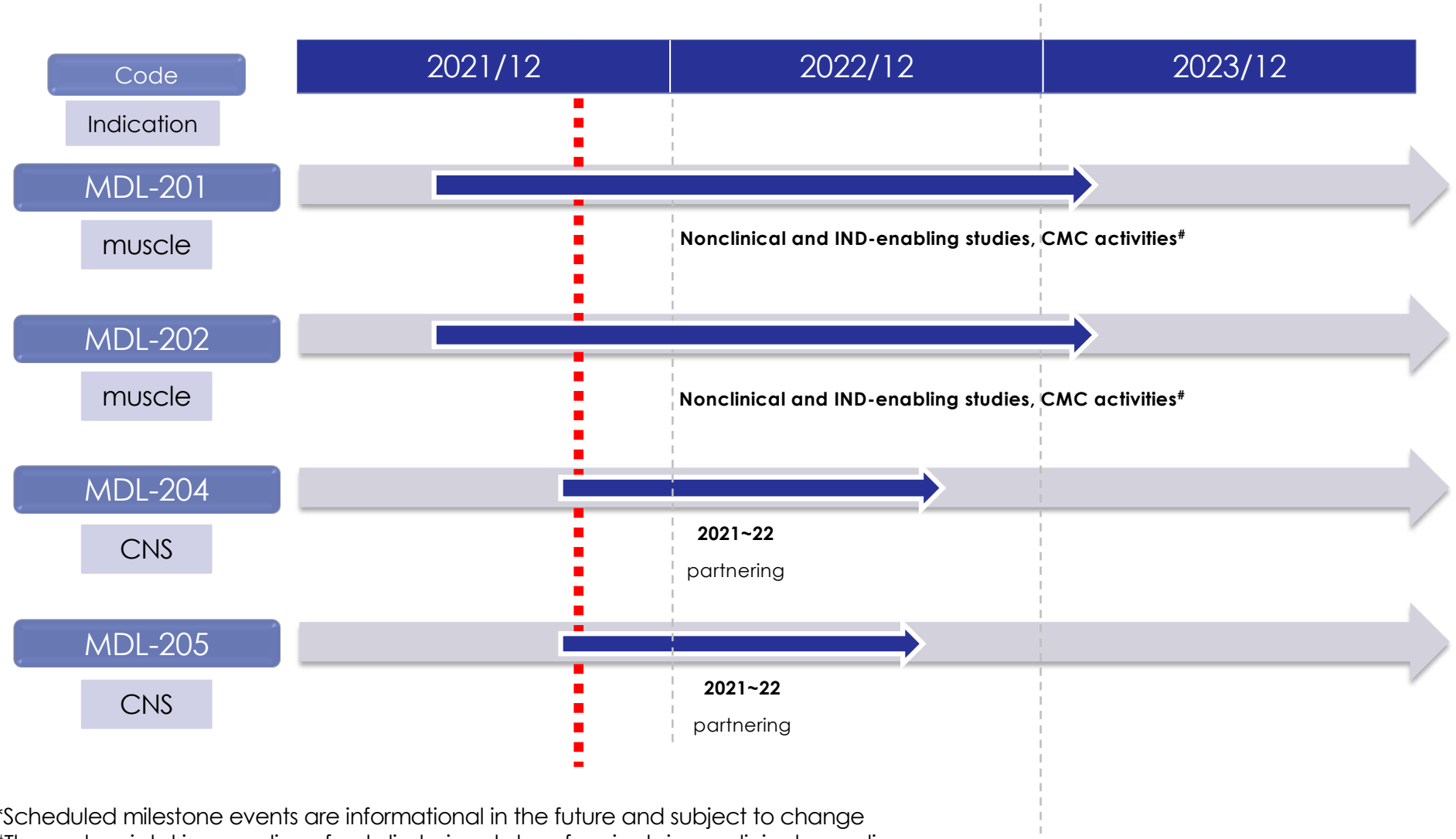
Composition of Modalis' value and measures for advance



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Collaboration pipeline

Achieved and expected Milestone events*

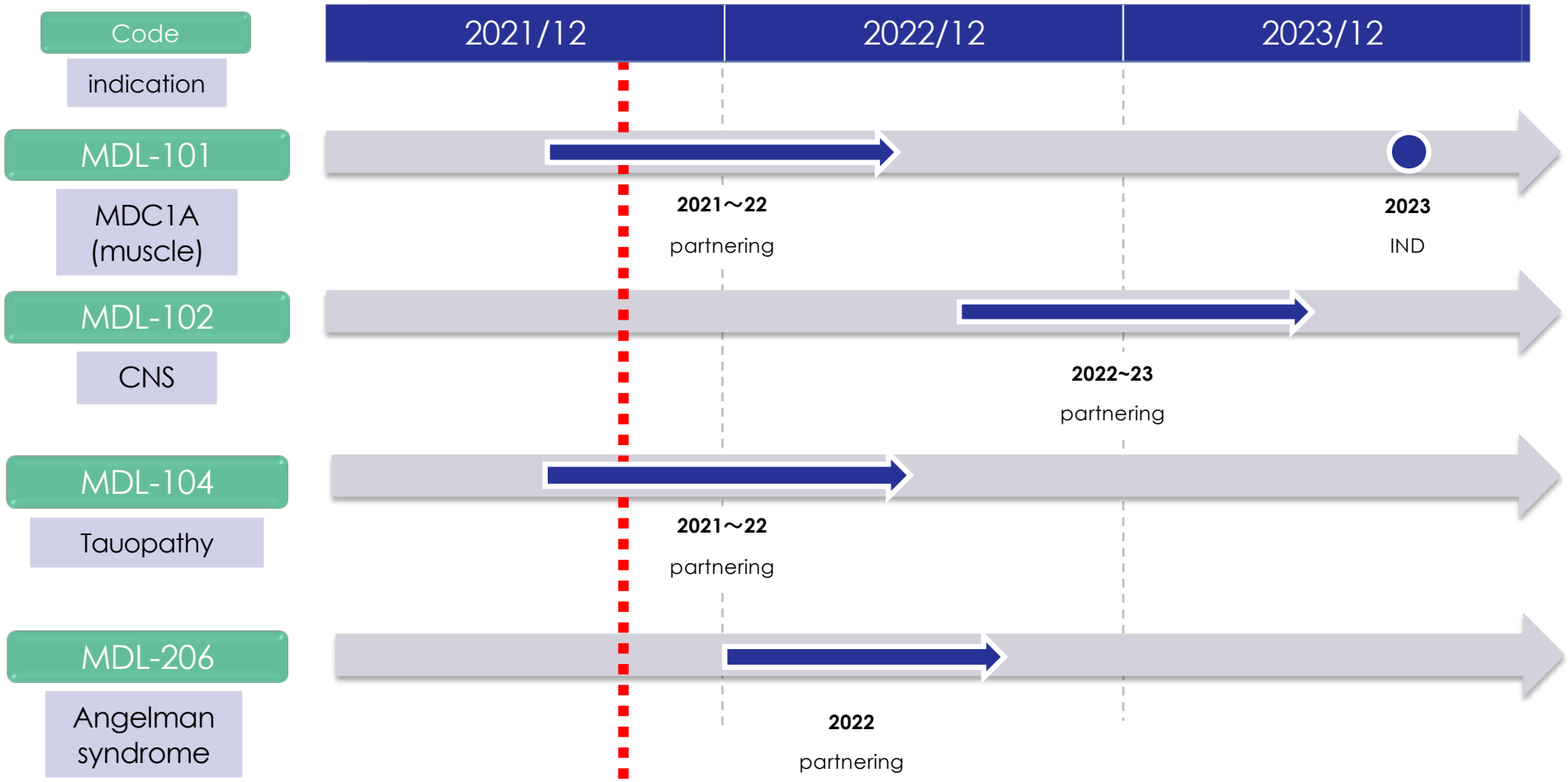


*Scheduled milestone events are informational in the future and subject to change
#The partner is taking a policy of not disclosing status of projects in preclinical or earlier

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Internal pipeline

Expected milestones by end 2023*



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

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4. Sustainability

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Social : Initiatives for Rare Disease



Corporate Philosophy

Every life deserves attention

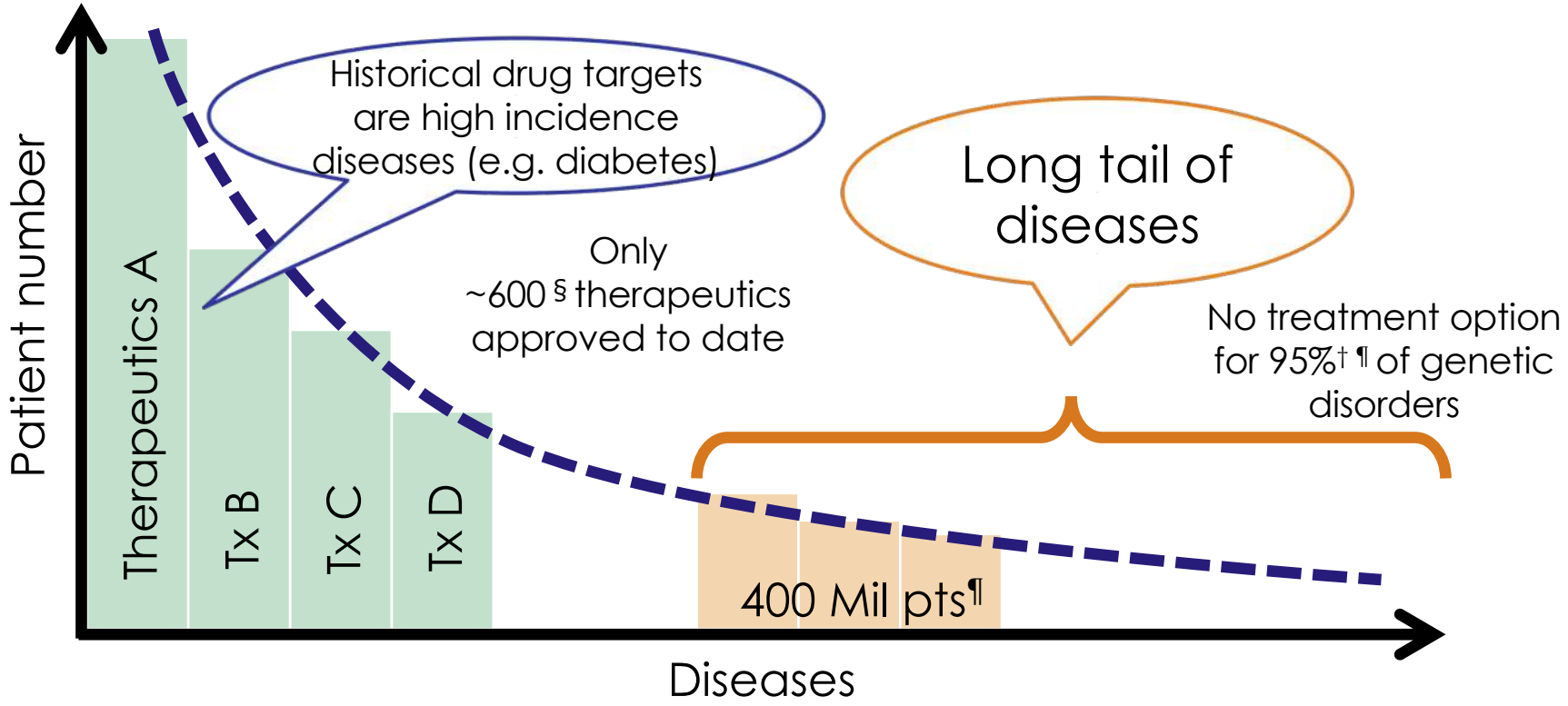
The company group, through drug discovery using the core platform technology "non-cutting CRISPR technology" (CRISPR-GNDM ® technology) to invent therapeutics targeting rare genetic disorders. True to our corporate philosophy of "every life deserves attention," we hope to contribute to society by giving patients hope to overcome their illness.

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Social : Initiatives for Rare Disease

It is believed that of10,000* human diseases, about 7,000#are rare diseases which consist of "long tail" diseases. Of these, 80%† overlap with genetic disorders and 95% remain untreated. The company is committed to identifying cures with our powerful novel technology.



Scalable efficient approach is required to tackle the divided population

reference: *21st Century Cure Act, #NIH GARD †innovation.org ¶GlobalGenes.org
§Active therapeutics of 491 NME, 106 BLA, 17 cellular and gene therapy products @FDA as of 2019.7.22 Source from KEGG

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Environment



Efficient Use & Preservation of Water

To preserve water and ensure it is used efficiently, wastewater from the laboratory is treated in accordance with environmental laws at our R&D facility in the US.



※ pH Neutralization System

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Environment

Global Warming・Measures to Reduce Carbon Footprint





With facilities that combine function and needs of our personnel, we are promoting reduction and optimization of energy consumption.
The company supports telework, and our recent relocation allows us to carry out business with energy efficiency in mind. Furthermore, our R&D facility in the US features a new HVAC system and state-of-the-art LED light fixtures.

The company group has made efforts to go paperless and is aiming to recycle 100% of items such as toner cartridges, etc. Proper separation and disposal of laboratory waste is strictly enforced in order to reduce our carbon footprint.



※ HVAC System（Energy Recovery Unit）

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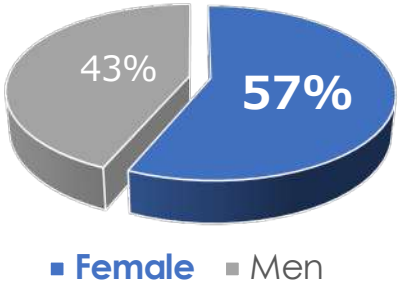
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Social

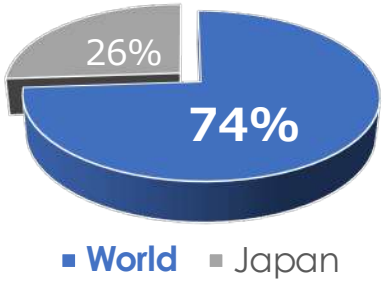
Valuing Human Rights・Diversity

The company group values the human rights and diversity of our employees and believes that improvement of the working environment is essential. The employees of our R&D facility in the US come from a wide range of backgrounds, regardless of nationality, gender, or age groups.

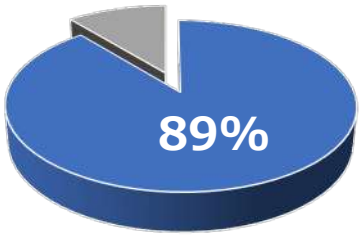
Ratio of Female Employees



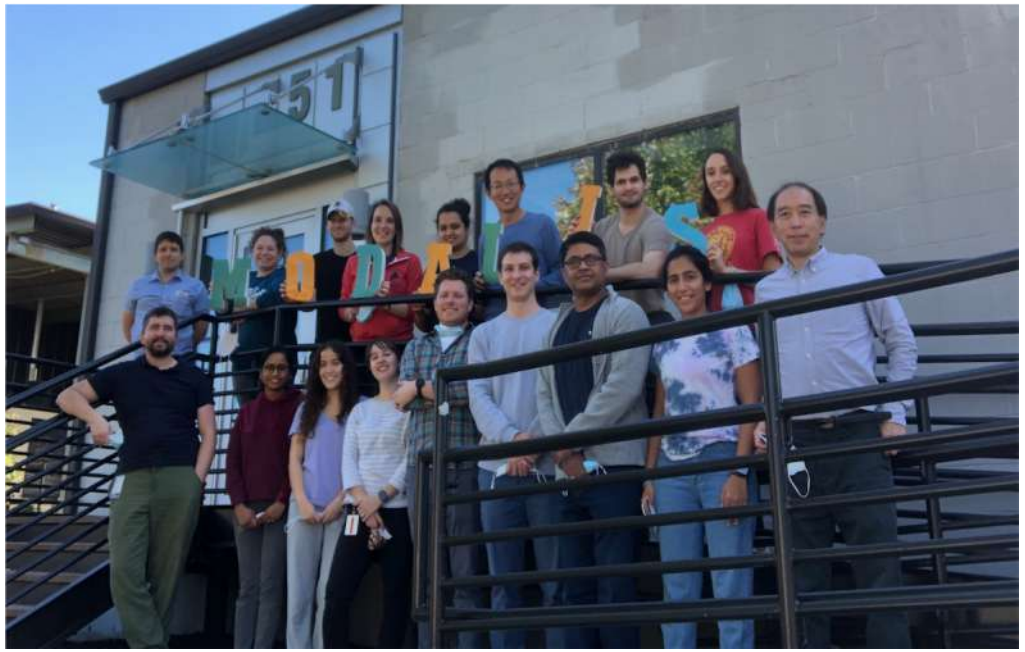
Ratio of International Employees



Ratio of Paid Vacation Days Used



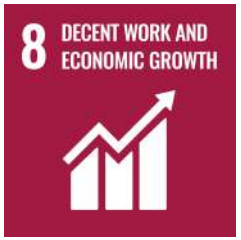
※Data from 10/1/2020 to 9/30/2021



※ members of our R&D facility in the US

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Social



Securing Human Resources & Way of Working

Flexible schedules and ongoing efforts to improve the working environment provide employees a source of motivation and sense of security as they carry out their duties. Additionally, we are making efforts to secure and develop talent among our scientists so they can drive innovation.



Use of CRISPR-GNDM® Technology

The company group's core platform technology "non-cutting CRISPR technology" (CRISPR-GNDM®) is made available to partners to promote open innovation in the realm of drug discovery and discover new therapeutics for genetic disorders. The technology is currently licensed out to one company and we have joint research and development agreements with three companies.

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Governance

Corporate Governance System



Five in six members of our Board of Directors are Outside Directors (of these, one is of foreign nationality and one is female) which creates a system that allows for internal checks and ensures accountability toward shareholders.

Our company has an established auditing committee, of which all three members have voting rights. As this decision making is related to business matters, we have created a system to reinforce the auditing and supervision of the Board of Directors.



The responsibility of business management is held by the Corporate Officers. Decision making related to business matters and auditing functions are separate from that of the Board of Directors, creating a system that ensures the improvement of business efficiency.

To ensure adherence to laws, business ethics, and other company regulations, a Compliance Committee has been established. In an effort to create a system that prevents unnecessary violations of compliance, relevant laws, company statutes, regulations, and a code of conduct provide concrete terms that must be followed while business is carried out.

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5. Q & A

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Q & A ①

Q)
What is current development status of MDL-101?

A)
With the very positive safety profile we confirmed in NHP and efficacy data in 2 mice disease models, Modalis works on IND enabling studies as well as regulatory meetings with FDA.

At the same time, our manufacturing team has initiated process development so that we can hand over the recipe of manufacturing to CDMO for scale up and large-scale manufacturing. This is one of the key element that rules the timeline in the gene therapy product development and should contribute to the value of the program.

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Q & A ②

Q)
Having got the animal data, what is the current partnering status of MDL-101?

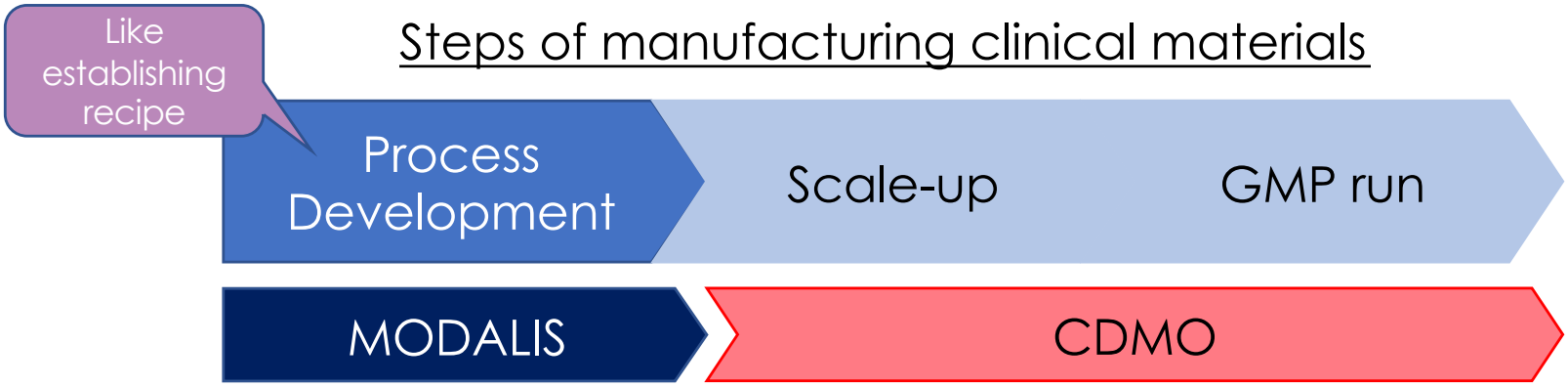
A)
While we continues to work on partnering discussion with aim to get it done within the year, but it may go beyond year-end.
As described in p10 of this document, Modalis believes the data we've got suffices partnering hurdle and the manufacturing agreement, which clarifies and outlines the whole manufacturing plan, added more value on the program.
So, we do not believe that delays in the partnering should not damage the value of the program itself.

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Q & A ③

Q)
How does the CDMO collaboration impacts on business?

A)
Manufacturing is one of the important element to start clinical trial of MDL-101. As Modalis does not have large-scale manufacturing capability, it needs to be transferred to the other party. The agreement with the 1st tier CDMO allows us to get access to its vector system and capability for manufacturing AAV and paves the way for sample production for GLP studies and clinical trials.



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Q & A ④

Q)
Why is the IND plan pushed back to 2023?

A)
Like in typical development of gene therapies, GMP manufacturing is the rate limiting step in MDL-101. Through out our discussion with the CDMO, both parties analyzed availability of manufacturing slot and procurement of materials and found it is more realistic that the clinical sample becomes available in 2023.

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Q & A ⑤

Q)
What does US lab relocation mean to the company?

A)
As of Oct 20, Modalis relocated its US operation to Waltham MA.
Since mid last year, the capacity of the US lab has become one of the limitation for our growth and we explored opportunities of relocation. But, due to supply-chain issues in US, our relocation had been pushed back by then.
With this relocation, we are able to accommodate process development function as well as further increase of research team. Thereby, we can expedite and deepen our product development including MDL-101.
The budget for this relocation was included in the plan for the current fiscal year.

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Q & A ⑥

Q)
How does the scale and process of manufacturing look like in product development for rare disorders?

A)
Although you might imagine manufacturing scale for rare disease product is also small, it may not be the case for some of the genetic disorders. For instance, many type of muscular disorders require systemic injection and 1000L scale of production, which is a largest batch in many of the GTx manufacturing facilities, can produce products only for single digit to low 2-digit patients.
It is important to manufacture those products in a way that complies with GMP, and it makes sense for us to work with CDMO, which has experience, capability, and capacity to manufacture.
Our current strategy is to work with the CDMO which we made an alliance this time and revisit the strategy when we establish clinical PoC and risk is well mitigated.

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Q & A ⑦

Q)
Any additional info regarding the “Notice Regarding Sales of Shares by A Major Shareholder”?

A)
After the press release, we we informed from the shareholder, professor Nureki, that he would follow the rules that were confirmed in the board meeting and would complies to the schedules and rules from this point on.

The company will follow this up and take the best measures.

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