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In case of any discrepancy, the Japanese version shall prevail

3Q/2024
Business and Financial report



(TSE：4883)

Modalis therapeutics Corporation

November 7, 2024

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About Modalis



MODALIS Value Highlights

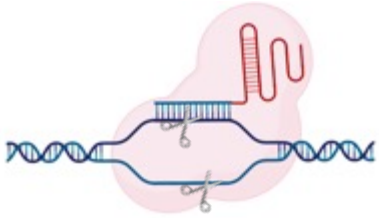
- Established the first robust **epigenetic platform** for activation and inhibition of endogenous genes using CRISPR-GNDM® platform
- Demonstrated sustained modulation of gene expression in multiple species (mouse, cyno) resulting in functional **efficacy without serious toxicities**
- Pipeline of preclinical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

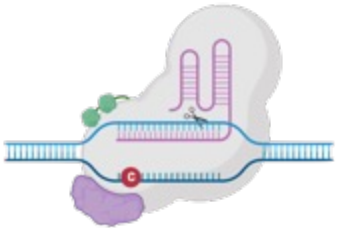
Enables treatment of genetic disorders by controlling epigenetic ON/OFF switch

GTx Technologies

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



Permanent Removal



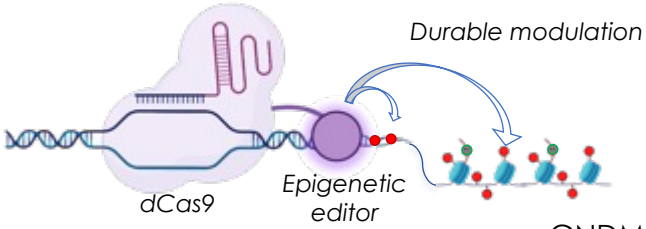
Permanent Replacement



Temporal silencing

Epigenome Editing(CRISPR-GNDM®)

Bind without cleaving
No DNA damage



GNDM=Guide Nucleotide Directed Modulation

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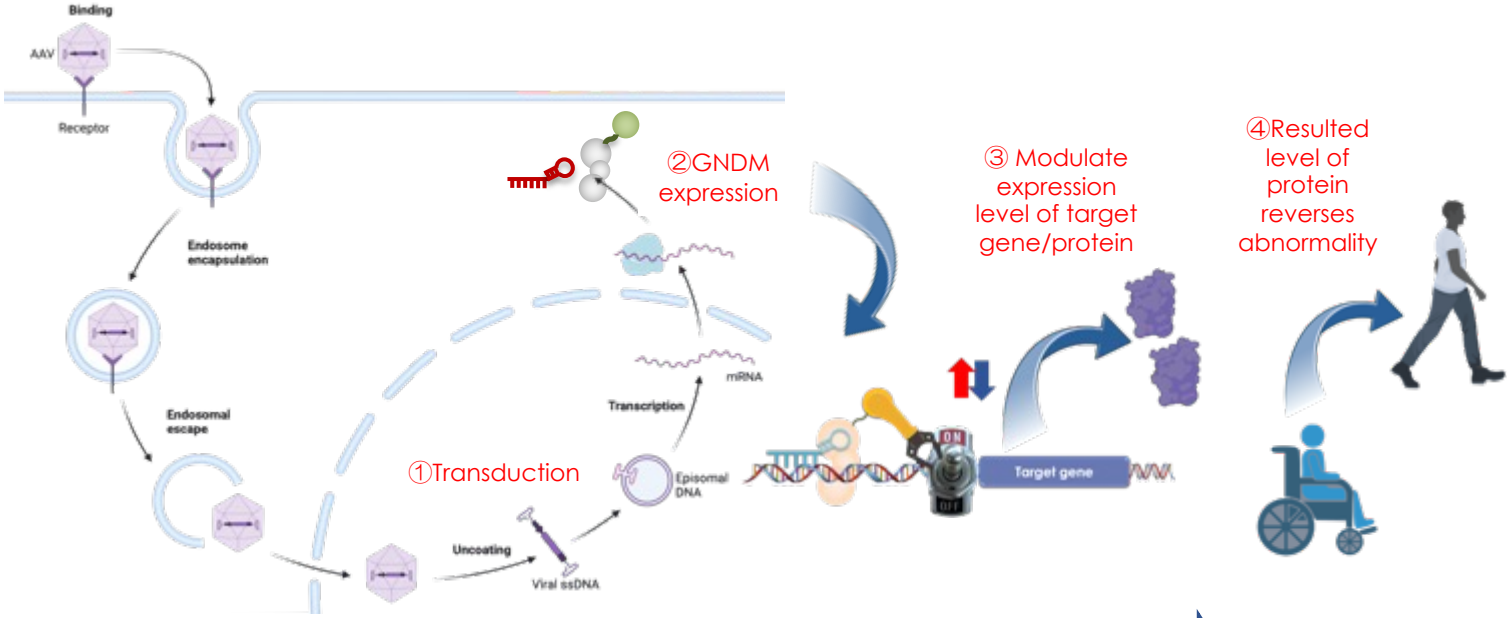
There are 3 steps for GNDM before providing efficacy

The GNDM is transduced, expressed and engages to the target to show efficacy



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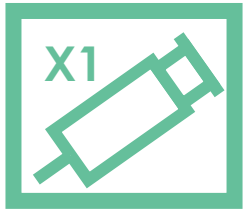
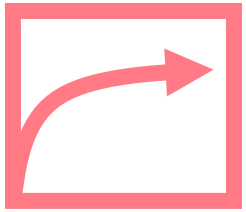
CRISPR-GNDM® is a promising new therapeutic modality

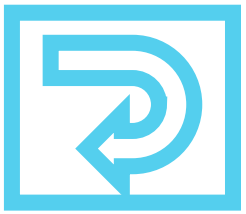
Potential benefits of CRISPR-GNDM® Technology



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

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 B1 ($120M, 2023)	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

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1. Key Takeaway of the 3Q/2024 outcome

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Paper and presentations

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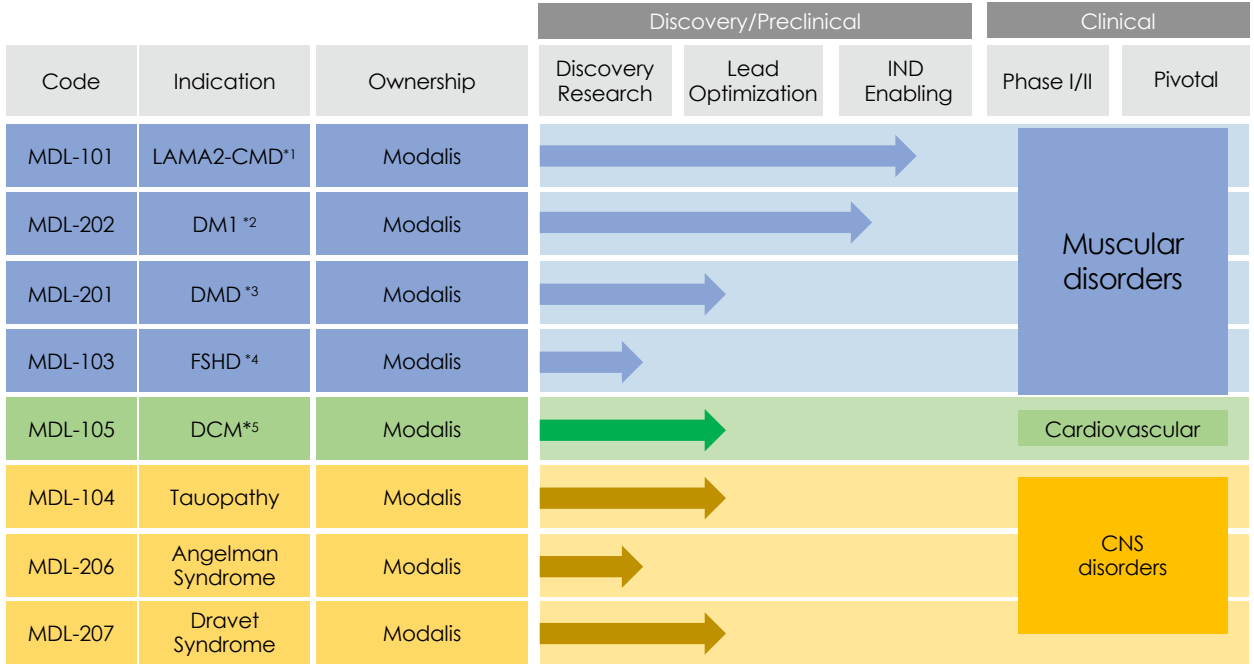
Finance and Others

The current pipeline of MODALIS

Set the muscular disease-centered strategy



*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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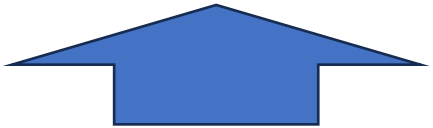
ODD and RPDD have been granted from FDA

- **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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MDL-101 is moving toward to IND

- The manufacturing process has been established
- Preparing of GLP-tox
- Organization and coordination of clinical trial operations

Reported on preclinical data for MDL-101 at four conferences held in Boston

CELL & GENE THERAPY SUMMIT-2024

Jul 8-10th



16TH ANNUAL BIOPROCESSING SUMMIT

SOLVING TODAY'S CHALLENGES, LEADING TO TOMORROW'S ADVANCES

Aug 19-22th



5th Annual Gene Therapy Immunogenicity Summit

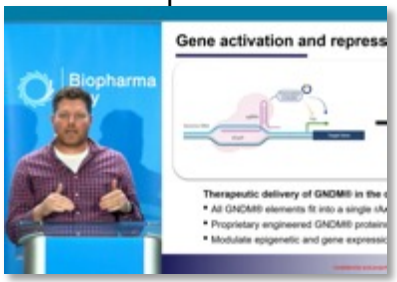
Prioritize Safety & Maximise Efficacy of Viral Gene Therapies

Aug 22



Nanopore Community Meeting Boston

Sep 16-17



The attention was focused on our company's achievements in leading the world in epigenome editing and development using modified capsids.

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We are scheduled to make a presentation at the Genome Editing Conference in December, together with major companies in the industry



Oral Presentation:
Title: **Epigenome editing with CRISPR-GNDM® as a treatment platform for unmet medical conditions**

Date: December 5, 2024 11-11:30PM EST

Session: Progressing Epigenome Editors into the Clinic
Content of the Presentation
Progress of our company's MDL-101 development and future strategy

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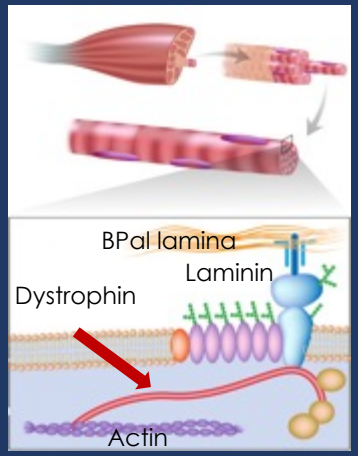
Duchenne Muscular Dystrophy (DMD)

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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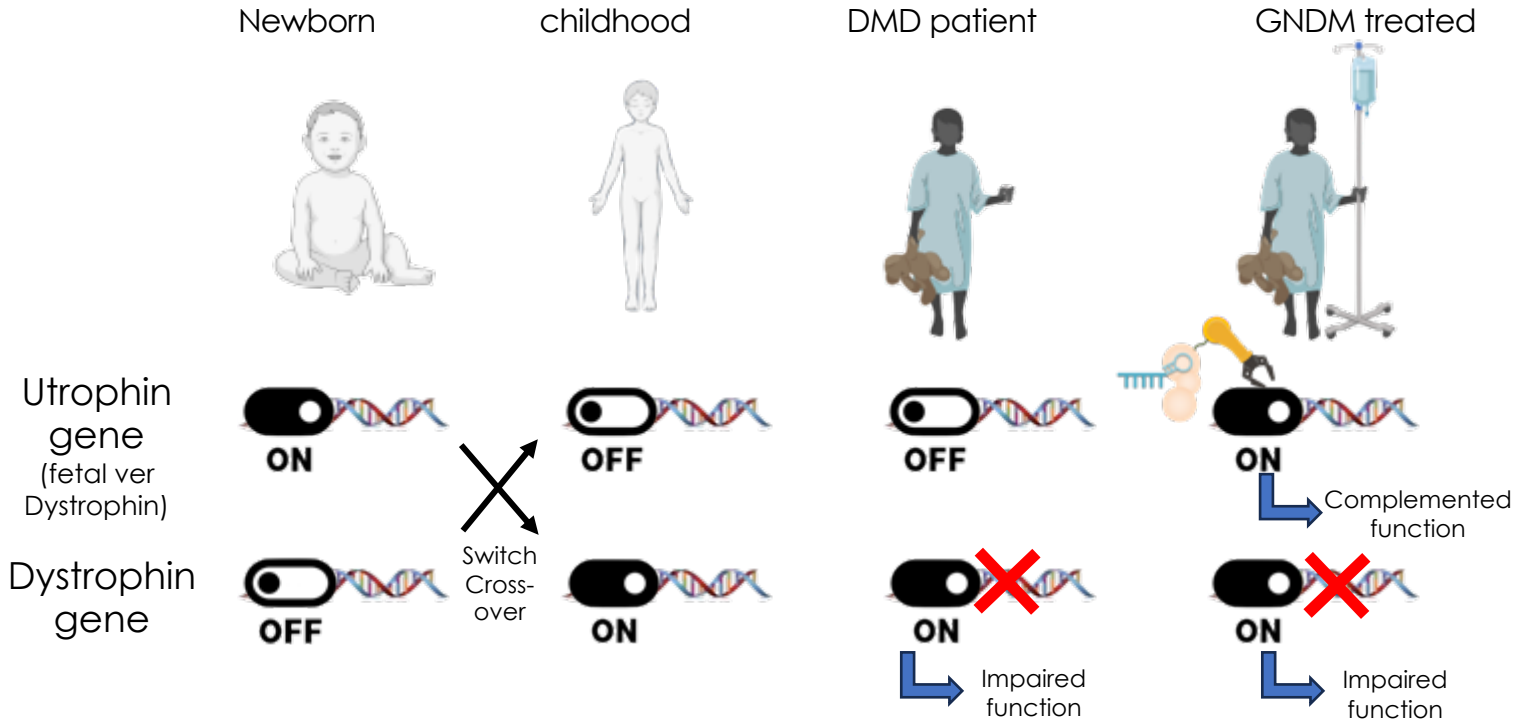
MDL-201 (UTRN-GNDM) Complementing Dystrophin Abnormalities

Reboot Utrophin genes in sleep mode during growth

MDL-201 (GNDM-UTRN) therapeutic concept



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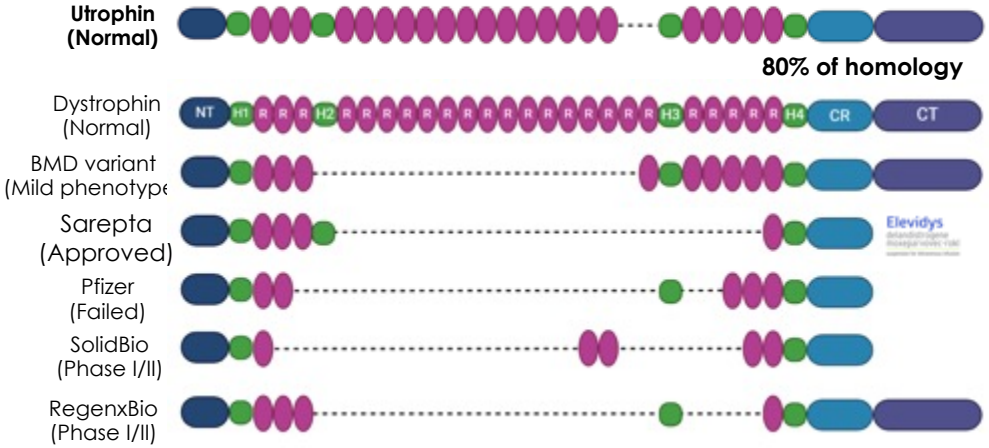
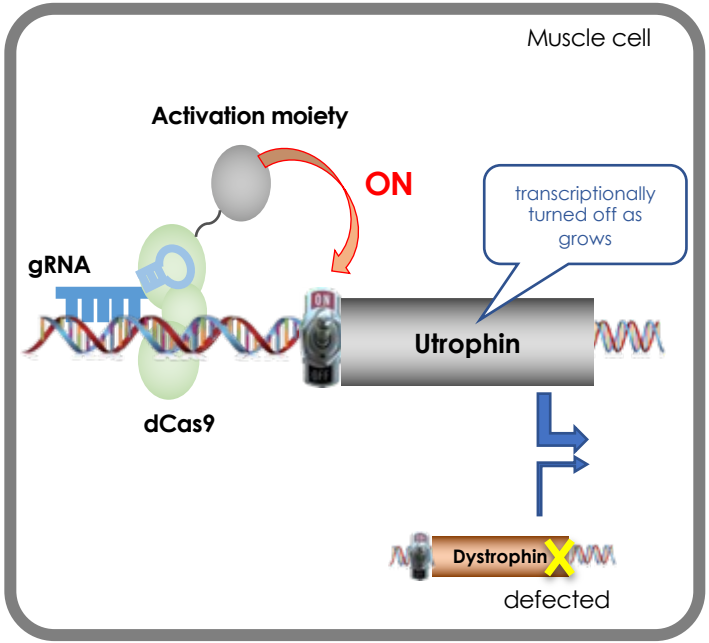
The mini-Dystrophin is missing many functional domains that exist in the full-length protein, but Utrophin retains most of these sites



MDL-201(GNDM-UTRN) mechanism 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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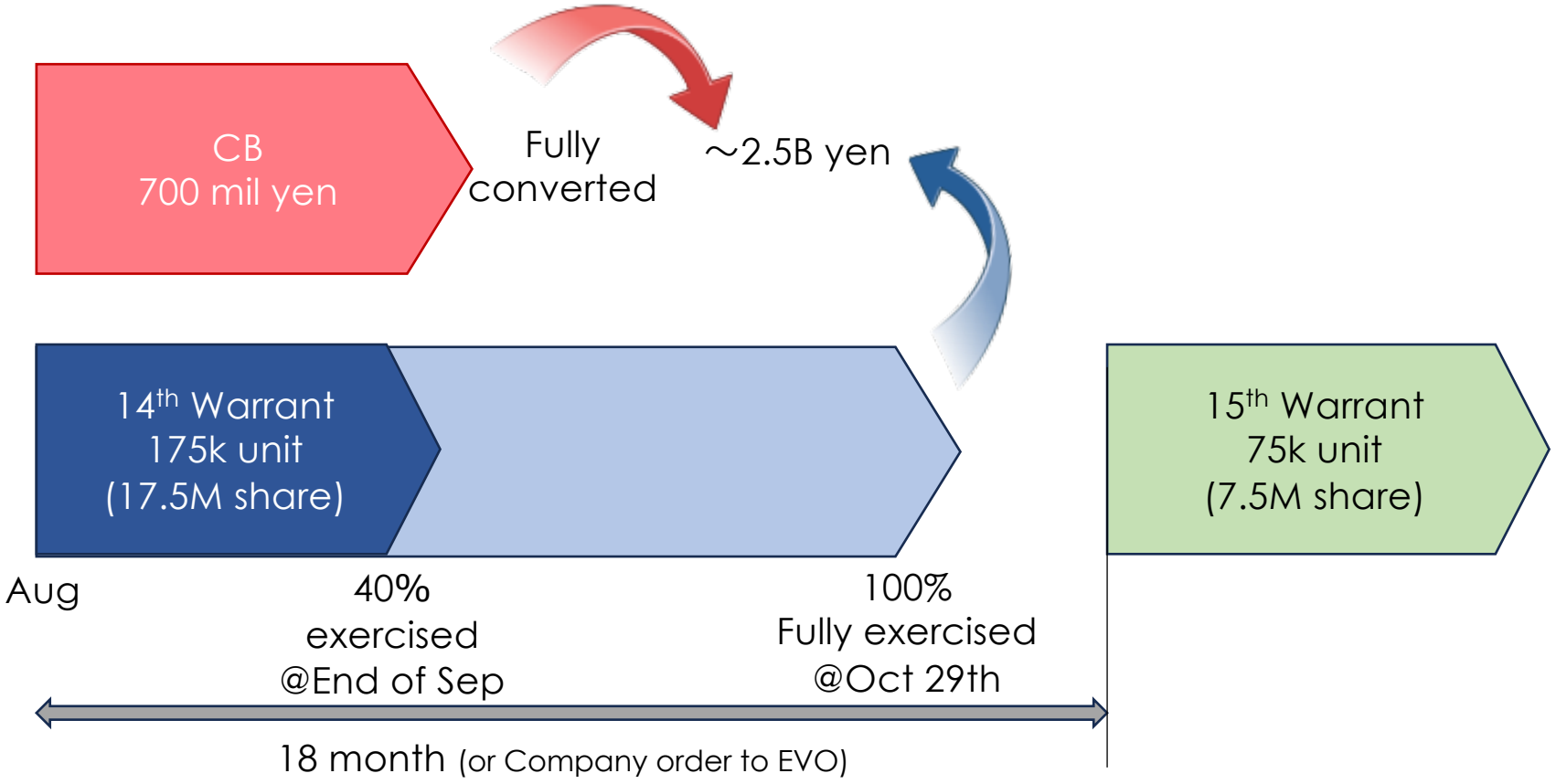
The conversion of the second convertible bond and the exercise of the 14th warrant have been completed, and approximately 2.5 billion yen in funds have been raised.



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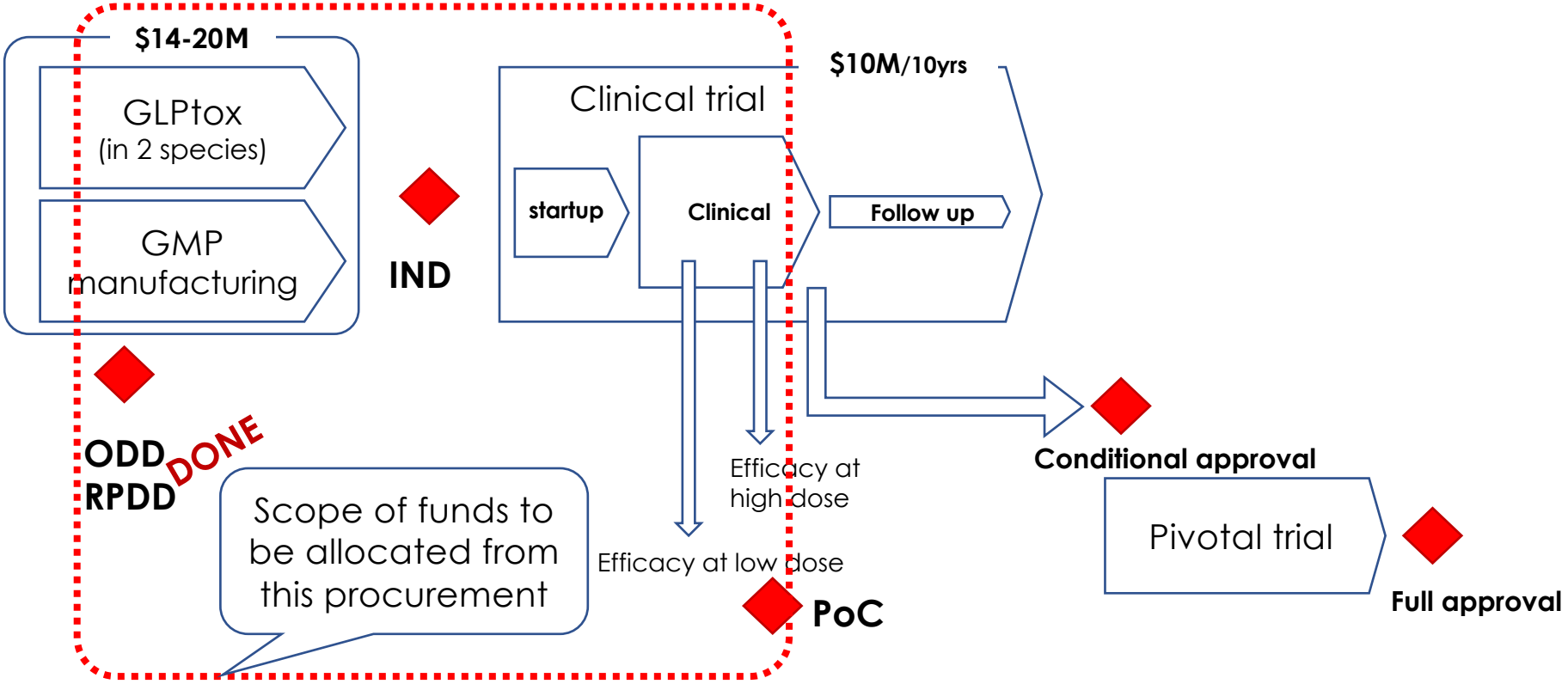
MDL-101 *Value Inflection Points and* Funds Needed to Reach Them



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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MDL-202-related patent granted in Japan

- Patent for modified Cas9 assessed in the US (September)
  - Modified cas9 protein, and use thereof
  - Co-filed with Univ of Tokyo
  - US18/058,823

- DMPK patent granted in Japan (September)
  - Treatment method for muscular dystrophy targeting DMPK gene
  - Patent application 2022-518586



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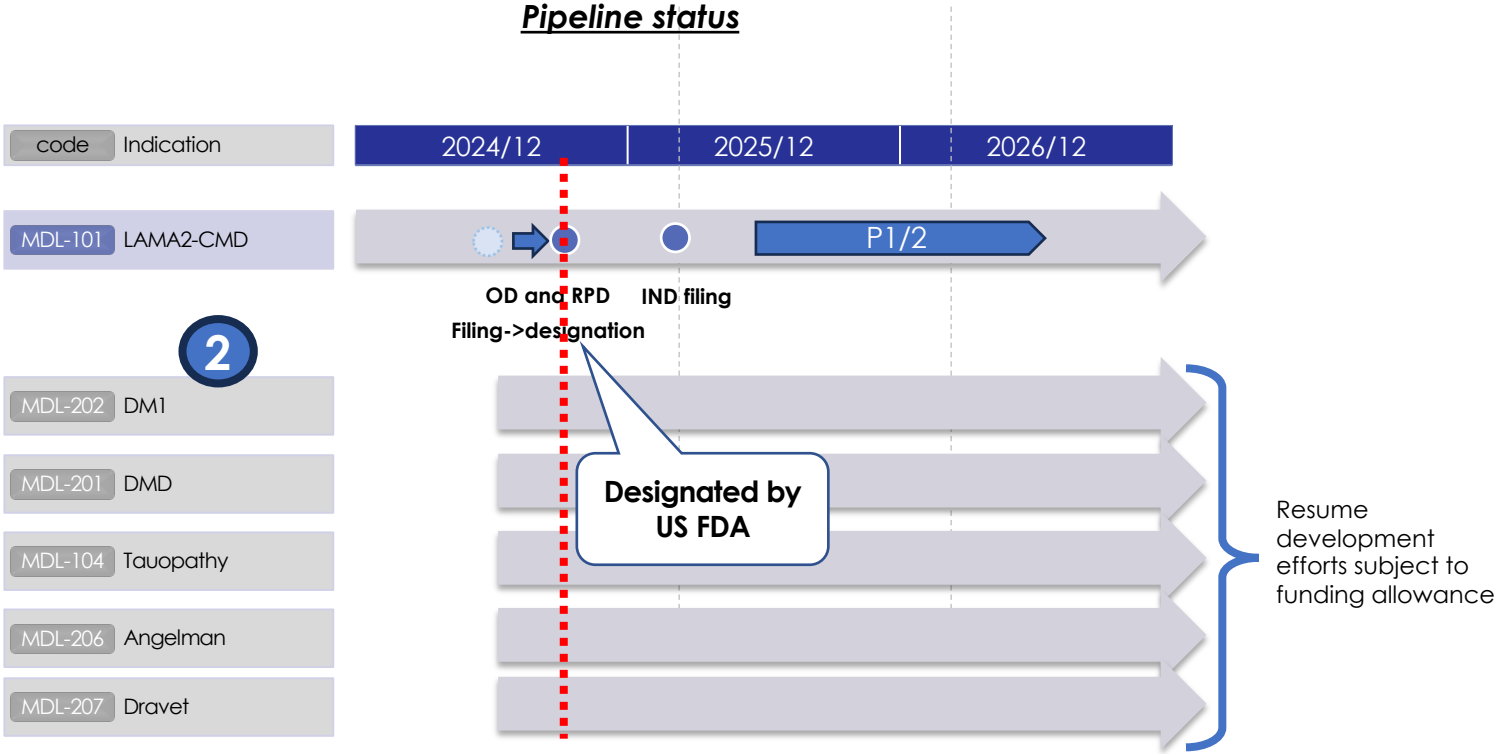
22

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, and Sep)**	• Data presentation in 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
	• 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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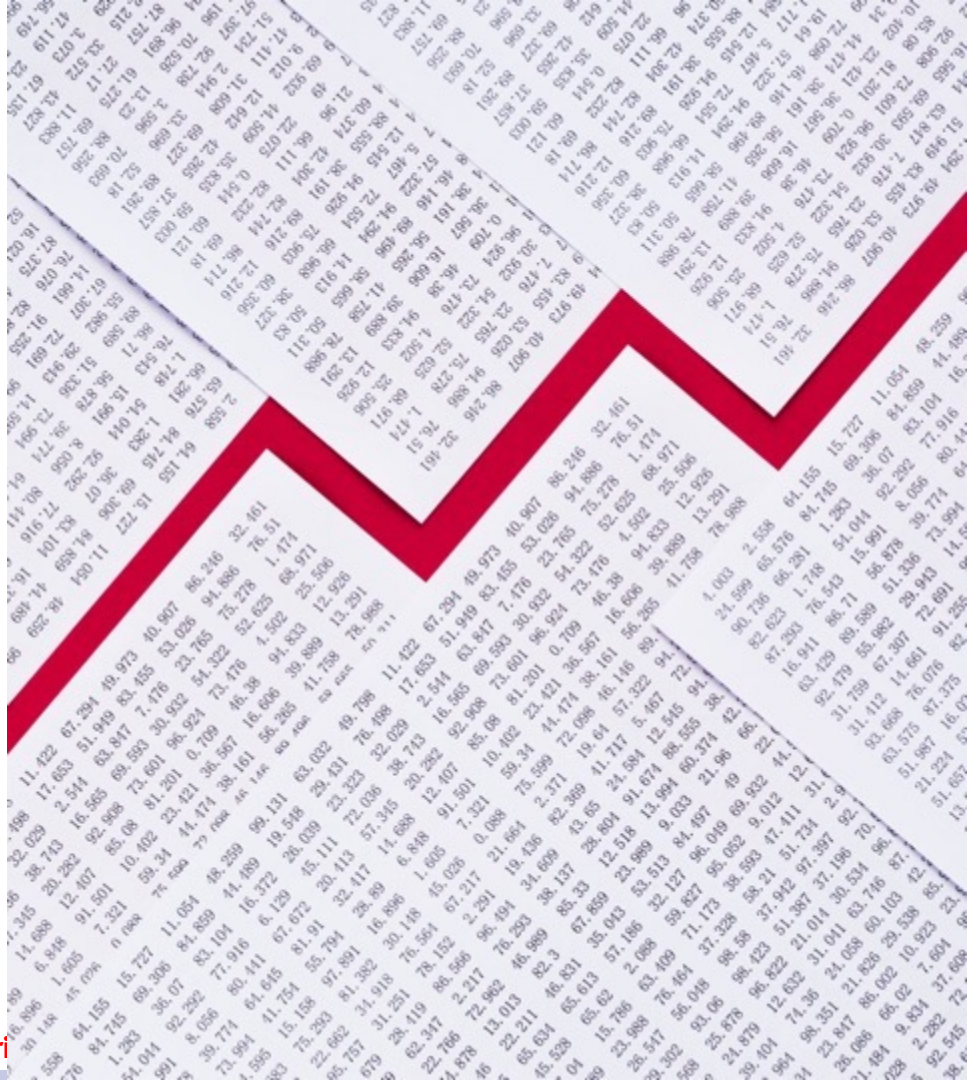
2. Financial reports



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BS & Financial Position

(Million Yen)

	End of FY2023 (A)	End of 3Q FY2024 (B)	(B) – (A)
Current assets	1,956	2,743	786
Cash & deposits	1,883	2,697	813
Non-current assets	69	67	△1
Total assets	2,025	2,811	785
Current liabilities	198	62	△135
Non-current liabilities	447	236	△211
Total liabilities	645	298	△346
Total net assets	1,380	2,512	1,131
Total liabilities and net assets	2,025	2,811	785
Capital adequacy ratio	66.8%	88.5%	

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)

	3Q FY2023 (A)	3Q FY2024 (B)	(B)−(A)
Operating revenue	-	-	-
Operating expenses	1,609	1,062	△547
R&D	1,401	882	△519
SGA	207	180	△27
Operating income	△1,609	△1,062	547
Ordinary income	△1,542	△1,059	483
Current Profit	△1,581	△1,060	521

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-201 (mainly personnel costs, research material costs such as reagents, and rent)

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3. Growth Strategy

Diversified pipeline with their own missions

Pioneer the gene modulation With highly suitable indications

MDL-101

Expand technology opportunity with products for larger opportunity

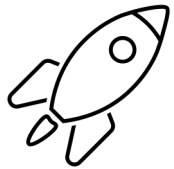
MDL-202

Further approach to challenging applications

Other programs

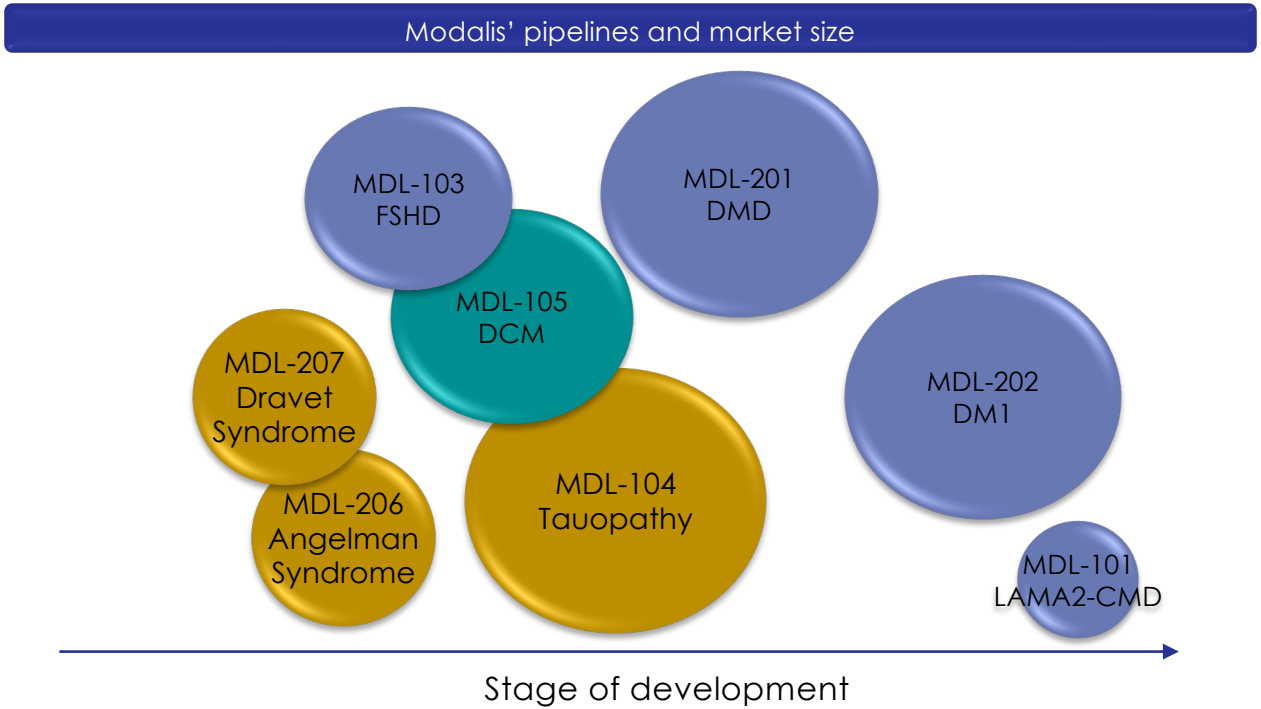






Modalis' pipelines and market size

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 3Q report

1. MODALIS is a lead program and is continuing to promote the development of MDL-101, a technology showcase
   - Received designation for **OD and RPD** filed in the previous quarter (ODD at the end of October)
   - IND enabling studies and GMP manufacturing are underway.

2. Development of **MDL-201**, which shares the mechanism of action with MDL-101, has been restarted. Potential to become a **best-in-class** product by overcoming the issues with the current marketed drugs

3. The conversion of the second convertible bond and the exercise of the 14th warrant have been completed in September and October, respectively, and raised approximately 2.5 billion yen

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4. Q&A

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Q1: When will the 15th series of stock acquisition rights start to be exercised?

- The details are as per the news released on August 7, but it is stipulated that the rights cannot be exercised for 18 months from August 26, 2024, which is the payment date for the stock acquisition rights, but at the Company's discretion, the exercise of all or part of the rights may be brought forward, and from the day after that, the allottees will be able to exercise their rights.
- At present, the Company currently has no plans to issue an instruction to bring forward the exercise period, and any decision to do so will be made in light of factors such as the progress of the business and the financial situation.
- In addition, all of the 15th series of stock acquisition rights have been converted into bonds, so the Company's Board of Directors has the authority to acquire all or part of the stock acquisition rights.

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