English translation for reference purposes only
In case of any discrepancy, the Japanese version shall prevail

2Q/2024
Business and Financial report



(TSE：4883)

Modalis therapeutics Corporation

August 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

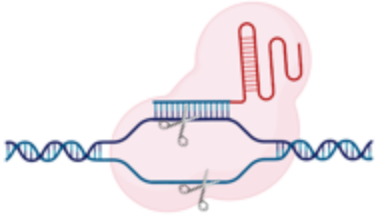
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Non-cleaving CRISPR = CRISPR-GNDM®

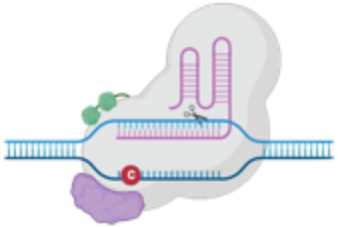
Enables treatment of genetic disorders by controlling epigenetic ON/OFF switch

GTx Technologies

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



Permanent Removal



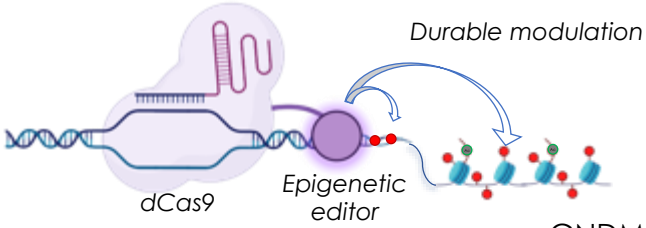
Permanent Replacement



Temporal silencing

Epigenome Editing(CRISPR-GNDM®)

Bind without cleaving
No DNA damage



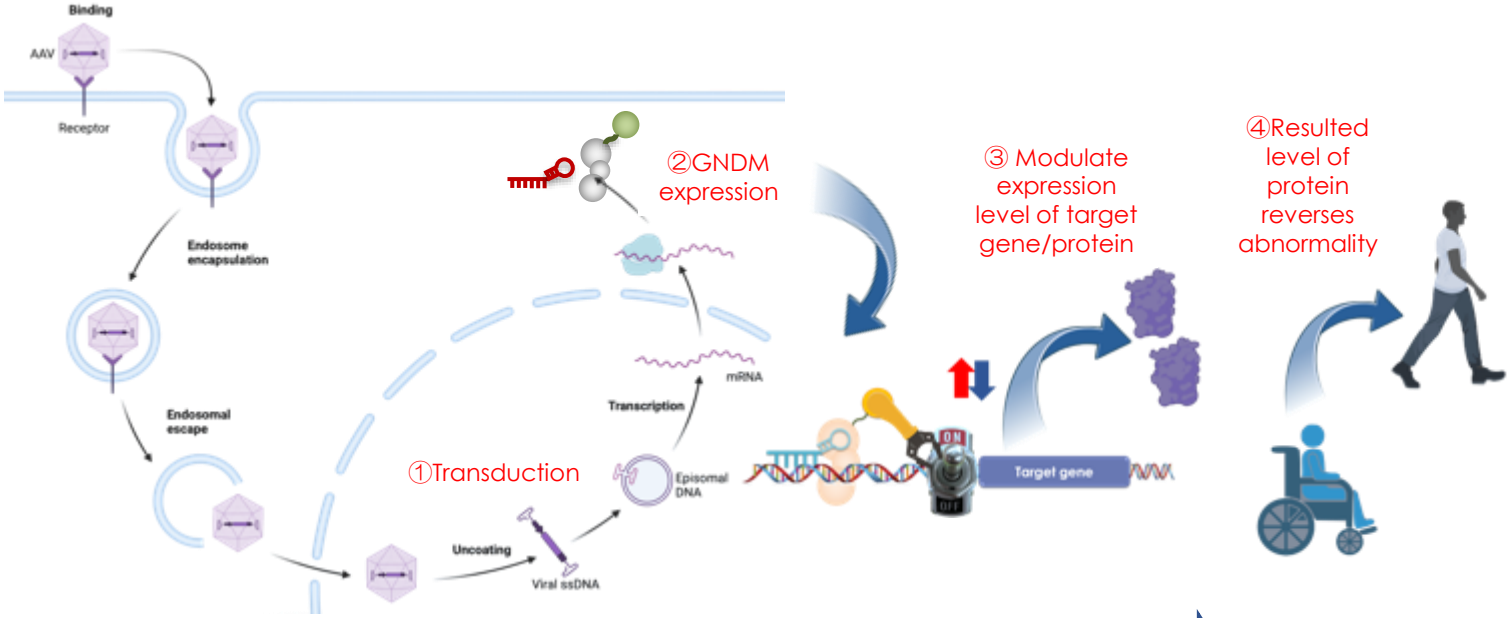
GNDM=Guide Nucleotide Directed Modulation

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There are 3 steps for GNDM before providing efficacy

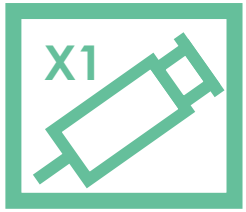
The GNDM is transduced, expressed and engages to the target to show efficacy



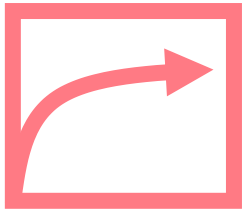
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CRISPR-GNDM® is a promising new therapeutic modality

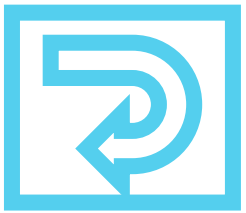
Potential benefits of CRISPR-GNDM® Technology



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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With the full approval of ELEVIDYS, 3 GTx have been approved in 2024

Based on recent successes, gene therapy is expanding its target 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 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]
LYFGENIA		$3.1M		Bluebird		
Lenmeldy	2024	$4.25M	Metachromatic Leukodystrophy	Orchard/KyowaKirin	1 in 100,000 live birth	?
beqvez		$3.5M	Hemophilia B	pfizer	1 in 30,000 male	$88M[#3]
ELEVIDYS		$3.2M	DMD	Sarepta	1 in 3,500 male birth	$4.1B[#4]

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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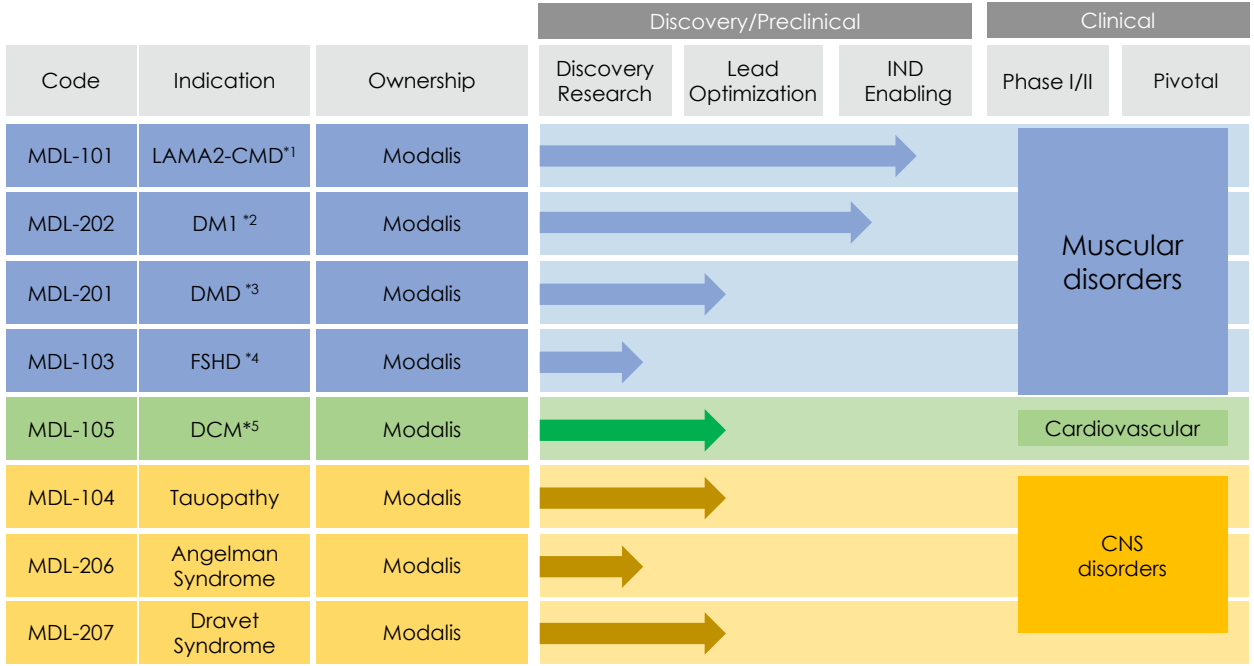
Table of contents

1. Topics of the 2Q/2024
2. Financial update
3. Growth strategy
   - About the finance just announced
4. Q&A

1. Key Takeaway of the 2Q/2024 outcome

01	02	03	04	05
MDL-101 moving forward to IND	Paper and presentations	New collaboration	additional business restructuring	Others

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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MDL-101 is moving toward to IND

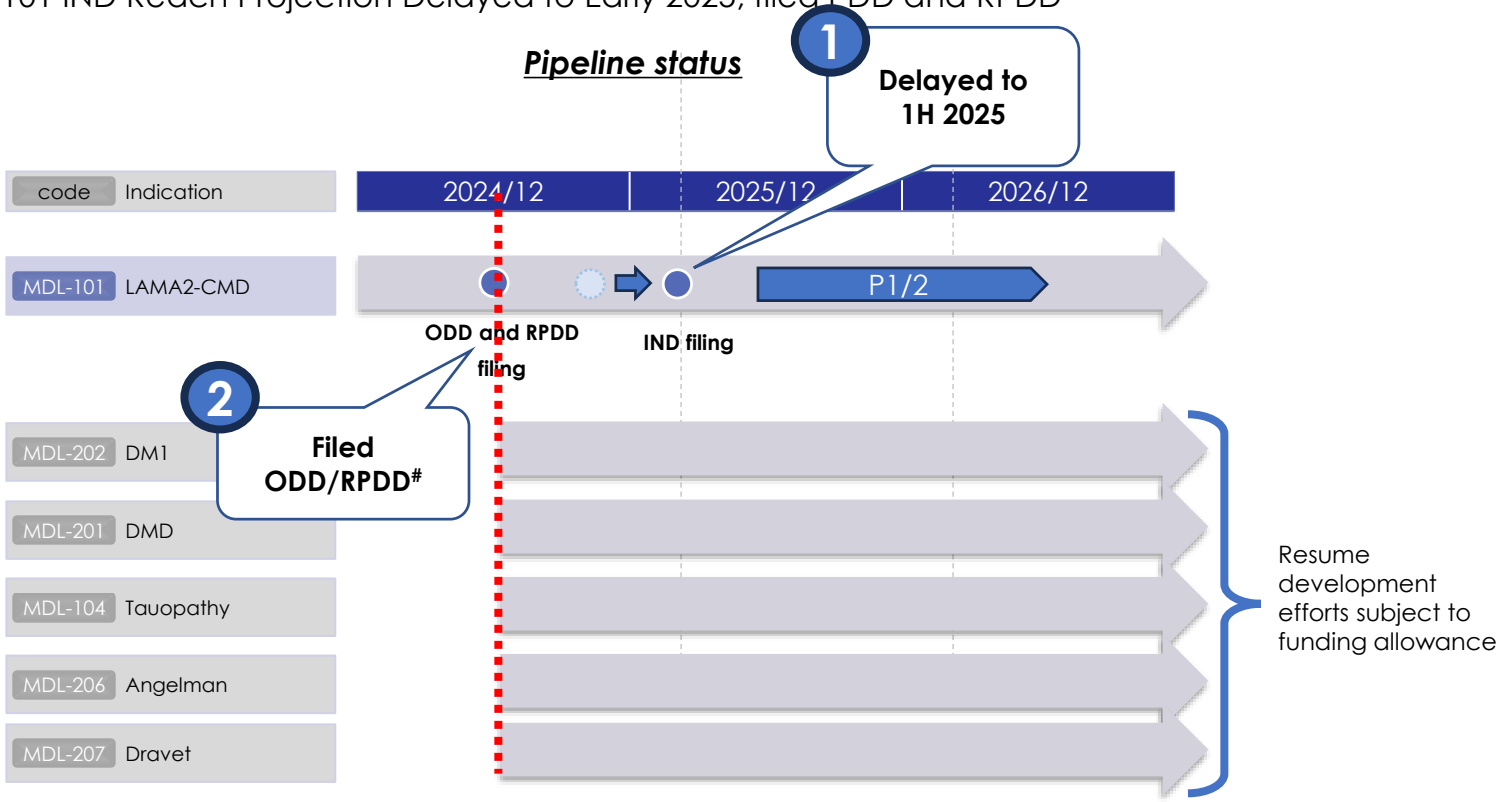
- The manufacturing process has been established
- Preparing of GLP-tox
- Organization and coordination of clinical trial operations

strategic pipeline prioritization and corporate restructuring

- Focus primarily on MDL-101
  - Continue the other program as research efforts.
- Modalis has reduced its US workforce to follow up to the downsizing done in April
  - Downsized including remaining manufacturing workforce as it completed their missions
- Joint research will be maintained as is.

Good news and bad news

While MDL-101 IND Reach Projection Delayed to Early 2025, filed PDD and RPDD



- 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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Background on IND filing delays

- Review of financial and development plans
- Reallocation of teams along with business consolidation

Advantages of ODD and RPDD are…

- **Orphan Drug Designation**
  - Tax deduction for clinical trial expenses
  - Exemption from application fees, etc.
  - Exclusive status for 7 years after market launch

- **Rare Pediatric Disease Designation and Priority Review Voucher Programs**
  - Granting priority review voucher after application for approval (The voucher program will end soon)



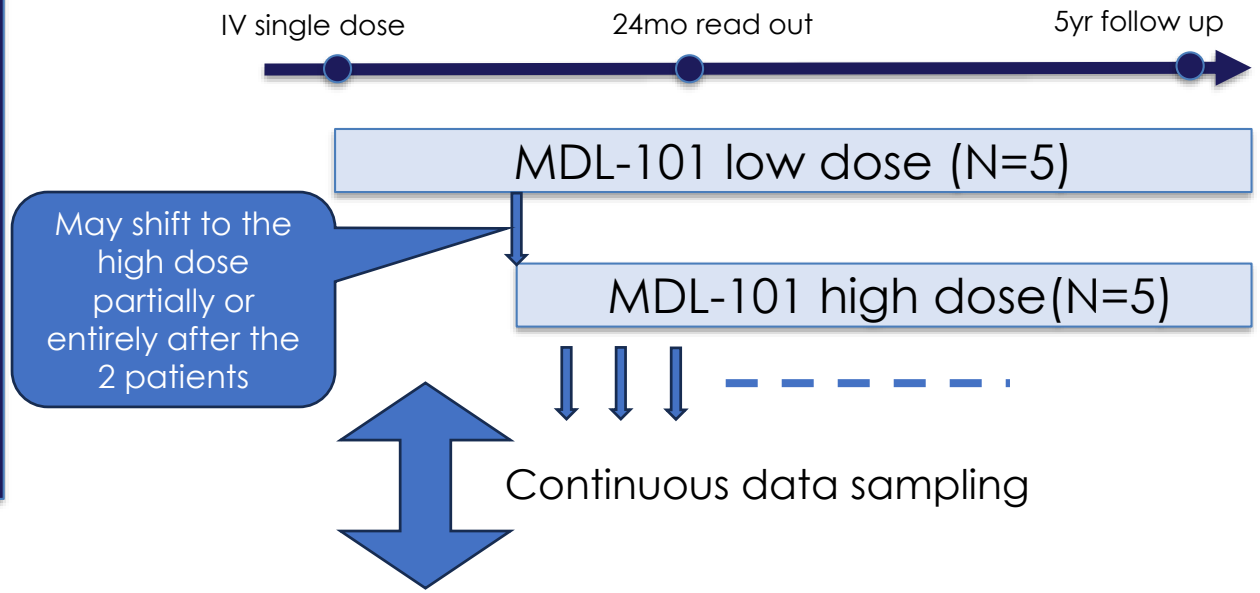
Reviewed by the rarity and medical relevance of the target disease, etc.

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The first-in-human clinical trial will be conducted in open label design

Summary of MDL-101-001 phase 1/2 Open-Label Dose-Escalation Study

- **Male or female LAMA2-CMD patients 36 months of age and younger**
- **Clinical phenotype and Lama2 gene mutations and/or decreased LAMA2 staining in muscle consistent with LAMA2-CMD**
- **Stable background medications**
- **No independent ambulation or sitting**



Comparison with Natural History Study (NCT06354790)

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Published paper on preclinical data on MDL-101 using CRISPR-GNDM®

MODALIS' first publication of CRISPR based epigenome editing



Cold Spring Harbor Laboratory

bioRxiv

THE PREPRINT SERVER FOR BIOLOGY

New Results

Efficient and durable gene activation by Cas9-mediated epigenome editing in vivo

Posted May 05, 2024.

Yuanbo Qin, Talha Akbulut, Rajakumar Mandraju, Keith Connolly, John Bechill, Farzaneh Assadian, Alison Shottek, Seth Levy, Jamie Benoit, Tetsuya Yamagata

doi: https://doi.org/10.1101/2024.05.03.592438

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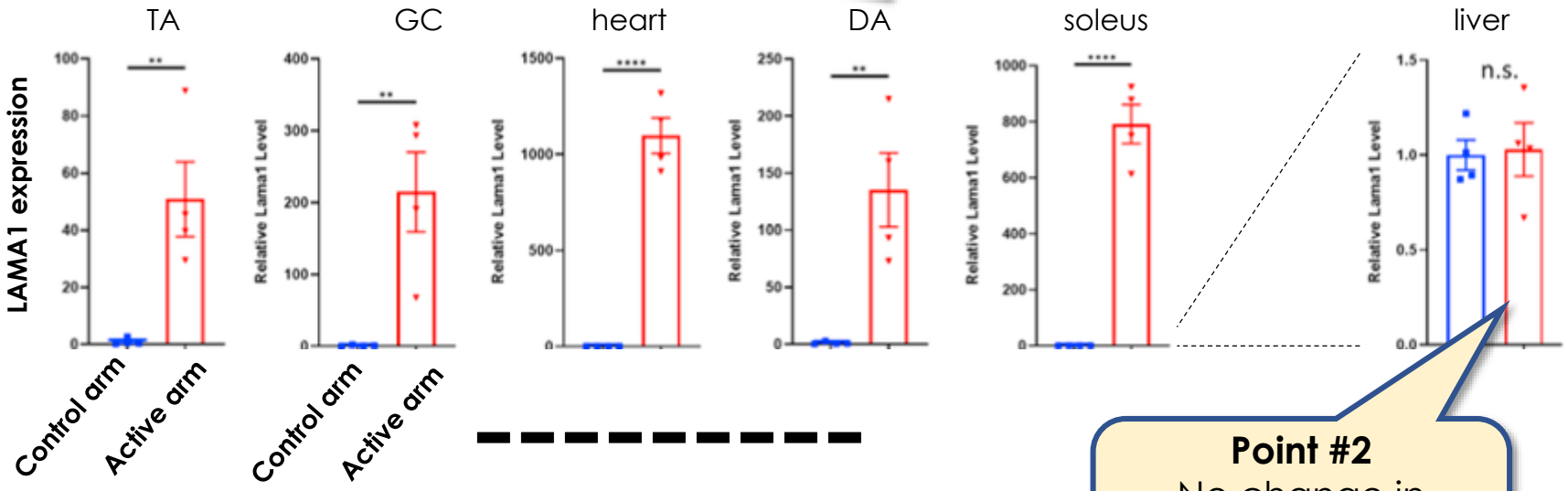
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From the paper

GNDM administration increased LAMA1 in a wide range of muscle tissues, with no change in non-muscle tissues

Point #1
LAMA1 is widely expresses in muscle tissues



Point #2
No change in expression level in liver

TA: tibialis anterior GC: Gastrocnemius DA: Diaphragm

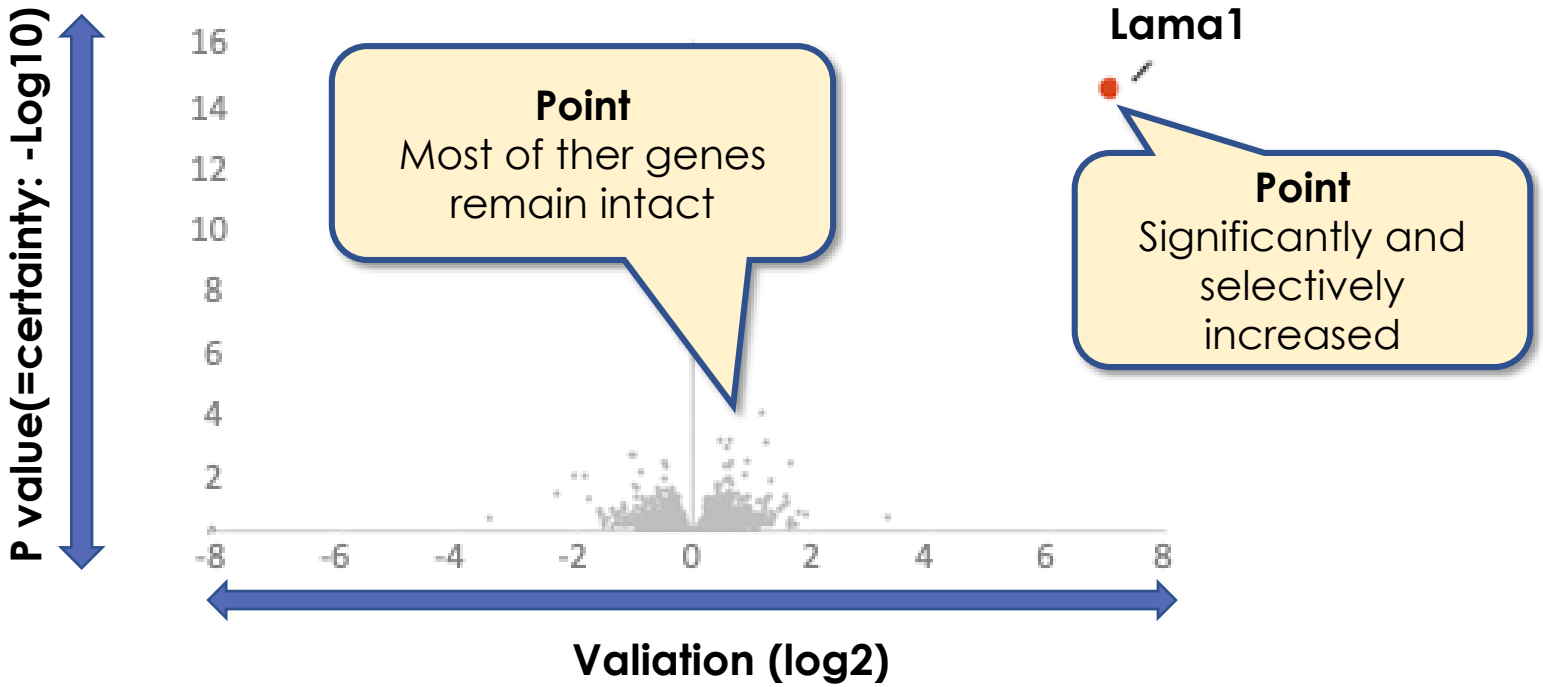
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From the paper

GNDM selectively upregulates LAMA1

gene perturbation by GNDM-LAMA1 in RNAseq

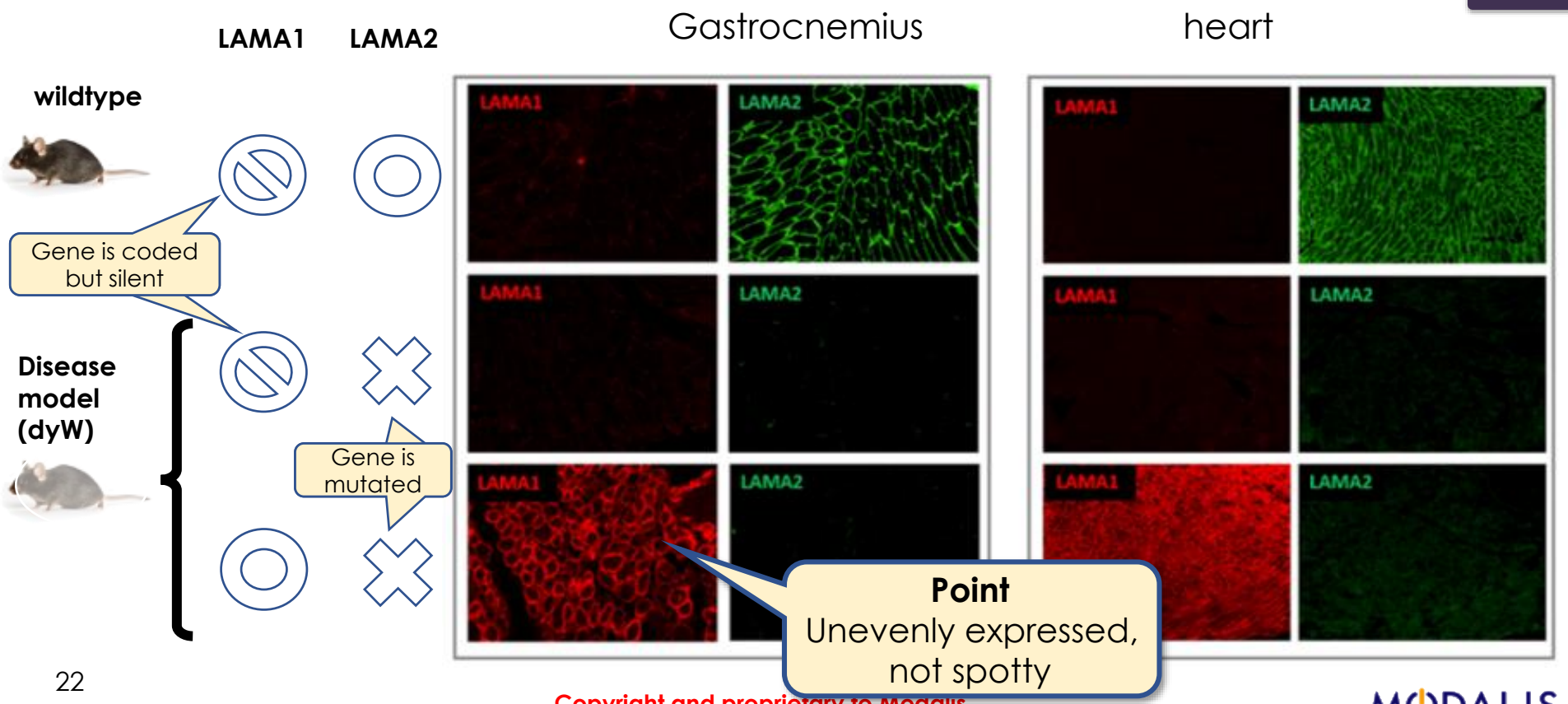


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From the paper

LAMA1 is distributed in many skeletal and heart muscles



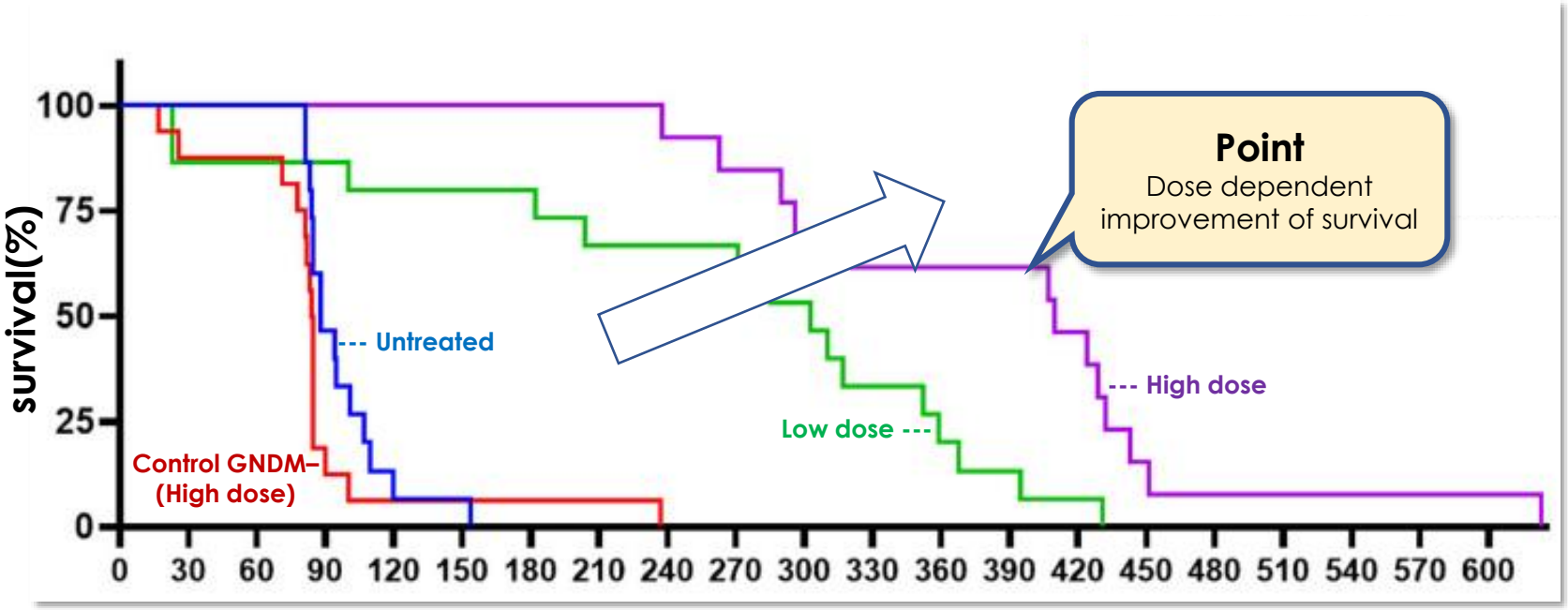
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From the paper

MDL-101 administration significantly improves survival

Survival curve of dyW(disease model)mice



Days post injection (d)

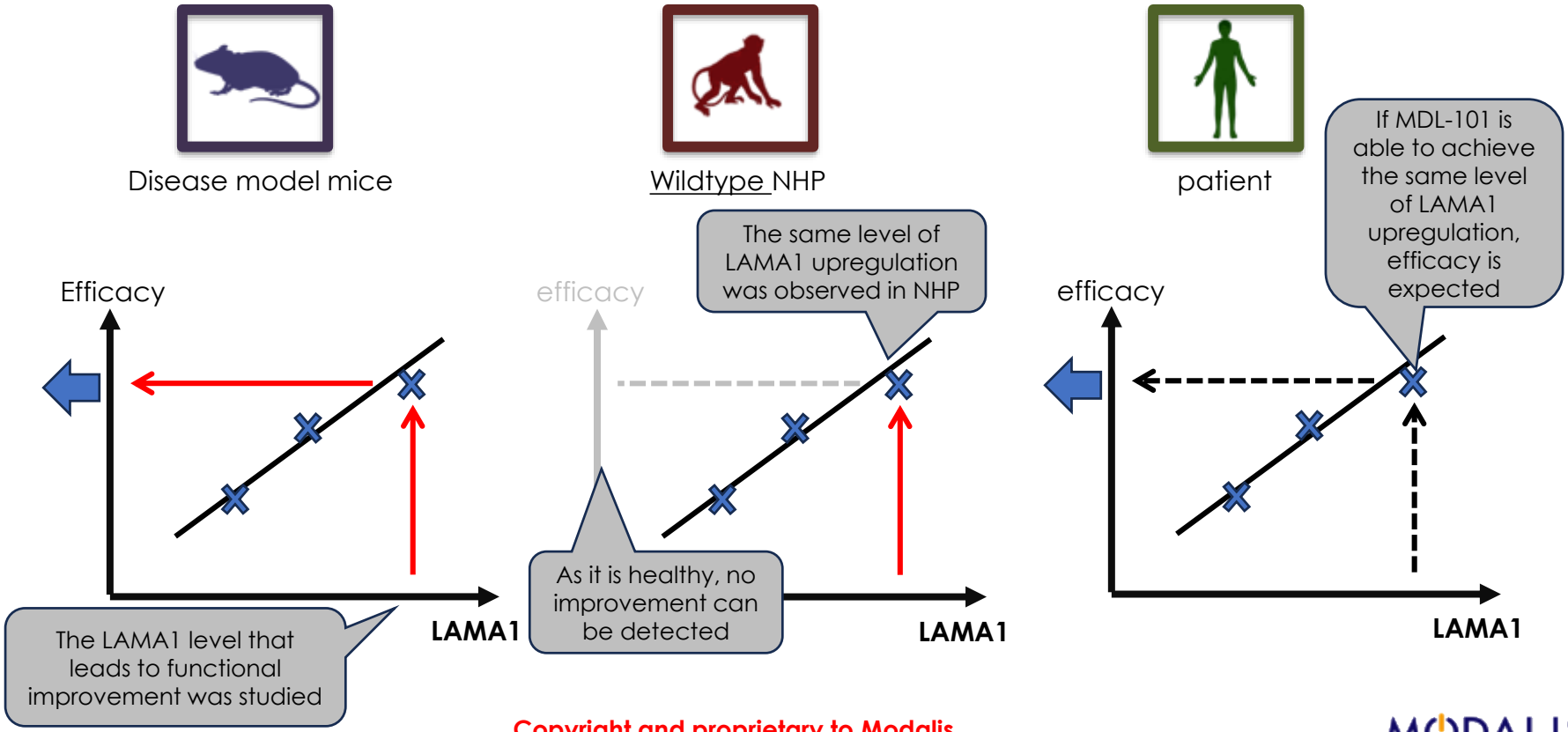
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From the paper

LAMA1 was upregulated to the potentially effective level

LAMA1 elevated in monkeys to the level of functional improvement at the mouse pathological condition observed

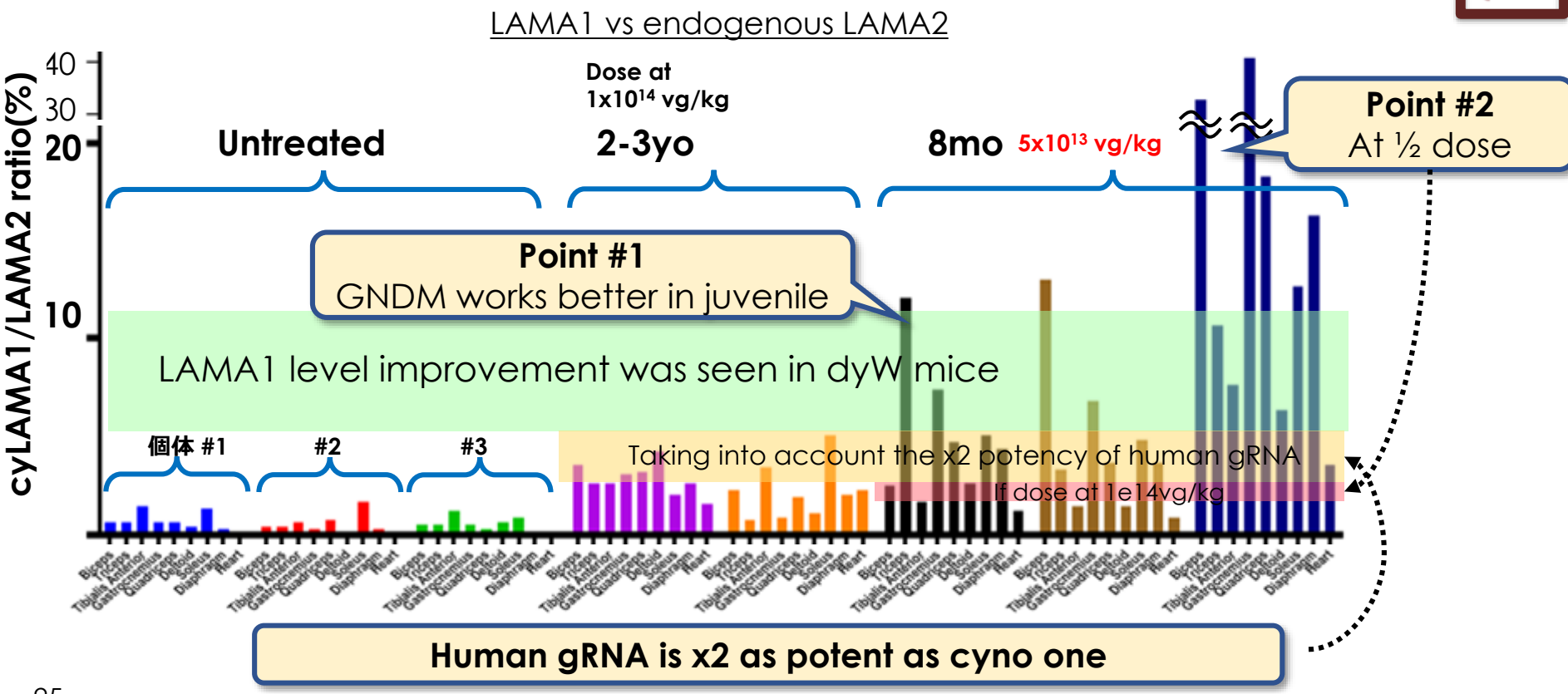


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From the paper

10-20% of endogenous LAMA2, which shall show efficacy, is expected in clinic



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Presented 101 preclinical data at 2 conferences

4th Annual
Next Generation
Gene Therapy Vectors
Innovating Gene Therapy Capsid & Payload Design

June 11-12 in Boston MA

CELL & GENE THERAPY SUMMIT-2024

July 8-10 in Boston MA



LAMA2 — EUROPE —

21 JUNE 2024 / Medical knowledge

Modalis Therapeutics advances a novel gene therapy for LAMA2-CMD

Modalis Therapeutics has made significant strides in developing a gene therapy technology aimed at treating LAMA2-congenital muscular dystrophy (LAMA2-CMD).

Earlier this year, the company released promising preclinical findings based on studies conducted in mice and non-human primates (monkeys). These studies have demonstrated the potential efficacy and safety of their approach, marking a pivotal step towards potential future clinical trials in humans.

Breakthrough Preclinical Results

Also, featured in LAMA2 CMD patient community

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Presenting manufacturing and immunology data in late August



Oral Presentation
Title : *"In-Process Stability Testing with Novel AAV Capsid Variants"*
Date : August 20, 2024 12-12:30PM EST
Session Title : Gene Therapy CMC & Analytics: Potency Assays, In-Process Testing

Reporting…
Production method and results of MDL-101, which employs muscle-specific modified AAV vectors



Oral Presentation
Title : "Counter-balanced immune response against Cas9-mediated epigenetic modulation induces durable therapeutic efficacy"
Date: August 22, 2024 at 12PM EST
Session Title : Talking Immunogenicity For Gene Edited Product

Reporting…
Data showing that MDL-101 (CRISPR-based epigenetic modulation technology) induces durable therapeutic efficacy and tolerability of immune response

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Impact of the presentations

- Multiple inquiries from pharmaceutical and biotech companies about partnerships
- Increased inquiries from around the world about participating in the clinical trial
  - The baby on the right is waiting for participating in MDL-101-001 trial. she was found to have muscle weakness, which was diagnosed as LAMA2-CMD shortly after birth. (Photo courtesy of parents)



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GENIXCURE is a Korean company with an AI-based AAV search platform

GENIXCURE

Developed its proprietary AI-based engineered AAV search platform, CARE™ (Cell-specific AAV Research Engine)



InsightMiner™: Hongik Univ.
AI system developed by Prof. Park Joon

1. AAV gene therapeutic drug development
   - CNS diseases (ALS, Lafora disease, dementia, etc.)
2. AAV contract manufacturing business
   - One-stop service for manufacturing, purification, and analysis



Elected as Baby unicorn(2024/6)
By The Ministry of SMEs and Startups



2024 Top Cell&Gene Tx company in APAC by Lifescience Review

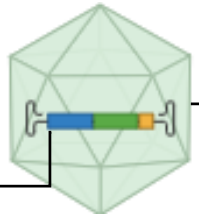
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Combining MDL-104 with GENIXCURE's next-generation delivery technology to co-develop innovative Alzheimer's disease therapies that are more selective, more effective, and less invasive

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Payload
MDL-104



GENIXCURE

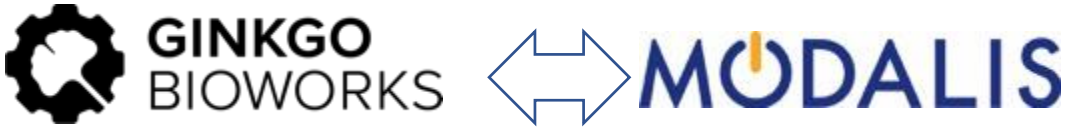
Engineered AAV capsid
XOB-031etc.

- The best-in-class molecule showing high suppression of neuronal tau protein expression in the brain
- Neuron-specific promoter use
- ICV administration
- Demonstrated in humanized mouse models of disease

- Neuron-specific capsid
- High transduction efficiency
- Liver detargeting
- Potential for IV administration (BBB transmission)

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Modalis' alliance network is expanding



Leading Synthetic Biology Company &
One of the world's largest biofoundry

New capsid area



Specialty Pharma in Rare Diseases



Emerging Biotech with
Novel AI-Based Capsid
Technology

Status of wholly owned pipelines

MDL-101:While conducting development to achieve clinical entry asap, also negotiating with potentials to realize partnering.

MDL-201, 202: Obtaining data with new version vector and will try to find a partner who funds development

MDL-104: Entered into MOU for Research Collaboration with Genixcure to develop next-generation therapeutics for Alzheimer's disease

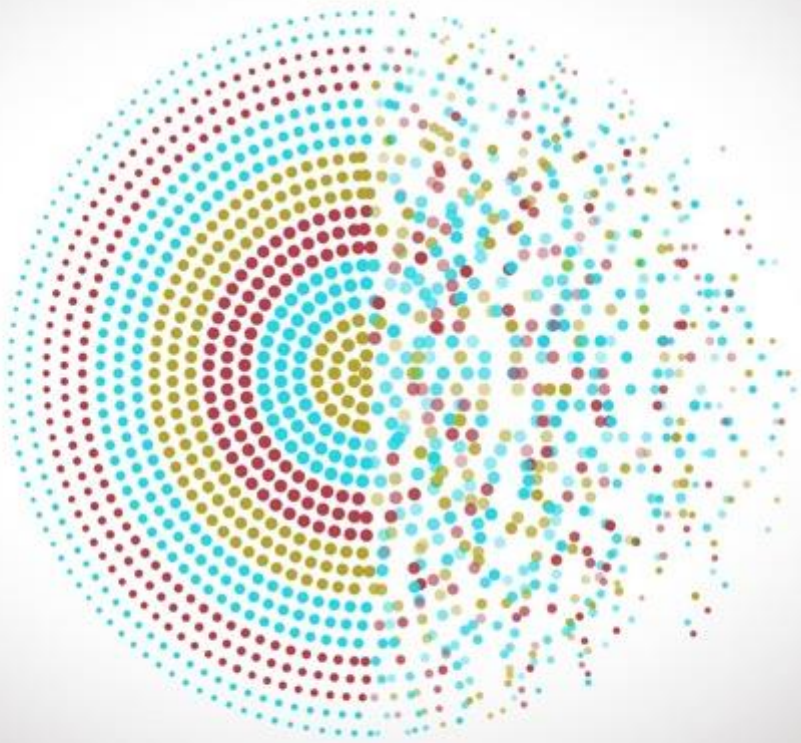
Other programs : R&D is ongoing. We plan to partner with the company when it reaches the appropriate stage of patent filing, acquisition of development data, and so on.

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Patents related to MDL-201 and 202 were granted and registered in China

- UTRN patent Granted in China(June)
  - METHOD FOR TREATING MUSCULAR DYSTROPHY BY TARGETING UTROPHIN GENE CHN 201980075173.0

- DMPK patent issued in China(June)
  - METHOD FOR TREATING MUSCULAR DYSTROPHY BY TARGETING DMPK GENE CN 113785066B



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Achievements of the programs and coming milestones

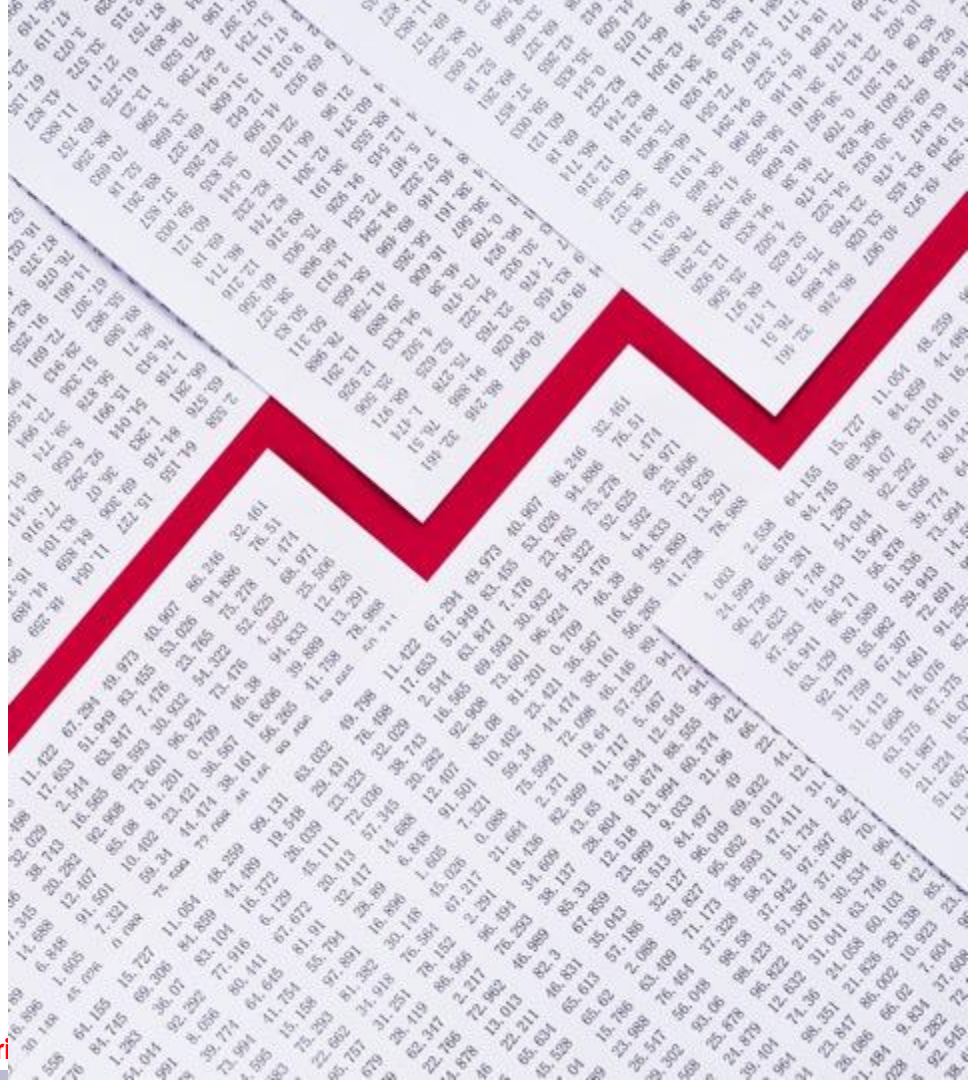
	Achievement so far	Coming milestones
MDL-101 LAMA2-CMD	• Animal PoC • Target engagement in monkeys • Pre-IND response • Establishment of manufacturing process • Publication of preclinical data (May) • Data presentation (June and July)	• Data presentation x2 in Aub • ODD and RPDD designation • GLP-Tox • GMP manufacturing • IND

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)
		• 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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PL & Business Result

(Million Yen)

	2Q FY2023 (A)	2Q FY2024 (B)	(B)−(A)
Operating revenue	-	-	-
Operating expenses	1,044	838	△206
R&D	906	716	△190
SGA	138	122	△16
Operating income	△1,044	△838	△206
Ordinary income	△995	△780	215
Current Profit	△1,033	△781	252

Operating expenses

- Advancement of clinical trial efforts for MDL-101 (process development costs for investigational drug manufacturing, etc., AAV change costs, etc.)
- Decrease in R&D expenses due to Decrease in in-house model pipeline including MDL-202 (mainly personnel expenses and research material expenses such as reagents)

Extraordinary loss

- Net loss increased due to lower impairment loss on fixed assets

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BS & Financial Position

(Million Yen)

	End of FY2023 (A)	End of 2Q FY2024 (B)	(B) – (A)
Current assets	1,956	1,332	△623
Cash & deposits	1,883	1,278	△605
Non-current assets	69	77	7
Total assets	2,025	1,409	△616
Current liabilities	198	103	△95
Non-current liabilities	447	193	△254
Total liabilities	645	297	△349
Total net assets	1,380	1,112	△267
Total liabilities and net assets	2,025	1,409	△616
Capital adequacy ratio	66.8%	77.9%	

Note

- Decrease in long-term liabilities due to conversion of convertible with stock acquisition rights (250 million yen)

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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

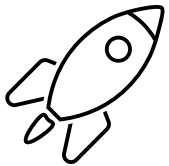
MDL-202

Further approach to challenging applications

Other programs

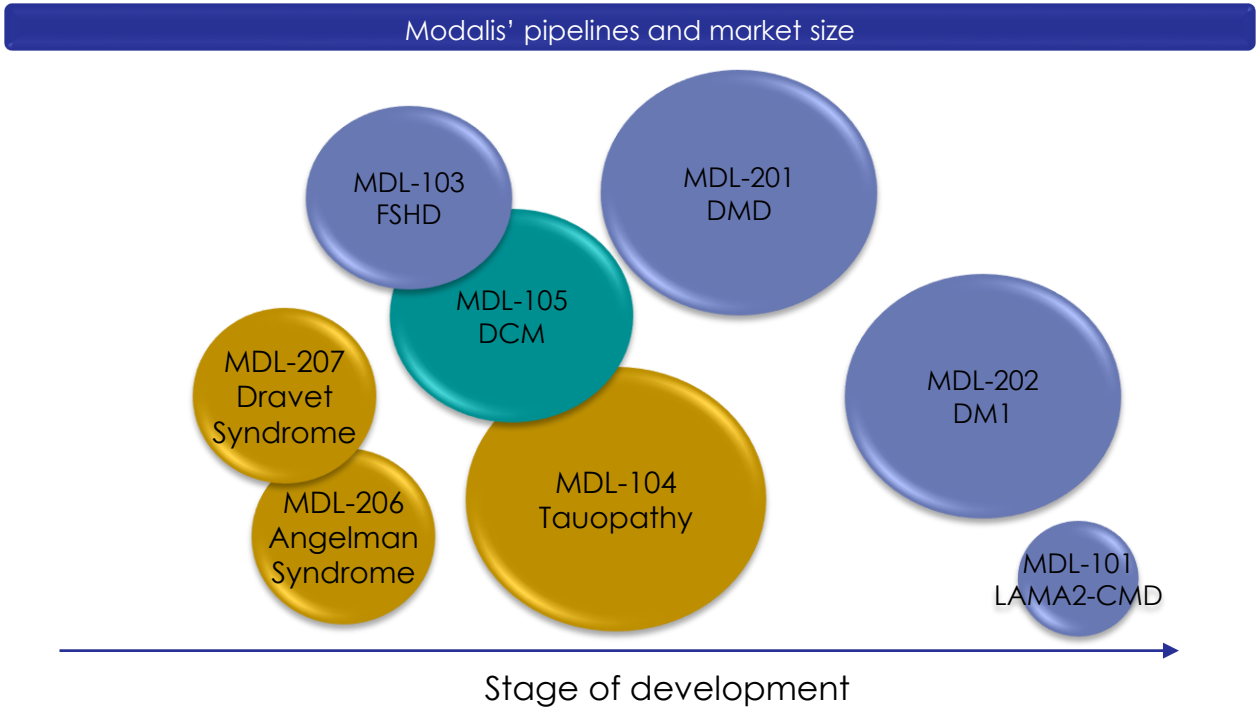






Modalis' pipelines and market size

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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Aim of Fundraising

↓

Secure funding until the next value inflection point

- As a result of the increased partnering hurdles in the biotech industry, P2 or PoC and beyond is a prerequisite.
  - Only 9.1% of assets in the P3 stage are partnered* according to 2023 data.
- Securing funds to reach PoC is key to winterizing through the biotech ice age
- Conversely, if a company is able to reach PoC on In-house sales (= higher profit margin potential) become in range

Source "Biopharma Dealmaking: Time for a Rethink?" by Lumanity at Swiss HLG Conference 2024

Outline of the Fund Procurement

	2nd Series of Unsecured Convertible Bonds with Stock Acquisition Rights (with conversion price amendment clause)	The 14th series of stock acquisition rights (1st tranche with exercise price amendment clause)	15th Series Stock Acquisition Rights (2nd tranche with exercise price amendment clause)
allottee	EVO FUND		
Amount to be procured	**700 million yen**	1,635 million yen (@101yen per share)	745 million yen (@101 yen per share)
Date of resolution to issue	Aug 7, 2024		
Date of pricing	Aug 6, 2024		
Date of allocation	Aug 23, 2024		
Term	2 year	5 year	5 year
Redemption price	100.0 yen	-	-
Interest rate	***0.0%***	-	-
Initial conversion/exercise price	93.4 yen		101 yen
Conversion and exercise price revision	**92.5%** of the last trading day		The price will be revised every three trading days after the issue date to the higher of the average closing price for the three preceding trading days x **100%** or the closing price for the immediately preceding trading day x **90%**.
Floor conversion/exercise price	**50.5 yen**		
Number of potential shares	7,494,640 – 13,861,360 share	**17,500,000 share**	**7,500,000 share**
Dilution ratio	19.0-35.1%	44.3%	19.0%
Total dilution ratio	82.4% - 98.5%		
supplementary clause	Call provision: any time after the issue date	Call provision: Requires agreement between the issuer and the allottee	Call provision: If no convertible bonds remain outstanding
	Put provision: If the share price falls below the minimum conversion price, early redemption can be requested at any time after that date.	-	-
	Conversion of bonds after the conversion of bonds has progressed to 350 million yen is possible only if the cumulative conversion amount of bonds does not exceed the cumulative exercise amount of stock acquisition rights.		

(1) The initial conversion/exercise price is based on the closing price of the Company's common stock **as of August 6, 2024**.
(2) The dilution ratio is based on the ratio of the number of shares outstanding to the number of shares of the Company's common stock as of **June 30, 2024**.
Please be noted this information is intended for the reader's understanding and is not intended as a solicitation to invest.

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Key points of this funding scheme are…

- 700 million yen will be deposited ahead of time by issuing bonds
  →As the funds to develop the development are available upfront, the development can be accelerated.

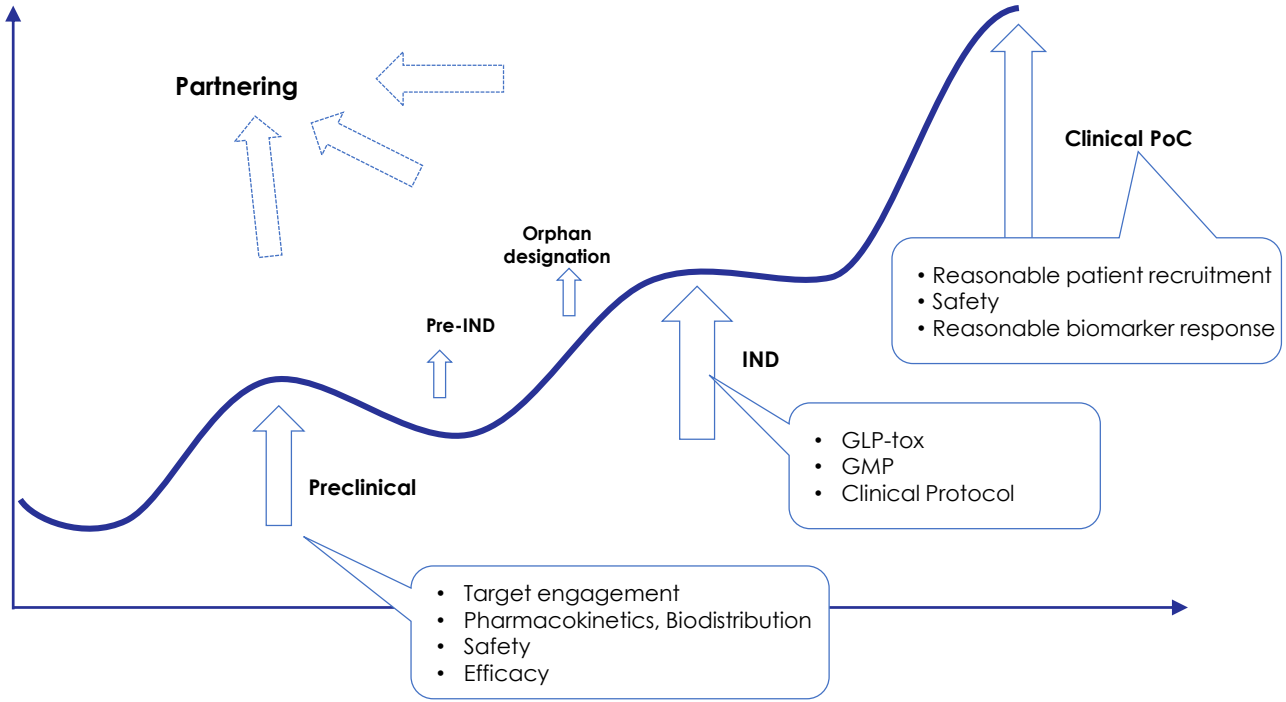
- After half of the bonds have been converted, exercise of stock option shall take priority over conversion of subscription rights..
  → After that point, financing will proceed in parallel

- 2nd tranche is cancellable
  → If the target amount to be raised is achieved by the 1st tranche, or if another funding source is available, the 2nd tranche may be cancelled → Unnecessary dilution can be avoided

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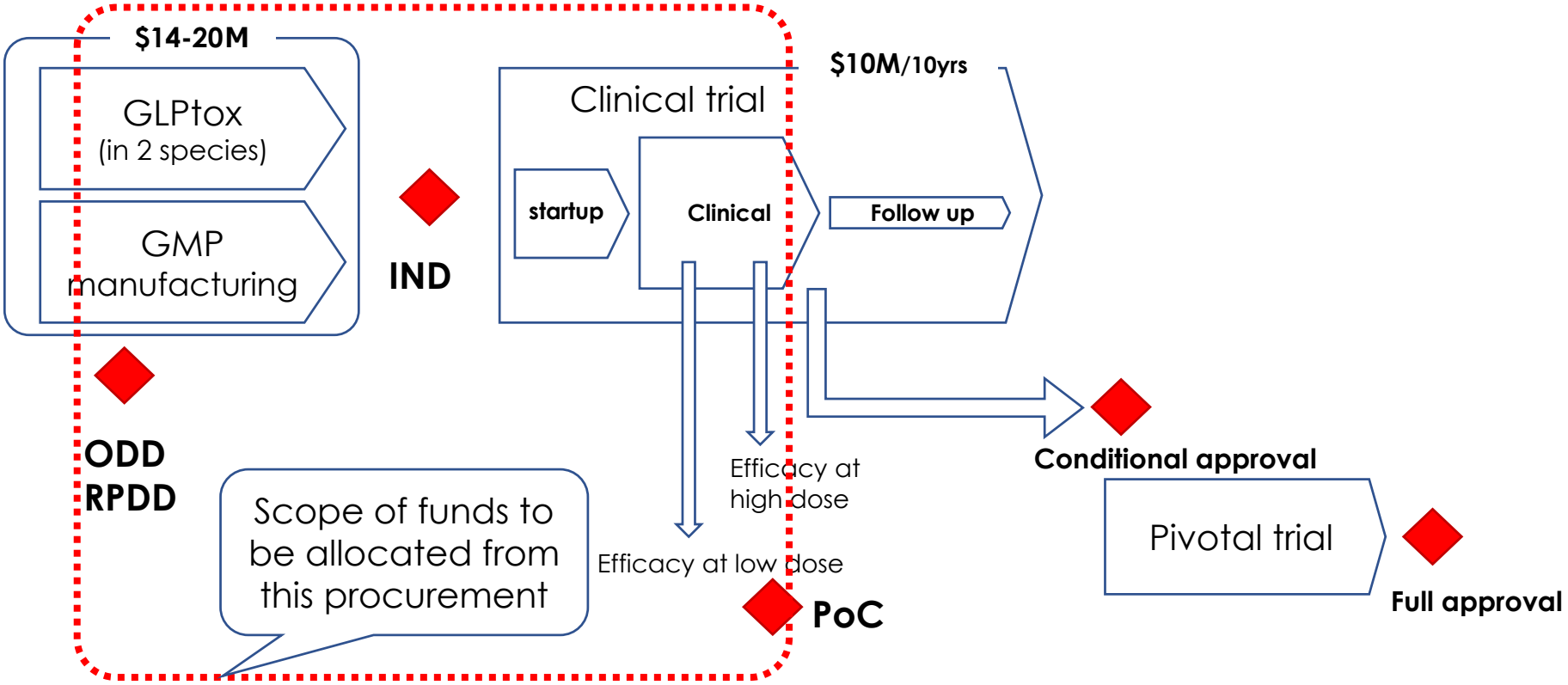
Future pre-clinical and clinical trials are expected to increase the value of the company.

Expected milestone events and impact on corporate value



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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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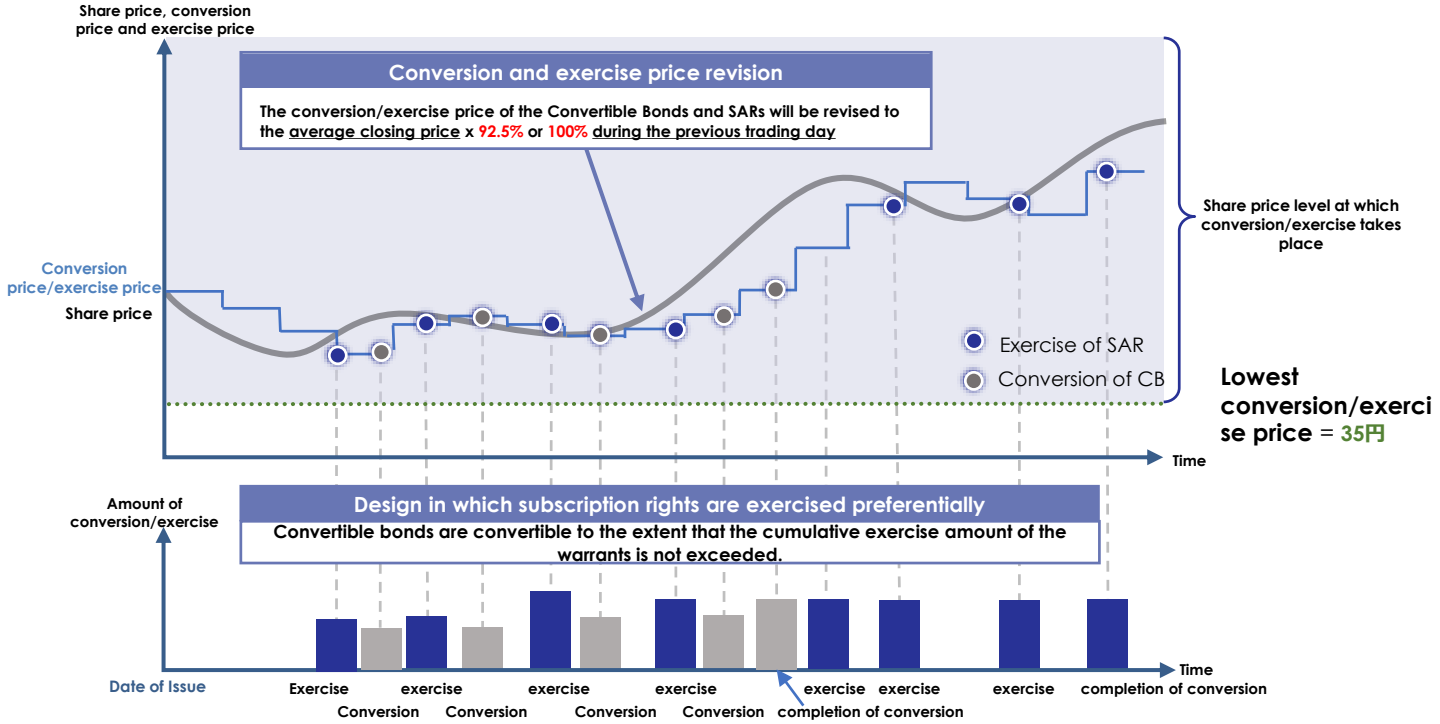
Use of Financing Funds

No.	Specific use of funds	Million yen	Scheduled date of expenditure
1	R&D expenses (excluding personnel expenses) for in-house pipeline (mainly for MDL-101)	2,335	Sep 2024～Aug 2027
2	Personnel and hiring expenses for researchers promoting research and development	700	Sep 2024～Aug 2027
3	Bond redemption funds (1st unsecured convertible bond-type bonds with subscription rights to shares)	38	Aug 2024
Total		3,073	

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Image of progress in exercising this fundraising

Simultaneous issuance of convertible bonds and stock acquisition rights(SAR)
Raise funds upfront through convertible bonds and raise additional funds in stages through warrants



※ The above chart is an image only and is not a forecast or guarantee of the actual share price movement of the Company or the timing of conversion or exercise.

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3. summary

Key Takeaway of 2024 2Q report

1. MODALIS is the lead program and continues to promote the development of MDL-101, a technology showcase
   - There are no issues with efficacy, toxicity, or manufacturing, and we are in a position to proceed solemnly with IND-enabling studies and GMP manufacturing.
   - With the reorganization of resources, the timing of the IND has been pushed back to 2025, but the approval of the most recently filed ODD and RPDD is expected to be realized within the next few months, and development will continue to be strongly pursued.
2. Other pipelines, including MDL-201, 202, and 104, are expected to have a **larger market size** and have the potential to resolve issues with prior products and become **best-in-class** products, respectively.
3. The new financing will be used to provide positive capital to continue these developments in a stable manner and to increase corporate value. We believe this will lift MDL-101 to the **next value inflection point**.

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4. Q&A

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Q1: How Modalis will streamline the JCR and Genixcure collaborations which are in the similar area

- While the target disease & pipeline is undisclosed, the one for JCR is different from that for GENIXCURE
- In addition, both JCR and GENIXCURE are developing neuron-specific capsids for CNS diseases, but in different strategies.
- We aim to select the most appropriate modified AAV capsid for each target disease & pipeline that will provide the best efficacy, safety, and optimal route of administration leading to a lower patient burden, and our collaboration with both companies does not limit that choice, and both agreements are non-exclusive.

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Q2: Wouldn't a large allotment give EVO control of management rights?

- EVO does not intend to hold the shares for a long period of time. In addition, according to the agreement with EVO, EVO cannot continue to hold more than a certain number of shares, and EVO does not intend to do so.
- The 2 million shares of EVO's stock that are included in the large shareholding report are shares lent by the asset management company of the CEO under a share lending agreement, and EVO is obligated to act in accordance with the wishes of the asset management company, including resolutions of the general meeting of shareholders.

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Q3: Where the foreign exchange gains from?

- We conduct all of our research and development at our U.S. subsidiary, and our Japanese subsidiary provides the funds, and in return, the Japanese subsidiary consolidates the results, including intellectual property, into the Japanese subsidiary.

- Under the weak yen environment that continued until July of this year, the loans converted to U.S. dollars generated foreign exchange gains, which were recorded in the accounting.

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