English translation for reference purposes only

Q&A regarding Notice of transition of MDL-101 to an improved version

In case of any discrepancy,
the Japanese version shall prevail

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Modalis Therapeutics Corporation
(TSE：4883)

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Q1 What is AAV? And what is the relationship between AAV and CRISPR-GNDM® ?

A) The Company's method of administering therapeutics is envisioned to deliver our proprietary CRISPR-GNDM® in an adeno-associated virus (AAV) vector to target cells in the body .

In other words, AAV is a delivery tool that delivers CRISPR-GNDM® to target cells.

For more information, see the following pages.

＊ Please note that this information is subject to change without notice. Please understand.

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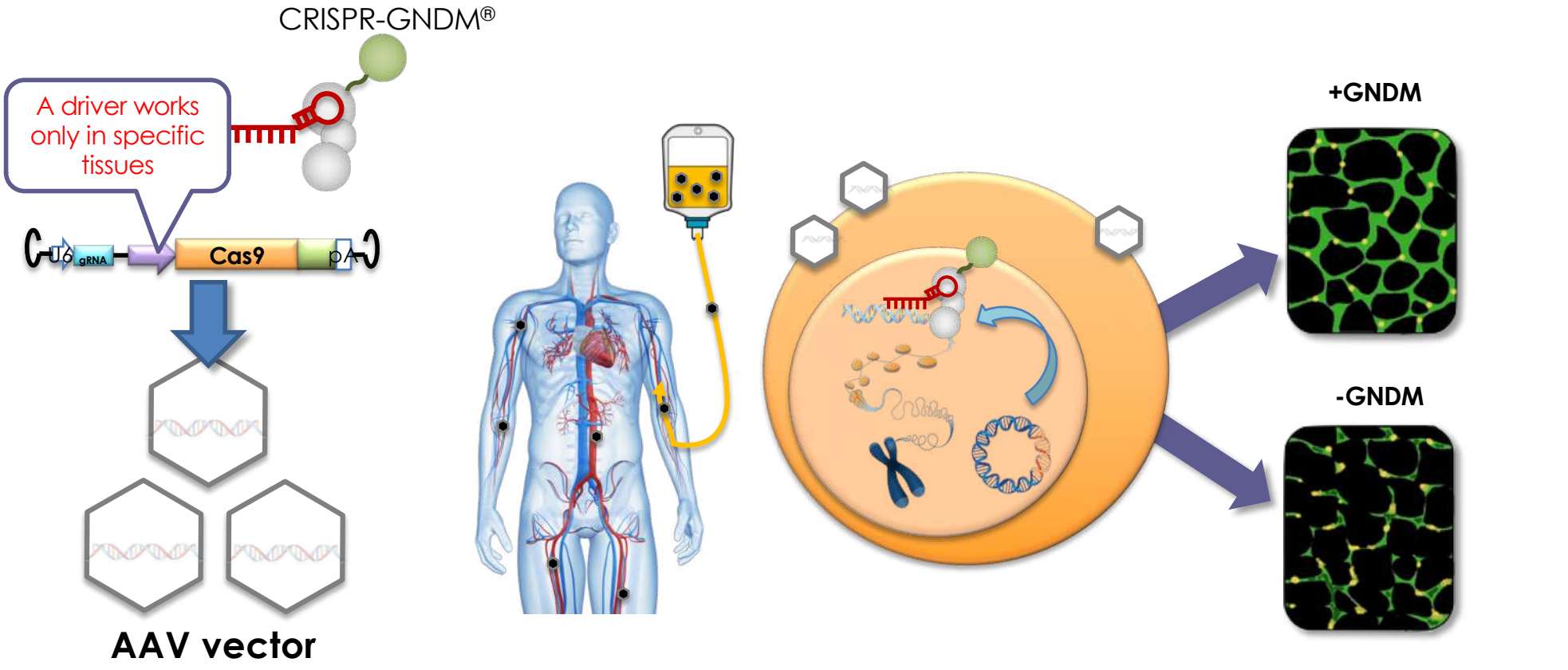
Delivery of CRISPR-GNDM® to target

Use AAV vector to deliver GNDM to target cell



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Q2 What is the reason for changing the AAV capsid at this time? And What is the advantages of the improved AAV.

A) The success of gene therapy since the 2010s has been largely due to adeno-associated virus (AAV) vectors, which are considered relatively safe and have a low risk as not self-replicating in the body mor inserting into chromosomes after transduction into cells. This was a major safety advantage over the previous generations.

Early gene therapies using AAV were developed initially for applications that requires local administration such as ophthalmology, and the remarkable results of these therapies have led to the expansion of their use to muscle diseases that require systemic high-dose administration. Currently, the pipelines of various companies for the treatment of Duchenne Muscular Dystrophy (DMD) are reaching to the late-stage clinical trials and regulatory submissions, and the results of clinical trials have led to discussions of various issues associated with large systemic dosing. To tackle these problems, academia and the pharmaceutical industry have developed improved AAV vectors with enhanced tropism to target tissues such as muscle, and several recently developed improved vectors have been confirmed to have more than 10-fold improved tropism and other characteristics compared to the conventional type. These profiles are expected to have a disruptive impact in terms of reduced toxicity in off-target organs such as the liver and lower manufacturing costs due to lower dosage requirements.

Under these circumstances, we have come to believe that the significance of continuing development with the current technology is largely lost and that ethical issues arise in administering products developed based on the old technology, which has concerns, when there are new technologies with higher safety standards.

We believe that products developed based on new technologies are superior in terms of efficacy, safety, manufacturing cost, and probability of success, and that although this may temporarily delay development in the short term, it will have a positive impact in the long term by increasing product and corporate value.

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Q3 Will modifying the MDL-101 AAV render the previous R&D effort useless?

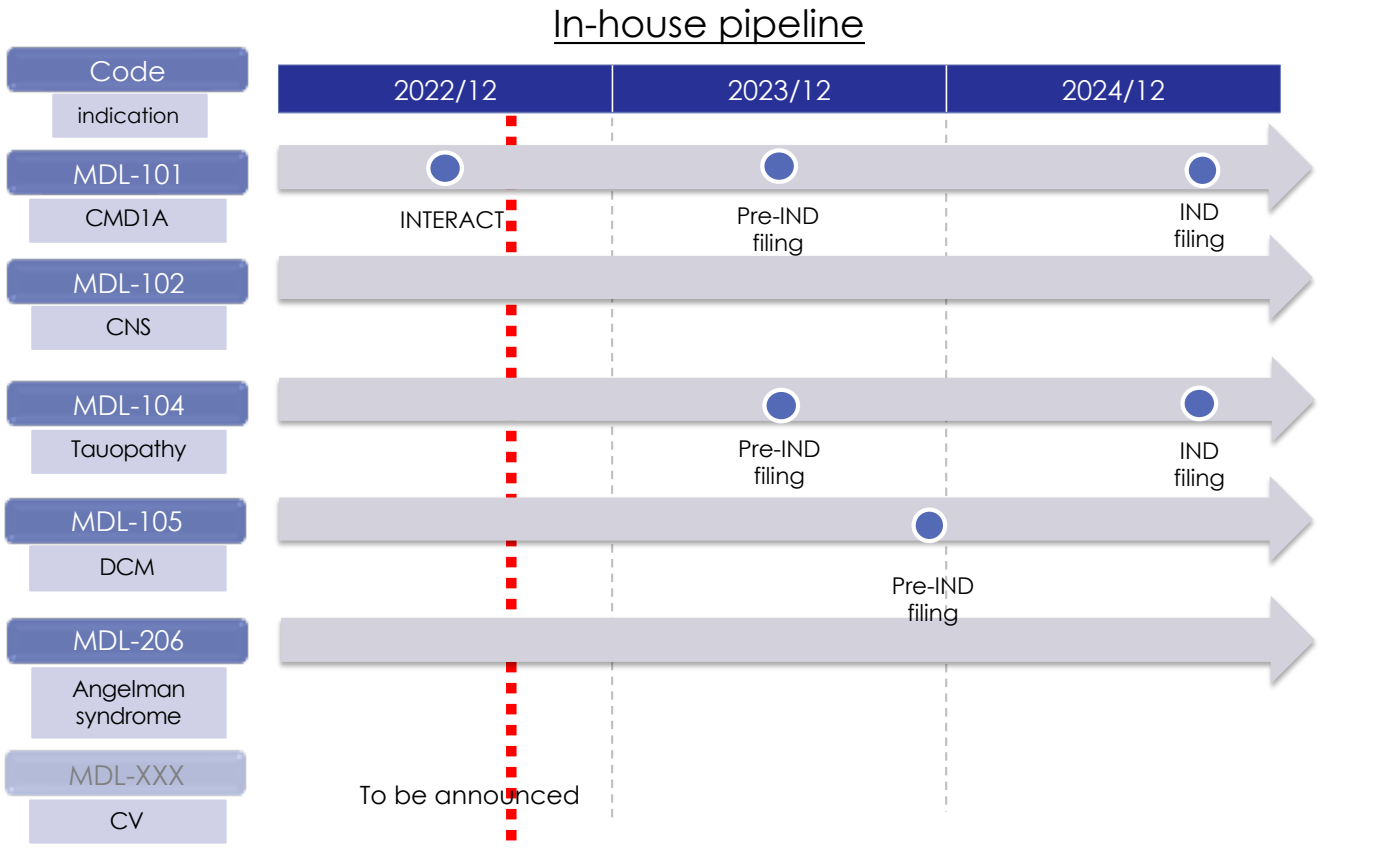
A) No.

The GNDM molecule to be mounted on the improved version AAV capsid will be basically the same molecule as before, so the drug efficacy and safety data obtained to date will be extrapolatable.

Since GMP(Good Manufacturing Practice) manufacturing has not yet started, some process development will have to be redone to accommodate the new molecule, but we believe that this will require only minimal backtracking.

Q4 Does this affect the license-out of MDL-101?

A) There may be some potential impact on the partnering schedule, but on the other hand, we believe that the improved MDL-101 configuration will be more strongly supported by the partners, so we believe that the results will be positive.



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

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Q5 Why company put higher priority on MDL-104, which has been a late starter?

A) Pipelines that require systemic administration, such as MDL-101, will be affected by the transition to improved AAV for the reasons described in Q1, but molecules that are intended for local administration to the CNS, such as MDL-104, MDL-205, and MDL-206, do not have the same risk.

When considering risk diversification of our pipeline portfolio, we believe it is reasonable to develop MDL-104 in parallel with MDL-101, as both have a different risk orientation.

Advantages of MDL-104 include: 1) local administration avoids systemic toxicity, 2) also local administration allows for much lower manufacturing of the clinically required dose, and 3) availability of humanized Tau mice that allows for direct estimation of clinical doses by mouse studies.

For the above and other reasons, the development timeline of MDL-104 could be shortened and becomes comparable to MDL-101 which will undergo improvements. As a result, we believe it makes sense to raise the priority of MDL-104

Q6 Will Company continue to disclose each revision to the development plan?

A) It is our policy to disclose any significant changes in development plans through press releases or other means. In the case of ordinary revisions, our policy is to disclose such revisions in each quarter and at other times.

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Inquiries are accepted on the "Contact" page of the Company's website.

https://www.modalistx.com/jp/contact/

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