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Company name: Modalis Therapeutics Corporation
Stock exchange listing: Tokyo Stock Exchange
Code number: 4883
URL: https://www.modalistx.com/en/
Representative: Haruhiko Morita

Modalis Therapeutics Reports Data Supporting Development of a Transformative Epigenome Editing Therapeutic, MDL-101: a First-in-Class Epigenome Editing approach for the Treatment of LAMA2-deficient congenital muscular dystrophy (LAMA2-CMD)

- *A breakthrough approach and supporting data using epigenome editing technology for the treatment of a type of muscular dystrophy, LAMA2-congenital muscular dystrophy (LAMA2-CMD), a genetic disorder, is presented.*
- *A single dose of MDL-101, using an AAV vector, demonstrated sustained upregulation of LAMA1 (Gene of Interest) in skeletal muscle tissues for up to 12 months, corrected muscle pathophysiology, significantly extended the lifespan, and increased the body weight of dyW mouse, a disease model of LAMA2-CMD.*
- *MYOAAV, an engineered AAV9 vector, significantly increased muscle tropism and consequently lowered the dose of the viral vectors at ten-times compared to conventional naturally occurring vectors.*
- *Systemic administration of MYOAAV version MDL-101 in adult and juvenile NHPs successfully demonstrated widespread muscle-specific vector distribution and induced LAMA1 (Gene of Interest) to levels that restore function across skeletal muscle tissues without adverse effect, suggesting the potential for clinical efficacy as a therapeutic approach for serious genetic disorders.*

7-May-2024 TOKYO & Waltham, Mass – Modalis Therapeutics Corporation (Tokyo Stock Exchange: 4883), a pioneering company developing innovative drugs for the treatment of rare genetic diseases, utilizing its proprietary CRISPR-based epigenome editing technology CRISPR-GNDM®, posted the preprint paper titled "Efficient and durable gene activation by Cas9-mediated epigenome editing *in vivo*" on bioRxiv. The company reported data

demonstrating exceptional durability, robust efficacy and safety in dyW mouse disease model of LAMA2-CMD and in adult and juvenile NHPs.

LAMA2-CMD is a severe, early onset congenital muscular dystrophy caused by the absence of the LAMA2 protein. Despite significant advances in gene therapy and the approval of about a dozen therapies, the size of the disease-causing gene of LAMA2-CMD, which exceeds 3,000 amino acids, hinders the conventional gene therapy approach using AAV vectors to deliver the healthy version of the mutated gene. No approved therapies to address the root cause of this condition exist or are in clinical trials. Modalis' proprietary CRISPR-GNDM®, is capable of specific modulation of the expression of disease-relevant genes, without introducing double-strand DNA breaks, and our MDL-101 is potentially the first-in-class therapeutics to solve the challenge and provide life-changing therapeutics for the patients of LAMA2-CMD.

"We are thrilled to post our comprehensive preclinical data supporting the development of MDL-101 on bioRxiv. This study represents one of the first demonstrations of successful systemic epigenome editing in NHPs in a viable therapeutic format, as evidenced by significant target engagement and induction of LAMA1 gene expression across muscle tissues," said Haru Morita, CEO of Modalis. "Additionally, our study is among the first to show that systemic Cas9 expression can be safe and well-tolerated in NHPs. These findings underscore the potential of CRISPR-GNDM® technology as a next-generation gene therapy platform for a variety of neuromuscular and other genetic disorders".

About bioRxiv (bioRxiv - the preprint server for Biology)

bioRxiv is a preprint server for life science, medical, and biological journals. It allows for early publication without waiting for long peer review periods. Most of the leading journals in life science, medical, and biology area are partnered with bioRxiv, so manuscript files and metadata submitted to bioRxiv can be directly transmitted to partnered journals when we submit. In addition, papers submitted to bioRxiv are assigned a DOI and are eligible for citation.

About MDL-101

MDL-101 is an experimental, epigenetic editing therapy under investigation for the treatment of LAMA2-Congenital Muscular Dystrophy (LAMA2-CMD). MDL-101 is comprised of a guide nucleotide targeting LAMA-1 gene, a highly homologous sister gene of the disease-causing gene LAMA-2, enzyme-null Cas9 (dCas9) fused with trans-activating domain driven by a muscle-specific promoter and coded in a muscle-specific AAV vector. MDL-101 upregulates LAMA-1 gene products in patients' muscle tissue to compensate for loss-of-

function caused by mutation of LAMA-2, and therefore has the potential to provide a one-time, durable treatment to benefit people living with LAMA2-CMD.

About Modalis:

Modalis Therapeutics develops precision genetic medicines using epigenome editing technology. Modalis is pursuing therapies for orphan genetic diseases using its proprietary CRISPR-GNDM® technology which enables the gene/locus-specific modulation of gene expression or epigenome editing without the need for DNA cleavage or altering DNA sequence. Headquartered in Tokyo with all research laboratories and development facilities in Waltham Massachusetts, the company is listed on the Tokyo Stock Exchange's Growth market. For additional information, visit www.modalistx.com.