News Releases & Research Results:

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Brogidirsen: A Dual-Targeting Exon 44 Skipping Antisense Oligonucleotide Shows Promising Safety and Efficacy in Phase I/II Trial for Duchenne Muscular Dystrophy

The National Center of Neurology and Psychiatry (NCNP; President: Kazuyuki Nakagome) is pleased to announce the publication of a research paper in *Cell Reports Medicine* detailing the results of an investigator-initiated trial for NS-089/NCNP-02, known as "brogidirsen." This innovative treatment for Duchenne muscular dystrophy (DMD), jointly developed with Nippon Shinyaku Co., Ltd. (President: Toru Nakai), represents a significant advancement in exon 44 skipping therapy.

Key Findings:

- **Brogidirsen shows dose-dependent dystrophin restoration in DMD patients' trials.**
- **High-dose brogidirsen reached 24.47% of normal dystrophin level in the DMD cohort.**
- **The trial demonstrated therapeutic benefits with stable or improved motor function and a favourable safety profile with no severe adverse events.**
- **Serum biomarkers for DMD were identified, including PADI2, TTN, MYOM2, and MYLPF.**
- **Brogidirsen showed high efficiency in DMD urine-derived cells, supporting human trials.**

The trial was conducted at NCNP Hospital and Kagoshima University Hospital. The six participants are now enrolled in an extension study led by Nippon Shinyaku further to evaluate the long-term efficacy and safety of brogidirsen.

About Brogidirsen:

It is the world's first dual-targeting exon 44 skipping antisense oligonucleotide. It has demonstrated high efficiency in promoting exon 44 skipping and dystrophin protein expression in patient-derived cells, showing the potential to slow disease progression in approximately 6% of DMD patients amenable to exon 44 skipping.

Background:

DMD is an X-linked, progressive muscle degenerative disorder caused by the absence of dystrophin protein. Previously, NCNP and Nippon Shinyaku Co., Ltd. jointly developed viltolarsen (Viltepso®), an exon 53 skipping drug conditionally approved in Japan and the USA, based on its ability to increase dystrophin production. While effective, exon-skipping therapies are mutation-specific, underscoring the need for treatments like brogidirsen to address other mutations.

Expert Comments:

- **Dr. Yoshitsugu Aoki, Research Director**:
  "We achieved a groundbreaking level of dystrophin restoration. Our novel evaluation method using urine-derived cells could reduce patient burden while discovering a therapeutic marker in the blood, which offers a promising tool for monitoring treatment efficacy."
- **Dr. Hirofumi Komaki, Clinical Director**:
  "This study marks the world's first success in restoring human dystrophin protein expression to over 24% on average, achieving results indicative of significant motor function improvement."

Acknowledgements:

NCNP extends its deepest gratitude to the study participants and their families for their invaluable contributions.

Looking Ahead:

With support from the Japan Agency for Medical Research and Development (AMED), Nippon Shinyaku is preparing for multinational clinical trials. The continued progress of brogidirsen highlights its potential as a transformative therapy for DMD.
For further details, please refer to the publication in *Cell Reports Medicine*.
（ https://www.cell.com/cell-reports-medicine/fulltext/S2666-3791(24)00672-4）

■ **Fundings**

The NS-089/NCNP-02 development project is subject to the following subsidies.

・**Japan Agency for Medical Research and Development (AMED)**
Practical Research Project for Rare/ Intractable Diseases, Step 1, 2015-2017: Intractable Diseases Practical Application Research Project “Development of a novel peptide-conjugated phosphorodiamidate morpholino therapy for

Duchenne muscular dystrophy".

Translational Research Grant, 2016-2019: "Implementation of investigator-initiated trials of muscular dystrophy with efficient utilization of the disease registry system, and implementation of clinical studies that contribute to drug development".

Translational Research Grant, Seeds C, 2018: The Translational Research program; Strategic Promotion for practical application of Innovative medical Technology "Systemic administration of the morpholino antisense for exon-44 skipping in Duchenne muscular dystrophy: An investigator-initiated clinical trial phase I/II study".

Translational Research Grant, Seeds C, 2019-2021: The Translational Research program; Strategic Promotion for practical application of Innovative medical Technology "Systemic administration of the morpholino antisense for exon-44 skipping in Duchenne muscular dystrophy: An investigator-initiated clinical trial phase I/II study".

■ Explanation of Terms

Duchenne Muscular Dystrophy (DMD)

DMD is the most common and severe genetic muscle disorder that primarily affects males. DMD is caused by a mutation in the DMD gene, which encodes dystrophin protein, resulting in progressive weakness and loss of skeletal, cardiac, and pulmonary muscles. Currently, corticosteroids are used to slow the progression of the disease. Since no other effective therapies are available, there is an urgent need to develop a new treatment.

Exon Skipping Therapy

In "exon skipping therapy," short synthetic nucleic acid (such as DNA) called antisense oligonucleotides are used to artificially remove (skip) part of a region (called exon, which is translated into protein) in the transcriptional product (mRNA), thereby correcting a shift of the amino acid reading frame (This correction is called in-framing). Although part of the resulting protein is shortened compared to normal dystrophin protein, partially functional dystrophin protein can be produced, leading to improved muscle function. An exon subject to this therapy varies depending on the *DMD* mutation. Brogidirsen is targeted at exon 44 of *DMD*.

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