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News Releases & Research Results

National Center of Neurology and Psychiatry (NCNP)

Study shows the efficacy of antisense oligonucleotide-based exon 44 skipping drug, NS-089/NCNP-02, for patients with Duchenne muscular dystrophy (DMD) - Investigator-initiated Clinical Trial (First-in-human Trial) may lead to the world's first effective drug for DMD amenable to exon 44 skipping -

National Center of Neurology and Psychiatry (President: Kazuyuki Nakagome) (hereinafter, "NCNP") has announced the results of the investigator-initiated Phase I/II study to evaluate the efficacy and safety of exon 44 skipping drug (NS-089/NCNP-02) as antisense oligonucleotide therapeutics, at the Muscular Dystrophy Association conference held from March 13 to 16, 2022.

NS-089/NCNP-02 is the world's first exon 44 skipping drug developed by NCNP in collaboration with Nippon Shinyaku Co., Ltd. (President: Toru Nakai). NS-089/NCNP-02 was developed based on a novel sequence design. Since it induced highly efficient exon 44 skipping and dystrophin protein expression in cells from DMD patients amenable to exon 44 skipping, we expect that it could slow the progression of the disease.

NS-089/NCNP-02 was administered intravenously every week for 24 weeks on six DMD patients at the NCNP hospital and the Kagoshima University Hospital to evaluate the safety, pharmacokinetics, dystrophin expression levels and motor function after the treatment. This study showed the increase in dystrophin protein expression on western blots to an average of 10.27% of normal in Cohort 1 (Dose: 40

mg/kg) and 15.79% of normal in Cohort 2 (Dose: 80 mg/kg). The North Star Ambulatory Assessment scores suggested a maintenance or improvement trend in their motor function. The drug is expected to have a therapeutic effect on DMD with these results. There was no discontinuation of administration due to adverse events during the trials. Nippon Shinyaku is preparing for the next phase of the trial based on the results. The six participants are also involved in an extension study conducted by Nippon Shinyaku to evaluate efficacy and safety in further administration.

We would like to express our deepest gratitude to the participants and their families.

Background

DMD is an incurable, X-linked progressive muscle degenerative disorder that results from the absence of dystrophin protein. We previously completed an investigator-initiated phase I study with systemic administration of the morpholino antisense NS-065/NCNP-01 (viltolarsen) for exon-53 skipping in DMD to achieve a highly favorable safety profile and favorable pharmacokinetics and efficacy (Sci Transl Med. 2018;10：437.). Viltolarsen (Viltepso®) was recently approved under accelerated approval based on increased dystrophin production in skeletal muscle observed in DMD patients in Japan and USA. However, a weakness of the current oligonucleotides-based exon-skipping approach is that it is mutation-specific. The Japan AMED has recently awarded us several project grants to address the problem of a limited number of patients by developing a highly efficient exon-44 skipping drug-using morpholino antisense in DMD, which are theoretically applicable for around 6% of all DMD boys.

Dr. Yoshitsugu Aoki (Research Director) stated, “Our preclinical studies using mouse models suggest that dystrophin restoration up to 10-15% of normal on western blots can be expected enough to improve skeletal muscle function.”

Dr. Hirofumi Komaki (Clinical Director) stated, “It is epoch-making that we succeeded first in the world in recovering the expression of human dystrophin protein

over on average 15%, and attained results suggesting sufficient efficacy for motor function."

■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, 2016-2020: "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 is 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. NS-089/NCNP-02 is targeted at exon 44 of *DMD*.

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