Angelman Syndrome Therapies Show Positive Results in Early Phase Clinical Trials

A clinical trial for a drug designed to treat the rare neurodevelopmental disorder known as Angelman syndrome (AS) has achieved a favorable safety profile and lessening of overall symptoms in trial participants.

In a recent press release, Ionis announced the detailed HALOS study results for the multiple ascending dose (MAD) portion of the Phase 1/2 open-label study of ION582. Consistent and encouraging results were demonstrated on measures assessing all functional domains, including communication, cognition, and gross and fine motor function. Many patients also displayed an improvement in daily living skills, socialization, sleep, and behavior.

The study, which included 51 people with AS ranging from ages two to 50, found favorable safety and tolerability in all dose levels, with no reports of lower limb weakness, ataxia, or radiculopathy.

Notably, after three doses and six months, 97% of people in the medium and high dose groups saw an improvement in overall AS symptoms as measured by the Symptoms of Angelman Syndrome–Clinician Global Impression-Change (SAS-CGI-C).

Additionally, in a formal survey, parents reported changes in their child's ability after four months of ION582 treatment, and caregivers reported improvement across all functional domains, including the ability to focus on what the caregiver directs the patient to do, communication, movement, sleep, and independence. As Lynne Bird, M.D., professor of clinical pediatrics at UC San Diego and HALOS study investigator, explained in the press release, "Angelman syndrome is a serious neurodevelopmental disorder with life-long impairments and

dependence on caregivers, for which we currently have only supportive care." As there is a significant burden on caregivers, it is encouraging that parents and caregivers saw such important improvements.

The therapy, ION582 is designed to un-silence the paternal copy of the *UBE3A* gene by targeting UBE3A-AS that silences the UBE3A gene. In June 2022, the drug won the FDA's Orphan Drug and Rare Pediatric Disease designation. Ionis plans to meet with the FDA to discuss the design for a Phase 3 study and hopes to begin testing in the first half of 2025.

The results position Ionis close to its competitor, Ultragenyx, who in April reported that its ASO treatment GTX-102, designed to treat Angelman syndrome, was generally safe and led to rapid and clinically meaningful improvements in cognition, communication, and sleep exceeding that of natural history data. Ultragenyx said the cognitive improvements were accompanied by strong behavioral, sleep, hyperactivity, gross motor, and receptive communication improvements after GTX-102 treatment.

GTX-102 works by the same mechanism as ION582, although they have different chemistry and sequence. Deletion or mutations of the maternal *UBE3A* allele causes Angelman syndrome (AS); because paternal *UBE3A* is epigenetically silenced by a long non-coding antisense (UBE3A-ATS) in neurons, this nearly eliminates UBE3A protein in the brain. Both of these antisense ASOs target UBE3A-ATS to unsilence the paternal gene, allowing a functional UBE3A protein to be produced, thus easing disease symptoms.

Trial participants included children 4-17 years old who received GTX-102 in an open-label trial without a control group. There were no unexpected serious adverse effects, although three participants experienced some lower extremity weakness, which rapidly resolved and did not disrupt their ability to continue treatment. Although the lower extremity weakness previously led to a clinical hold in 2020, the hold was lifted in 2021 after the study's protocol was changed to narrow the dose range and switch to intrathecal administration.

Ultragenyx CMO Eric Crombez stated in the press release that the interim data shows treatment with GTX-102 resulted in a rapid, multi-domain improvement that continued throughout maintenance dosing, which could have a meaningful impact on patients and their families. Notably, some children have been able to start eating independently and communicating with their families. Ultragenyx expects to meet with the FDA by mid-year to discuss the results and has created a design for a Phase 3 trial that is expected to start by year-end.

A novel strategy for prenatal treatment is also being explored. All three of these treatments are discussed in greater detail in this previous OTS article.

The news of two therapies preparing for a Phase 3 trial is positive for both the caregivers and those suffering from the symptoms of Angelman syndrome, as they both provide hope of improvement and a better quality of life.