September 2026

Dear Angelman Syndrome Community,

At Ionis, we share the Angelman syndrome community's disappointment with the recent announcement of a negative outcome from the ASPIRE Phase 3 clinical trial evaluating GTX-102 (apazunersen).[1] We recognize how frustrating this result is, given the need for a meaningful therapy for those living with Angelman syndrome. We have heard from many in the Angelman syndrome community in recent days and want to take the opportunity to address some of the questions we have received.

About obudanersen (ION582)

Ionis does not believe that the ASPIRE results impact obudanersen as a potential therapy for Angelman syndrome. Importantly, obudanersen uses different chemistry from apazunersen. Ionis has used this same chemistry across multiple approved medicines for rare neurologic diseases, including SPINRAZA® (nusinersen) for spinal muscular atrophy, QALSODY® (tofersen) for a genetic form of amyotrophic lateral sclerosis (ALS), and ZANVASTRO™ (zilganersen), which the FDA approved last week for Alexander disease.[2] Obudanersen builds on decades of Ionis knowledge and success in developing RNA-targeted medicines.

Our expertise allows us to develop potential therapies optimized for both their potency and safety profile. Data from our Phase 1/2 HALOS trial showed that all dose levels of obudanersen studied showed favorable safety and tolerability.[3,4] This encouraging safety profile enabled us to select the highest dose of obudanersen studied in HALOS (80mg) for study in REVEAL and CHAMPION.[5,6]

Status of obudanersen (ION582) clinical development program

Ionis remains committed to continue evaluating the safety and efficacy of obudanersen through three clinical trials: HALOS (an ongoing Phase 1/2 trial); REVEAL (an ongoing Phase 3 pivotal trial); and CHAMPION (a recently announced Phase 3 trial to study obudanersen in people with uniparental disomy or imprinting defects (UPD/ID) genotypes).[3,5,6] Ionis has confirmed with all clinical trial investigators that all three trials will continue as planned.

About HALOS, REVEAL and CHAMPION

HALOS, REVEAL, and CHAMPION were designed in close collaboration with scientists, doctors, regulators, advocacy leaders, and Angelman syndrome caregivers. The Phase 3

REVEAL study is evaluating obudanersen in a broad age group (ages 2-17) and genotype (deletion and mutation) population.[5] The primary endpoint being used in our Phase 3 trials (REVEAL and CHAMPION) is change from baseline in expressive communication.[5,6]

We believe our trials have been designed to generate the clinical evidence needed to determine whether obudanersen is a safe and effective treatment for people living with Angelman syndrome. However, we will not know the outcome until the trials are completed and the data are thoroughly analyzed. We anticipate initial results from our pivotal Phase 3 trial, REVEAL, in the second half of 2027.[5]

Our Commitment

The Angelman syndrome community's resilience in moments like this inspires us. Ionis joins the community in recognizing the tremendous contributions that all trial participants and caregivers make in driving clinical trials forward. Ionis will continue to appropriately collaborate with the Angelman syndrome community to advance our obudanersen clinical development program and continue to provide updates as our research advances.

Sincerely,

Rob Komorowski, Rob Goldstein-Mahon, and Jeff Smith on behalf of the obudanersen team

References: 1. Ultragenyx.com Press Releases September 2026, 2. Ionis.com Medicines September 2026, 3. Clinicaltrials.gov NCT05127226 HALOS, 4. Ionis.com Press Releases July 2024, 5. Clinicaltrials.gov NCT06914609 REVEAL, 6. Clinicaltrial.gov NCT07782827 CHAMPION

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