December 2025

Dear Angelman Syndrome Community,

We are writing to update you on the ION582 clinical development program, including the Phase 1/2 HALOS and Phase 3 REVEAL trials, as well as the recently announced CHAMPION trial to explore ION582 in additional genotypes.[1,2,3]

All of us at Ionis express our gratitude to every Angelman syndrome (AS) patient, caregiver, family member, and friend who has chosen to participate in research and clinical trials. Medical and scientific knowledge about Angelman syndrome advances only because of you. Thank you!

REVEAL approved in multiple regions, recruitment underway, more trial sites to activate

REVEAL is a Phase 3, pivotal, placebo-controlled clinical trial to determine the safety and efficacy of ION582 in children and adults with AS.[1] Ionis has active clinical trial sites for REVEAL in Australia, Canada, Japan, Singapore, South Korea, the United Kingdom, and the United States (U.S.), and gained regulatory approval to open sites in Israel.[3] Ionis is pursuing approval in additional regions and activating additional REVEAL trial sites. A complete list of REVEAL sites is available online here.

Ionis to focus pivotal clinical trial on the highest dose (80 mg) of ION582

Over the coming months, Ionis will be working with sites to transition individuals over the age of 2 years who are already enrolled in HALOS or REVEAL and were assigned to the 40 milligram (mg) cohorts to the 80 mg cohort in each study. This change is based on an ongoing review of HALOS data showing that the 80 mg dose of ION582 was associated with encouraging efficacy results and comparable safety and tolerability.[4] Study site staff will discuss this transition with individuals enrolled in these studies.

The ability to focus on a single dose level also means fewer participants need to enroll in REVEAL to achieve the study's objectives. The projected enrollment for REVEAL has been reduced from approximately 210 to approximately 158 patients.[1]

Clinical trial of ION582 in UPD/ID patients anticipated to initiate in 2026

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CHAMPION is a planned Phase 3 study in individuals with AS and a genetic diagnosis of uniparental disomy (UPD) or imprinting center defect (ID).[3] Ionis is collaborating with clinicians, researchers, advocacy leaders, and regulators on the design and conduct of the clinical trial. Importantly, Ionis is also convening a group of caregivers from the UPD and ID community as part of this process.

Expansion of HALOS to include people with AS under the age of two

HALOS is our ongoing Phase 1/2 open-label clinical trial exploring the safety, tolerability, pharmacokinetics, and pharmacodynamics of ION582.[2] Results from HALOS have been encouraging and have supported Ionis' decision to advance ION582 into the Phase 3 REVEAL trial.[4] Recently, Ionis expanded HALOS to include individuals under 2 years of age. HALOS participants under 2 years of age will continue to receive a lower dose of ION582.[2] A list of HALOS trial sites recruiting people under 2 years old is available online here.

Finally, Ionis thanks everyone in the AS community who took the time to speak with members of our team at community events and conferences this past year, including through the Angelman Syndrome Foundation's Angelman Strong events, the FAST Summit and Gala, and events outside the U.S., including conferences in Australia, Italy, and elsewhere. Your inspirational stories have impacted our team and shaped our understanding of AS and our research. We look forward to engaging with you at community events in 2026 and beyond.

Ionis encourages individuals to discuss any questions they may have about the clinical trial topics covered in this community statement with their doctor. Ionis will continue to provide updates on its AS research and community engagement activities.

Sincerely,
The Ionis Angelman syndrome research team

Abbreviations: AS, Angelman Syndrome; U.S., United States of America; mg, milligram; UPD, uniparental disomy; ID, imprinting center defect; FAST, Foundation for Angelman Syndrome Therapeutics.

References:

1. REVEAL: A Phase 3 Study of ION582 in Angelman Syndrome. Updated December 22, 2025. Accessed December 22, 2025. https://clinicaltrials.gov/study/NCT06914609.
2. HALOS: A Safety, Tolerability, Pharmacokinetics and Pharmacodynamics Study of Multiple Ascending Doses of ION582 in Participants With Angelman Syndrome. Updated November 14, 2025. Accessed December 2, 2025. https://clinicaltrials.gov/study/NCT05127226.
3. Update on the Ionis Development Program for Angelman Syndrome. 2025 FAST Global Science Summit. Orlando, Florida. Presented November 8, 2025.
4. Data on file.

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