April 2026

Dear Angelman Syndrome Community,

Ionis is pleased to inform you that we have activated our first REVEAL (NCT: NCT06914609) clinical trial sites in the European Union (EU); the Klinikum der Ludwig-Maximilians-Universitaet Muenchen in Muenchen, Germany, and Corporacio Sanitaria Parc Tauli at the Hospital de Sabadell in Sabadell, Spain.[1]

Ionis is excited to open the first enrollment site for REVEAL in the EU and thanks the Angelman syndrome (AS) community for its continued support. Ionis is working with regulators and investigators to open additional REVEAL enrollment sites in Germany, Italy, Poland, and Spain. These sites will join the global network of sites already enrolling people into REVEAL in Australia, Canada, Israel, Japan, Singapore, South Korea, the United Kingdom, and the United States. As additional sites in the EU, and elsewhere, become activated, they will be added to the trial's information page on clinicaltrials.gov.[1,2]

REVEAL is Ionis' pivotal Phase 3 clinical trial of ION582, also known as obudanersen. ION582, an antisense oligonucleotide (ASO), is an investigational medicine designed to increase UBE3A protein production in people with AS. REVEAL is designed to evaluate the efficacy and safety of ION582 in children and adults with AS. Approximately 158 individuals with *UBE3A* mutation- or deletion-positive AS will be enrolled in REVEAL.[1]

REVEAL is a double-blind controlled study. Participants will be randomly assigned to the ION582 (80mg) or to the control arm during the double-blind, controlled period of the study. In the EU, individuals assigned to the control arm will undergo a skin-prick sham procedure during the double-blind, controlled period. The double-blind, controlled period lasts approximately 60 weeks. All participants who complete the double-blind controlled treatment period may transition to a 25-month long-term extension (LTE) period, during which all participants will receive ION582 (80 mg).[1,2]

Ionis thanks the EU Angelman syndrome community for its support in advancing our efforts to bring REVEAL to the region. We also express our sincere gratitude to individuals with AS and their families in the EU who are already enrolled in our HALOS study, which has contributed to our understanding of ION582's potential as a treatment for AS.[3]

Individuals with questions about participating in a clinical trial, such as REVEAL, should speak with their doctor. Ionis will continue to share updates on the status of its research into ION582 as a potential treatment for Angelman syndrome.

Sincerely,

The Ionis ION582 Team

Additional information that you may find helpful can be found on the following page

Where can someone go for more information about REVEAL?

A person's doctor should be their primary source of information on health-related topics, including clinical trials. You can also find more information about REVEAL online here: https://clinicaltrials.gov/study/NCT06914609.

What is ION582?

ION582 is an investigational antisense oligonucleotide (ASO) medicine designed by Ionis to increase the production of UBE3A protein for the potential treatment of Angelman syndrome. An ASO is a type of medicine that is designed to target the body's RNA to help address a genetic disorder or condition. Each ASO is different and targets RNA in a specific way. ION582 is being evaluated in global clinical trials of children and adults with Angelman syndrome called HALOS (Phase 2) and REVEAL (Phase 3).[3,4]

Why is the control arm different in the EU from other regions where REVEAL is enrolling?

All data collected in REVEAL will be critical to understanding the potential safety and efficacy of ION582 as a treatment for Angelman syndrome. The use of different control-arm procedures across regions is common in clinical trials. Ionis and EU regulators aligned on the use of a "skin-prick sham" procedure in the control arm of REVEAL in the EU, whereas Ionis aligned on administering a placebo in all other regions where the trial is taking place.

Ionis has aligned with regulators, including the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), to evaluate data from both control-arm approaches together as a single dataset to inform the safety and effectiveness of ION582.

What is a "skin-prick sham" procedure?

A skin-prick sham procedure involves a healthcare professional inserting a needle into the skin. The needle does not penetrate the spinal cord; no cerebrospinal fluid is collected, nor is any fluid administered during this procedure. The study participant and family will not know whether the participant is assigned to receive the skin-prick sham procedure or ION582 during the double-blind, controlled period of the study. Study doctors and staff will discuss this procedure, as well as pre- and post-procedure activities, with study participants.

The Angelman Syndrome Foundation and the Foundation for Angelman Syndrome Therapeutics (FAST) are community organizations that provide resources and support to patients, caregivers, and others impacted by Angelman syndrome. For more information about Ionis, visit www.ionis.com or email padvocacy@ionis.com.

References: 1. REVEAL: A Phase 3 Study of ION582 in Angelman Syndrome. https://clinicaltrials.gov/study/NCT06914609. Updated April 24, 2025. Accessed April 24 2026., 2. REVEAL Study: Phase 3 Study of the Efficacy and Safety of ION582 in Children and Adults with Angelman Syndrome. https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2024-519711-33-01. Accessed April 20 2026., 3. HALOS: A Safety, Tolerability, Pharmacokinetics and Pharmacodynamics Study of Multiple Ascending Doses of ION582 in Participants With Angelman Syndrome. https://clinicaltrials.gov/study/NCT05127226. Updated November 14, 2025. Accessed April 20 2026, 4. Collotta D, et al. *Front. Pharmacol*. 2023;14:1304342.

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