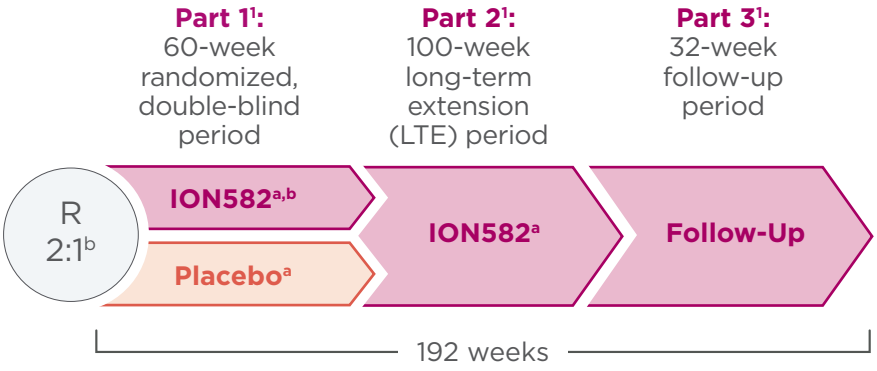
REVEAL: A Phase 3 Study to Evaluate the Efficacy and Safety of Intrathecally Administered ION582 in Children and Adults with Angelman Syndrome (AS)[1]

The REVEAL trial is a Phase 3, randomized, double-blind, placebo-controlled clinical trial[1]

Study objective:

To evaluate the safety and efficacy of an investigational RNA-targeted antisense therapeutic, ION582, in individuals with AS.[1,2]



This is a global, multicenter, three-part study of ION582. **Part 1** consists of individuals who will be randomized 2:1 to receive ION582 Q12W or placebo for a period of 60 weeks. This will be followed by **Part 2**, an open-label, LTE period during which individuals who complete Part 1 will receive ION582 for 100 weeks. **Part 3** is a follow-up period for 32 weeks for participants who completed Part 2.[1]

Select inclusion/exclusion criteria[1,c]:

- Males or females aged ≥2 to ≤50 years
- Documented diagnosis of AS due to either *UBE3A* deletion or mutation and individuals must be on stable standard-of-care treatment[d]
- Individuals with paternal uniparental disomy or imprinting center defects or clinically significant abnormalities rendering them unsuitable for participation are excluded[e]

For more study information scan here:

All information accurate as of 04/2025, for most updated information please scan QR code.

Key Clinical Endpoints[1,c]	
Primary Endpoint	Change from baseline to Week 52 in the Performance on the Expressive Communication subdomain raw score of the Bayley-4 compared to placebo in cohort 1
Secondary Endpoints	Change from baseline to Week 52 in • Bayley-4 ◦ Cognition Subdomain raw score ◦ Fine Motor Subdomain raw score • Symptoms of AS-Clinical Global Impression of Change ◦ Overall AS ◦ Sleep problems • Vineland Adaptive Behavior Scale-3 ◦ Daily Living Skills, Personal Subdomain raw score • Observer-Reported Communication Ability ◦ Overall *T* score

ION582 has not been evaluated for safety and efficacy by any regulatory authorities and is not indicated for the treatment of any disease.

[a]Administered by lumbar intrathecal bolus injection.[1] [b]Two dosing cohorts will be evaluated in the study.[1] [c]This is not an exhaustive list. [d]Includes but is not limited to antiepileptic medication, behavioral management medications, sleep medications, gabapentin, cannabidiol, special diets, supplements, and nutritional support.[1] [e]These include but are not limited to known brain or spinal disease that would interfere with the lumbar puncture procedure; any condition that, in the opinion of the investigator, would make the participant unsuitable for inclusion or could interfere with the participant participating in or completing the study.[1]

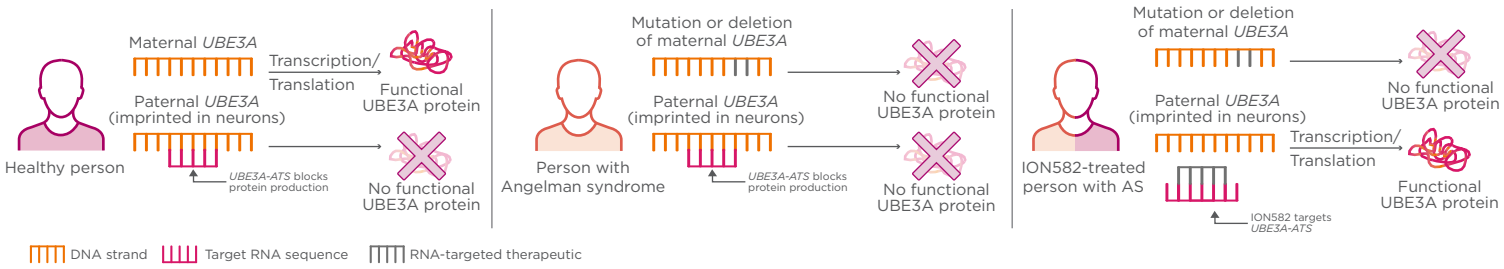
Bayley-4, Bayley Scales of Infant and Toddler Development-4; Q12W, every 12 weeks; R, randomized; *UBE3A*, ubiquitin protein ligase E3A gene.

1. ClinicalTrials.gov identifier: NCT06914609. Accessed April 7, 2025. https://www.clinicaltrials.gov/study/NCT06914609/ 2. Ionis Pharmaceuticals. Pipeline. Accessed February 6, 2025. https://www.ionis.com/science-and-innovation/pipeline

ION582 Is an Investigational RNA-Targeted Therapeutic (RTT) Designed to Increase Neuronal Expression of *UBE3A*[1]

- In Angelman syndrome, UBE3A expression is lost on the maternal gene. UBE3A expression is healthy on the paternal strand but silenced by *UBE3A-ATS*[2]
- The loss of UBE3A expression is the cause of many symptoms associated with Angelman syndrome[2]

Proposed ION582-Mediated Upregulation of *UBE3A*[1-3]



RTTs downregulate *UBE3A-ATS*, unsilencing paternal UBE3A expression and restoring brain-wide UBE3A protein levels in mouse models[2-4]

Administration of a single dose of *UBE3A-ATS*-targeting antisense RTT in mouse models reduced *UBE3A-ATS* levels in the CNS for 16 weeks.[4]

Both *UBE3A* mRNA and UBE3A protein levels were significantly higher in RTT-treated mice than in control mice at 2 to 16 weeks after treatment.[4]

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For more information or questions about participating sites, please contact us at **IonisION582-CS2@clinicaltrialmedia.com** or **844-285-7172.**[5]

AS, Angelman syndrome; CNS, central nervous system; mRNA, messenger RNA; UBE3A, ubiquitin protein ligase E3A protein; *UBE3A*, ubiquitin protein ligase E3A gene; *UBE3A-ATS*, ubiquitin protein ligase E3A antisense transcript gene.

1. Ionis Pharmaceuticals. Pipeline. Accessed February 6, 2025. https://www.ionis.com/science-and-innovation/pipeline/ 2. O'Geen H, et al. *Mol Ther*. 2023;31(4):1088-1105. 3. Milazzo C, et al. *JCI Insight*. 2021;6(15):e145991. 4. Meng L, et al. *Nature*. 2015;518(7539):409-412. 5. ClinicalTrials.gov identifier: NCT06914609. Accessed April 7, 2025. https://www.clinicaltrials.gov/study/NCT06914609/