IONIS' COMMITMENT TO NEUROLOGY[1-3,a,b]

	Investigational RNA-Targeted Therapeutic	Disease State	Gene/Target
Ionis-owned	Zilganersen	Alexander disease	*GFAP*
	Obudanersen[c]	Angelman syndrome	*UBE3A-ATS*
	ION717[d]	Prion disease	*PRNP*
	ION440	*MECP2* duplication syndrome	*MECP2*
	ION356	Pelizaeus-Merzbacher disease	*PLP1*
	ION464[e]	Multiple system atrophy and Parkinson's disease	*SNCA*
Ionis-Biogen	Tofersen	Superoxide dismutase 1 amyotrophic lateral sclerosis	*SOD1*
	IONIS-MAPT$_{Rx}$[e]	Alzheimer's disease	*TAU*
	Salanersen	Spinal muscular atrophy	*SMN2*
Ionis-Otsuka	Ulefnersen	Fused in sarcoma amyotrophic lateral sclerosis	*FUS*
Ionis-Roche	Tominersen	Huntington's disease	*HTT*
	ION993	Huntington's disease	*HTT-SNP*

Phase 1 | Phase 2 | Phase 3

[a]Content in the table subject to change pending updates to Ionis pipeline. [b]Safety and efficacy have not been evaluated by any regulatory authorities for the indications described. [c]The US Food and Drug Administration has granted both orphan drug designation and rare pediatric disease designation for its investigational drug obudanersen.[4] [d]This investigational antisense therapeutic is in a Phase 1/2a study.[1] [e]This investigational antisense therapeutic is in a Phase 1 study. The primary purpose of the study is the evaluation of the therapeutic's safety profile. It is listed here as Phase 2 because the therapeutic is being tested in patients and not healthy volunteers. This study may be categorized by partners or on regulatory sites, such as ClinicalTrials.gov, as a Phase 1 study.[1]

FUS, fused in sarcoma protein gene; *GFAP*, glial fibrillary acidic protein gene; *HTT*, huntingtin gene; *MECP2*, methyl-CpG-binding protein 2 gene (human); *PLP1*, proteolipid protein 1 gene; *PRNP*, prion protein gene; *SMN2*, survival of motor neuron 2 gene; *SNCA*, synuclein alpha gene; *SNP*, single nucleotide polymorphism; *SOD1*, superoxide dismutase 1 gene; *TAU*, tau protein gene; *UBE3A-ATS*, ubiquitin protein ligase E3A-antisense transcript gene.

1. Ionis Pharmaceuticals. Ionis Innovation Day. October 4, 2023. Accessed March 5, 2026. https://ir.ionis.com/static-files/8b71dc65-dad9-4368-9014-604c5b203ca1/ 2. Ionis Pharmaceuticals. Data on file. 3. Ionis Pharmaceuticals. Pipeline. Accessed March 5, 2026. https://www.ionis.com/science-and-innovation/pipeline 4. Ionis reports second quarter financial results and recent business achievements. US Securities and Exchange Commission. August 9, 2022. Accessed March 5, 2026. https://www.sec.gov/Archives/edgar/data/874015/000114036122028849/brhc10040582_ex99-1.htm

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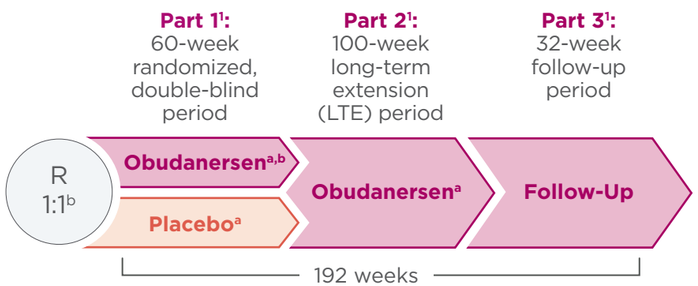
REVEAL: A Phase 3 Study to Evaluate the Efficacy and Safety of Intrathecally Administered Obudanersen in Children and Adults With Angelman Syndrome (AS)[1,2]

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, obudanersen, in individuals with AS.[1,2]



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

Select inclusion/exclusion criteria[1,c]:

- Males or females aged 2 to 50 years
- Clinical 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, imprinting center defects, mosaic findings, or clinically significant abnormalities that render them unsuitable for participation are excluded[e]

Key Clinical Endpoints[1,c]	
Primary Endpoint	Change from baseline to Week 52 in the Bayley-4 Expressive Communication subdomain raw score (without caregiver input) compared with placebo in cohort 1
Secondary Endpoints	Change from baseline to Week 52 in • Bayley-4 ° Cognition Subdomain raw score without caregiver input ° Fine Motor Subdomain raw score without caregiver input • 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 emerging T-score

For more study information, scan here:

All information is accurate as of 02/2026. For the most up-to-date information, please scan QR code.

Obudanersen 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]The study was initiated in 2024 with two dosing cohorts: 40 mg obudanersen and 80 mg obudanersen. Following additional review of data from the ongoing Phase 1/2 trial of obudanersen (HALOS), REVEAL was amended in December 2025 to its current form as a two-arm study: 80 mg obudanersen and placebo. Following the amendment, participants randomized to receive 40 mg obudanersen will be transitioned to receive 80 mg obudanersen.[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 study participation or completion.[1]

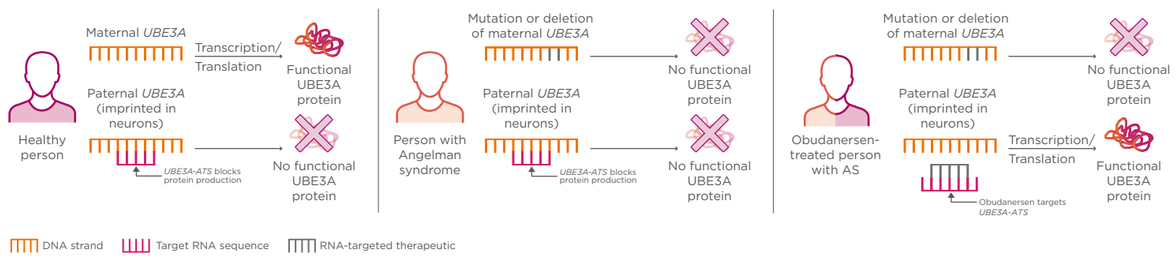
Bayley-4, Bayley Scales of Infant and Toddler Development-4; Q12W, every 12 weeks; R, randomized; *UBE3A*, ubiquitin protein ligase E3A gene.

1. ClinicalTrials.gov identifier: NCT06914609. Accessed March 5, 2026. https://www.clinicaltrials.gov/study/NCT06914609/ 2. Ionis Pharmaceuticals. Pipeline. Accessed March 5, 2026. https://www.ionis.com/science-and-innovation/pipeline

Obudanersen 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 Obudanersen-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 from 2 to 16 weeks after treatment.[4]

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

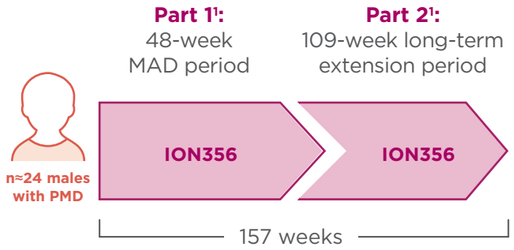
For more information or questions about participating sites, please contact us at **IonisION582-CS2@clinicaltrialmedia.com** or **844-285-7172**.[5]

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 March 5, 2026. 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 March 5, 2026. https://www.clinicaltrials.gov/study/NCT06914609/

Orbit Study: A Phase 1b Study to Evaluate the Safety, Pharmacokinetics (PK), and Pharmacodynamics of Intrathecally Administered ION356 in Patients With Pelizaeus-Merzbacher Disease (PMD)[1]

Study objective:
To evaluate the safety and tolerability of an investigational RNA-targeted therapeutic (RTT), ION356, in patients with PMD and *PLP1* duplication. This study will also evaluate PK, biomarkers, and outcomes relevant to PMD.[1,2]



This is a multicenter, MAD, multipart study of ION356. **Part 1** is the MAD treatment period, in which patients will receive ION356 at multiple ascending doses for 48 weeks. This will be followed by **Part 2**, a 109-week long-term extension period. Multiple dosing cohorts will be evaluated in the study.[1,2]

Select inclusion/exclusion criteria[1]:

- Diagnosis of PMD with genetic confirmation of *PLP1* gene duplication[a]
- Clinical phenotype and brain imaging consistent with a diagnosis of PMD
- Males aged 2 to 17 years[b]
- Persons with clinically significant abnormalities rendering them unsuitable for participation are excluded[c]

Table: Key Clinical Endpoints[1,2,d]

Primary Endpoints	Incidence of treatment-emergent adverse events and serious treatment-emergent adverse events from Day 1 to final study visit Change from baseline over the course of the study in: • Laboratory assessments • Neurological exam and vital signs • Electrocardiography • Concomitant medication use
Secondary Endpoints	Characterization of the CSF and plasma PK of ascending dose levels of multiple intrathecal administrations of ION356

For more study information, scan here:

All information is accurate as of 02/2026. For the most up-to-date information, please scan QR code.

ION356 has not been evaluated for safety and efficacy by any regulatory authorities and is not indicated for the treatment of any disease.

[a]Patients with >2 copies of *PLP1* are excluded.[1] [b]Patients can have a trial partner (parent, caregiver, or other).[1] [c]Abnormalities include, but are not limited to, obstructive hydrocephalus and known brain or spinal disease or previous spinal surgery that would interfere with the lumbar puncture process, CSF circulation, or safety assessment.[1] [d]This is not an exhaustive list.
CSF, cerebrospinal fluid; MAD, multiple ascending dose; *PLP1*, proteolipid protein 1 gene.
1. ClinicalTrials.gov identifier: NCT06150716. Accessed March 5, 2026. https://clinicaltrials.gov/study/NCT06150716/ 2. Ionis Pharmaceuticals. Data on file.

ION356 Is an Investigational RNA-Targeted Therapeutic (RTT) Designed to Reduce CNS Expression of *PLP1*[1-4]

Proposed ION356-Mediated Downregulation of *PLP1*[1-4]

ION356 is administered directly to the CNS via lumbar intrathecal bolus injection[4]

ION356 has not been evaluated for safety and efficacy by any regulatory authorities and is not indicated for the treatment of any disease.

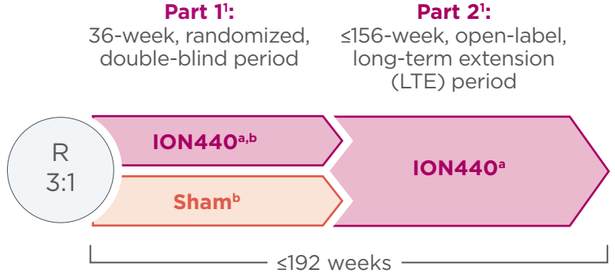
For more information or questions about participating sites, please contact us at **IonisPelizaeusMerzbacherStudy2@clinicaltrialmedia.com** or **(844) 387-9520**.[4]

CNS, central nervous system; dsDNA, double-stranded DNA; mRNA, messenger RNA; PLP1, proteolipid protein 1; *PLP1*, proteolipid protein 1 gene.
1. Bennett CF, et al. *Annu Rev Pharmacol Toxicol*. 2021;61:831-852. 2. Dhuri K, et al. *J Clin Med*. 2020;9(6):2004. 3. Ionis Pharmaceuticals. Data on file.
4. ClinicalTrials.gov identifier: NCT06150716. Accessed March 5, 2026. https://clinicaltrials.gov/study/NCT06150716/

ATTUNE: A Phase 1/2 Study to Evaluate the Safety, Tolerability, Pharmacokinetics (PK), and Pharmacodynamics (PD) of Intrathecally Administered ION440 in Patients With *MECP2* Duplication Syndrome (MDS)[1]

The Phase 1/2, randomized, double-blind, sham-controlled, multiple ascending dose clinical trial is currently underway[1]

Study objective[1,2]:
To evaluate the safety and tolerability of an investigational RNA-targeted antisense therapeutic, ION440, in patients with MDS. This study will evaluate adverse events, PK, PD, and outcomes relevant to MDS.



This is a multicenter, two-part study of ION440. **Part 1** consists of patients who will be randomized 3:1 to receive ION440 or sham for a 36-week period.[b] This will be followed by **Part 2**, an open-label LTE period during which patients who complete Part 1 will receive ION440 for up to approximately 156 weeks. Multiple dosing cohorts will be evaluated in the study.[1]

Select inclusion/exclusion criteria[1,c]:

- Males aged ≥2 to ≤65 years[b]
- Documented diagnosis of MDS and genetic confirmation of *MECP2* duplication
- Patients with clinically significant abnormalities rendering them unsuitable for participation are excluded[d]

For more study information, scan here:

All information is accurate as of 02/2026. For the most up-to-date information, please scan QR code.

Key Clinical Endpoints[1,c]	
Primary Endpoints	Number of patients with treatment-emergent adverse events from baseline up to approximately 36 weeks (Part 1) or 192 weeks (Part 2)
	Clinically significant change from baseline up to approximately 36 weeks (Part 1) or 192 weeks (Part 2) in • Vital signs, physical and neurological examination findings • Laboratory assessments • Electrocardiogram
Secondary Endpoints	Characterization of the PK of ION440 in the CSF and plasma
	Predose and postdose up to Week 36 • Maximum observed concentration of ION440 in plasma • Area under the concentration-time curve of ION440 in plasma • Plasma terminal elimination half-life • Plasma concentration
	Up to approximately 192 weeks • Trough concentration in plasma and CSF

ION440 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]Each cohort will be divided into two subcohorts based on participant age (A: ≥8 to ≤65 years old or B: 2 to 7 years old, inclusive) at time of informed consent.[1] [c]This is not an exhaustive list. [d]These include, but are not limited to, known brain or spinal disease that would interfere with the lumbar puncture procedure or CSF circulation; presence of other factors that would affect the safety of the lumbar puncture procedure; any concomitant disease or condition that, in the opinion of the investigator, makes the patient unsuitable for enrollment, could interfere with the conduct of the study, or that would pose an unacceptable risk to the patient in the study.[1]
CSF, cerebrospinal fluid; *MECP2*, methyl-CpG-binding protein 2 gene (human); R, randomized.
1. ClinicalTrials.gov identifier: NCT06430385. Accessed March 5, 2026. https://www.clinicaltrials.gov/study/NCT06430385/ 2. Ionis Pharmaceuticals. Data on file.

ION440 Is an Investigational RNA-Targeted Therapeutic (RTT) Designed to Reduce CNS Expression of *MECP2*[1]

ATTUNE

Proposed ION440-Mediated Downregulation of *MECP2*[1-5]

MECP2-targeting antisense RTT administration in animal models reduced MeCP2 levels and reduced expression of MeCP2-regulated genes in a dose-dependent manner.[2]

Preclinical animal models of MDS have also demonstrated that RTT-mediated suppression of MeCP2 rescued behavioral impairments, reduced epileptiform activity, and reduced behavioral seizures.[3]

ION440 has not been evaluated for safety and efficacy by any regulatory authorities and is not indicated for the treatment of any disease.

For more information or questions about participating sites, please contact us at **IonisMECP2study@clinicaltrialmedia.com** or **844-779-1497**.[6]

CNS, central nervous system; dsDNA, double-stranded DNA; MDS, *MECP2* duplication syndrome; MeCP2, methyl-CpG-binding protein 2; *MECP2*, methyl-CpG-binding protein 2 gene (human); mRNA, messenger RNA.
1. Ionis Pharmaceuticals. Data on file. 2. Shao Y, et al. *Sci Transl Med*. 2021;13(583):eaaz7785. 3. Sztainberg Y, et al. *Nature*. 2015;528(7580):123-126. 4. Bennett CF, et al. *Annu Rev Pharmacol Toxicol*. 2021;61:831-852. 5. Bajan S, Hutvagner G. *Cells*. 2020;9(1):137. 6. ClinicalTrials.gov identifier: NCT06430385. Accessed March 5, 2026. https://www.clinicaltrials.gov/study/NCT06430385/