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

	Investigational RNA-Targeted Therapeutic	Disease State	Gene/Target	Phase 1	Phase 2	Phase 3
Ionis-owned	Zilganersen	Alexander disease	*GFAP*			
	ION582[c]	Angelman syndrome	*UBE3A-ATS*			
	ION269[d]	Alzheimer's disease in Down syndrome	*APP*			
	ION717[e]	Prion disease	*PRNP*			
	ION440	*MECP2* duplication syndrome	*MECP2*			
	ION356	Pelizaeus-Merzbacher disease	*PLP1*			
	ION859[f]	Parkinson's disease	*LRRK2*			
	ION464[f]	Multiple system atrophy and Parkinson's disease	*SNCA*			
Ionis-Biogen	Tofersen	Superoxide dismutase 1 amyotrophic lateral sclerosis	*SOD1*			
	IONIS-MAPT$_{Rx}$	Alzheimer's disease	*TAU*			
	ION306	Spinal muscular atrophy	*SMN2*			
Ionis-Otsuka	Ulefnersen	Fused in sarcoma amyotrophic lateral sclerosis	*FUS*			
Ionis-Roche	Tominersen	Huntington's disease	*HTT*			

[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 ION582.[4] [d]This investigational antisense oligonucleotide therapeutic is in a Phase 1b study. It is listed here in Phase 2 because the therapeutic is being tested in people living with Down syndrome.[3] [e]This investigational antisense therapeutic is in a Phase 1/2a study.[3] [f]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 in 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.[3]
MECP2, methyl-CpG-binding protein 2 gene (human).

1. Ionis Pharmaceuticals. Ionis Innovation Day. October 4, 2023. Accessed January 29, 2025. https://ir.ionis.com/static-files/8b71dc65-dad9-4368-9014-604c5b203ca1/ 2. Ionis Pharmaceuticals. Data on file. 3. Ionis Pharmaceuticals. The Ionis antisense pipeline. Accessed January 29, 2025. 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 January 29, 2025. https://www.sec.gov/Archives/edgar/data/874015/000114036122028849/brhc10040582_ex99-1.htm

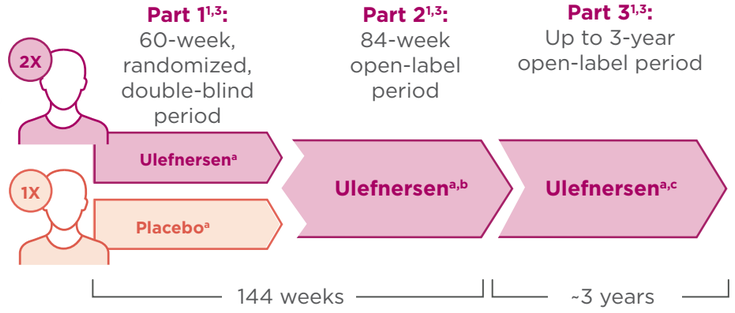
TABLE OF CONTENTS

IONIS®

The FUSION Study Is Evaluating Ulefnersen, an Investigational RNA-Targeted Therapeutic (RTT), for People With FUS-ALS[1-3]

The Phase 1-3, double-blind, placebo-controlled clinical trial is currently underway[1,2]

Study objective:
To determine if an investigational RNA-targeted antisense therapeutic, ulefnersen, is safe and capable of halting, reversing, or slowing deterioration based on clinical functioning and biomarkers in people with FUS-ALS.[1-3]



This is a multicenter, three-part study of ulefnersen. **Part 1** will consist of participants who will be randomized in a 2:1 ratio to receive a multidose regimen of ulefnersen or placebo for a period of 60 weeks, followed by **Part 2**, which will be an open-label period where all participants will receive ulefnersen for a period of 84 weeks. Participants may continue to receive ulefnersen in **Part 3.**[1,3]

Select inclusion/exclusion criteria[1,d]:

- People aged ≥10 years with signs or symptoms consistent with ALS
- Confirmed genetic mutation in *FUS*[e]
- Upright SVC[f] ≥50% of predicted value or if SVC is <50%[g] of predicted value
- People who require permanent ventilation[h] and/or tracheostomy are excluded
- People who have any known ALS-associated mutations, other than *FUS,* are excluded

Table: Key Clinical Endpoints[1]

Primary Endpoint	Change From Baseline (Day 1) Through Study Day 505 in Part 1 in Functional Impairment[i]
Secondary Endpoints[j]	Change From Baseline in ALSSQOL-R Change From Baseline in In-Clinic ALSFRS-R Survival and Ventilation Assistance-Free Survival (VAFS) Change From Baseline in In-Clinic SVC Change From Baseline in HHD Change From Baseline in CSF NfL Concentration Change from Baseline in FUS Concentration in Cerebrospinal Fluid (CSF) to Day 505

For more study information scan here:

All information accurate as of 01/2025, for most updated information please scan QR code.

Ulefnersen 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]Participants who complete Part 2 will have the opportunity to enroll in Part 3, an open-label extension with continued access to ulefnersen and monitoring until ulefnersen receives marketing authorization or its development is discontinued.[1] [c]Participants may continue to receive open-label ulefnersen for up to 3 additional years or until ulefnersen becomes commercially available or until the sponsor discontinues the ulefnersen development program.[1] [d]This is not an exhaustive list. [e]By a certified, CE-marked, or equivalent testing laboratory, mutations must be reviewed and approved by a variant classification committee.[1] [f]As adjusted for sex, age, and height.[1] [g]Must be 10 to 30 years of age (inclusive) at the time of informed consent AND had ALS symptom onset within 12 months before the time of informed consent[1] [h]More than 22 hours of mechanical ventilation (invasive or noninvasive) per day for >21 consecutive days.[1] [i]Functional impairment to be measured by joint rank analysis of the combined assessment of function and survival.[1] [j]All secondary endpoints are measured up to Day 505 from baseline.[1]

ALS, amyotrophic lateral sclerosis; ALSFRS-R, Revised Amyotrophic Lateral Sclerosis Functional Rating Scale; ALSSQOL-R, Revised Amyotrophic Lateral Sclerosis Specific Quality of Life; CSF, cerebrospinal fluid; FUS, fused in sarcoma protein; *FUS*, fused in sarcoma gene; FUS-ALS, fused in sarcoma amyotrophic lateral sclerosis; HHD, handheld dynamometry; NfL, neurofilament light chain; SVC, slow vital capacity.

1. ClinicalTrials.gov identifier: NCT04768972. Accessed January 29, 2025. https://clinicaltrials.gov/study/NCT04768972/ 2. Ionis Pharmaceuticals. Data on file. 3. Ionis Pharmaceuticals. The Ionis antisense pipeline. Accessed January 29, 2025. https://www.ionis.com/science-and-innovation/pipeline/

Ulefnersen Is an Investigational RNA-Targeted Therapeutic (RTT) That Has Been Designed to Reduce CNS Expression of *FUS*[1-4]

FUSION

Proposed Ulefnersen-Mediated Downregulation of *FUS*[1-4]

Ulefnersen lowered levels of wild-type and mutant FUS in the CNS, which resulted in a marked reduction in the burden of FUS aggregates, a pathological hallmark of the disease, in animal models and a compassionate use authorization in a single human patient.[4]

Ulefnersen 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 **ionisNCT04768972study@clinicaltrialmedia.com** or **844-421-0104**.[5]

CNS, central nervous system; dsDNA, double-stranded DNA; *FUS*, fused in sarcoma gene; FUS, fused in sarcoma protein; mRNA, messenger RNA.

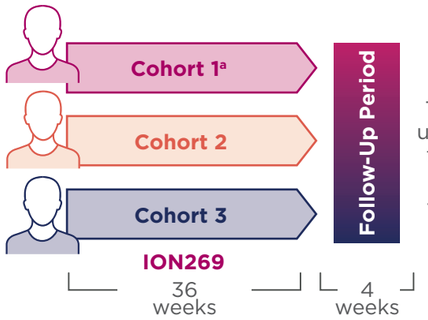
1. Bennett CF, et al. *Annu Rev Pharmacol Toxicol*. 2021;61:831-852. 2. Ionis Pharmaceuticals. The Ionis antisense pipeline. Accessed January 29, 2025. https://www.ionis.com/science-and-innovation/pipeline/ 3. Bajan S, Hutvagner G. *Cells*. 2020;9(1):137. 4. Korobeynikov VA, et al. *Nat Med*. 2022;28(1):104-116. 5. ClinicalTrials.gov identifier: NCT04768972. Accessed January 29, 2025. https://clinicaltrials.gov/study/NCT04768972/

HERO: A Study to Evaluate the Safety, Tolerability, and Pharmacokinetics (PK) and Pharmacodynamics (PD) of ION269 in Participants With Down Syndrome (DS) at Risk for Alzheimer's Disease (AD)

The Phase 1b, multicenter, open-label, single ascending dose (SAD) clinical trial is currently underway

Study objective:

To evaluate the safety and tolerability of an investigational RNA-targeted antisense therapeutic, ION269, in adults with Down syndrome with evidence of brain amyloid positivity. This study will evaluate PK, PD, safety, and tolerability.



Study Design
Three cohorts will undergo a 36-week treatment period, followed by a 4-week follow-up period

This is a multicenter, open-label, SAD study of ION269. Participants will be examined in three separate cohorts and will receive a single dose of the study drug administered as an intrathecal (IT) injection during the 36-week treatment period, followed by a 4-week follow-up period.

Select inclusion/exclusion criteria:

- Has a reliable study partner[b]
- Has a diagnosis of Down syndrome and has an intelligence quotient (IQ) ≥45
- Has evidence of amyloid pathology on amyloid-positron emission tomography (PET) scan
- Must be cognitively stable
- Persons with any unstable medical condition[c] or unstable psychiatric illness will be excluded[d]
- Persons with any contraindications to having a brain MRI will be excluded

For more study information scan here:

All information accurate as of 01/2025, for most updated information please scan QR code.

Primary Endpoints

- Number of Participants With Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)
- Number of Participants With Change from Baseline in Laboratory Assessments
- Number of Participants With Change from Baseline in Cerebrospinal fluid (CSF) Safety Laboratory Assessments
- Number of Participants With Change From Baseline in Vital Signs
- Number of Participants With Change From Baseline in Weight
- Number of Participants With Change From Baseline in Electrocardiogram (ECG)
- Number of Participants With Change From Baseline in Suicide Risk Measured by Columbia Suicide Severity Rating Scale [C-SSRS] Child Version
- Number of Participants With Change From Baseline in Physical and Neurological Examination Findings

Secondary Endpoints

- CSF Concentrations of ION269
- Area Under the Plasma Concentration-time Curve (AUC) of ION269 From Time 0 to Time of Last Measurable Concentration
- Maximum Observed Plasma Concentration (Cmax) of ION269
- Time to reach Cmax (Tmax) of ION269
- Change From Baseline in Concentration of CSF Soluble Amyloid Precursor Protein Alpha (sAPPα)
- Change From Baseline in Concentration of CSF Soluble Amyloid Precursor Protein Beta (sAPPβ)

ION269 has not been evaluated for safety and efficacy by any regulatory authorities and is not indicated for the treatment of any disease.

[a]United States only includes Cohort 1. [b]Defined as a parent, sibling, or caregiver ≥21 years of age, who has known the participant for >6 months (ie, a reliable and competent individual with a close relationship with the participant) and is capable of providing accurate information about the participant's history, can attend all scheduled study visits and provide feedback regarding the participant's symptoms and performance as described in the protocol, and can comply with all study requirements and activities. [c]Defined as an unstable medical condition likely to hamper the evaluation of safety and/or efficacy of the study drug (eg, moderate or severe untreated obstructive sleep apnea, medical history of clinically significant B12 or folate deficiency that is currently uncontrolled, clinically significant abnormalities of thyroid function, stroke, or other cerebrovascular conditions) as per Investigator's judgment. [d]Defined as unstable psychiatric illness, including psychosis, or untreated major depression within 90 days before screening, as determined by the Investigator.
MRI, magnetic resonance imaging.
ClinicalTrials.gov identifier: NCT06673069. Accessed January 12, 2025. https://www.clinicaltrials.gov/study/NCT06673069/

ION269 Is an Investigational RNA-Targeted Therapeutic (RTT) Designed to Reduce Expression of *APP*[1-5]

HERO

APP gene overexpression is strongly associated with Alzheimer's disease (AD) pathogenesis[1,6]

Individuals with Down syndrome have three copies of the *APP* gene, which leads to significantly elevated levels of amyloid-β (Aβ) peptide in the brain, increasing risk of AD in these individuals[1,3,7]

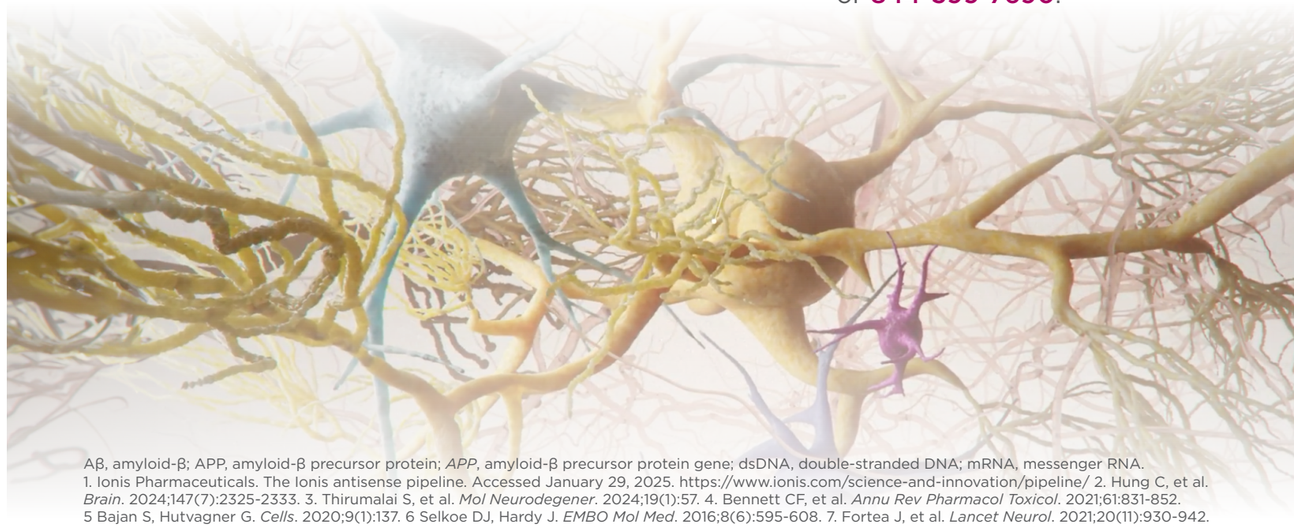
Proposed ION269-Mediated Downregulation of *APP*[1-5]

ION269 RTT is designed to reduce expression of *APP* mRNA and APP protein, which may lead to downstream reductions in proteolytic products, such as Aβ

APP-targeting antisense RTT administration in mouse models of AD has shown a reduction in *APP* expression and improvement in cognition after administration of three doses[8]

ION269 has not been evaluated for safety and efficacy by any regulatory authorities and is not indicated for the treatment of any disease.

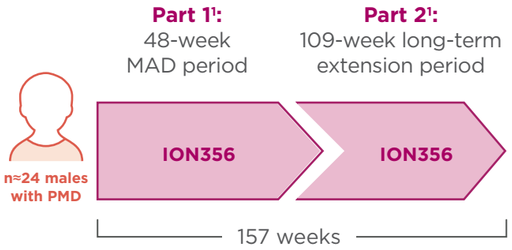
For more information or questions about participating sites, please contact us at **IonisHEROStudy@clinicaltrialmedia.com** or **844-599-7690**.[9]



Aβ, amyloid-β; APP, amyloid-β precursor protein; *APP*, amyloid-β precursor protein gene; dsDNA, double-stranded DNA; mRNA, messenger RNA.
1. Ionis Pharmaceuticals. The Ionis antisense pipeline. Accessed January 29, 2025. https://www.ionis.com/science-and-innovation/pipeline/ 2. Hung C, et al. *Brain*. 2024;147(7):2325-2333. 3. Thirumalai S, et al. *Mol Neurodegener*. 2024;19(1):57. 4. Bennett CF, et al. *Annu Rev Pharmacol Toxicol*. 2021;61:831-852. 5 Bajan S, Hutvagner G. *Cells*. 2020;9(1):137. 6 Selkoe DJ, Hardy J. *EMBO Mol Med*. 2016;8(6):595-608. 7. Fortea J, et al. *Lancet Neurol*. 2021;20(11):930-942. 8. Farr SA, et al. *J Alzheimers Dis*. 2014;40(4):1005-1016. 9. ClinicalTrials.gov identifier: NCT06673069. Accessed January 12, 2025. https://www.clinicaltrials.gov/study/NCT06673069/

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 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 dosages for 48 weeks. This is 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]

For more study information scan here:

All information accurate as of 01/2025, for most updated information please scan QR code.

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

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 January 9, 2025. https://clinicaltrials.gov/study/NCT06150716/ 2. Ionis Pharmaceuticals. Data on file.

ION356 Is an Investigational RNA-Targeted Therapeutic (RTT) That Has Been 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.

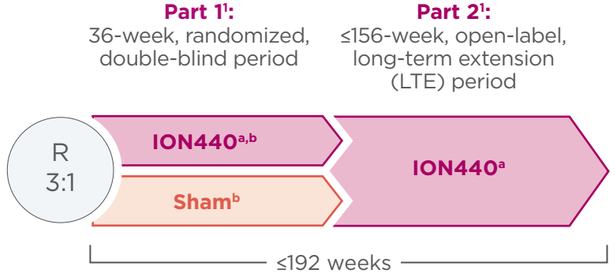
For more information or questions about participating sites, please contact us at **IonisPelizaeusMerzbacherStudy2@clinicaltrialmedia.com** or **(844) 387-9520**.[4]

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 January 9, 2025. 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 period of 36 weeks.[b] This is followed by **Part 2**, which is 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 accurate as of 01/2025, for most updated 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 October 24, 2024. 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 October 24, 2024. https://www.clinicaltrials.gov/study/NCT06430385/

NOTES

NOTES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THERAPEUTICS
for neurologic diseases
With a history of major breakthroughs in RNA-targeted technology, Ionis' robust pipeline is filled with potential.
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