

IONIS' COMMITMENT TO NEUROLOGY^{1-3,a,b}

Investigational RNA-Targeted Therapeutic	Disease State	Gene/Target	Phase 1	Phase 2	Phase 3
Ionis-owned	Obudanersen ^c	Angelman syndrome	<i>UBE3A-ATS</i>		
	ION717 ^d	Prion disease	<i>PRNP</i>		
	ION440	<i>MECP2</i> duplication syndrome	<i>MECP2</i>		
	ION356 ^e	Pelizaeus-Merzbacher disease	<i>PLP1</i>		
	ION464 ^f	Multiple system atrophy and Parkinson's disease	<i>SNCA</i>		
	ION337	Dravet syndrome	<i>SCN1A</i>		
	Tominersen	Huntington's disease	<i>HTT</i>		
Ionis-Biogen	Tofersen	Presymptomatic superoxide 1 dismutase amyotrophic lateral sclerosis	<i>SOD1</i>		
	Diranersen	Alzheimer's disease	<i>TAU</i>		
	Salanersen	Spinal muscular atrophy	<i>SMN2</i>		
Ionis-Otsuka	Ulefneresen	Fused in sarcoma amyotrophic lateral sclerosis	<i>FUS</i>		
Ionis-Roche	ION892	Alzheimer's disease	<i>APOE</i>		

^aContent in the table subject to change pending updates to Ionis pipeline. ^bSafety and efficacy have not been evaluated by any regulatory authorities for the indications described. ^cThe US Food and Drug Administration has granted both orphan drug designation and rare pediatric disease designation for its investigational drug obudanersen.⁴ ^dThis investigational antisense therapeutic is in a Phase 1/2a study. ^eThis investigational RNA-targeted medicine is in a Phase 1b study. It is listed here in Phase 2 because the medicine is being tested in patients and not healthy volunteers. ^fThis 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.

APOE, apolipoprotein E gene; *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; *SCN1A*, sodium voltage-gated channel alpha subunit 1 gene; *SMN2*, survival of motor neuron 2 gene; *SNCA*, synuclein alpha gene; *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 August 14, 2026. <https://ir.ionis.com/static-files/8b71dc65-dad9-4368-9014-604c5b203ca1/> 2. Ionis Pharmaceuticals. Data on file. 3. Ionis Pharmaceuticals. Pipeline. Accessed August 14, 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 August 14, 2026. <https://www.sec.gov/Archives/edgar/data/874015/000114036122028849/>

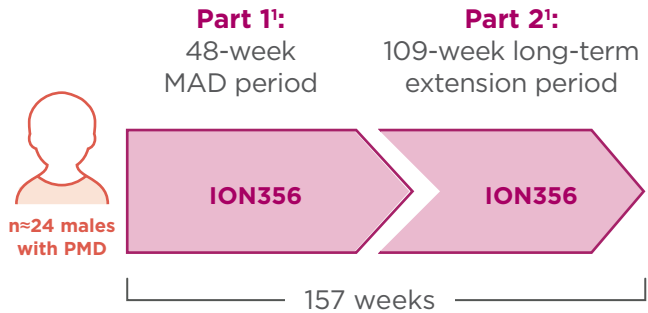
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Orbit Study: A Phase 1b Study to Evaluate the Safety, Pharmacokinetics (PK), and Pharmacodynamics of Intrathecally Administered ION356 in Patients With Pelizaeus-Merzbacher Disease (PMD)¹



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 criteria¹:

- 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 is accurate as of 09/01/2026. 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.

^aPatients with >2 copies of *PLP1* are excluded.¹ ^bPatients can have a trial partner (parent, caregiver, or other).¹ ^cAbnormalities 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 ^dThis is not an exhaustive list.
CSF, cerebrospinal fluid; MAD, multiple ascending dose; *PLP1*, proteolipid protein 1 gene.
1. ClinicalTrials.gov identifier: NCT06150716. Accessed August 14, 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 injection⁴



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



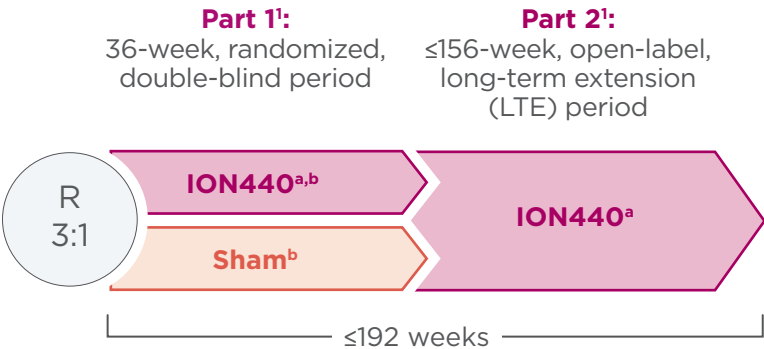
CNS, central nervous system; dsDNA, double-stranded DNA; mRNA, messenger RNA; PLP1, proteolipid protein 1; *PLP1*, proteolipid protein 1 gene.
1. Bennett CF, et al. *Annu Rev Pharmacol Toxicol*. 2021;61:831-852. 2. Dhuri K, et al. *J Clin Med*. 2020;9(6):2004. 3. Ionis Pharmaceuticals. Data on file.
4. ClinicalTrials.gov identifier: NCT06150716. Accessed August 14, 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 underway¹



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 09/01/2026. For the most up-to-date information, please scan QR code.



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

^aAdministered by lumbar intrathecal bolus injection.¹ ^bEach 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 ^cThis is not an exhaustive list of eligibility criteria. Additional protocol-defined inclusion and exclusion criteria apply. For complete eligibility information, please scan the QR code above.¹ ^dThese 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 August 14, 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



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

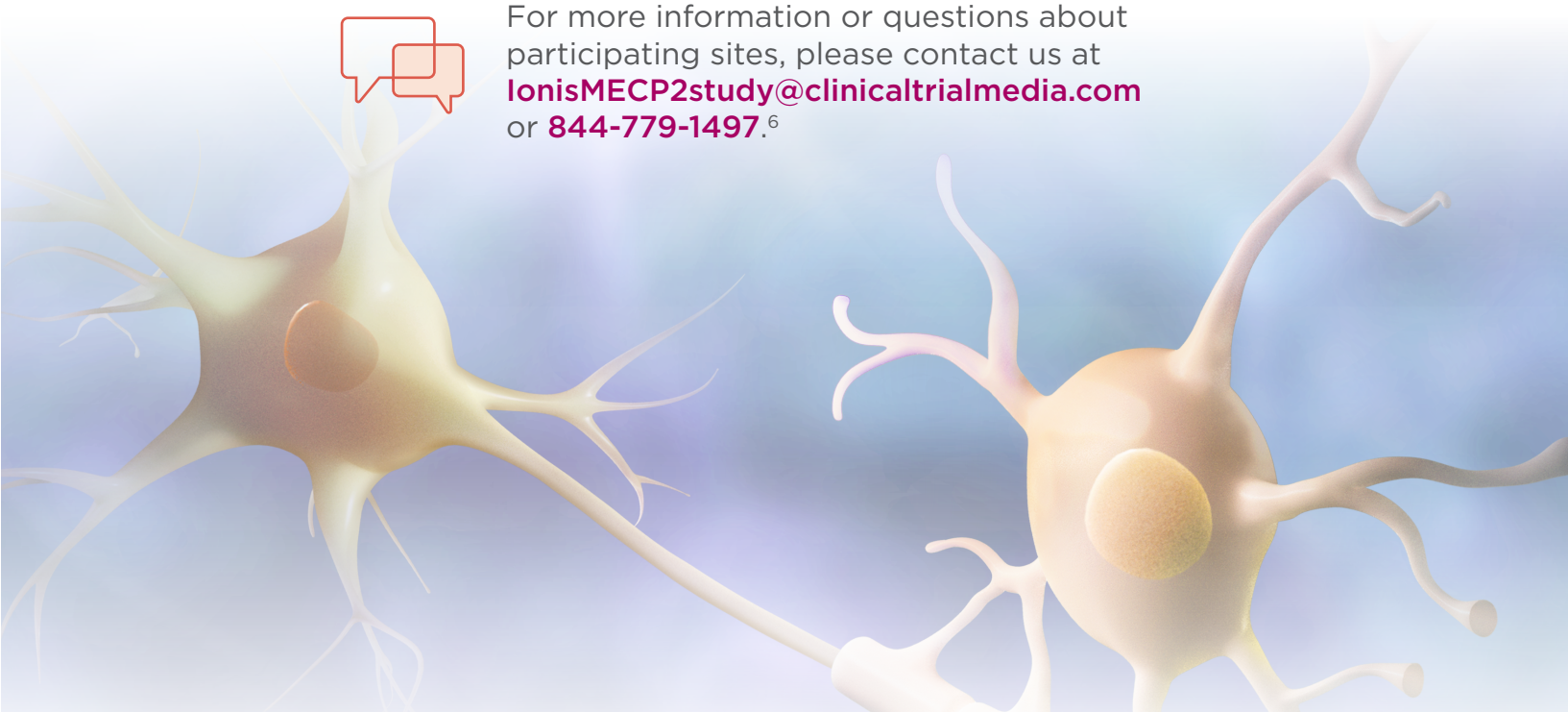
Preclinical animal models of MDS have also demonstrated that RTT-mediated suppression of MeCP2 rescued behavioral impairments, reduced epileptiform activity, and reduced behavioral seizures.³



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 August 14, 2026. <https://www.clinicaltrials.gov/study/NCT06430385>

HORIZON

HORIZON

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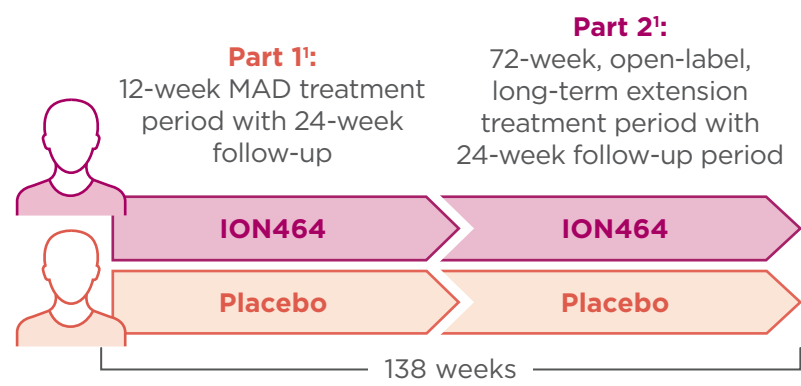
HORIZON Is a Phase 1b Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Intrathecally Administered ION464 in Adult Patients With Multiple System Atrophy (MSA)¹

The Phase 1/2, multiple-ascending-dose (MAD) clinical trial is currently underway¹



Study objectives^{1,2}:

To evaluate the safety and tolerability of an investigational RNA-targeted therapeutic (RTT), ION464, in patients with MSA. This study will evaluate pharmacodynamics, pharmacokinetics, and biomarkers relevant to MSA.



This is a multicenter, MAD, two-part study of ION464. In **Part 1**, participants will be randomized to receive a multidose regimen of ION464 or placebo. Patients who are eligible^a for **Part 2**, a long-term extension study, will receive ION464 or placebo for a period of 72 weeks with a 24-week post-treatment follow-up period.¹

Select inclusion/exclusion criteria¹:

- Patients aged 40 to 70 years
- Diagnosed with probable or possible MSA^b
- Patients with cognitive dysfunction are excluded^c
- Patients with known family history of ataxia or parkinsonism and known genetic cause of ataxia or parkinsonism are excluded

Table: Key Clinical Endpoints ¹	
Primary Endpoints	Number of participants with adverse events
	Number of participants with serious adverse events
Secondary Endpoints	Changes from baseline in cerebrospinal fluid (CSF) levels of total α-synuclein
	Serum concentration of ION464
	Area under the concentration-time curve from time zero to time of last measurable concentration of ION464
	Maximum observed concentration of ION464
	Time to reach maximum observed concentration of ION464

For more study information, scan here:



All information is accurate as of 09/01/2026. For the most up-to-date information, please scan QR code.



ION464 has not been evaluated for safety and efficacy by any regulatory authorities and is not indicated for the treatment of any disease.

^aParticipants who completed Part 1 of the study (including all planned doses of study drug, except those prematurely terminated from the study by the Sponsor due to tolerability or safety findings related to participation in the study) will be allowed to participate in Part 2 if they can provide consent or have a legally authorized representative, as appropriate and applicable, who can provide consent on their behalf to reconfirm their eligibility.²^bBased on Gilman's criteria, of either parkinsonian or cerebellar type.²^cDefined as having a Montreal Cognitive Assessment <25.¹

1. ClinicalTrials.gov. Accessed August 14, 2026. <https://www.clinicaltrials.gov/study/NCT04165486> 2. Ionis Pharmaceuticals. Data on file.

HORIZON

HORIZON

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ION464 Is an Investigational RNA-Targeted Therapeutic (RTT) Designed to Reduce CNS Expression of α-Synuclein (α-Syn)¹⁻⁴

Proposed ION464-Mediated Downregulation of α-Synuclein (SNCA)¹⁻⁴



SNCA-targeting antisense RTT administration in animal models decreased SNCA mRNA and α-syn throughout the cortex and midbrain and prevented progression of α-syn-mediated pathology.³

Preclinical studies demonstrated that SNCA-targeting antisense RTT administration reduced α-syn pathology, and restored dopaminergic cell numbers and motor function.³



ION464 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 IonisHORIZONStudy@clinicaltrialmedia.com or (844) 748-5844.⁵

CNS, central nervous system; dsDNA, double-stranded DNA; mRNA, messenger RNA; SNCA, synuclein alpha gene.

1. Ionis Pharmaceuticals. Pipeline. Accessed August 14, 2026. <https://www.ionis.com/science-and-innovation/pipeline>

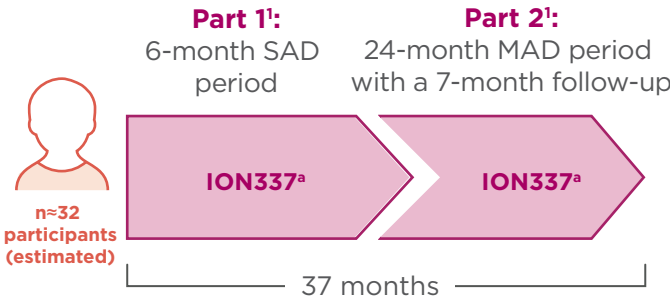
2. Dhuri K, et al. *J Clin Med*. 2020;9(6):2004. 3. Cole TA, et al. *JCI Insight*. 2021;6(5):e135633. 4. Bennett CF, et al. *Annu Rev Pharmacol Toxicol*. 2021; 61:831-852. 5. ClinicalTrials.gov. Accessed August 14, 2026. <https://www.clinicaltrials.gov/study/NCT04165486>

ASCEND: A Phase 1/2 Open-Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics (PK), and Pharmacodynamics (PD) of Intrathecally Administered ION337 in Patients With Dravet Syndrome (DS)¹



Study objective:

To evaluate the safety and tolerability of the investigational RNA-targeted therapeutic (RTT) ION337 in patients with DS. The study will also evaluate PK, PD, biomarkers, and clinical outcomes relevant to DS.¹



This is a multicenter, open-label, multipart study of ION337. **Part 1** is the single-ascending-dose treatment period, in which patients will receive a single dose of ION337 and be monitored over 6 months. This will be followed by **Part 2**, a 24-month multiple-ascending-dose treatment period in which patients who complete Part 1 will receive multiple doses of ION337. The study will conclude with a 7-month safety follow-up period. Up to 4 dose levels will be evaluated in the study within distinct cohorts.¹

Select inclusion/exclusion criteria^{1,b:}

- Children aged ≥2 to ≤12 years
- Documented diagnosis of DS
- Confirmed pathogenic or likely pathogenic *SCN1A* variant
- Persons with clinically significant abnormalities rendering them unsuitable for participation are excluded^c

Table: Key Clinical Endpoints^{1,d}

Primary Endpoints

Number of participants with treatment-emergent adverse events and serious adverse events

Change from baseline over the course of the study in:

- Laboratory assessments
- Vital signs
- Electrocardiograms (ECGs)
- Physical and neurological examinations
- Columbia-Suicide Severity Rating Scale (C-SSRS)

Secondary Endpoints

- Plasma pharmacokinetics of ION337
- CSF exposure and concentration of ION337
- Percent change from baseline in 28-day normalized major motor seizure frequency

For more study information, scan here:



All information is accurate as of 09/01/2026. For the most up-to-date information, please scan QR code.



ION337 has not been evaluated for safety and efficacy by any regulatory authorities and is not indicated for the treatment of any disease.

^aAdministered by lumbar intrathecal bolus injection.¹ ^bThis is not an exhaustive list of eligibility criteria. Additional protocol-defined inclusion and exclusion criteria apply. For complete eligibility information, please scan the QR code above.¹ ^cThese 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; pathogenic or likely pathogenic variant in another gene that causes epilepsy.¹ ^dThis is not an exhaustive list.¹

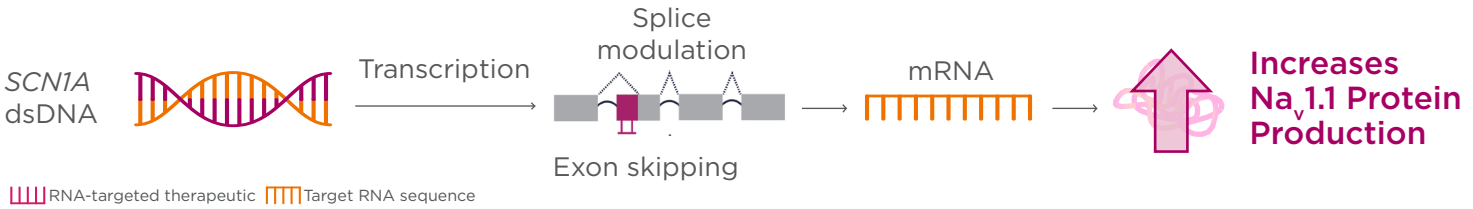
CSF, cerebrospinal fluid; MAD, multiple ascending dose; SAD, single ascending dose; *SCN1A*, sodium voltage-gated channel alpha subunit 1 gene.

1. ClinicalTrials.gov identifier: NCT07531745. Accessed August 14, 2026. <https://clinicaltrials.gov/study/NCT07531745>

ION337 Is an Investigational RNA-Targeted Therapeutic (RTT) Designed to Increase Production of the Na_v1.1 Protein^{1,2}



Proposed ION337-Mediated Upregulation of Na_v1.1^{1,2}



ION337 is an investigational RNA-targeted therapeutic designed to increase production of the Na_v1.1 protein, which is reduced in people with Dravet syndrome caused by certain *SCN1A* gene variants.¹



ION337 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 IonisDravetSyndrome@clinicaltrialmedia.com or (844) 867-4309.³

dsDNA, double-stranded DNA; mRNA, messenger RNA; *SCN1A*, sodium voltage-gated channel alpha subunit 1 gene.

1. Ionis doses first participant in Phase 1-2 ASCEND study of ION337 in Dravet syndrome. August 14, 2026. Accessed August 14, 2026. <https://ir.ionis.com/node/34931/pdf> 2. Dravet Syndrome Foundation. ASCEND trial launches for Dravet syndrome: what families should know. May 15, 2026. Accessed August 14, 2026. <https://dravetfoundation.org/ascend-trial-launches-for-dravet-syndrome-what-families-should-know/>

3. ClinicalTrials.gov identifier: NCT07531745. Accessed August 14, 2026. <https://clinicaltrials.gov/study/NCT07531745>

The image is a full-page background for a notebook. It features a light blue and white gradient. On the left side, there is a faint, stylized illustration of a neuron with a pink cell body and yellow branching processes. The word "NOTES" is written in bold, purple, uppercase letters at the top center. Below the title, the page is filled with horizontal grey lines for writing.

A background image of a neuron with a pink cell body and yellow branching processes, set against a light blue and white gradient. The word "NOTES" is written in bold purple capital letters at the top center. Below the title, there are 21 horizontal lines for writing, alternating between light blue and white backgrounds.



LEADING THE WAY IN RNA-TARGETED 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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