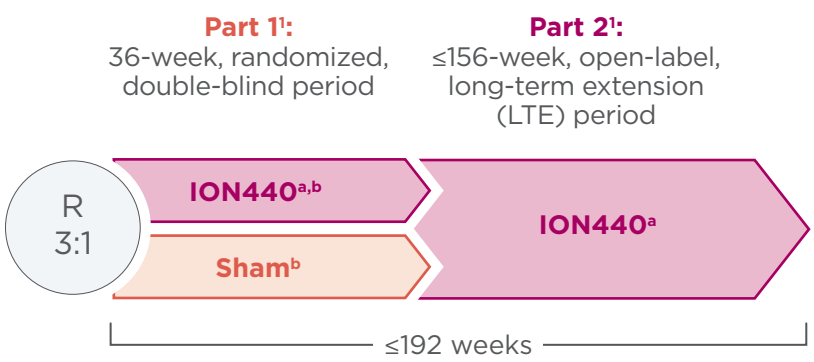
ATTUNE: A Phase 1-2 Study to Evaluate the Safety, Tolerability, Pharmacokinetics (PK), and Pharmacodynamics (PD) of Intrathecally (IT) Administered ION440 in Patients With *MECP2* Duplication Syndrome (MDS)[1]

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 medicine, 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 age ≥2 years to ≤65 years old[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:

Key Clinical Endpoints[1,c]

Primary Endpoints	Number of patients with treatment-emergent adverse events 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 cerebrospinal fluid (CSF) and plasma Predose and postdose up to Week 26 • 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 the US Food and Drug Administration 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]

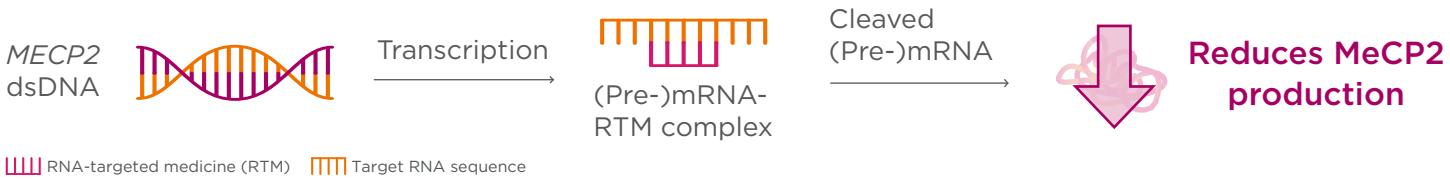
MECP2, methyl CpG binding protein-2 gene (human).

1. ClinicalTrials.gov identifier: NCT06430385. Accessed August 5, 2024. https://www.clinicaltrials.gov/study/NCT06430385/
2. Ionis Pharmaceuticals. Data on file.

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

ATTUNE

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



MECP2-targeting antisense RTM 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 RTM-mediated suppression of MeCP2 rescued behavioral impairments, reduced epileptiform activity, and reduced behavioral seizures.[3]

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

LEADING THE RNA REVOLUTION

in the treatment of neurologic disease

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

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 September 4, 2024. https://www.clinicaltrials.gov/study/NCT06430385/

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