Poster **#198**

DESIGN AND RATIONALE OF THE ATTUNE STUDY IN PATIENTS WITH MECP2 DUPLICATION SYNDROME

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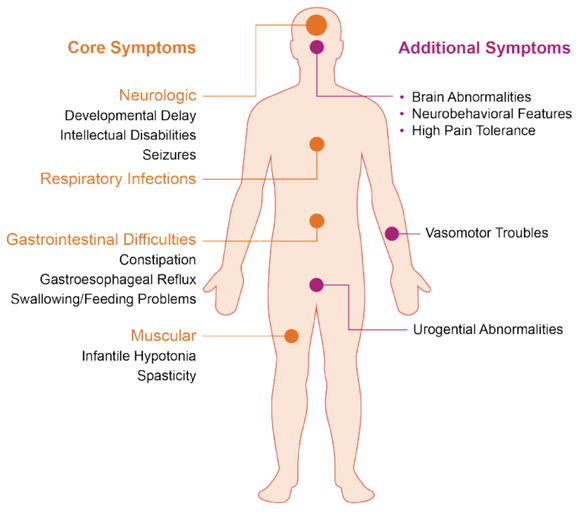
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OBJECTIVE

MECP2 Duplication Syndrome (MDS) is a rare X-linked disorder caused by overexpression of the MECP2 gene. Cardinal symptoms include infantile hypotonia, progressive spasticity, developmental delay in childhood resulting in severe to profound intellectual disability, minimal or absent speech, recurrent respiratory infections, gastrointestinal symptoms, development of refractory seizures, and shortened lifespan. ION440 is a modified antisense drug that selectively targets MeCP2 pre-mRNA. In preclinical MDS models, lowering MeCP2 resulted in a reduction in seizures, improvement in motor and social skills, and normalization of an aberrant gene expression profile. This study aims to evaluate safety, tolerability, and pharmacokinetics of ION440 in MDS patients.

METHODS

Introduction to MECP2 Duplication Syndrome



- **MECP2 Duplication Syndrome (MDS)** is a rare X-linked disorder affecting predominantly males, that is caused by overexpression of the chromosomal region (Xq28) containing the methyl CpG binding protein-2 (MECP2) gene
  - MeCP2 regulates brain development and maintains the function of mature neurons during adulthood
    - The overexpression of MECP2 protein can be due to a duplication [including translocation], or triplication of the *MeCP2* gene
    - Multiple factors have been associated with severity; more recently genetic variant structure (triplications and translocation), and age, have been linked to functional severity
- Symptoms may begin as early as birth and have overlap with other neurodevelopmental disorders
- MDS is a progressively debilitating disease, with significant burden on patients and caregivers, often regression is seen over time with age, and a shortened lifespan has been observed

Study Design

Phase 1-2 randomized, double-blind, sham-controlled, multiple-ascending dose (MAD) study to evaluate ION440 in male pediatric and adult participants with MDS and will be conducted in two parts:

Part 1: Multiple Ascending Dose (MAD) Study

Randomized in a 3:1 ratio to receive ION440 or sham for 36 weeks

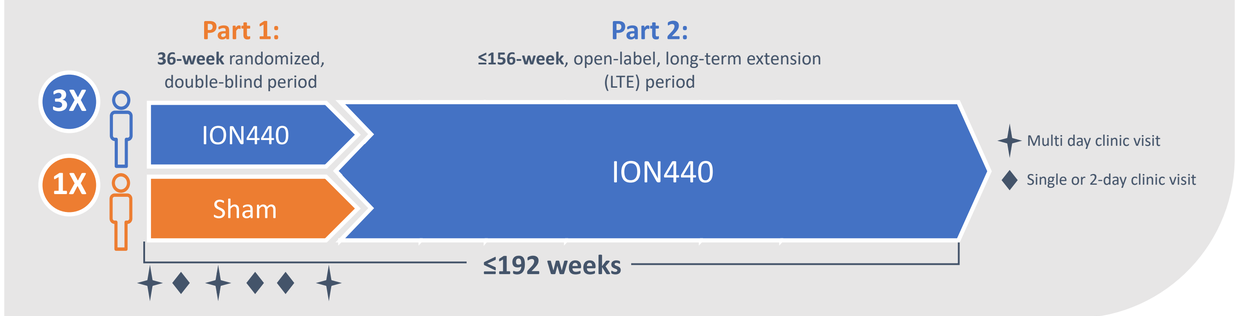
Part 2: Open Label Long-term Extension Study (LTE)

All patients will receive ION440 for up to 156 weeks

Multiple dose cohorts (Dose A, Dose B, and Dose C) will be evaluated in the study:

- **Sub cohort A**: ≥8 to ≤65 years of age
- **Sub cohort B:** ≥2 to ≤7 years of age
- *Dosing cohorts will be enrolled sequentially with sub cohort A initiating prior to sub cohort B. Dose escalation in sub cohort A is independent of sub cohort B*
- **Study Duration:**

  Part 1 (MAD): 36 Weeks **Part 2 (LTE): ~156 Weeks**



Study Objectives

Primary Safety Objective
To assess the safety and tolerability of ION440

Corresponding Endpoint

- Incidence of treatment-emergent adverse events (TEAEs) and clinically significant change from Baseline in vital signs, physical examination, laboratory assessments, and ECG over the course of the study.

Secondary Objectives PK
To characterize the pharmacokinetics of ION440 in the CSF and plasma

Corresponding Endpoint(s)

- Maximum plasma concentration (C_{max}), area under the concentration-time curve (AUC), elimination half-life ($t_{½}$), and trough (pre-dose) and post-treatment ION440 concentrations, where appropriate
- ION440 trough (pre-dose) and post-treatment concentrations in CSF

Key Exploratory Endpoints have been identified that look to establish early signs of clinical efficacy based on the most bothersome symptoms (seizures, motor skills and communication skills), and symptoms that have the biggest impact on quality of life and activities of daily living

Study Design and Rationale

The proposed study design allows for a thorough characterization of the effects of ION440 in patients and provide an opportunity to demonstrate effects on target engagement, disease biomarkers, and clinical measures

MAD and Seamless LTE: Detailed Safety, Tolerability, and PK Analysis + Early Look at Efficacy Signals

- Evaluation of safety and tolerability between initial and subsequent dose(s)
- Identification of potential safety issues and pharmacodynamic effects due to prolonged dosing and drug accumulation
- Follow-up period to fully characterize PK and PD effects, to optimize dosing interval in subsequent trials
- Seamless LTE provides prospect of direct benefit for all participants

Double Blind Sham Control: Increased Study Integrity and Reduced Bias

- Maintain scientific integrity given lack of published natural history (NH) [retrospective and prospective NH study ongoing - NCT06014541]
- Distinguish adverse events (AE) related to lumbar puncture (LP) [including sedation] from ION440 effects
- Caregiver/clinician-reported outcomes, are less likely to experience bias when double-blinded
- Ideal for informing endpoint selection, study design, and statistical analyses of subsequent clinical studies

Proposed Patient Population: Enhanced Genetic Understanding of MDS and Early Intervention

- Male MDS patients with “simple duplications” represent likely 50% of the patient population, and have approximately 2-fold MeCP2 compared to typically developing individuals which supports PK/PD modeling efforts and lays the foundation for evaluation in patients with complex structures and females with complex inheritance patterns and structures
- Part 1/MAD includes evaluation of patients down to 2 years old since earlier intervention may result in greater benefit

Key Inclusion Criteria

Inclusion Criteria for Part 1:

- Males age ≥ 2 years to ≤ 65 years old, depending on specific cohort and group, at the time of informed consent.
  - **Group A:** ≥ 8 to ≤ 65 years old
  - **Group B:** 2 to 7 years old, inclusive
- Participant has at least one parent or caregiver ≥ 18 years old capable of providing informed consent (signed and dated), and able to attend all scheduled study visits and provide feedback regarding the participant's symptoms and performance as described in the protocol, and able to comply with all study requirements and activities
- Participant has a documented diagnosis of MDS, with genetic confirmation of MECP2 duplication
- Is currently receiving stable doses of concomitant medications for at least 3 months prior to baseline. If recent changes (< 3 months stable) in medications, the participant may be allowed per Investigator judgment in consult with Sponsor Medical Monitor
- Able to complete all study procedures, measurements and visits and caregiver/participant has adequately supportive psychosocial circumstances, in the opinion of the Investigator

Inclusion Criteria for Part 2:

- Completed ION440-CS1, Part 1/MAD. Completers are defined as participants who received at least one dose of Study Drug and attended all study visits through Follow Up
- All inclusion criteria in Part 1/MAD apply (participants will not be required to undergo new Screening bloodwork)

For more information on inclusion and exclusion criteria, please visit clinicaltrials.gov

RESULTS & CONCLUSIONS

The ATTUNE study will investigate safety and tolerability of ION440 in patients who have MDS, a disease for which there are currently no treatment options beyond symptom management.

ATTUNE (NCT06430385) is a clinical study that is actively recruiting patients.

For more information on the ATTUNE study, please visit the clinicaltrials.gov listing (NCT06430385) or send inquiries to: IonisMECP2study@clinicaltrialmedia.com

For more information about participation in clinical trials, please visit https://ionistrials.com/

For more information about Ionis, please visit https://www.ionis.com/

ACKNOWLEDGEMENTS & REFERENCES

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