Poster #8

Prospective and Retrospective Observational/Non-interventional Study to Characterize Biomarkers and Disease Progression in Patients with MECP2 Duplication Syndrome (NH00006)

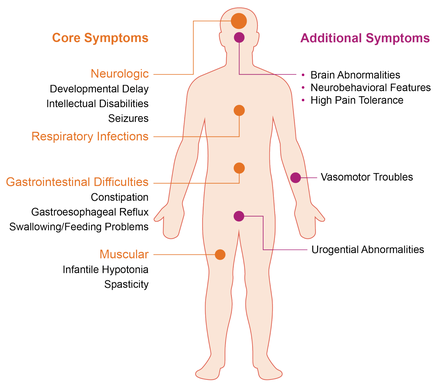
Christine Coquery[1], Aaron Yarlas[1], Davut Pehlivan[2], Eric Marsh[3], Jeffrey Neul[4], Sarika Peters[4], Bernhard Suter[2], David Lieberman[5], Holly Harris[2,6]

1. Ionis; 2. Baylor College of Medicine; 3. Children's Hospital of Philadelphia; 4. Vanderbilt University Medical Center; 5. Boston Children's Hospital; 6. Texas Children's Hospital

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INTRODUCTION

MECP2 DUPLICATION SYNDROME

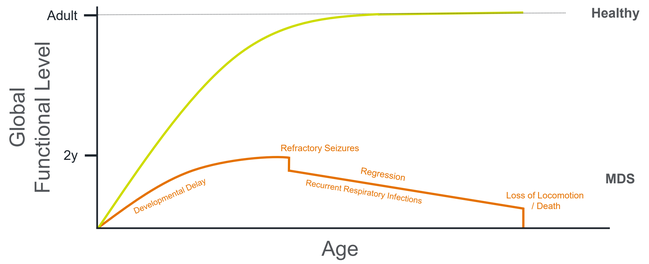


- MECP2 Duplication Syndrome (MDS) is a rare X-linked disorder affecting predominantly males, that is caused by overexpression of the chromosomal region (Xq28) containing the methyl CpG binding protein-2 (*MECP2*) gene
  - MeCP2 regulates brain development and maintains the function of mature neurons during adulthood
    - The overexpression of MeCP2 protein can be due to a duplication, translocation, or triplication of the *MECP2* gene
    - Duplication size, presence of specific duplication genes beyond *MECP2*, genetic variant structure (triplications and translocation), and age, have been linked to functional severity
- MDS is characterized by several debilitating cardinal symptoms including infantile hypotonia, progressive spasticity, intellectual disability, respiratory infections, gastrointestinal disorders, seizures, and motor and language delays
- 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

BACKGROUND & RATIONALE

ESTIMATED DISEASE COURSE OF MDS

Based on Existing Literature



MDS may present with a limited period of normal development (<12 months), entering into a phase of slow but steady growth (achieving up to a ~21 to 24 month developmental age equivalence which is variable across domains), followed by a plateau around age 4-5 years and regression around 6-7 years which generally coincides with seizure onset. A small proportion of patients do not experience seizures and tend to regress later in life.

- While the overall symptomology is established, there is a need to characterize MDS (and its progression) in key domains
  - Quantify symptomology with clinical scales longitudinally
  - Capture meaningful deficits within the disease
  - Assess clinical relevance of biomarker effects
- Metrics that can provide longitudinal, quantitative information, and potential prognostic factors that predict the rate of disease progression will add important information that can be used to support participant selection and stratification strategies as well as future clinical study design
- There are currently limited outcome measures validated in MDS. We identified both single domain and multi-domain outcome measures that may have utility in future clinical trials

STUDY DESIGN & OBJECTIVES

DESIGN

NH00006 (NCT06014541) is a multi-center, non-randomized, non-interventional prospective and retrospective study in participants with genetically-confirmed MDS who are able to complete study procedures, to be used in support of the clinical development of therapies for MDS.

~40 patients



Key Inclusion Criteria:

Male patients ≥1 month and ≤ 65 years of age

Diagnosis with genetic confirmation of *MECP2* duplication (or triplication)

Patients do not have any contraindications to undergo a lumbar puncture, sedation, or general anesthesia

OBJECTIVES

The study seeks to confirm the utility and clinical relevance of biomarkers for translational research and drug development in MDS

- A biomarker is a characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an intervention
- Biomarkers that may support translational research and drug development for MDS will fulfill one or more of the following criteria
  - A biomarker is a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions.
  - A biomarker is not an assessment of how a patient feels, functions, or survives but may be used for diagnostic, monitoring, predictive prognostic, safety, and pharmacodynamic evaluation purposes.
  - The study will measure both soluble and non-soluble biomarkers and evaluate correlations between changes in biomarkers and changes in clinical/caregiver reported outcomes over time. The biomarker is correlated with measures of disease severity (i.e., the current clinical picture)

The study seeks to characterize performance and changes in single domain and multiple domain outcome measures related to the known clinical presentation in MDS

- Characterize longitudinal changes in performance on clinical scales (clinician-reported measures of neurodevelopment and functioning) and caregiver-reported outcome assessments (communication, gastrointestinal, social-emotional-adaptive behavioral measures);
- Evaluate longitudinal changes in caregiver-reported health-related quality-of-life measures; and
- Assess the frequency, type, and severity of seizures over time
- Evaluate the content validity and psychometric properties of selected COAs to determine which are most appropriate and fit-for-purpose for capturing key outcomes in this patient population

MAPPING COA/PROCEDURE ASSESSMENTS TO CLINICAL PRESENTATION

Single and Multi Domain Approach

Developmental
Developmental delays observed in 100% of patients
- BSID-III
- Vineland-3
- ABC-2-C

Neurological
Seizures present in >50% of MDS patients
- EEG/ERP
- Seizure Diary
- Pupillometry

Communication
Low to no verbal communication seen in most MDS patients
- ORCA
- CSBS-DP

Quality of Life and Caregiver Burden
To assess both patient quality of life and caregiver impact
- QI-D Inventory Disability
- EQ-5D-Y
- RETT CIA
- MDS Caregiver Burden Scale
- WPAI-CG

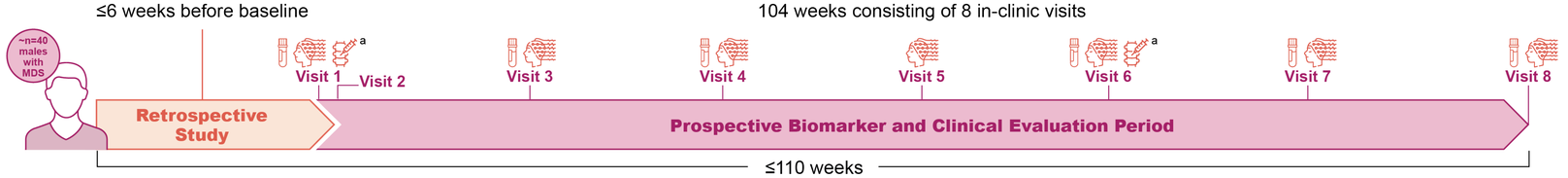
Multi-Domain/Other
Multi-domain assessments are needed to adequately categorize disease severity
- MDS CGI-C/S
- R-MBA
- GHS

Abbreviations: ABC-2-C – Aberrant Behavioral Checklist Second Edition Community; BSID-III – Bayley Scales of Infant and Toddler Development, Third Edition; CGI-C – clinical global impression – change; CGI-S – clinical global impression – severity; EEG – electroencephalogram; ERP – event related potentials; EQ-5D-Y – EuroQol five-dimensions questionnaire/youth; CSBS-DP – Communication and Symbolic Behavior Scales Developmental Profile; GHS – Gastrointestinal Health Questionnaire; ORCA – Observer Reported Communication Ability; QI-D – Quality of Life Inventory – Disability; RETT CIA – Rett Syndrome Caregiver Inventory Assessment; R-MBA – Revised Motor Behavioral Assessment; Vineland-3 – Vineland Adaptive Behavior Scales™, Third Edition; WPAI-CG – Work Productivity and Activity Impairment – Caregiver

Study Duration:
- approximately 110 weeks (Wks) including:
  - Screening (up to 6 Wks)
  - Prospective Period (104 Wks)

Screening Period[1,2]:
≤6 weeks before baseline

Prospective Period[1,2]:
104 weeks consisting of 8 in-clinic visits



Lumbar puncture | Quantitative electroencephalogram | Blood collection

[a]Participants will undergo cerebral spinal fluid collection at 2 timepoints. Participants will undergo the 2nd lumbar puncture based on their entry into the study as follows: Participants 1-10 (Visit 6), Participants 11-20 (Visit 5), Participants 21-30 (Visit 4), Participants 31-40 (Visit 3).

1. ClinicalTrials.gov. Accessed August 29, 2023. https://clinicaltrials.gov/ct2/show/NCT06014541/
2. Ionis Pharmaceuticals. Data on file.

CONCLUSIONS



- The NH00006 study is ongoing with enrollment expected to complete by the end of 2024 with study completion in 2026. The results from the study are anticipated to; confirm, in a second group of MDS patients, relevant target engagement, safety and disease biomarkers, establish longitudinal performance across single and multi-domain clinical trial relevant outcome measures, identify key stratification and covariate factors and facilitate enrollment and data interpretation for an upcoming interventional trial.
- For more information on the NH00006 study, please visit the clinicaltrials.gov listing (NCT06014541) or send inquiries to: ionisMDSNaturalHistorystudy@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/

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contact: CCoquery@ionis.com