A PROSPECTIVE, LONGITUDINAL STUDY OF POTENTIAL TREATMENT-RESPONSIVE BIOMARKERS AND CLINICAL OUTCOMES IN HUNTER SYNDROME

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The objective of this study is to identify and develop laboratory measurements and other tests that may help develop treatments for Hunter Syndrome and, potentially, related diseases. The information learned from this study may also help doctors,...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Metabolic and nutritional disorders congenital
Study type	Observational invasive

Summary

ID

NL-OMON55328

Source
ToetsingOnline

Brief title
DENA 208800_BIOMARKERS IN HUNTER SYNDROME

Condition

- Metabolic and nutritional disorders congenital

Synonym
Hunter syndrome, mucopolysaccharidosis type II (MPS II)

Research involving
Human

Sponsors and support

Primary sponsor: Denali Therapeutics Inc.

Source(s) of monetary or material Support: Denali

Intervention

Keyword: Biomarkers, Hunter syndrome

Outcome measures

Primary outcome

* To characterize the progression of adaptive behavior as measured by the Vineland Adaptive Behavior Scales (VABS)

* To characterize the progression of neurocognition as measured by the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III); Kaufman Assessment Battery for Children*, Second Edition (KABC-II); or Wechsler Intelligence Scale for Children*, Fifth Edition (WISC-V)

* To assess levels of potential disease-related or treatment-responsive biomarkers in blood, urine, and/or cerebrospinal fluid (CSF) samples from MPS II participants

Secondary outcome

The exploratory objectives of the study are as follows:

*To explore correlations between disease-related biomarkers and clinical measures of disease severity (e.g., function, cognition, and behavior)

*To characterize glycosaminoglycan (GAG) levels in serum and urine of MPS II participants

*To characterize GAG levels in the CSF of MPS II participants

Study description

Background summary

Early medical care is likely required to prevent the disabling damages to the brain seen in Hunters syndrome. Currently known biomarkers do not reliably predict disease severity, disease progression, and treatment response in Hunters syndrome, especially in younger children, and evaluation of new potential biomarkers is needed.

Study objective

The objective of this study is to identify and develop laboratory measurements and other tests that may help develop treatments for Hunter Syndrome and, potentially, related diseases. The information learned from this study may also help doctors, healthcare professionals and researchers understand more about your child*s condition and other people with Hunter Syndrome.
Some of the laboratory tests in this investigational study will be done to find out how Hunter Syndrome works in the body and to determine how your child*s body is managing Hunter Syndrome. These tests measure substances called biomarkers. The research being done in this study may determine how future therapies (medications and procedures) can work to help manage Hunter Syndrome. In this study, the biomarkers being measured can be found in blood, urine and cerebrospinal fluid (CSF), samples of which are planned to be collected during this trial .

Study design

This is a nonrandomized, prospective, observational study of patients diagnosed with MPS II, also known as Hunter syndrome. There are no experimental therapies in this study. The primary focus is to evaluate biomarkers and assess the clinical outcomes of disease in patients with MPS II, including the neuronopathic form of mucopolysaccharidosis type II (nMPS II),and the non-neuronopathic form of mucopolysaccharidosis type II (nnMPS II), that Biomarkers and their correlation to clinical progressiont may serve as markers of disease severity or treatment response, and thereby advance clinical trials of new MPS II therapeutics.

Documented diagnosis of MPS II is required for study entry in all parts of the study. This diagnosis will include genetic analysis (mutation analysis of the iduronate-2 sulfatase [IDS] gene) and biochemical assessment (e.g., IDS enzyme activity in plasma, white blood cells, or fibroblasts).

Before enrollment for Parts 3 and 4 begins,Part 1 of the study will have enrolled approximately 11 participant from 2 through 10 years of age who have MPS II and Part 2 of the study will have enrolled approximately 2 participants from 2 through 30 years of age who have MPS II.
Part 3 will enroll approximately 12 participants who are < 8 years of age at

screening and have nMPS II, and Part 4 will enroll approximately 12 participants aged 6 to < 17 years at screening who have nnMPS II.
In Part 1, biomarker sample collections will occur primarily in the first month of the study and at Month 6, and patients will be followed for up to 18 months, or until they enroll into Part 3 or 4 of the study or one of the planned treatment trials. In Parts 3 and 4, clinical outcome assessments and blood and urine biomarker sample collections will be performed, and participants will be followed for up to 24 months.

In Part 1, approximately 11participants aged 2 through 10 years who have MPS II will be enrolled, as follows:
*Approximately 5 (one-half) or more of enrolled patients will be aged 2 through 5 years.
*Approximately 3 (one-third) or more of all enrolled patients will have aneuronopathic phenotype.

In Part 2, Approximately 2 patients from 2 through 30 years of age who have MPS II will be enrolled; Part 2 will entail a single collection of urine, and blood. Clinical assessments are optional in Part 2 for patients aged 18 years or younger;
no clinical assessments are planned for patients older than 18 years.
Approximately 4 or more of enrolled patients in Part 2 will have a neuronopathic phenotype.

Part 1 and Part 2 will be conducted concurrently. until approval of Version 6 of the DNLI-E-0001 Protocol has been obtained from each site. After the amendment has been approved, no further participants will be enrolled in Part 1 or 2 of the study. Ongoing participants active in Part 1 at the time of approval have the option of being screened for Part 3 or 4 and switching to Part 3 or 4, if eligible. Otherwise, participants will complete the remaining Part 1 assessments per the schedule of assessments.

In Part 3, approximately 12 participants aged < 8 years at screening who have nMPS II will be enrolled as follows:
* At least 6 (or one-half) of the enrolled participants will be < 3 years of age at screening, including newborns.

In Part 4, approximately 12 participants aged 6 to < 17 years at screening who have nnMPS II will be enrolled as follows:
* At least 8 (or two-thirds) of the enrolled participants will be < 13 years of age at screening.

Study burden and risks

Patients age 19 to 30 years old; study participation will last for approximately 2 months. This time will include the screening period, visit Day 1 and safety follow-up. A visit will take about 3 to 4 hours.

Patients age 16 to 18 and agree to undergo optional assessments will take part in the study for up to approximately 5 months. This time will include the screening period, visit Day 1, additional, optional tests provided with agreement from you and at the discretion of the doctor, and the safety follow-up. The visits with optional assessments will take about 4 to 5 hours.

While being in this study, blood, urine, saliva (if required) and cerebrospinal fluid samples are taken. If required, approximately 1-2 mL of saliva will be collected. During the screening visit approximately 5 mL and during visit Day 1 approximately 10 mL of blood may be collected. If the entire study is completed, the total amount of blood collected will be approximately 15 mL. At the study visits where cerebrospinal fluid is collected, up to approximately 10 mL of cerebrospinal fluid may be collected during each lumbar puncture. If a CSF sample is provided and complications develop, it may be necessary to collect additional blood for safety purposes.

Some of the questions on the rating scales and questionnaires may seem personal. Patients may refuse to answer any of the questions.

Patients in the current study will not receive any additional medical therapy for MPS II, and, as such, are not expected to receive direct therapeutic benefit. However, they may benefit from participation in this study via the included assessments of health status and information that may be used to request educational, medical, or other services. For example, some patients will undergo neurocognitive evaluations, and the test results will be provided to the parent(s)/legally authorized representative (LAR), which may be used to determine and request additional educational services. Hearing loss is a common feature of MPS II; audiology assessments performed in this study will characterize patients* hearing performance, and the results may be used to plan treatments or interventions.

The risks of participation in the current study are primarily those associated with the study procedures, including blood draws. All procedures will be performed by medical staff with expertise in the care of MPS II patients.

Contacts

Public
Denali Therapeutics Inc.

Oyster Point Blvd. 161
South San Francisco CA 94080
US
Scientific

Denali Therapeutics Inc.

Oyster Point Blvd. 161
South San Francisco CA 94080
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)

Inclusion criteria

Part 1 and 2
Participants in Parts 1 and 2 must have a confirmed diagnosis of MPS II based on the following:
1) A documented mutation in the IDS gene, AND
2) Reduced IDS activity in plasma, WBCs, and/or skin fibroblasts consistent with MPS II (e.g., *10% of the lower limit of the normal range, based on the testing laboratory*s range)
For nMPS II subgroups in Parts 1 and 2participants will have a neuronopathic phenotype at the time of enrollment based on the following criteria:
* In addition to a diagnosis of MPS II, have a development quotient (DQ) <85 and/or a decline of at least 7.5 points in DQ, assessed at least 6 months apart, or have the same genetic mutation as a blood relative with confirmed nMPS II

Part 1
Participants in Part 1 must also meet the following criteria for study entry:
* Informed consent signed by the parent(s) or LAR and participant assent if required based on local regulations, IRB/IEC requirements, and patient age
* Aged 2 through 10 years at time of consent
* Participant and parent(s) or LAR are willing and able to comply with study

visits and study procedures
* Have the ability to comply with protocol requirements according to the investigator*s judgment

Part 2
Participants in Part 2 must also meet the following criteria for study entry:
* Consent:
o For minors: informed consent signed by the parent(s) or LAR and participant assent if required based on local regulations and patient age
o For nonminors: informed consent signed by the participant
* Aged 2 through 30 years at time of consent
* Participant and parent(s) or LAR are willing and able to comply with study visits and study procedures
* Have the ability to comply with protocol requirements according to the investigator*s judgment
* Scheduled to undergo CSF sampling for non-study-related medical reasons and participant or parent(s)/LAR consent to donate CSF for research purposes during that procedure.

Part 3
Participants in Part 3 must meet the following criteria for study entry:
* Have informed consent signed by the parent(s) or LAR and participant assent if required based on local regulations, IRB/IEC requirements, and participant age
* Be < 8 years of age at time of consent
* At least 6 (or one-half) of the participants enrolled must be < 3 years of age at screening
* Have a confirmed diagnosis of MPS II based on all of the following criteria:
* 1. Documented reduced IDS activity in plasma, WBCs, and/or skin fibroblasts consistent with MPS II (10% or less of the lower limit of the normal range, based on the testing laboratory*s range)
* 2. Elevated urine GAG levels consistent with MPS II diagnosis:
* a. At screening in standard-of-care ERT treatment-naïve participants
* b. Pretreatment in participants receiving standard-of-care ERT, if available by historical report
* 3. A documented likely pathogenic variant in the IDS gene, as determined by an independent external review panel
* *Have nMPS II based on at least one of the criteria (1, 2, or 3) below:
1. Have a large deletion(s) or rearrangement(s) in the IDS gene or other definitive mutation indicative of nMPS II, as determined by an independent external review panel
2. Have a DQ > 55 and < 85 at the baseline neurocognitive assessment and/or a documented decline of at least 7.5 points in DQ in the previous 6 to 18 months
3. Have the same IDS gene variant as a blood relative with confirmed nMPS II
* Participant and parent(s) or LAR are willing and able to comply with study

visits and study procedures.
* Have the ability to comply with protocol requirements according to the investigator*s judgment

Part 4
Participants in Part 4 must meet the following criteria for study entry:
* Have informed consent signed by the parent(s) or LAR and participant assent if required based on local regulations, IRB/IEC requirements, and participant age
* Be 6 to < 17 years of age at time of consent
* At least 8 (or two-thirds) of the participants enrolled must be < 13 years of age at screening
* Have a confirmed diagnosis of MPS II based on all of the following:
* 1. Documented reduced IDS activity in plasma, WBCs, and/or skin fibroblasts consistent with MPS II (10% or less of the lower limit of the normal range, based on the testing laboratory*s range)
* 2. Elevated urine GAG levels consistent with MPS II diagnosis:
At screening in standard-of-care ERT treatment-naïve participants
b. Pretreatment in participants receiving standard-of-care ERT, if available by historical report
3. A documented likely pathogenic variant in the IDS gene, as determined by an independent external review panel
* Have nnMPS II based on both of the following:
1. Do not have a large deletion(s) or rearrangement(s) in the IDS gene or other definitive mutation indicative of nMPS II, as determined by an independent external review panel
2. The participant has a General Ability Index (GAI) score * 70 at the baseline assessment based on the WISC-V, performed without clinically significant hearing loss or with hearing aids presentHave a full-scale intelligence quotient (IQ) above 70 at the baseline assessment based on the WISC-V performed
* Participant and parent(s) or LAR are willing and able to comply with study visits and study procedures.
* Have the ability to comply with protocol requirements according to the investigator*s judgment

Exclusion criteria

Patients who meet any of the following criteria will be excluded from study entry (Part 1 and Part 2):
* Have an unstable medical condition that would make participation in the study unsafe or would interfere with necessary medical care, in the opinion of the investigator
* Have received any CNS-targeted MPS II investigational therapy (e.g., intrathecal IDS, transferrin or insulin receptor*mediated IDS delivery to CNS,

or stem cell transplantation) within the previous 6 months. Patients may rescreen for this study after the 6-month washout completes.
* Have received an MPS II gene therapy at any time
* Have a mutation of other genes, including loci adjacent to the IDS gene (e.g., fragile X mental retardation 1 [FMR1] or AF4/FMR2 family member 2 [i.e., AFF2 or FMR2]), that are known to be associated with developmental delay, seizures, or other significant CNS disorders
* Have documented loss of activity of sulfatases other than IDS, indicating multiple sulfatase deficiency

Patients in Part 2 who meet any of the following criteria will be excluded from study entry:
* Have a history of complications from previous LPs or are anticipated to pose significant technical challenges or unacceptable safety risk in receiving an LP, in the judgment of the investigator

* Have any bleeding disorders, or any other medical condition or circumstance in which an LP (for collection of CSF) is contraindicated according to local institutional policy

Participants who meet any of the following criteria will be excluded from Parts 3 and 4 study entry:
* Have an unstable medical condition that would make participation in the study unsafe or would interfere with necessary medical care, in the opinion of the investigator
* Have received any CNS-targeted MPS II investigational therapy (e.g., intrathecal IDS, transferrin or insulin receptor*mediated IDS delivery to CNS, or stem cell transplantation) within the previous 6 months
* Have received an MPS II gene therapy or hematopoietic stem cell transplant at any time unless prior Sponsor approval has been received
* Have a mutation of other genes, including loci adjacent to the IDS gene (e.g., fragile X mental retardation 1 [FMR1] or AF4/FMR2 family member 2 [i.e., AFF2 or FMR2]), that is known to be associated with developmental delay, seizures, or other significant CNS disorders
* Have documented loss of activity of sulfatases other than IDS, indicating multiple sulfatase deficiency

Study design

Design

Study type: Observational invasive
Masking: Open (masking not used)

Control:	Uncontrolled
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-03-2021
Enrollment:	3
Type:	Actual

Ethics review

Approved WMO Date:	24-08-2020
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-03-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-06-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT04007536
CCMO	NL72007.078.19