A 12-month Longitudinal, Prospective, Observational, Natural History Study of Patients with Sanfilippo Syndrome Type A (MPS IIIA)

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1. Primary Objective(s) The primary objective(s) of this study are to:* Evaluate the course of disease progression in patients with MPS IIIA who are untreated with any investigational products to inform possible future treatment studies * Determine...

Ethical review	-
Status	Will not start
Health condition type	Metabolic and nutritional disorders congenital
Study type	Observational invasive

Summary

ID

NL-OMON32977

Source
ToetsingOnline

Brief title
MPS IIIA study

Condition

- Metabolic and nutritional disorders congenital
- Mental impairment disorders

Synonym
MPS IIIA, Sanfilippo syndrome Type A

Research involving
Human

Sponsors and support

Primary sponsor: Shire Human Genetic Therapies
Source(s) of monetary or material Support: Shire HGT

Intervention

Keyword: MPS IIIA, Natural History, Sanfilippo Syndrome Type A, Surrogate Endpoint Study

Outcome measures

Primary outcome

The primary endpoints of this study are to evaluate the severity and progression of MPS IIIA on clinical and laboratory parameters, including:

* Developmental age in general and acquisition/loss of specific developmental milestones

* CNS function, including global and subsystem development for cognition, speech, and motor system functions

* Determination of serum, urine, and CSF levels of heparan sulfate and its breakdown products

Secondary outcome

The secondary endpoints of this study are to:

* Assess change from baseline in additional clinical parameters (eg, standardized neurocognitive and development assessments, neurologic function, Developmental Quotient [DQ], sleep, brain Magnetic Resonance Imaging [MRI] volumes, and Auditory Brainstem Response [ABR])

* Quantitate additional biomarkers of CNS health in CSF such as markers of neuronal and astrocyte cell integrity

Study description

Background summary

Sanfilippo syndrome, or MPS (Mucopolysaccharidosis) III, is a lysosomal storage disease (LSD) caused by loss in activity of one of four enzymes necessary for degradation of the glycosaminoglycan (GAG) heparan sulfate in lysosomes. Four different subtypes (A, B, C, and D) have been identified and are each due to a specific enzyme deficiency involved in the lysosomal catabolism of heparan sulfate. MPS IIIA results from deficiency of the enzyme heparan-N-sulfatase (sulfamidase). In the absence of this enzyme, intermediates of the heparan sulfate degradation process dramatically accumulate in the lysosomes of neurons and glial cells, with lesser accumulation outside the brain.
MPS III is the most prevalent of all mucopolysaccharidoses; MPS IIIA is the most frequent subtype in the Nederlands. Subtypes A and B together account for approximately 90% of all cases of MPS III worldwide. The birth prevalence of MPS IIIA has been estimated as 1.28 per 100,000 in Australia, 1.16 per 100,000 in the Netherlands, and 0.88 in 100,000 in Germany.1-3 In summary, there is widespread geographic prevalence of MPS IIIA, with an average global birth incidence of approximately 1 in 100,000.
MPS IIIA symptoms arise between 2 to 6 years of age for the majority of patients who are severely affected; however, diagnosis often lags behind the earliest symptoms. Patients present a wide spectrum and severity of clinical symptoms. The central nervous system (CNS) is the most severely affected organ system in patients with MPS IIIA, evidenced by deficits in language development, motor skills, and intellectual development. In addition, there are abnormal behaviors including but not limited to aggression and excess motor activity/hyperactivity that contributes to disturbances in sleep.4-6 In contrast with other MPS types, the viscera are mildly affected, with enlargement of liver and spleen with no evidence of dysfunction. There are also reports of unexplained, recurrent and severe diarrhea.7 Overall, individuals with MPS IIIA have a marked developmental delay and significantly reduced lifespan of 15 years of age on average. A milder variant has recently been identified with slower progression and survival to later age in approximately 10% of German patients with MPS IIIA.
A preliminary diagnosis of MPS III can sometimes be established by finding elevated heparan sulfate in urine, although some tests can be false negatives. The preferred diagnostic method is quantification of sulfamidase activity in the leucocytes and/ or fibroblasts. Additionally, genotyping patients with known pathogenic mutations strongly support a diagnosis.
A long range goal of Shire Human Genetic Therapies (Shire HGT) is to develop recombinant human heparan-N-sulfatase (rhHNS) enzyme replacement therapy (ERT) for patients with MPS IIIA. A particular challenge for treating lysosomal storage disorders that damage the brain (such as MPS III) is how to target ERT to the brain. In ongoing animal studies, ERT is being administered into the

cerebral spinal fluid (CSF) via an intrathecal (IT) route, because when administered intravenously (IV) it does not cross the blood brain barrier (BBB) after the immediate postnatal period of life. The first precedent for intraspinal ERT has been shown to be both safe and effective for spinal cord compression in patients with MPS I.

To determine the primary pharmacodynamic activity of an IT-administered ERT, it is essential to understand the levels of heparan sulfate and its breakdown products in a tissue that manifests the pathology of MPS IIIA. The CSF will be analyzed as a surrogate for the brain and spinal cord levels of heparan sulfate and its breakdown products. There are no published studies of the levels of substrate for sulfamidase (ie, heparan sulfate or its breakdown products) in CSF. Hence, an objective of this study is to determine the levels of heparan sulfate and sulfated oligosaccharides derived from this GAG in CSF from patients with MPS IIIA who are untreated with any investigational products.
Data on the natural disease course of MPS IIIA in patients is essential to inform the efficacy measures that will be required to evaluate the MPS IIIA ERT in the future. Prospective natural history studies have not been performed to date in individuals with MPS IIIA. This longitudinal, prospective, observational, natural history study of patients with MPS IIIA will be conducted to document the natural progression of the disease, and to provide data that will assist in the development of future treatment studies with MPS III, such as ERT with rhHNS. This study will attempt to correlate disease progression with biochemical, developmental, brain imaging, neurophysiological, and neurocognitive measurements.
MPS IIIA has devastating consequences on the CNS of patients with MPS IIIA, with no effective treatment currently available. Therefore, a clear unmet medical need exists for this condition. It is hoped that this natural history study will provide clinical and biomarker reference data necessary to inform the development of future ERT studies for MPS IIIA.

Study objective

1. Primary Objective(s)
The primary objective(s) of this study are to:
* Evaluate the course of disease progression in patients with MPS IIIA who are untreated with any investigational products to inform possible future treatment studies
* Determine the level of heparan sulfate and heparan sulfate breakdown products in serum, urine, and CSF as measured over 12 months

2. Secondary Objective(s)
The secondary objective of this study is to:
* Obtain clinical assessments and biological samples that may provide indicators or markers of disease severity and progression

3. Exploratory Objectives

The exploratory objectives of this study are to:
* Compare serum, urine and CSF levels of GAG related biomarkers (total GAG, heparan sulfate and its breakdown products) for relative performance in diagnostic utility
* Provide a reference group with which to compare subsequent ERT (rhHNS) treated patients in the context of potential future clinical trials
* Investigate functional activities of daily living and quality of life

Study design

This is a two-center longitudinal, prospective, observational, natural history study of patients with MPS IIIA designed to assess the potential surrogate endpoints that will be utilized in potential future ERT trials of MPS IIIA via defined assessments including standardized clinical, biochemical, neurocognitive, development, and imaging measures. This study will have 5 assessment periods as follows:
* Screening: Within 30 days of the study baseline evaluation.
* Baseline (Assessment Day 0): Within 30 days of consent and the first screening assessment.
* Assessment: The 6-month visit (±14 days) from baseline (Assessment Day 0).
* Assessment: The 12-month (±14 days) or EOS visit from baseline (Assessment Day 0).
The EOS visit will occur if the patient withdraws before the 12-month visit. He/she will participate in an EOS visit that will occur as soon as possible (+14 days) after the patient ends participation in the study. The EOS assessments will be the 12-month visit assessments.
* Safety follow-up contact: 7 (±2 days) from the 12-month (or EOS) visit.

Written informed consent (assent if applicable) will be obtained prior to screening, ie, the start of any study related procedures. Patients will be screened for entry into the study initially on a confirmed diagnosis of MPS IIIA via biochemical enzyme assay (if not already performed prior to this study at a laboratory acceptable by Shire HGT). They will also undergo additional screening procedures, eg, assessment of inclusion and exclusion criteria; as outlined in Appendix 1 Schedule of Events.
Patients who successfully meet the screening criteria will be enrolled in the study. Following enrollment, the patient will complete baseline procedures. The baseline assessments will include (the complete list is provided in the Schedule of Assessments):
* Sleep questionnaire
* Child Health Questionnaire* (CHQ) Parent Form 50 Questions
* Child Health Questionnaire* (CHQ) Child Form 87
* Infant Toddler Quality of Life Questionnaire* (ITQOL)
* MRI
* Lumbar puncture (LP)
* Measurement of intracranial pressure (ICP)
* CSF sample

* ABR

Note: The Baseline, Months 6, and 12 (or EOS) assessments may take from 2 days (consecutive) to 5 days (maximum); the neurocognitive and developmental testing must be completed before the patient receives sedation or anesthesia.
Study procedures that require sedation or general anesthesia will include appropriate procedures to minimize the anesthesia risks. Specifically, the assessments will include the following tests: head MRI, ABR, ICP, LP, and CSF sampling.
Each time these assessments are done, a single administration of sedation/anesthesia will be given under carefully controlled and monitored conditions. Although these procedures may contribute substantially to the knowledge gained regarding the natural course of MPS IIIA and potentially inform future trials related to treatment development, the procedures by themselves offer no clear direct benefit to the patient. It is possible that results from the various assessments (eg, MRI) would identify the presence of other pathology or conditions, which could be responsible for, or contribute to, the clinical symptoms attributed to MPS IIIA.
All patients will undergo a Safety follow-up call or on-site visit (7±2) days after the 12-months (or EOS) visit.
The sponsor may terminate the study at any time. Patients may withdraw from the study at any time and for any reason without prejudice to any future medical care or research opportunities. An Investigator may withdraw a patient from the study for medical or administrative reasons at any time. Patients who discontinue or are withdrawn prior to study completion should undergo end of study procedures at time of discontinuation.
Patients who complete this study will be notified by the Investigator of any subsequent treatment studies to be conducted by the sponsor and may be provided the opportunity to enroll in any subsequent trials should such be developed by the sponsor, and if the patient also satisfies the specified enrollment criteria. However, the sponsor cannot guarantee that such studies will occur, or that any particular patient will be guaranteed a place in subsequent trials.
See Appendix 1, Schedule of Events, for the complete schedule of study procedures.

Study burden and risks

The risks of the study are associated with various procedures. The risk to anesthesia are not common but can include irregular heartbeat, increase or decrease in blood pressure, a fast increase in body temperature, difficulty breathing, heart attack or stroke, a reaction to a medication used in anesthesia, or death from complications of changes in heartbeat, blood pressure, body temperature, or breathing.

A lumbar puncture can cause a mild to severe headache, which may last for several days. Risks associated with lumbar puncture include pain at the injection site, meningitis (infection of the nervous system), failed procedure,

bleeding and spinal fluid leakage. To decrease the risk of headaches associated with lumbar punctures, the subject will be asked to stay flat in bed for about 2 hours after the procedure is completed.

The risk of blood sampling may be mild pain and discomfort at the site of needle entry. There is a slight risk of fainting, bruising, swelling or infection at the site of needle entry.

Benefit: The subject will receive very close attention by the study staff during the time involved in this study. Research is designed to benefit society by gaining new knowledge, so the information gained may benefit others diagnosed with MPS IIIA.

Contacts

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Scientific
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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)
Elderly (65 years and older)

Inclusion criteria

1.The patient has a documented deficiency in HNS enzyme activity of *10% of the lower limit of the normal range as measured in fibroblasts or leukocytes (based on normal range for diagnosis of MPS IIIA by a laboratory that is acceptable to Shire HGT).
AND
2.The patient has a normal enzyme activity level of at least one other sulfatase (to rule out multiple sulfatase deficiency) as measured in fibroblasts or leukocytes (based on normal range by a laboratory that is acceptable to Shire HGT).
3. The patient is * 3 years of age and has a developmental age above 1 year.
4. The patient is medically stable, in the opinion of the investigator, to accommodate the protocol requirements, including travel and assessments, without placing an undue burden on the patient/patient's family.
5. The patient*s parent(s) or legal guardian(s) has voluntarily signed an Institutional Review Board/Independent Ethics Committee-approved informed consent (assent if applicable) form after all relevant aspects of the study have been explained and discussed with the patient*s parent(s), or legal guardian(s). The patient's parents or legal guardian*s consent and patient*s assent as appropriate, must be obtained.

Exclusion criteria

1. The patient has significant non-MPS IIIA related CNS impairment or behavioral disturbances, which would confound the scientific integrity or interpretation of study assessments, as determined by the Investigator.
2. Patients who, for MPS IIIA behavioral-related reasons, in the opinion of the Investigator, would preclude performance of study neurocognitive and developmental testing procedures.
3. Patients who are pregnant, or female patients of childbearing potential, who will not or cannot comply with the use of an acceptable method of birth control such as condoms, barrier method, oral contraception, etc.
4. The patient is blind and/or deaf.
5. The patient has any known or suspected hypersensitivity to anesthesia or is thought to be at an unacceptably high risk for anesthesia due to airway compromise or other conditions.
6. The patient or the patient's family has a history of neuroleptic malignant syndrome, malignant hyperthermia, or other anesthesia-related concerns.
7. The patient has a history of complications from previous lumbar punctures or technical challenges in conducting lumbar punctures such that the Investigator does not recommend performing lumbar punctures.
8. The patient has a history of poorly controlled seizure disorder.
9.The patient has a history of an intracranial pressure (ICP) or opening CSF pressure upon lumbar puncture that exceeds the accepted normal limit of 30 cm H2O that has not been definitively treated.

10. The patient is currently receiving psychotropic or other medications, which in the Investigator*s opinion, would be likely to substantially confound test results.
11. The patient cannot sustain absence from aspirin, non-steroidals, or medications that affect blood clotting within 1 week prior to a relevant study related procedure (eg, lumbar puncture if applicable), or has ingested such medications within 1 week before any procedures in which any change in clotting activity would be deleterious.
12. The patient has received treatment with any investigational drug or a device intended as a treatment for MPS IIIA within the 30 days prior to, or during the study, or is currently enrolled in another study that involves an investigational drug or device (enrollment through Safety follow-up contact).
13. The patient has received a cord blood or bone marrow transplant.
14. The patient*s assent is unattainable, or the patient*s parent(s) or patient*s legal guardian(s) is/are unable to understand the nature, scope, and possible consequences of the study, or do/does not agree to comply with the protocol defined schedule of assessments.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Start date (anticipated):	01-07-2009
Enrollment:	5
Type:	Anticipated

Ethics review

Not available

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
CCMO	NL27898.018.09