A Phase I/II Safety, Tolerability, Ascending Dose and Dose Frequency Study of Recombinant Human Heparan-N-sulfatase (rhHNS) Intrathecal Administration via an Intrathecal Drug Delivery Device in Patients With Sanfilippo Syndrome Type A (MPS IIIA)

Published: 20-07-2010
Last updated: 02-05-2024

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Inborn errors of metabolism
Study type	Interventional

Summary

ID

NL-OMON36295

Source
ToetsingOnline

Brief title
MPS IIIA ERT study

Condition

- Inborn errors of metabolism

Synonym
MPS IIIA, Sanfilippo syndrome Type A

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Enzyme replacement therapy, MPS IIIA, Phase I/II study, Sanfilippo Syndrome Type A

Outcome measures

Primary outcome

* To determine the safety of intrathecal rhHNS administration, as measured by

adverse events

(by type and severity), changes in clinical laboratory testing (serum chemistry

including liver

function tests, hematology, and urinalysis), electrocardiograms, CSF chemistries

(including cell counts and inflammatory markers), and anti-rhHNS antibodies (in

CSF and

serum).

Secondary outcome

* To determine (by dose group) the effects of IT administration of rhHNS, as

measured by

(1) change from baseline values, and (2) comparison to values obtained in a

longitudinal,

12-month, natural history study of untreated patients with MPS IIIA in the Shire

HGT-SAN-053 Surrogate Endpoint Trial, on the following measurements/

assessments over

a 6-month period:

* Standardized neurocognitive and behavioral assessments as measured by the

Bayley

Scales of Infant Development, Third Edition (BSID-III), and the Kaufman

Assessment

Battery for Children, Second Edition (KABC-II).

* Sanfilippo-specific behavioral rating scales, as measured by the Four-Point

Scoring

System/Total Disability Score (FPSS/TDS) and the Sanfilippo Behavioral Rating

Scale

(SBRS).

* Gross and fine motor skills assessment and voluntary movement, as measured by

the

Movement Assessment Battery for Children, Second Edition (MABC-2).

* Functional adaptive behavior as measured by the Vineland Adaptive Behavioral

Scales,

Second Edition (VABS-II).

* Quality of life (QoL), as measured by the Child Health Questionnaire* Parent

Form 50

(CHQ-50) Questions and Child Health Questionnaire* Child Form 87 (CHQ-87),

Infant

Toddler Quality of Life Questionnaire* (ITQOL), and Children*s Sleep Habits

Rating

Scale.

* Concentration of rhHNS in CSF and serum.

* Concentration of inflammatory cytokines in serum and CSF.

* Concentration of heparan sulfate and heparan sulfate derivatives in urine and

CSF, and, if

possible, in serum.

* Concentration of exploratory biomarkers in CSF, serum, and urine (potential

surrogate

markers of efficacy).

* Brain magnetic resonance imaging (MRI) and auditory brainstem response (ABR),

aka

Brainstem Auditory Evoked Potentials.

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 Netherlands. 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. 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 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.

In the current study recombinant human heparan-N-sulfatase (rhHNS) will be administered via an inthrathecal route, and safety and efficicy will be investigated.

Study objective

The primary objectives of this study is:
* To determine the safety and tolerability of rhHNS via ascending doses administered via a surgically implanted intrathecal drug device (IDDD) once monthly for 6 months, in patients
with MPS IIIA.
The secondary objectives of this study are:
* To determine by dose group the effects of IT administration of rhHNS, as measured as
(1) change from baseline values, and (2) comparison to values obtained in a longitudinal,
12-month, natural history study of untreated patients with MPS IIIA in the Shire HGT-SAN-053 Surrogate Endpoint Trial, on the following measurements/assessments over a
6-month period:

* Standardized neurocognitive and behavioral assessments, Sanfilippo-specific behavioral
rating scales, gross and fine motor assessments, functional adaptive rating scales, quality
of life questionnaires, and Children*s Sleep Habits Rating Scale.
* Concentration of rhHNS in cerebrospinal fluid (CSF) and serum.
* Concentration of safety and potential surrogate efficacy biomarkers in CSF, urine, and
serum.
* Concentration of heparan sulfate and heparan sulfate derivatives in urine and CSF as
measured over approximately 6 months.
* Brain magnetic resonance imaging (MRI) and auditory brainstem response (ABR), aka
Brainstem Auditory Evoked Potentials.

Study design

This is a multicenter, multiple-dose, dose escalation study designed to evaluate the safety,
tolerability, and clinical activity of up to 3 dose levels (10, 45 and 90 mg) monthly for 6 months of rhHNS administered via an IDDD in patients with Sanfilippo syndrome Type A.

Patients will be assigned to 1 of 3 treatment groups:
* Group 1: rhHNS administered by IT injection 10 mg once per month for a total of 6 months
* Group 2: rhHNS administered by IT injection 45 mg once per month for a total of 6 months
* Group 3: rhHNS administered by IT injection 90 mg once per month for a total of 6 months
This study will have 7 periods as follows:
* Screening: Within 60 days prior to the implantation of the IDDD.
* Surgical implantation of the IDDD: Week 1, Days 1 through 7. Includes pre-surgical
assessments, surgical implantation of the IDDD on Day 2, and follow-up assessments on
Days 3 through 7 after operative procedure.
* Baseline: Week 2, Days 1 and 2. Assessments for safety, biochemical, and neurological
baseline measures (Day 1) will occur on the day before the first IT injection. CSF sample
assessment will be obtained from patients on Day 2, immediately prior to the first IT study
drug injection.
* Treatment period: Week 2 (first IT administration) through Week 22, (last IT administration). Intrathecal administration of rhHNS will occur on Day 2

(±2) days of
each dosing week (Weeks 2, 6, 10, 14, 18, and 22).
* End of study procedures: Week 26, 30 (±7) daysafter the last rhHNS administration for patients who complete the study, and 30 (±7) days after the last rhHNS administration for patients who discontinue prior to the end of the study.
* Safety follow-up: Week 30, 30 (±7) days after the end of study procedures.

Intervention

At the start of the study patients will receive a surgically implanted intrathecal drug
delivery device (IDDD). After this patients will receive Monthly or EOW inthrathecal enzyme therapy.

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

Public

Shire

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US
Scientific
Shire

300 Shire Way
MA 02421,Lexington
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)
Elderly (65 years and older)

Inclusion criteria

1. a.)Patients have a documented deficiency in sulfamidase enzyme activity of *10% of the lower limit of the normal range as measured in fibroblasts or leukocytes (based on measurements by a laboratory that is acceptable to Shire HGT).
AND EITHER b or C
b.)Patients have a normal enzyme activity level of at least 1 other sulfatase (to rule out multiple sulfatase deficiency) as measured in fibroblasts or leukocytes (based on measurements by a laboratory that is acceptable to Shire HGT).
c.) Patients have 2 documented mutations (based on assessments by a laboratory that is acceptable to Shire HGT).
2. The patient is *3 years of age and has a developmental age above 1 year (developmental age will be determined by the screening neurocognitive and developmental tests).
3. Patients must be medically stable, in the opinion of the Investigator, to accommodate the protocol requirements, including travel, assessments, and IDDD surgery, without placing an

undue burden on the patient/patient's family.
4. The patient*s parent(s) or legal guardian must have voluntarily signed an Institutional Review Board/Independent Ethics Committee-approved informed consent form

Exclusion criteria

1. The patient has significant non-MPS IIIA related central nervous system (CNS) impairment or behavioral disturbances that would confound the scientific integrity or interpretation of study assessments, as determined by the Investigator.
2. The patient has MPS IIIA behavioral-related issues, as determined by the Investigator that would preclude performance of study neurocognitive and developmental testing procedures.
3. The patient is pregnant, breast feeding, or is a female patient of childbearing potential who will not or cannot comply with the use of an acceptable method of birth control
4. The patient is blind and/or deaf
5. The patient has any known or suspected hypersensitivity to anesthesia or is thought to have 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 Investigator may choose to exclude patients who have had complications resulting from prior lumbar punctures.
8. The patient has a CNS shunt.
9. The patient has skeletomuscular/spinal abnormalities or other contraindications for the surgical implantation of the IDDD.
10. The patient has a history of poorly controlled seizure disorder.
11. The patient is currently receiving psychotropic or other medications, which in the Investigator*s opinion, would be likely to substantially confound test results and the dose and regimen of which cannot be kept constant throughout the study.
12. The patient cannot sustain absence from aspirin, non-steroidal medications, or medications that affect blood clotting within 1 week prior to a relevant study-related procedure (eg, device implantation if applicable), or has ingested such medications within 1 week before any procedures in which any change in clotting activity would be deleterious.
13. 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 (screening through safety follow-up contact).
14. The patient has received a hematopoietic stem cell or bone marrow transplant.
15. The patient*s parent(s), or patient*s legal guardian(s) is/are unable to provide consent or the patient cannot provide assent,

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	06-09-2010
Enrollment:	8
Type:	Actual

Medical products/devices used

Generic name:	intrathecal drug delivery device (IDDD)
Registration:	Yes - CE intended use
Product type:	Medicine
Brand name:	Recombinant human heparan N-sulfatase (rhHNS)
Generic name:	n.v.t.

Ethics review

Approved WMO

Date:	20-07-2010
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	09-12-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	29-03-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-08-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-09-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-03-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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
EudraCT	EUCTR2009-015984-15-NL
CCMO	NL31033.018.10

Study results

Date completed:	13-08-2012

Actual enrolment: 6

Summary results
Trial is onging in other countries