A Randomized, Controlled, Open-label, Multicenter, Phase IIb Safety and Efficacy Study of HGT-1410 (Recombinant Human Heparan N Sulfatase) Administration via an Intrathecal Drug Delivery Device in Pediatric Patients with Early Stage Mucopolysaccharidosis Type IIIA Disease

Published: 21-11-2013
Last updated: 23-04-2024

The primary objective of this study is to assess the potential clinical efficacy of HGT-1410administered via a surgically implanted IDDD in patients with MPS IIIA. Efficacy will bemeasured as a meaningful amelioration in the progression of cognitive...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Metabolism disorders NEC
Study type	Interventional

Summary

ID

NL-OMON40318

Source
ToetsingOnline

Brief title
HGT-SAN-093

Condition

- Metabolism disorders NEC

Synonym
mucopolysaccharide, Sanfilippo syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Shire
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: Early Stage Mucopolysaccharidosis Type IIIA Disease, HGT-1410, Intrathecal Drug Delivery Device, Pediatric Patients

Outcome measures

Primary outcome

Achievement of response, defined as a maximum decline in cognitive DQ of 10

points

over 48 weeks, as assessed by the Bayley Scales of Infant Development, 3rd

Edition.

Secondary outcome

- Safety endpoints including the assessment of adverse events (AEs), IDDD

related

issues, laboratory values, anti-rhHNS antibody development, vital signs,

physical

examination findings, and ECG results

-The change from baseline to Week 48 in adaptive behavioral function, assessed

by

VABS II, using raw scores and age equivalent score

- The change from baseline to Week 48 in the DQ assessed by neurocognitive

testing, using the BSID-III age equivalent scores

- The change from Baseline to Week 48 in total cortical grey matter volume, as

assessed by MRI

- The change from Baseline to Week 48 in concentrations of GAG in the CSF and

urine

- The concentration of HGT-1410 in CSF and serum

Study description

Background summary

MPS IIIA is a rare, inherited genetic disorder in which an enzyme called heparan N-sulfatase (HNS) or sulfamidase is missing or not working properly. This enzyme is important in the breakdown of mucopolysaccharides (MPSs) or glycosaminoglycan (s) (or GAGs), which are large complex sugars used in the building of tissues of the body. When sulfamidase is missing, or not working properly, it causes GAGs to build up in the body, in the small parts of the cells, called lysosomes. As time goes on, cells in the body become clogged with the sugar and are injured. As a result, patients with MPS IIIA develop problems affecting the body, especially the central nervous system (CNS: the brain and spinal cord). These patients typically do not develop normal abilities regarding language, learning, and many of the normal tasks that are part of growing up or the patients may develop these abilities and then lose them as time goes on and the GAGs build up within their body. The study Sponsor, Shire HGT, is developing the study drug, recombinant human heparan N-sulfatase (rhHNS; HGT-1410) as an enzyme replacement therapy (ERT) for patients with MPS IIIA.

Study objective

The primary objective of this study is to assess the potential clinical efficacy of HGT-1410
administered via a surgically implanted IDDD in patients with MPS IIIA. Efficacy will be
measured as a meaningful amelioration in the progression of cognitive decline,

and will be
measured using the Bayley Scales of Infant and Toddler Development, 3rd Edition (BSID-III).

Secondary objectives:
To determine:
* The safety and tolerability of HGT-1410 IT
* The effect of HGT-1410 administration on BSID-III Age-equivalent and development
quotient (DQ) scores
* The effect of HGT-1410 IT on adaptive behavioral function, assessed by Vineland Adaptive
Behavior Scales, Second Edition (VABS II)
* The effect of HGT-1410 IT treatment on the total cortical grey matter volume, as assessed by
volumetric MRI of the brain
* The effect of HGT-1410 IT treatment on the concentration of GAGs in CSF and urine
* The pharmacokinetics of HGT-1410 in CSF and serum.

Study design

This is an open-label, randomized, parallel group, controlled, multicenter study designed
to evaluate the efficacy and safety of 45 mg HGT-1410 administered IT Q2W and 45 mg
of HGT-1410 administered IT Q4W via an IDDD versus no treatment in patients at a relatively early stage of MPS IIIA disease. Cognitive assessments, which support the primary objective of the trial, will be performed by assessors who are blinded to the treatment assignment of the patient.

Intervention

HGT-1410 at a dose of 45 mg administered every 2 weeks (Q2W) or 45 mg administered
every 4 weeks (Q4W). HGT-1410 will be administered intrathecally (IT) by an indwelling
intrathecal drug delivery device (IDDD).

The SOPH-A-PORT® Mini S is a system intended for implantation by physicians. The SOPH-A-PORT Mini S, once implanted, allows healthcare personnel to administer HGT-1410 indicated for IT delivery intermittently over a long period.

The comparator group will receive no treatment with HGT-1410. A placebo will not be
used, since the IDDD will not be implanted in patients who are randomized to

the control
group.

HGT-1410 Q2W (ie, every 14 days), or Q4W (ie, every 28 days) for 48 weeks via a surgically implanted intrathecal drug delivery device (IDDD), or lumbar puncture (LP)

Study burden and risks

Please refer to the overview of procedures in the protocol (appendix 1) for a complete overview.
The following procedures will be performed in the context of the research and are different/additional in comparison with the standard treatment:
All treatment groups:
-complete questionnaires (3 times)
-lumbar punction (3 times in non-treatment group), in the treatment groups if cerebrospinal fluid cannot be collected by IDDD device;
-MRI (3 times)

Only treatment groups:
-intake IP
-implementation of IDDD
-x-rays (2 times). Possibly 12 additional x-ray studies to verify proper placement of the device if there are problems accessing the device.

Pain and headache during or after the injection of study drug are possible. The injection procedure may be performed incorrectly, including injecting the wrong medicine through the port, injecting study drug outside the port into the surrounding tissue, or using the wrong type of needle or improper technique while injecting medicine into the port.
Injection of HGT-1410, as with any protein, carries with it the risk of an infusion-related reaction.
Tingling or painful sensation to the lower legs.

Contacts

Public
Shire

Shire Way 300
Lexington MA, 02421
US
Scientific
Shire

Shire Way 300
Lexington MA, 02421
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

1. Documented MPS IIIA diagnosis:
a) All patients must show a documented deficiency in sulfamidase enzyme activity of *10% of the lower limit of the normal range as measured in fibroblasts or leukocytes
AND
b) patients must show documented mutations in each SGSH allele OR there must be documentation of mutations in each SGSH allele in a sibling affected by MPSIIIA, provided parental consent is obtained to use this information.
2. Age *12 months and * 48 months
3. The patient has a Developmental Quotient score *60%, assessed by cognitive evaluation at screening assessment using the Bayley Scales of Infant and Toddler Development *3rd Edition (BSID-III)
4. The patient is medically stable, in the opinion of the Investigator, and able to accommodate the protocol requirements, including travel, assessments, and IDDD surgery, without placing an undue burden on the patient/patient's family
5. The patient, and patient's parent(s) or legal guardian must have voluntarily signed an Independent Ethics Committee-approved informed consent form after all relevant aspects of the study have been explained and discussed with the patient's parent(s), or legal guardian. Consent of the patient's parent(s) or legally authorized guardian(s) must be obtained prior to the start of any study procedures.

Exclusion criteria

1. The presence of 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 presence of the S298P mutation in either or both SGSH alleles, associated with attenuated disease OR there must be documentation of mutations in each SGSH allele in a sibling affected by MPSIIIA, provided parental consent is obtained to use this information.
3. The presence of relatively attenuated MPS IIIA disease in an older sibling, defined as preservation of any comprehensible speech beyond the age of 10 years
4. Visual or hearing impairment, in the clinical judgement of the investigator, sufficient to preclude cooperation with neurodevelopmental testing.
5. In the opinion of the Investigator, the patient is assessed as having an unacceptably high risk for anesthesia due to airway compromise, drug hypersensitivity, or other conditions (such as neuroleptic malignant syndrome, malignant hyperthermia, or other anesthesia-related concerns).
6. The patient has a history of poorly controlled seizure disorder.
7. The patient is currently receiving psychotropic or other medications, which in the Investigator's opinion would be likely to substantially confound test results.
8. The patient has a history of bleeding disorder or is unable to abstain from medications that, in the opinion of the investigator, place them at risk of bleeding following surgery or lumbar puncture..
9. The patient participated in a clinical trial of another investigational medicinal product, within the 30 days prior to the study (or within 5 elimination half lives of the investigational product), or is currently enrolled in another study that involves an investigational drug or device. NOTE: Nutritional supplements, including genistein are permitted if they are taken or administered outside the context of a formal investigation.
10. The patient has received a hematopoietic stem cell or bone marrow transplant, or gene therapy.
11. The patient has a condition that is contraindicated as described in the SOPH-A-PORT Mini S IDDD Instructions for Use, including:
a) The patient has had an allergic reaction to the materials of construction of the SOPH-A-PORT Mini S device
b) The patient's body size is too small to support the size of the SOPH-APORT Mini S Access Port, as judged by the Investigator
c) The patient has a known or suspected local or general infection
d) The patient has one or more spinal abnormalities that could complicate safe implantation or fixation
e) The patient has a functioning CSF shunt device

f) The patient has shown an intolerance to an implanted device
12. 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.
13. The patient is unable to comply with the protocol (eg, has a clinically relevant medical condition making implementation of the protocol difficult, unstable social situation, or otherwise unlikely to complete the study) or is, in the opinion of the Investigator, otherwise unsuited for the study.
14. The patient has any item (braces, tattoos, etc.) which would exclude the patient from being able to undergo MRI according to local Institutional Policy, or the patient has any other situation that would exclude the patient from undergoing any other procedure required in this study.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-09-2014
Enrollment:	2
Type:	Actual

Medical products/devices used

Generic name:	intrathecal drug delivery device (IDDD)
Registration:	Yes - CE intended use
Product type:	Medicine

Brand name:	rhHNS (recombinant human heparan-N-sulfatase)
Generic name:	rhHNS (recombinant human heparan-N-sulfatase)

Ethics review

Approved WMO Date:	21-11-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-03-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-04-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-05-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-06-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-07-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-02-2015
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	EUCTR2013-003450-24-NL
ClinicalTrials.gov	NCT02060526
CCMO	NL46471.018.13