An open-label, single-arm, multicenter study of intracerebral administration of adeno-associated viral vectors serotype rh.10 carrying the human N-sulfoglycosamine sulfohydrolase (SGSH) cDNA for the treatment of mucopolysaccharidosis type IIIA (MPS IIIA)

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Primary: To assess the efficacy of intracerebral delivery of AAVrh.10SGSH gene therapy (LYS-SAF302) in improving or stabilizing the neurodevelopmental status of MPS IIIA patients after 24 months (main cohort), compared to the expected evolution...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Metabolic and nutritional disorders congenital
Study type	Interventional

Summary

ID

NL-OMON52445

Source
ToetsingOnline

Brief title
P4-SAF-302

Condition

- Metabolic and nutritional disorders congenital
- Mental impairment disorders

Synonym
MPS III; Sanfilippo syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Blue Daisy
Source(s) of monetary or material Support: Non profit organization (Blue Daisy)

Intervention

Keyword: gene therapy, MPS IIIA, mucopolysaccharidosis type IIIA

Outcome measures

Primary outcome

The primary endpoint is the observed (post-surgery) evolution of cognitive developmental quotient (DQ) expressed by the ratio (DQ24/DQ0) between baseline and 24 months. Actual values will be compared to the ones expected based on modeling from natural history studies. Cognitive DQ will be assessed by neurocognitive testing using the Bayley Scale for Infant and Toddler Development, 3rd Edition (BSIDIII) or the Kaufman Assessment Battery for Children, 2nd Edition (KABCII), depending on child's age and ability. Primary and secondary analyses will be performed separately on the main and the ancillary cohorts.

Secondary outcome

Secondary endpoints include:

• The change from baseline in the cognitive developmental age (DA) and cognitive developmental quotient (DQ) assessed by neurocognitive tests (BSID III or KABC-II) at all timepoints

• The change from baseline in other DA and DQ (language and motor) assessed by neurocognitive tests (BSID III or KABC-II) at all timepoints

• The percentage of patients with stabilized developmental age (DA) at 12 months and 24 months

• The change from baseline in the total adaptive behavior composite standard score as measured by the Vineland Adaptive Behavior Scales (VABS-II) at 12 months and 24 months and change from baseline in total behavior problem as measured by the Child Behavior Checklist (CBCL) at 12 and 24 months

• The change in sleep pattern as measured by the Children Sleep Habits Questionnaire (CSHQ) at 12 months and 24 months

• The change from baseline in the patient/parent quality of life

• The change from baseline in total cortical grey matter volume and white matter volume on MRI at 12 months and 24 months

• The change from baseline in relevant disease biomarkers in CSF and PBMC

Study description

Background summary

There is no disease-modifying treatment currently available for MPS IIIA, although a number of approaches are being explored.
The rationale for therapeutic approaches in MPS is based on the observation that delivery of the missing enzyme reverses phenotypic abnormalities in genetically deficient cells. Although enzyme replacement therapy (ERT) is being explored, it is not currently available for MPS IIIA.
On the other hand, MPS have long been recognized as prime candidate diseases for gene therapy as it was shown that the missing enzyme might be produced and distributed to the organism by a group of genetically modified cells.
Indeed, numerous studies in animal models of MPS have described the effects of genetic modification of tissues including bone marrow, skin, muscle, liver and brain, resulting in the production of a therapeutically active enzyme.

When vectors are administered in the periphery, the produced enzymes do not cross the blood-brain barrier. Only very high doses of enzyme in the circulation may result in detectable transport into the brain.
Due to the predominant neurological involvement in MPS IIIA, therapy must be delivered to the CNS with a broad distribution throughout the brain to ensure that deficient enzyme can be sustainably produced where it is most needed.

Study objective

Primary: To assess the efficacy of intracerebral delivery of AAVrh.10SGSH gene therapy (LYS-SAF302) in improving or stabilizing the neurodevelopmental status of MPS IIIA patients after 24 months (main cohort), compared to the expected evolution based on natural history data.
Secondary: To assess the safety and tolerability of intracranial delivery of LYS-SAF302 and to assess the treatment efficacy on the behavioral, sleep disturbances of the patients and on quality of life for both patient and parents.

Study design

The study is interventional, single arm, and multicenter. Evolution under treatment will be compared to expected natural evolution based on natural history studies (Shapiro et. al., 2016 and ongoing Lysogene study P3-LYS-SAF). The main cohort will enroll patients aged >30 months with a 2-year duration (primary and key secondary efficacy analysis). An interim analysis will be performed one-year post-surgery. An extension phase will be carried out for an additional 3-year period for each patient for long-term efficacy analysis and safety assessment up to 5 years post treatment.
An ancillary cohort will include up to 6 MPS IIIA patients more than 6 months and less than 30 months of age and followed for 5 years. Interim analysis of the main cohort at one year post-surgery will not include the ancillary cohort. The ancillary cohort will be analyzed separately from the main cohort. Initial analysis of the ancillary cohort will be performed when all patients in the ancillary cohort have reached 4 years of age.
Treatment will involve direct injections of the investigational product into both sides of the brain through image-guided tracks, in a single neurosurgical session.
Patients will receive immunosuppression for at least one year post-surgery. After surgery, safety and toxicity will be evaluated by regular contact between the investigators and the families, as well as during in-person visits. At each visit, clinical progression will be assessed and blood and urine analyses carried out.
Brain imaging (MRI) will be performed at inclusion (baseline), before and after surgery, every 3 months during the first year, at 18 and 24-month, and then annually up to 5 years post treatment. In case hyperintensities are observed at injection sites, additional follow up safety MRIs should be done every 3 months

until the images stabilize or regress. When required, cerebrospinal fluid (CSF) will be collected at the opportunity of MRI and analyzed for disease biomarkers.
Neuropsychological and behavioral tests will be carried out at baseline, then every 6 months for 24 months, then every year up to 5 years post treatment.
Safety will be monitored throughout the entire study period.

Intervention

LYS-SAF302 is the adeno-associated viral vector serotype rh.10 (AAVrh.10) carrying the human N-sulfoglucosamine sulfohydrolase (SGSH) gene (LYS-SAF302), suspension for injection.
The level of residual enzyme activity collected at baseline and the type of mutation will determine the duration of immunosuppression treatment.
All patients will receive short-term corticosteroids (Prednisolone 1mg/Kg/day) for 10 days with initiation the day before surgery to prevent primarily immune reaction against the vector. In addition, to prevent long-term immune reaction against the transgene SGSH, all patients will receive:
• Mycophenolate mofetil started 7 days before surgery and for 2 months (8 weeks post-surgery)
• Tacrolimus started 7 days before surgery and during at least one year post-surgery

Study burden and risks

Risks of LYS-SAF302 and neurosurgery:
Possible unwanted effects from the surgery and administration of LYS-SAF302 may include bleeding at the injection site, leakage of cerebrospinal fluid (fluid that surrounds the brain and spinal cord), bacterial infection of the skin, swelling of the brain, inflammation of the brain, risk of motor deficit (muscles not functioning), or uncontrolled movements. If any of these or something unexpected happens, patient will be treated for any side effects by the neurosurgeon team and the clinical site investigator.

Risks related to administration of LYS-SAF302 during neurosurgical procedure are expected to occur within 2 weeks following the surgery.

Following surgery, all subjects have white matter lesions that developed within 3-6 months following intraparenchymal administration of LYS-SAF302. The pattern of lesion evolution with stabilization in subjects with more than 12 months of follow-up is consistent with the hypothesis that high levels of expression of SGSH at the injection site may lead to dysfunction of oligodendrocytes and astrocytes, resulting in local cystic white matter lesions. To date, no clinical symptoms have been observed that could be directly attributed to the observed MR lesions. The MRI findings seem to be self-limiting and clinically barely manifest. Evolution of the lesions is followed up by MRI on a regular

basis, as per protocol.

Risks associated with anesthesia during the surgery or for the MRI:
Side effects may occur with chloral hydrate as a sedative: Stomach irritation, bloating, and excessive gas in the stomach or abdomen may occur. Feelings of great enthusiasm, allergic skin reactions, headache, and the presence of abnormally high amounts of certain molecules in urine, which are created during cell break down, have occasionally been reported. Minor side effects such as a sore throat, nausea, and vomiting, can be common. Major complications from anesthesia are rare. If you have any concerns, please ask your anesthesiologist.

Risks associated with immune-suppressive agents:
Immune-suppression drugs will be prescribed to lower any risk of reaction to and rejection of the study medication. These medications (tacrolimus, mycophenolate mofetil, and prednisolone) also have known side effects when administered alone or in combination with each other.

Risks associated with spinal tap puncture and cerebral spinal fluid collection:
In approximately 25% of the patients, spinal tap puncture can cause a mild-to-severe headache, which may last for several days. Other risks associated with the spinal tap puncture include pain or discomfort at the site where the needle entered the spinal canal. Much rarer complications (less than 1% of spinal tap puncture) include meningitis (an infection of the membrane covering of the spine/brain), bleeding, spinal fluid leakage, nerve damage, and paralysis (palsy).

Most frequent side effects associated with blood draw:
In addition to unwanted effects, certain procedures may cause pain or discomfort at the site where the needle enters the skin. Also, a vein becoming inflamed, or in very rare cases a blood clot (venous thrombosis) cannot be entirely ruled out. These risks will be minimized by having only qualified personnel collect the blood. Sometimes blood will be collected when patient is under general anesthesia.
Most frequent side effects associated with magnetic resonance imaging:
On very rare occasions, patients experienced side effects from the contrast agent used for brain imaging (MRI); those include nausea, headache, and pain at the injection site. Very rarely, allergic reactions to the contrast agent happened with hives, itchy eyes, or other reactions.
Due to the investigational nature of this study, there may be other risks that are not currently known.

The overall benefit expected for patients is to prevent, stabilize, or possibly improve the symptoms of the disease. Improvement in patient's behavior as a result of this therapeutic procedure may be also expected. Most of the benefits are expected to affect the central nervous system.

Other collective benefit is an increased knowledge about MPS IIIA and this kind

of treatment, and the proposed study should confirm that gene therapy is an approach for treating MPS IIIA. Any proof of tolerance and safety is highly likely to be relevant for other diseases involving the central nervous system, including but not limited to similar diseases, which are characterized by brain function worsening due to abnormal build-up of various toxic materials in the body*s cells.
Because people respond differently to therapy and because the study drug is experimental, no one can predict in advance if patient will benefit.

Contacts

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Blue Daisy

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)
Babies and toddlers (28 days-23 months)

Inclusion criteria

1. Documented MPS IIIA diagnosis based on genotyping confirming the SGSH gene mutations

2. Age >= 30 months at screening (main cohort) or >= 6 months and < 30 months (ancillary cohort)
3. Cognitive DQ score on BSID-III >= 50%
4. Signed written informed consent before any study related procedure is performed
5. Medical status sufficiently stable, in the opinion of the investigator, to adhere to the study visit schedule and other protocol procedures
6. Confirmation by the study neurosurgeon and anesthesiologist of the feasibility of the neurosurgical procedure.

Exclusion criteria

1. Homozygous for the S298P mutation or non-severe form of MPS IIIA, based on investigator*s judgement
2. Past participation in another gene or cell therapy clinical trial
3. Past use of SGSH enzyme replacement therapy for a cumulative period exceeding 3 months. In addition, a washout period of at least 2 months is required prior to screening
4. Current participation in a clinical trial of another investigational medicinal product. NOTE: Nutritional supplements, including Genistein are permitted if they are taken outside the context of an investigational trial
5. History of bleeding disorder or current use of medications that, in the opinion of the investigator, place them at risk of bleeding following surgery
6. Presence of concomitant medical condition precluding lumbar puncture
7. Presence of any item (e.g., metal braces) precluding undergoing MRI
8. Any condition that would contraindicate treatment with immunosuppressants such as tacrolimus, mycophenolate mofetil or steroids
9. History of significant non-MPS IIIA related CNS impairment or behavioral disturbances that would confound scientific rigor or interpretation of results.
10. Rare and unrelated serious comorbidities e.g. Down syndrome, intraventricular hemorrhage in the new-born period, or extreme low birth weight (<1500 grams)
11. History of poorly controlled seizure disorder
12. Any vaccination 1 month prior to the planned surgery
13. Serology consistent with HIV exposure or consistent with active hepatitis B or C infection
14. Grade 2 or higher lab abnormalities for LFT, bilirubin, creatinine, hemoglobin, WBC count, platelet count, PT, and a PTT
15. Visual or hearing impairment sufficient, in the clinical judgment of the investigator, to preclude cooperation with neurodevelopmental testing. Use of hearing aids is permitted.

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	30-04-2019
Enrollment:	10
Type:	Actual

Medical products/devices used

Generic name:	SmartFlow Neuro Venticular Cannula
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	10-09-2018
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-03-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-03-2019

Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-04-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-11-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	03-02-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-03-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-03-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-04-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-05-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	23-06-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-10-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	29-10-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	30-07-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-10-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-06-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-07-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-11-2022
Application type:	Amendment

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	09-12-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-10-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	EUCTR2018-000195-15-NL
ClinicalTrials.gov	NCT03612869
CCMO	NL65877.000.18