A Phase I/II Open Label, Dose Escalation, Safety Study in Subjects with Mucopolysaccharidosis type VI (MPS VI) Using Adeno-Associated Viral Vector 8 to Deliver the human ARSB gene to Liver.

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Primary safety objective: To evaluate the safety of systemic intravenous administration of the Investigational Medicinal Product (IMP) in pediatric and adult MPS VI patients.Primary efficacy objective: To investigate the efficacy of the IMP through...

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

Summary

ID

NL-OMON47624

Source
ToetsingOnline

Brief title
Phase I/II Study in MPS VI with viral vector

Condition

- Inborn errors of metabolism

Synonym
enzyme impairment - Lysosomal disorder

Research involving
Human

Sponsors and support

Primary sponsor: Fondazione Telethon
Source(s) of monetary or material Support: EU Meusix grant and Fondazione Telethon

Intervention

Keyword: adeno-associated viral vector (AAV), ARSB gene, Gene Therapy, Mucopolysaccharidosis

Outcome measures

Primary outcome

The primary safety endpoints will be based on physical examination and

laboratory tests.

• Overall short-term and long-term safety and tolerability measured by

recording of adverse events, physical examination including vital signs,

laboratory tests and liver ultrasound.

• Inflammation of the liver, as shown by an elevation in transaminases.

• Kidney fuction by monitoring of parameters: creatinine, albumin, total

protein and BUN

• Presence of immune-complexes by monitoring of C3 and C4 complement protein

level

The primary efficacy endpoint will be urinary GAG excretion levels.

Secondary outcome

Secondary efficacy endpoints will include:

• Leukocyte ARSB levels (enzyme activity),

• Endurance measured by 6-minute walk test (6MWT) and 3-minute stair climb

test (3MSCT),

• Forced vital capacity (FVC) and forced expiratory volume at 1 minute (FEV1)

in cooperative subjects.

Tertiary efficacy endpoints will include:

• Height and Weight

• Health Assessment Questionnaire and Childhood Health Assessment Questionnaire

(HAQ, CHAQ) scores,

• Visual acuity and ocular abnormalities by full ocular examination.

• Cardiac function through ECG and echocardiography to monitoring cardiac

parameters

Additional exploratory endpoints will include:

• Urinary and serum GAG levels by more sensitive assays that are under

investigation.

• ARSB protein level

• Anti-AAV Antibodies

Study description

Background summary

Mucopolysaccharidosis VI is an autosomal recessive lysosomal storage disorder (LSD), belonging to the group of mucopolysaccharidoses (MPS). The MPS are caused by defects in lysosomal enzymes resulting in widespread intra- and extra-cellular accumulation of glycosaminoglycans (GAGs).
MPS VI, also known as Maroteaux-Lamy syndrome, is caused by deficiency of the enzyme arylsulfatase B
Deficiency of ARSB results in the intralysosomal storage and urinary excretion of these partially degraded GAGs.

The biochemical diagnosis of MPS VI is based on the detection of elevated urinary dermatan sulfate levels and is confirmed by reduced ARSB activity in cell extracts. The diagnosis is generally confirmed by ARSB enzyme activity below 10% of the lower limit of normal range in cultured fibroblasts or isolated leukocytes.
The rate of clinical progression in MPS VI subjects varies considerably, generating a spectrum of clinical presentation ranging from rapidly to slowly progressive disease. Nevertheless, all subjects within this spectrum will eventually experience significant morbidity and in most cases early mortality.
The classic features of MPS VI include hydrocephalus and spinal cord compression, coarse facial features, hearing loss, corneal clouding, macroglossia, heart valve disease, respiratory difficulties, hepatosplenomegaly, inguinal and abdominal hernias, dwarfism/growth retardation, skeletal dysplasia, and joint stiffness. Mental development is usually normal, although physical and visual impairments affect psychomotor performances .
Communicating hydrocephalus is a typical feature in MPS VI . Increased intracranial pressure is thought to be caused by dural thickening and dysfunction of arachnoid villi. Typical signs of obstructive hydrocephalus such as early morning headache, vomiting, and papilledema are often absent, although some subjects may present with rapid visual deterioration.
Visual impairment is common and occurs in about 40% of subjects with MPS VI. Ocular abnormalities include corneal clouding, glaucoma, and abnormal optic disk.
Aortic and mitral valvular dysfunction, due primarily to thickened calcified stenotic valves, are the most prominent cardiac involvement.
Disease complications related to the anatomical and pathological changes in the airways of subjects are obstructive sleep apnea, pneumonia, and hearing loss . Upper-airway obstruction and decreased lung capacity often lead to obstructive sleep apnea. Less frequently, daytime somnolence, failure to thrive, pulmonary hypertension, and cor pulmonale may develop. Behavioral and learning problems may also occur as a consequence of disrupted sleep. Recurrent pneumonia may be secondary to decreased pulmonary functions and poor clearance of airway secretions. Recurrent otitis and conductive hearing loss are common in MPS VI.
Hepatomegaly is always present and enlarged spleen is found in about half the subjects . Umbilical and/or inguinal hernias are common.
The skeletal changes are striking examples of dysostosis multiplex. An enlarged head and a deformed chest may be present at birth. Claw-hand deformities are classic features and nerve entrapment syndromes, particularly of the carpal tunnel, are common.
Advances in the understanding of the biochemical and molecular bases of LSDs have led to the development of specific treatment regimens. In addition to supportive care, specific therapies have been developed to provide the deficient enzyme by hematopoietic stem cell transplantation (HSCT) and enzyme replacement therapy (ERT).
Enzyme replacement therapy (ERT), approved by FDA has several limitations 1) rhARSB has a short half-life requiring weekly intravenous infusions that

carry a risk of allergic reaction and often require a central venous access
2) some organs and tissues are not corrected, likely because of limited biodistribution of rhARSB. For example, in MPS VI subjects, ERT failed to ameliorate cardiac function, visual impairment
3) the cost of ERT is extremely high, thus representing a significant burden for the health system

Study objective

Primary safety objective: To evaluate the safety of systemic intravenous administration of the Investigational Medicinal Product (IMP) in pediatric and adult MPS VI patients.

Primary efficacy objective: To investigate the efficacy of the IMP through measurements of a clinically relevant biochemical endpoint in pediatric and adult MPS VI patients.

Study design

This Phase I/II clinical trial is designed as an open label dose escalation study and will be carried out as a multi-center clinical trial, involving the Department of Translational Medicine (DISMET) of *Federico II* University, Naples, Italy as the primary site and the following secondary sites:

- Center for Lysosomal and Metabolic Diseases, Department of paediatrics, Erasmus MC University Medical Center, Rotterdam, The Netherlands
- Children*s Hospital, Hacettepe University, Ankara, Turkey.

IMP administration will be performed at the primary site, the DISMET of *Federico II University, Naples, Italy; primary and secondary sites will perform screening and follow-up visits and evaluations.

The study follows an adaptive design and the starting dose is 6x10^11 genome copies (gc) of vector per kg of body weight.
Depending on safety parameters collected in the first three subjects at the starting dose, dose escalation to the higher dose (2x10^12 gc/kg) or enrollment of additional two subjects at the same dose level or moving to three subjects at the lower dose (2x10^11 gc/kg) will be performed.
The time interval between each subject within the two lower dose cohort s will be at least 6 weeks. The time interval between subjects within the high dose will be at least 14 weeks.
Dose escalation to the higher dose level will be performed after at least 6 weeks from the IMP administration in the last individual of the starting dose cohort, once safety outcome measures have been collected. .
Every DLT or every phase requiring an escalation or de-escalation will be reported and discussed with the DSMB

Five protocol phases are foreseen:
1) Recruitment phase, with signature of informed consent.
2) Screening phase, during which the conditions required by the clinical protocol for patients* inclusion/exclusion will be evaluated.
3) Baseline phase, from the end of the screening phase to the IMP administration phase.
4) Treatment phase, day 0, i.e. the day of IMP administration.
5) Follow-up phase, from IMP injection until + 3 years from IMP

Intervention

IMP administration will be performed by peripheral intravenous access using a commercially available infusion pump and devices that have been designed for administration of intravenous medications and solutions

Study burden and risks

Advantages of gene therapy vs. ERT
As described before, ERT with rhARSB (Naglazyme) has been approved by the FDA and the EMA and is currently recommended for MPS VI (Giugliani et al., 2007 ; Giugliani et al., 2014). Three clinical studies using Naglazyme ERT have been reported and the largest study including 56 MPS VI subjects showed long-term reduction in urinary GAGs and improvements in endurance (Harmatz et al., 2008). However, ERT has several limitations. First, rhARSB has a short half-life requiring weekly intravenous infusions that carry a risk of allergic reaction and often require a central venous access, which carries risks of sepsis. Second, some organs and tissues are not corrected likely because of limited biodistribution. For example, in MPS VI subjects, ERT failed to ameliorate cardiac function, visual impairment, and bone density while inconsistent results have been reported in lung volumes (FEV1 and FVC), obstructive apnea parameters, joint range of motion and stiffness (Harmatz et al., 2006; Harmatz et al., 2008; Harmatz et al., 2005a; Harmatz et al., 2004). Third, ERT costs are extremely high, thus preventing access to therapy to several subjects especially in underdeveloped countries.
For these reasons, we believe gene therapy with a single systemic administration has enormous potential to provide long-term expression and secretion of ARSB enzyme from liver resulting in biochemical correction and ultimately in clinical benefit in MPS VI subjects, as observed in animal models (Cotugno et al., 2011; Cotugno et al., 2010; Ferla et al., 2014; Ferla et al., 2013; Tessitore et al., 2008).

Our results in non-clinical models suggest that gene therapy:
-may be more effective than ERT. We believe that this is possible, and even likely, based on the stable and long-term expression and phenotypic rescue we have obtained using gene transfer in large animal models (Cotugno et al., 2011; Ferla et al., 2013). In sharp contrast to the gene therapy, during ERT the

levels of ARSB drop to baseline within a few hours after the protein infusion (Harmatz et al., 2005d). Thus, given the significant difference in ARSB pharmacokinetics between the two approaches, we hypothesize that the stable levels of enzyme mediated by gene therapy result in improved enzyme biodistribution to body districts which are more resistant to ERT, such as bone or cartilage. The potential for long-term disease correction is indeed supported by the hemophilia B clinical trial with AAV2/8 expressing the factor IX (Nathwani et al., 2011.,Nathwani et al., 2014). This trial showed long-term expression of factor IX at levels, which were sufficient to improve the bleeding diathesis, with few side effects;

-may avoid the multiple infusions associated with ERT: our data in non-clinical models of MPS VI show that a single intravascular administration of AAV2/8.TBG.felineARSB results in expression of therapeutic levels of ARSB for up to 6 years, the last time point of our observation (Ferla et al., 2014, Cotugno et al 2011, Ferla unpublished data). Therefore, gene therapy may overcome the inconvenience and discomforts related to weekly infusions of recombinant enzyme. In addition, infusions of rhARSB may be associated with immune-mediated anaphylactoid reactions, presumably due to frequent infusions of the recombinant protein. The risk of such reactions may be avoided by the single administration of the gene therapy vector expressing ARSB.

Risks associated with gene therapy
However, gene transfer is a fairly new area of medicine and the long-term health effects are not fully known.
The gene therapy vector we propose to use may cause toxic response related to:

-Infusion of the IMP
The infusion itself may cause toxic reactions (fever, hives, skin rashes, low blood pressure, difficulty breathing, or death).

-Immune response to the IMP
The immune response system may generate antibodies to the vector as it does with all viruses. This antibody response will preclude any future administration of the same vector serotype in the subject receiving the vector, because the neutralizing antibodies (NAB) to AAV will completely prevent liver transduction (Ferla et al., 2013; Wang et al., 2010). However, participation in gene transfer studies using a different vector or different AAV vector serotypes may still be possible.

-Inflammation of the liver
In a clinical trial study with the AAV2/2 vector expressing the human Factor IX, an unexpected transient elevation in transaminases, beginning several weeks after vector infusion, was observed in 2 of 7 enrolled subjects. This increase in liver enzymes was asymptomatic and transient as the transaminases normalised after 6-8 weeks (Manno et al., 2006). This complication is thought to be secondary to previous exposure of the participants to the same virus. It is not

known if this liver inflammation, if it occurs, would be transient or would result in longer-lasting damage. In the most recent clinical trial for hemophilia B performed using the same AAV vector serotype proposed in our study, the increase in liver enzymes was observed with the higher dose and was controlled with a short course of prednisolone (Nathwani et al., 2011; Nathwani et al., 2014).

-Spread of the vector to other body tissues, including semen
Following IMP infusion, it is possible that the vector may spread into different tissues of the body. There is a theoretical risk that vector particles can enter the genetic information of germ cells or semen. In dose escalation clinical studies with AAV2/2 and AAV2/8 vectors expressing the human Factor IX, vector DNA was detected in the semen based on PCR analysis, raising the possibility of germline transmission (Manno et al., 2006; Nathwani et al., 2011; Nathwani et al., 2014). However, the presence of viral vector DNA in the semen was proved to be transient in all subjects, with younger subjects clearing more quickly than older ones. Moreover, animal studies suggested that AAV2/2 does not transduce spermatogonia directly (Arruda et al., 2001; Couto et al., 2004). Additionally, vector shedding in rabbit semen is transient and no late recurrence of AAV serotypes 2, 5, 6 and 8 was found over several consecutive cycle of spermatogenesis (Favaro et al. 2011; Favaro et al. 2009; Schuettrumpf et al. 2006; Arruda et al. 2001). We also performed a GLP germline transmission study in male rabbits (nr. 20140052TLP), which demonstrated that AAV2/8.TBG.hARSB shedding in semen is transient. This argues against the possibility of transduction of early spermatogenesis precursor exposed to AAV8 during the blood dissemination to the gonads. Therefore the risk of germline transmission can be considered minimal. However, in previous clinical trials based on systemic administration of AAVs, this potential complication was managed by recommending to all subjects to bank sperm before enrolment and to use barrier contraception methods until semen was negative for vector sequences.

-Potential risk of the IMP to cause cancer
The first evidence about the risk of cancer came from a study in MPSVII mice that were found to develop hepatocellular carcinoma following neonatal AAV injections (Donsante et al., 2007). These findings were also observed more recently in methylmalonic acidemia mice which also developed hepatocellular carcinoma several months after neonatal AAV injections and showed vector integration and overexpression of microRNA-341 (Mir341) proximal to the Rian locus, that has no orthologues in humans (Chandler et al., 2015). Similarly, a higher frequency of hepatocellular carcinoma was observed in molybdenum cofactor deficient mice injected with AAV as newborns (Reiss and Hahnewald, 2011). In contrast, no evidence of insertional mutagenesis and cancer were observed in adult mice for 18 months (Li et al., 2011), in dogs for a period of 8 years (Niemeyer et al., 2009), and in nonhuman primates for up to 5 years (Nathwani et al., 2011).
A recent study found clonal integration of AAV2 in 11 of 193 cases of

hepatocellular carcinoma. These AAV2 integrations occurred in known cancer driver genes (CCNA2, TERT, CCNE1, TNFSF10, and KMT2B) leading to overexpression of the target genes. Tumors with viral integration mainly developed in non-cirrhotic liver (9 of 11 cases) and without known risk factors (6 of 11 cases), suggesting a pathogenic role for AAV2 in these patients (Nault et al., 2015). However, integration pattern of recombinant AAVs is different than that of wild type AAVs (Huser et al 2014) and the gap between the high rate of AAV2 infection in human population and the rare occurrence of HCC with AAV2 integration come out in favor of its safety. Additionally, a recent study showed recombinant AAV5 integration is not associated with hepatic genotoxicity in non human primates and patients (Gil-Farina et al 2016)

Contacts

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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. Subjects must have a documented biochemical and molecular diagnosis of MPS VI.
2. Subjects must be 4 years old or older.
3. Subjects should have received Enzyme Replacement Therapy (ERT) for at least 12 months before enrolment, and should continue to receive treatment until 7-14 days before IMP administration.
4. Documented informed consent; willingness to adhere to protocol and required long-term follow-up as evidenced by written informed consent.

Exclusion criteria

1. Subjects unable or unwilling to meet requirements of the study.
2. Participation in a clinical study with an investigational drug in the 6 months prior to enrolment in this trial.
3. Subjects who are unable to perform the 6MWT.
4. History of severe anaphylactoid reaction to Naglazyme in subjects receiving ERT that could affect the safety (severe reaction is meant to be an event with respiratory impairment that is life-threatening).
5. Presence of tracheostomy or need of ventilatory assistance.
6. Subjects with evidence of progressive severe myelomalacia that is predicted to require neck surgery in the first six months after enrolment.
7. Serum AST or ALT above the upper limit of normal range at the baseline evaluations (Baseline 2, -5 days).
8. Co-existence of chronic diseases or clinically relevant abnormal baseline laboratory values; infections with hepatitis B, C, or HIV (Baseline 1).
9. Systemic corticosteroid therapy or other immunosuppressive/immunomodulating drugs within 2 weeks prior to IMP administration.
10. Female individuals of childbearing age who are pregnant or nursing or unwilling to use effective contraception for at least one year post-IMP administration.
11. Fertile male individuals who are unwilling to use male barrier contraceptives such as condom.
12. Any other condition that would not allow the subject to complete follow-up examinations during the course of the study and that, in the opinion of the Investigator, would make the subject unsuitable for the study.
13. Detectable serum neutralizing antibodies (NAB) against AAV8 vector (Screening)
14. Presence of serum antibodies anti-ARSB above the limit of detection of the assay (antibodies anti-ARSB titer >31250 or positive to the value of dilution 1:10 according to the performed assay) at Screening.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	31-05-2017
Enrollment:	4
Type:	Anticipated

Ethics review

Approved WMO Date:	05-03-2018
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	29-10-2018
Application type:	First submission
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	EUCTR2016-002328-10-NL
CCMO	NL60768.000.17