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Gene therapy in children with mucopolysaccharidosis II (MPSII) consented below the age of 22 months

Submission date
06/05/2022

Recruitment status
Recruiting

Registration date
07/09/2022

Overall study status
Ongoing

Last Edited
10/06/2025

Condition category
Genetic Diseases

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Mucopolysaccharidosis Type II is also referred to as MPS II or Hunter Syndrome. This is one of a family of diseases referred to as lysosomal storage diseases. MPS II is an x-linked inherited disease that means the person affected is missing a gene which codes for a specific enzyme (iduronate-2-sulphastase [IDS]). Without this enzyme, two waste products build up in cells in the body causing the symptoms seen in MPS II – delayed development, progressive deteriorating mental status and behavioural problems. Currently, enzyme replacement therapy (ERT) is the only approved treatment available for patients diagnosed with MPSII. However, ERT is a supportive therapy and is intended to alleviate symptoms and improve patient quality of life, rather than addressing the pathogenic mechanisms of the disease. To date, there is no effective disease-modifying treatment. In children with other MPS conditions it has been shown that it is possible to provide enzyme to cells in the body by a bone marrow transplant – transplanted cells from a donor, able to make the absent enzyme and secrete to other cells through the blood, however, in MPS II a bone marrow transplant does not seem to deliver enough enzyme to the cells to get rid of the waste product. The treatment proposed hopes to deliver increased amounts of the enzyme to the cells by genetic manipulation of the patient's own cells to include the missing IDS gene.

Who can participate?
Patients aged between 3 months and 22 months at consent into the trial, with the severe (progressive neuronopathic) phenotype of MPSII.

What does the study involve?
The treatment process can be broken down into three stages: stem cell collection, chemotherapy conditioning and infusion of gene-modified cells. Patients will be followed up at regular intervals for 2 years initially. All of the treatment and follow-up conducted will be at Manchester University Foundation Trust.

What are the possible benefits and risks of participating?
This a new treatment for children with MPS II and carries a series of risks associated with

haematopoietic stem cell transplant as well as the gene therapy component. Some of these risks are predictable and can be closely monitored for and treated. Some risks are unpredictable and will require quick recognition and appropriate response from the medical team. The risks can be divided into three categories:

1. Stem cell collection:
The medicines used to move stem cells from the bone marrow to the bloodstream (GCS-F and Plerixafor) can cause some children to feel unwell with fevers, aches and pains. This can usually be well controlled with pain medication. The process of cell collection can also cause some children nausea, tingling sensations or changes in blood pressure. Children are closely monitored and appropriate treatment given as required.

2. Chemotherapy conditioning and transplant:
Busulfan is the chemotherapy agent used to prepare the patient's bone marrow prior to transplant. It can cause patients to feel sick, have diarrhoea, mucositis (sore mouth/ulcers) stomach pain, hair loss, bone marrow failure and in some cases seizures and blood clots in the liver (veno-occlusive disease [VOD]). Children are closely monitored during and after the administration of busulfan. Medicine to help with nausea, sickness, pain and to prevent blood clots will be given as part of the planned treatment to reduce some of the side effects of busulfan.
During transplant a patient will often need support with blood products including infusions of red cells and platelets. They may also require support with eating and drinking which can be given through a central line.
The chemotherapy used during transplant can increase the risk of a patient developing infections which could be bacterial, viral or fungal. Medicine is used to try and prevent including penicillin, aciclovir, itraconazole and co-trimoxazole.
Infection can be serious and can be fatal, even with drugs to both prevent and treat infection and despite intensive surveillance of infection. The infection management is the same as for other children undergoing bone marrow transplant.
During both the process of stem cell collection and transplant a central line will be required. The insertion of central venous lines carries the risks of bleeding, infection and clots. The risks of these events occurring is low, however, the staff within the children's hospital are well-trained in managing these potential events.
The gene-modified cells are frozen using a chemical called dimethylsulfoxide (DMSO) which is used to protect the cells. When the cells are defrosting they can have a strong odour and make some people feel nauseated. Children will be closely monitored during the infusion.
Lumbar punctures (where a needle is inserted in the lower spine) are needed periodically to collect cerebrospinal fluid (CSF) whilst under local anaesthetic. This procedure frequently causes headaches, nausea and backache. More rarely, this can cause delayed bleeding at site of insertion, or infection. Rarer complications include collection of blood in the lining outside the brain, lower limb weakness, movement of the brain, and injury to the nerves of the face. These effects can be treated and can be resolved in almost all cases.

3. Gene-modified cells:
As a novel treatment there remains some uncertainty around the potential for these gene-modified cells to cause side effects. Some proposed potential side effects include:
3.1. The risk of the gene being inserted near an area of DNA which may cause cancer. In the studies done in both animals and humans using similar techniques to this treatment, this has not been recognised, however, will be monitored for.
3.2. The risk that the virus being used to insert the missing enzyme is able to replicate its pathological DNA and cause infection in the patient. This is thought to be very unlikely, as the required DNA to package pathological material has been removed. No studies using this or

similar viruses have ever reported this happening.
3.3. A small risk that the ApoEII tag that is part of the modified IDS gene may cause adverse immune responses. This has not been observed in pre-clinical tests.
3.4. That there may be allergic or immunological reactions to the enzyme expressed or the products used to store the cell product safely.
3.5. That the insertion of the gene will interfere with the ability of the modified stem cells to engraft in the marrow. If graft failure were to happen, then we would infuse stem cells stored as a backup at the time of stem cell collection, which have not been gene-modified.
Being aware and prepared for the possibility of these risks will help in planning ways to manage them if they were to arise.

Where is the study run from?
University of Manchester (UK)

When is the study starting and how long is it expected to run for?
May 2022 to April 2028

Who is funding the study?
LifeArc (UK)

Who is the main contact?
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Additional identifiers

EudraCT/CTIS number
2021-000400-38

IRAS number
1004283

ClinicalTrials.gov number
NCT05665166

Secondary identifying numbers
R125432, IRAS 1004283

Study information

Scientific Title
A Phase I/II, study of autologous CD34+ haematopoietic stem cells transduced ex vivo with CD11B lentiviral vector encoding human IDS tagged with ApoEII in patients with neuronopathic mucopolysaccharidosis type II (nMPS II, Hunters syndrome)

Study objectives
The main objective is to look at the safety of the gene therapy in patients. Safety includes engraftment of the gene therapy, short-term safety and longer term safety.

Safety of the transplant will include adverse events from the transplant itself and the chemotherapy required before transplant. Following transplant, the researchers will monitor how long it takes for engraftment of the modified cells via production of new gene modified blood cells. They will also look at how the body responds and whether there are any serious reactions to the therapy.

Over the next 24 months the researchers will look at safety around the therapy, checking that there is no unusual growth of the modified cells, no live virus present and no adverse reactions to the newly expressed IDS enzyme.

The secondary and exploratory objectives will be used to evaluate the effectiveness of the therapy in patients.

The researchers will monitor how the body responds to the therapy by looking at changes in IDS enzyme activity throughout the body as a direct result of the introduction of a normal copy of the IDS gene from the gene therapy and how many copies of the gene have been added. They will also look at the substrate of the IDS enzyme and see whether the build up of heparan and dermatan sulphate are changed.

Untreated, MPSII patients show a decline in development so the researchers will look at patient behaviour, sleep and quality of life on them and their families using tests and questionnaires. They will also look for changes in symptoms throughout the body such as breathing problems, hearing issues and changes in height and weight.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 06/09/2022, London – West London & GTAC (The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS, UK; +44 (0)207 1048 007; westlondon.rec@hra.nhs.uk), ref: 22/LO/0386

Study design
Non-randomized single-arm open-label study

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)

Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Mucopolysaccharidosis type II (MPS II or Hunter Syndrome)

Interventions
The protocol treatment is a cryopreserved formulation of autologous CD34+ cells transduced with a lentiviral vector containing the human IDS gene tagged with ApoEII (IMP). The recommended IMP dose range is between 3.0 to 30.0 x106 CD34+ cells/kg. The actual dose will depend on the yield of cells available from the leukapheresis of the patient and the subsequent yield after transduction. The IMP is a one-time gene therapy treatment delivered intravenously. The study is non-randomised, single-arm and open-label.

Intervention Type
Biological/Vaccine

Phase
Phase I/II

Drug/device/biological/vaccine name(s)
Cryopreserved autologous CD34+ haematopoietic stem cells transduced ex vivo with CD11B lentiviral vector encoding human IDS tagged with ApoEII

Primary outcome measure
Safety of the IMP, including engraftment, absence of significant regimen-related toxicity, absence of short term infusion reactions and of long term vector related integration events. Safety and tolerability will be assessed throughout the full 2 years of the study from IMP administration by evaluating adverse events (AEs), clinical laboratory test results (haematology, chemistry and urinalysis), vital signs measurements, electrocardiogram (ECG), physical examination results, and concomitant medication usage.

Secondary outcome measures
1. Heparan sulphate in cerebrospinal fluid (CSF) (at baseline, 3, 6, 12, and 24 months post-IMP), plasma (at baseline, 1, 3, 6, 9, 12, 18 and 24 months post-IMP) and urine (at baseline, 1, 3, 6, 9, 12, 18 and 24 months post-IMP) (and glycosaminoglycan (GAG) ratio in urine by dimethylmethylene blue [DMB]) measured using total GAG analysis
2. IDS enzyme activity in plasma (at baseline, 1, 3, 6, 9, 12, 18 and 24 months post-IMP), total leucocytes (at baseline, 1, 3, 6, 9, 12, 18 and 24 months post-IMP) and CSF (at baseline, 3, 6, 12, and 24 months post-IMP) within or above normal range measured using an IDS enzyme activity assay
3. VCN in total leucocyte (at baseline and 1, 3, 6, 9, 12, 18 and 24 months post-IMP) and the bone marrow (at baseline and 1, 6, 12 and 24 months post-IMP) measured using RT-qPCR
4. Proportion of cells containing the inserted IDS.ApoEII gene in total bone marrow colony forming units (CFUs) measured using RT-qPCR at baseline, 1, 6, 12 and 24 month’s post-IMP

5. IDS enzyme activity in the bone marrow within or above normal range measured using an IDS enzyme activity assay at baseline, 6, 12 and 24 months post-IMP treatment
6. Cognitive scores (standard scores, age-equivalent scores and development quotient) measured using the Bayley Scales of Infant Development, 3rd Edition (BSID-III) or Kaufman Assessment Battery for Children, 2nd Edition (KABC-II) at baseline, 6, 12, 18 and 24 months post-IMP treatment
7. Adaptive behaviour (age-equivalent scores) measured using the Vineland Adaptive Behaviour Scales, 3rd Edition (VABS-III) at baseline, 6, 12, 18 and 24 months post-IMP treatment
9. Parent/caregiver quality of life (QoL) measured at baseline, 6, 12 and 24 months post-IMP treatment using:
9.1. Parenting Stress Index (overall level of parenting stress experienced by parents of children)
9.2. Beck Depression Inventory, second edition
9.3. Paediatric QoL Inventory (PedsQL) Family Impact Module

Exploratory:
1. Dermatan sulphate in CSF (at baseline, 3, 6, 12, and 24 months post-IMP), plasma (at baseline, 1, 3, 6, 9, 12, 18 and 24 months post-IMP) and urine (at baseline, 1, 3, 6, 9, 12, 18 and 24 months post-IMP) (and GAG ratio in urine by DMB) measured using total GAG analysis
2. IDS enzyme activity in subpopulations (i.e., CD3+, CD15+, CD19+ cells) measured using IDS enzyme activity assay at baseline, 1, 3, 6, 9, 12, 18 and 24 months post-IMP
3. VCN in blood subpopulations (CD3+, CD15+, CD19+ cells) measured using RT-qPCR at baseline, 1, 3, 6, 9, 12, 18 and 24 months post-IMP
4. Obstructive sleep apnoea assessed by polysomnography (using the apnoea-hypopnoea index [AHI]) at baseline, 6, 12 and 24 months post-IMP
5. Presence and persistence of anti-IDS antibodies in blood (at baseline, 1, 3, 6, 9, 12, 18 and 24 months post-IMP) and CSF (at baseline, 3, 6, 12, and 24 months post-IMP) measured using an anti-IDS antibody assay
6. Hearing measured using age-appropriate hearing assessments at baseline, 12 and 24 months post-IMP
7. Height measured by standard calibrated stadiometer from the age they can stand independently, prior to this measuring length, at baseline, 1, 3, 6, 9, 12, 18 and 24 months post-IMP
8. Presence of exploratory biomarkers in bodily fluids measured using differing laboratory assays at baseline, 1, 3, 6, 9, 12, 18 and 24 months post-IMP
9. Cognitive score (GSV) measured using the Bayley Scales of Infant Development, 3rd Edition (BSID-III) or Kaufman Assessment Battery for Children, 2nd Edition (KABC-II) at baseline and 6, 12, 18 and 24 months post-IMP
10. Adaptive behaviour (GSV) measured using the Vineland Adaptive Behaviour Scales, 3rd Edition (VABS-III) at baseline and 6, 12, 18 and 24 months post-IMP
11. Rate of fidelity analysis of neurocognitive assessments looking at the quality of interactions at baseline, 6, 12, 18 and 24 months post-IMP treatment
12. Parental reported observations of child's development at baseline, 6, 12, 18 and 24 months post-IMP treatment

Overall study start date
03/05/2022

Completion date
30/04/2028

Eligibility

Key inclusion criteria
1. Written informed consent from a legally authorized guardian
2. Male, age at consent ≥3 months and ≤12 months - updated 16/09/2024: ≥3 months and ≤22 months
3. Normal cognitive function or mild cognitive dysfunction (patient has a Development Quotient [DQ] score ≥70 at screening as determined by the Bayley Scale of Infant Development-third edition (BSID-III), cognitive domain), or assessed as normal or only mildly impaired by experienced neuropsychologist
4. Close male relative with known severe (progressive neuronopathic) phenotype of MPSII, or genotype associated with progressive neuronopathic phenotype. This is to be confirmed by the independent expert reviewers.
5. IDS activity ≤10% of the Lower Limit of Normal as measured in leucocytes or plasma, plus either:
5.1. A normal enzyme activity level of at least one other sulfatase (to rule out multiple sulfatase deficiency) as measured in leucocytes, or
5.2. A documented mutation in the IDS gene
6. Medically stable and able to accommodate the protocol requirements, including travel without placing an undue burden on the patient/patient's family, as determined by the CI
7. Patients and their parents/legal guardians must be willing and able to comply with study restrictions and to commit to attend clinic for the required duration during the study and follow-up period as specified in the protocol

Participant type(s)
Patient

Age group
Child

Lower age limit
3 Months

Upper age limit
22 Months

Sex
Male

Target number of participants
5

Key exclusion criteria
1. The patient has previously received stem cell or gene therapy
2. The patient has received modified intravenous ERT or intrathecal ERT in a trial setting
3. Patient currently enrolled in another interventional clinical trial
4. The patient has a history of poorly controlled seizures
5. Hemizygous for mutation known to be associated with non-neuropathic phenotype
6. The patient is currently receiving psychotropic or other medications which, in the CI's opinion, would be likely to substantially confound test results
7. The patient has received any investigational medicinal product (including Genistein) within 30 days prior to the Baseline visit or is scheduled to receive any investigational medicinal product

during the course of the study
8. Documented Human Immunodeficiency Virus (HIV) infection (positive HIV RNA and/or anti-p24 antibodies)
9. Malignant neoplasia (except local skin cancer) or a documented history of hereditary cancer syndrome. Patients with a prior successfully treated malignancy and a sufficient follow-up to exclude recurrence (based on oncologist opinion) can be included after discussion and approval by the Medical Monitor
10. Myelodysplasia, cytogenetic alterations characteristic of myelodysplastic syndrome and acute myeloid leukaemia, or other serious haematological disorders
11. The patient has a medical condition or extenuating circumstance that, in the opinion of the CI, might compromise the patient's ability to comply with protocol requirements, the patient's well-being or safety, or the interpretability of the patient's clinical data
12. Visual or hearing impairment sufficient to preclude adequate neurodevelopmental testing
13. Severe behavioural disturbances due to reasons other than MPS II and likely to interfere with protocol compliance, as determined by the CI
14. Known sensitivity to Busulfan
15. The receipt of live vaccinations within 30 days prior to treatment start
16. Known sensitivity to DMSO

Date of first enrolment
24/03/2023

Date of final enrolment
31/03/2026

Locations

Countries of recruitment
United Kingdom

Study participating centre
Not provided at time of registration
United Kingdom
-

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ROR
https://ror.org/027m9bs27

Funder(s)

Funder type
Charity

Funder Name
LifeArc

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Results and Publications

Publication and dissemination plan
1. Peer-reviewed scientific journals
2. Conference presentation
3. Publication on website
4. Information in the PIS and statement in the Consent Form for participants samples and anonymised data being transferred to commercial entities such as the funder and other authorised representatives for the purposes of research and the development of gene therapy products, services and therapies for commercialisation as described in the Information Sheet.

Intention to publish date
01/10/2026

Individual participant data (IPD) sharing plan

The data-sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary

Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No