ISRCTN19853672 https://doi.org/10.1186/ISRCTN19853672

Intra-cerebral gene therapy for Sanfilippo type B syndrome

Submission date	Recruitment status	[X] Prospectively registered
30/09/2010	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
03/08/2011	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
30/09/2021	Nutritional, Metabolic, Endocrine	

Plain English summary of protocol

Background and study aims
Sanfilippo syndrome, also known as mucopolysaccharidosis type III (MPS III), is a rare genetic disorder. There are four types (A to D). Sanfilippo syndrome subtype B, or mucopolysaccharidosis type IIIB (MPSIIIB), is caused by a genetic defect of the enzyme α-N-acetylglucosaminidase (NAGLU). This enzyme is involved in breaking down long chains of sugar molecules. In its absence, these molecules build up. This causes brain damage starting most often during the first 5 years of life. Affected children require specific care and death occurs at the average age of 15, although some patients are still alive after the age of 20. MPSIIIB could be treated by delivering the correct gene for the missing enzyme using a virus (gene therapy). The aim of this study is to test this gene therapy approach in patients with MPSIIIB.

Who can participate?
Patients age 18 months to 5 years with MPSIIIB

What does the study involve?
Participants receive gene therapy combined with immunosuppressant drugs (to suppress the strength of the body's immune system). The virus is injected into the brain at 6 injection sites in a single session. Clinical and x-ray examinations are carried out and blood and cerebrospinal fluid samples are taken before and after treatment, with daily follow-up during 1 week after the injections, then 14 and 21 days, 1, 3, 6 and 12 months after treatment.

What are the possible benefits and risks of participating?
Not provided at time of registration

Where is the study run from?
Hôpital Bicêtre (France)

When is the study starting and how long is it expected to run for?
September 2013 to November 2015

Who is funding the study?
1. French Patient Association (France)
2. Private donations (France)

Who is the main contact?
Prof. Marc Tardieu

Contact information

Type(s)
Scientific

Contact name
Prof Marc Tardieu

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Additional identifiers

Protocol serial number
MPS3-IP-01

Study information

Scientific Title
A phase I/II, open-label, study of intracerebral administration of adeno-associated viral vectors carrying human NaGlu cDNA for the treatment of Sanfilippo type B syndrome

Acronym
MPS3B

Study objectives
There is currently no available treatment for Sanfilippo syndrome. The rationale for therapeutic approaches in mucopolysaccharidoses (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, there is still not currently available for MPSIIIB.

On the other hand, MPS have long been recognized as prime candidate diseases for gene therapy as it was shown that the missing enzyme may 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.

However, 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.

In MPSIII, a direct administration into the brain would be required, since most lesions take place in this organ.

Ethics approval required
Old ethics approval format

Ethics approval(s)
CCP Il-de-France II, 17/04/2013, ref: 2013-03-17

Primary study design
Interventional

Study design
Phase I/II single-arm open-label study

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Mucopolysaccharidose - neurodegenerative disease

Interventions
Patients will receive gene therapy combined with immunosuppressant regimen. The vector is a serotype 2 AAV genome encoding the human α-N-acetylglucosaminidase cDNA packaged in a serotype 5 capsid called AAV-NAGLU. Vector suspensions will be simultaneously injected into the brain parenchyma at 6 injections sites in a single neurosurgical session. Combined immunosuppression (Tacrolimus, Cell-Cept) is justified by previous studies in children receiving recombinant enzyme infusions and investigations of AAV-mediated gene therapy in Sanfilippo and Hurler dogs.

Clinical and radiological examination, collection of biological products including blood, peripheral blood mononucleated cells and cerebrospinal fluid (CSF) > 6 weeks prior to treatment, at inclusion, baseline, 14 days prior to treatment, observation and -2 and -1 days, daily follow-up during 1 week post-injection, then 14 and 21 days, 1, 3, 6 and 12 months post-treatment.

The total duration of follow up is 1 year.

Added 02/08/2013:
Vectors will be delivered through 8 small burr holes. Two in the posterior fossa to target the white matter of the cerebellar hemisphers and six supratentorially, to target the white matter adjacent to the putamen. Two deposits will be done on each track, one deep and one superficial, in a single neurosurgical session.

Intervention Type
Drug

Phase
Phase I/II

Drug/device/biological/vaccine name(s)
Intra-cerebral gene therapy

Primary outcome(s)
Clinical, radiological, biological tolerance associated to the proposed treatment

Key secondary outcome(s)
Collection of data to define exploratory tests that will become evaluation criteria for further clinical phase III efficacy studies (brain MRI; neurological and biological markers)

Completion date
01/11/2015

Eligibility

Key inclusion criteria
1. Age: 18 months to the end of the 5th year
2. Onset of clinical manifestations related to MPSIIIB during the first 5 years of life
3. NaGlu activity in peripheral blood cell and/or cultured fibroblast extracts of less than 10% of controls
4. Patient affiliated to a social security regimen
5. Family understanding the procedure and the informed consent
6. Vital laboratory parameters within normal range

Sanfilippo disease is a rare disease and so the countries of recruitment will depend on the availabilities of the patient at the time of recruitment. There will be one study centre in France.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Child

Lower age limit
18 Months

Upper age limit
5 Years

Sex
All

Total final enrolment
4

Key exclusion criteria
1. Presence of brain atrophy on pre-inclusion MRI judged on a cortico-dural distance of more than 1 cm
2. Any condition that would contraindicate permanently anaesthesia
3. Any other permanent medical condition not related to MPSIIIB
4. No independent walking (Ability to walk without help)
5. Any vaccination 1 month before vector injection
6. Receipt of aspirin within one month
7. Any medication aiming at modifying the natural course of MPSIIIB given during the 6 months before vector injection

Date of first enrolment
01/09/2013

Date of final enrolment
01/11/2015

Locations

Countries of recruitment
France

Study participating centre
Hôpital Bicêtre
Le Bicêtre-Bicêtre
France
94275

Sponsor information

Organisation
Institut Pasteur (France)

ROR
https://ror.org/0495fxg12

Funder(s)

Funder type
Charity

Funder Name
French Patient Association (France)

Funder Name
Private donations (France)

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/09/2017	18/12/2020	Yes	No
Results article	results	10/05/2021	30/09/2021	Yes	No