# Clinical trial results:
# A phase I/II, open-label, study of intracerebral administration of adeno-associated viral vector containing the human alpha-N-acetylglucosaminidase cDNA in children with Sanfilippo type B syndrome

## Summary

| | |
|---|---|
| EudraCT number | 2012-000856-33 |
| Trial protocol | FR |
| Global end of trial date | 27 November 2019 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 12 December 2020 |
| First version publication date | 12 December 2020 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | AMT110-CD-001 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | ISRCTN19853672 |
| ClinicalTrials.gov id (NCT number) | NCT03300453 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | uniQure biopharma B.V |
| Sponsor organisation address | Paasheuvelweg 25A, Amsterdam, Netherlands, 1105BP |
| Public contact | Elise Destree, Elise Destree, +31 20 240 6000, E.Destree@uniqure.com |
| Scientific contact | Elise Destree, Elise Destree, +31 20 240 6000, E.Destree@uniqure.com |

Notes:

**Paediatric regulatory details**

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 27 November 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 27 November 2019 |
| Global end of trial reached? | Yes |
| Global end of trial date | 27 November 2019 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the clinical, radiological, biological tolerance associated to the proposed treatment

Protection of trial subjects:

Appropriate inclusion and exclusion criteria were applied.
An IDMC was appointed to
- be informed on the research protocol, informed consent documents and data safety reporting plans and monitoring plan;
- review the study performance and safety data and make recommendation(s) to the Sponsor on further study conduct, including:
o inclusion of the next patient in the protocol depending on clinical evolution of the already/previously treated subjects at 1 month after the immediate previous one,
o continuation of the trial,
o termination of the trial,
o modification to the trial;
by assessing the study progress, safety data and especially SUSARs.

Background therapy:

The following immunosupressive/anti-inflammatory agents were used:
- Modigraf (tacrolimus) - starting at 10 - 15 ng/mL, reducing progressively over the course of the study.
- Cellcept (mycophenolate mofetil) - 1200 mg/m2 for 2 weeks pre-surgery and 6 weeks post surgery.
- Prednisolone - 1mg/kg - for 10 days, starting on the day of surgery.

Evidence for comparator:

n/a

| | |
|---|---|
| Actual start date of recruitment | 17 September 2013 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety |
| Long term follow-up duration | 66 Months |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | France: 4 |
| Worldwide total number of subjects | 4 |
| EEA total number of subjects | 4 |

Notes:

| Subjects enrolled per age group | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 1 |
| Children (2-11 years) | 3 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

The study began on 17 September 2013 and 4 patients were enrolled on the study.

### Pre-assignment

Screening details:

Patients were screened against the eligibility criteria.
As the study consisted of a first in human trial, the patient recruitment was sequential.

### Period 1

| | |
|---|---|
| Period 1 title | Initial Phase (Until M12) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Blinding implementation details:

n/a

### Arms

| | |
|---|---|
| **Arm title** | Human NAGLU gene - initial |

Arm description:

Patients received a one-time treatment with human NAGLU gene

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | rAAV2/5-hNaGlu |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intracerebral use |

Dosage and administration details:

Administration of the investigational product (solution for injection) into the brain parenchyma and cerebellum at 8 image-guided tracks (6 cortical white matter, 2 cerebellum), with 2 deposits per track at different depths, in a single neurosurgical session. Each patient received 960 µL of vector suspension at 16 simultaneous vector deposit each containing 2.4x1011 vg (4x1012 vg in total) on Day 0 (study initial phase).

| **Number of subjects in period 1** | Human NAGLU gene - initial |
|---|---|
| Started | 4 |
| Completed | 4 |

| **Period 2** | |
|---|---|
| Period 2 title | Extension Phase 1 (M12 to M30) |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |
| Blinding implementation details:<br>n/a | |

| **Arms** | |
|---|---|
| **Arm title** | Extension Phase 1 |
| Arm description:<br>Follow up -Extension Phase 1 | |
| Arm type | Follow Up |
| No investigational medicinal product assigned in this arm | |

| **Number of subjects in period 2** | Extension Phase 1 |
|---|---|
| Started | 4 |
| Completed | 4 |

| **Period 3** | |
|---|---|
| Period 3 title | Extension Phase 2 (M30 to M66) |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |
| Blinding implementation details:<br>n/a | |

| **Arms** | |
|---|---|
| **Arm title** | Extension Phase 2 |
| Arm description:<br>Follow-up - Extension Phase 2 | |
| Arm type | Follow Up |
| No investigational medicinal product assigned in this arm | |

| **Number of subjects in period 3** | Extension Phase 2 |
|---|---|
| Started | 4 |
| Completed | 4 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Human NAGLU gene - initial |
| Reporting group description: | |
| Patients received a one-time treatment with human NAGLU gene | |

| Reporting group values | Human NAGLU gene - initial | Total | |
|---|---|---|---|
| Number of subjects | 4 | 4 | |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 1 | 1 | |
| Children (2-11 years) | 3 | 3 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 0 | 0 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Gender categorical<br>Units: Subjects | | | |
| Not specified | 4 | 4 | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Human NAGLU gene - initial |
| Reporting group description: | |
| Patients received a one-time treatment with human NAGLU gene | |
| Reporting group title | Extension Phase 1 |
| Reporting group description: | |
| Follow up -Extension Phase 1 | |
| Reporting group title | Extension Phase 2 |
| Reporting group description: | |
| Follow-up - Extension Phase 2 | |

### Primary: Adverse Events

| | |
|---|---|
| End point title | Adverse Events[1] |
| End point description: | |
| All AEs identified in the period | |
| End point type | Primary |
| End point timeframe: | |
| As specified by the period | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical tests were performed. All patients received the same treatment. The primary objective was to look at safety.

| End point values | Human NAGLU gene - initial | Extension Phase 1 | Extension Phase 2 | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 4 | 4 | 4 | |
| Units: Number of events | 63 | 60 | 32 | |

### Statistical analyses

No statistical analyses for this end point

### Primary: Serious Adverse Events

| | |
|---|---|
| End point title | Serious Adverse Events[2] |
| End point description: | |
| | |
| End point type | Primary |
| End point timeframe: | |
| As specified by the period | |

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical tests were performed. All patients received the same treatment. The primary objective was to look at safety.

| End point values | Human NAGLU gene - initial | Extension Phase 1 | Extension Phase 2 | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 4 | 4 | 4 | |
| Units: Number of SAEs | 1 | 6 | 3 | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Assessed throughout study

Adverse event reporting additional description:

Adverse events were assessed throughout the study. They data was collected in 3 time periods:
- Initial Phase (Until M12)
- Extension Phase 1 (M12 to M30)
- Extension Phase 2 (M30 to M66)

| | |
|---|---|
| Assessment type | Non-systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 18 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Initial Phase |

Reporting group description:

Adverse events collected in the Initial Phase 1

| | |
|---|---|
| Reporting group title | Extension Period 1 |

Reporting group description:

Adverse events collected in Extension Phase 1 (M12 to M30)

| | |
|---|---|
| Reporting group title | Extension Period 2 |

Reporting group description:

Adverse events collected in Extension Phase 2 (M30 to M66)

| Serious adverse events | Initial Phase | Extension Period 1 | Extension Period 2 |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 2 / 4 (50.00%) | 3 / 4 (75.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Nasal polyps | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 4 (0.00%) | 1 / 4 (25.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Transaminases increased | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 4 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |

| | | | |
|---|---|---|---|
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 4 (25.00%) | 2 / 4 (50.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pneumonia respiratory syncytial viral | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 4 (25.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia adenoviral | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 4 (25.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Escherichia pyelonephritis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 4 (25.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Electrolyte imbalance | Additional description: Hydroelectolytic disorders linked to the bacterial infection | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 4 (25.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

Frequency threshold for reporting non-serious adverse events: 0 %

| **Non-serious adverse events** | Initial Phase | Extension Period 1 | Extension Period 2 |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 4 / 4 (100.00%) | 4 / 4 (100.00%) | 4 / 4 (100.00%) |
| Surgical and medical procedures | | | |
| Central venous catheterisation | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 4 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Adenoidectomy | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 4 (25.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|---|---|---|---|
| Ear tube insertion | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 4 (25.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 3 / 4 (75.00%) | 3 / 4 (75.00%) | 2 / 4 (50.00%) |
| occurrences (all) | 5 | 7 | 2 |
| Gait disturbance | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 4 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hyperthermia | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 4 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Inflammation | | | |
| subjects affected / exposed | 2 / 4 (50.00%) | 0 / 4 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 4 (25.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Reproductive system and breast disorders | | | |
| Balanoposthitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 4 (25.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Rhinitis | | | |
| subjects affected / exposed | 4 / 4 (100.00%) | 1 / 4 (25.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 9 | 1 | 2 |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 2 / 4 (50.00%) | 2 / 4 (50.00%) |
| occurrences (all) | 1 | 3 | 4 |
| Bronchitis chronic | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 4 (25.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cough | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 4 (0.00%) | 2 / 4 (50.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 3 | 1 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 4 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Psychiatric disorders | | | |
| Abnormal behaviour | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 4 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Agitation | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 4 (0.00%) | 2 / 4 (50.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Sleep disorder | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 4 (25.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 1 | 1 |
| Investigations | | | |
| Carbon dioxide decreased | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 4 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Haematocrit decreased | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 4 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 4 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Protein total decreased | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 4 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Red blood cell count decreased | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 4 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Transaminases increased | | | |
| subjects affected / exposed | 2 / 4 (50.00%) | 0 / 4 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Alanine aminotransferase increased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 4 (0.00%) | 2 / 4 (50.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 4 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Epstein-Barr virus test positive | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 4 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Carbon dioxide increased | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 4 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 4 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Immunosuppressant drug level increased | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 4 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Magnetic resonance imaging brain abnormal | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 4 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Varicella virus test positive | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 4 (25.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Vitamin D decreased | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 4 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Cardiac disorders | | | |
| Left ventricular dysfunction | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 4 (25.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Mitral valve incompetence | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 4 (25.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nervous system disorders | | | |

| | | | |
|---|---|---|---|
| Cerebellar atrophy | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 4 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Cerebral haemosiderin deposition | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 4 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Psychomotor hyperactivity | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 2 / 4 (50.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Presyncope | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 4 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 2 / 4 (50.00%) | 1 / 4 (25.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 2 | 1 | 1 |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 4 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Splenomegaly | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 4 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Ear and labyrinth disorders | | | |
| Otitis media | | | |
| subjects affected / exposed | 2 / 4 (50.00%) | 2 / 4 (50.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 3 | 3 | 1 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 2 / 4 (50.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 1 | 4 | 1 |
| Tonsillectomy | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 4 (25.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 4 (75.00%) | 3 / 4 (75.00%) | 2 / 4 (50.00%) |
| occurrences (all) | 6 | 6 | 2 |
| Vomiting | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 4 (25.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 2 / 4 (50.00%) | 0 / 4 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Hepatobiliary disorders | | | |
| Hepatotoxicity | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 4 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hypertransaminasaemia | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 4 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis allergic | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 4 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dermatitis atopic | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 4 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Infections and infestations | | | |
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 4 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Ear infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 2 / 4 (50.00%) | 3 / 4 (75.00%) |
| occurrences (all) | 0 | 3 | 3 |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 4 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Infectious mononucleosis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 4 (25.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Otitis externa | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 4 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Viral infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 4 (75.00%) | 2 / 4 (50.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 3 | 2 | 0 |
| Lung disorder | Additional description: Lung infection | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 4 (25.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Varicella | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 4 (25.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pharyngitis | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 1 / 4 (25.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 4 (25.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 05 November 2013 | Amendment 1:<br>At the request of HCB and transmitted by the ANSM during the clinical and pharmaceutical evaluation of the AEC file, it was asked to specify the procedures for the transfer of the material (catheters) under a PSMII for purging. |
| 22 May 2014 | Amendment 2:<br>In order to follow up on the 4 patients included in the clinical trial, the period of observation and follow-up of the safety of the test treatment is prolonged until 30 months post-surgery with the continuation of the treatment. immunosuppressive therapy (tacrolimus Modigraf®). This will track the progress of patients' health status and collect additional safety data and samples to meet protocol objectives. |
| 07 January 2016 | Amendment 3:<br>1) Change of the Promoter of the study. The Institut Pasteur transfers the legal and operational responsibility of this trial to a Dutch biotech company, uniQure biopharma B.V. (Tafelbergweg 51, 1105 BD Amsterdam, the Netherlands).<br><br>2) Extension of follow-up of 4 patients included in the 36-month clinical trial. Version 5 of protocol consisted in extending the follow-up of the 4 patients to 18 months post-surgery. With this second phase of extension, the total follow-up of the children will be 5 years, in accordance with the recommendations of the European Medicines Agency on the follow-up of patients administered with a gene therapy (EMEA / CHMP / GTWP / 60436 / 2007). It should be noted that during this second phase of extension, the dose of tacrolimus will continue to be reduced and potentially stopped from month 48 post-surgery, depending on the results of available immunological data.<br><br>3) Addition of serologies to Cytomegalovirus (CMV) and Varicella-Zoster Virus (VZV) at visits V23-M12 and V41-M30 when previous serologies are negative (note that these serologies are performed by the center at the same time as the Epstein-Barr virus serology (EBV), the results will be retrospectively collected for the V23-M12 visit that has already been performed for the 4 patients included).<br><br>4) Addition of a blood sample (volume = 3 ml) at visit V41-M30 for the analysis of total and neutralizing antibodies against transgene<br><br>5) Clarification that any adverse event spontaneously reported by the patient / parents, observed by the investigator as well as any laboratory or radiological abnormalities that occurred during the extension phase should be documented in the CRF and added a section describing the monitoring and reporting of adverse events qualified for special notification (in agreement with EMEA / CHMP / GTWP / 60436/2007) |
| 09 January 2018 | Amendment 4:<br>The purpose of the amendment is to incorporate the tacrolimus tapering and discontinuation plan into the current protocol. This includes addition of a new Appendix which outlines the process, as well as adaptation of the protocol itself to include a new M51 (V48) sample and associated updates. In addition, administrative updates related to personnel and address changes were made, as well as correction of some typographical errors identified in the previous version. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial?  No

## Limitations and caveats

None reported