# Clinical trial results:
# A phase I/II study evaluating safety and efficacy of autologous hematopoietic stem cells genetically modified with GLOBE lentiviral vector encoding for the human beta-globin gene for the treatment of patients affected by transfusion dependent beta-thalassemia

## Summary

| | |
|---|---|
| EudraCT number | 2014-004860-39 |
| Trial protocol | IT |
| Global end of trial date | 25 November 2019 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 15 October 2020 |
| First version publication date | 15 October 2020 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | TIGET-BTHAL |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02453477 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Ospedale San Raffaele |
| Sponsor organisation address | Via Olgettina 60, Milan, Italy, 20132 |
| Public contact | TIGET Clinical Trial Office (TCTO), OSPEDALE SAN RAFFAELE, tcto@hsr.postcert.it |
| Scientific contact | San Raffaele Telethon Institute for Gene Therapy (SR-TIGET), OSPEDALE SAN RAFFAELE, tcto@hsr.postcert.it |

Notes:

### Paediatric regulatory details

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMEA-001933-PIP01-16 |
| 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? | Yes |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 31 July 2020 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 25 November 2019 |
| Global end of trial reached? | Yes |
| Global end of trial date | 25 November 2019 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

1. To evaluate the safety and tolerability of autologous CD34+ cell enriched fraction that contains Hematopoietic Stem Cells (HSC) transduced with Lentiviral Vector (LV) encoding the beta-globin gene in pediatric and adult patients with transfusion dependent beta-thalassemia following a reduced toxicity conditioning regimen.
2. To evaluate the efficacy of autologous CD34+ cell enriched fraction that contains Hematopoietic Stem Cells (HSC) transduced with Lentiviral Vector (LV) encoding the beta-globin gene in pediatric and adult patients with transfusion dependent beta-thalassemia following a reduced toxicity conditioning regimen.

Protection of trial subjects:

The study was conducted in accordance with the protocol, consistent to ICH-GCP and applicable local regulatory requirements. The written informed consent with a declaration of data privacy was signed and dated by the subject or by the subject's legally acceptable representative. For pediatric subjects or subjects unable to give free consent to the trial, subject's parents or subject's legally acceptable representative signed the informed consent. An independent Data Safety Monitoring Board (DSMB) was assigned to monitor the trial.
Long-term follow-up will be conducted under a separate protocol.

Background therapy:

Regular red blood cell transfusions and iron chelator therapy

Evidence for comparator:

No acceptable comparator therapy was available.

| | |
|---|---|
| Actual start date of recruitment | 29 May 2015 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy |
| Long term follow-up duration | 6 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Italy: 10 |
| Worldwide total number of subjects | 10 |
| EEA total number of subjects | 10 |

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) | 0 |
| Children (2-11 years) | 4 |
| Adolescents (12-17 years) | 3 |
| Adults (18-64 years) | 3 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

This study enrolled subjects aged ≥3 and <65 years with a diagnosis of Transfusion dependent beta-thalassemia (TDBT) (any genotype). Enrolment started with adult subjects. The ensuing enrolment of older children, and then of younger children, was conducted after Data Safety Monitoring Board (DSMB) approval for both of these age groups.

### Pre-assignment

Screening details:

The conditions required by the clinical protocol for subject inclusion/exclusion were assessed during the screening phase.

### Period 1

| | |
|---|---|
| Period 1 title | OTL-300 (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Blinding implementation details:

This was a single-arm open-label study.

### Arms

| | |
|---|---|
| **Arm title** | OTL-300 |

Arm description:

Each subject received the Advanced therapy investigational medicinal product (ATIMP), OTL-300 (autologous CD34+ cell enriched fraction containing HSPC transduced with the GLOBE LVV encoding for the beta-globin gene), on a single occasion via intraosseous infusion.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | OTL-300 (autologous CD34+ cell enriched fraction) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intraosseous use |

Dosage and administration details:

5 x 10e6 CD34+ cells/kg, with a minimum dose of 2 x 10e6 CD34+ cells/kg and a maximum dose of 20 x 10e6 CD34+ cells/kg, depending on the yield of cells.

| **Number of subjects in period 1[1]** | OTL-300 |
|---|---|
| Started | 9 |
| ATIMP infusion/Ly infusion | 9 |
| Completed | 9 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Ten subjects have been enrolled in the study. Nine subjects received the conditioning regimen, received the OTL-300 infusion, and completed the 2-year study. One younger child discontinued the study after PBSC mobilization and transduction, and did not receive the conditioning regimen or the OTL-300 infusion.

## Baseline characteristics

### Reporting groups

| Reporting group title | OTL-300 |
|---|---|

Reporting group description:

All patients were affected by transfusion dependent beta-thalassemia. Enrolment started with adult subjects. The ensuing enrolment of older children, and then of younger children, was conducted after DSMB approval for both of these age groups. Ten subjects underwent Peripheral blood stem cell (PBSC) mobilization and harvest: four younger children, three older children, and three adults. Nine subjects received the conditioning regimen, received the OTL-300 infusion, and completed the 2-year study; these subjects comprised the modified Intention-to-Treat (mITT) Population. One younger child discontinued the study after PBSC mobilization and transduction, and did not receive the conditioning regimen or the OTL-300 infusion.
Mean age in the mITT Population was 5.7 years for younger children, 13.5 years for older children, and 33.8 years for adult subjects. The majority of subjects were male (66.7%) and all subjects were White.

| Reporting group values | OTL-300 | Total | |
|---|---|---|---|
| Number of subjects | 9 | 9 | |
| Age categorical<br>Units: Subjects | | | |
| Younger children (3-7 years) | 3 | 3 | |
| Older children (8-17 years) | 3 | 3 | |
| Adults (≥18 years) | 3 | 3 | |
| Age continuous<br>Units: years | | | |
| median | 17.64 | | |
| full range (min-max) | 4.6 to 35.7 | - | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 3 | 3 | |
| Male | 6 | 6 | |

### Subject analysis sets

| Subject analysis set title | mITT Population |
|---|---|
| Subject analysis set type | Modified intention-to-treat |

Subject analysis set description:

mITT Population comprised of subjects received mobilization + conditioning + OTL-300 and completed the 2-year study.

| Reporting group values | mITT Population | | |
|---|---|---|---|
| Number of subjects | 9 | | |
| Age categorical<br>Units: Subjects | | | |
| Younger children (3-7 years) | 3 | | |
| Older children (8-17 years) | 3 | | |
| Adults (≥18 years) | 3 | | |
| Age continuous<br>Units: years | | | |
| median | 17.64 | | |
| full range (min-max) | 4.6 to 35.7 | | |

| Gender categorical<br>Units: Subjects | | | |
|---|---|---|---|
| Female | 3 | | |
| Male | 6 | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | OTL-300 |

Reporting group description:

Each subject received the Advanced therapy investigational medicinal product (ATIMP), OTL-300 (autologous CD34+ cell enriched fraction containing HSPC transduced with the GLOBE LVV encoding for the beta-globin gene), on a single occasion via intraosseous infusion.

| | |
|---|---|
| Subject analysis set title | mITT Population |
| Subject analysis set type | Modified intention-to-treat |

Subject analysis set description:

mITT Population comprised of subjects received mobilization + conditioning + OTL-300 and completed the 2-year study.

### Primary: Overall survival

| | |
|---|---|
| End point title | Overall survival[1] |

End point description:

Overall survival of all nine subjects in the mITT Population at the end of the 24-month follow up.

| | |
|---|---|
| End point type | Primary |

End point timeframe:

Day 1 -2 Years

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 analysis has been specified for this endpoint as it is a single arm study with no comparator.

| End point values | OTL-300 | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 9 | | | |
| Units: percent | | | | |
| number (confidence interval 95%) | | | | |
| Proportion surviving at end of follow-up | 100 (66.37 to 100) | | | |
| Kaplan-Meier estimate of survival | 100 (100 to 100) | | | |

### Statistical analyses

No statistical analyses for this end point

### Primary: Achievement of hematological engraftment

| | |
|---|---|
| End point title | Achievement of hematological engraftment[2] |

End point description:

Hematological engraftment was defined as neutrophil count >500/mm^3 and platelets >20,000/mm^3 on three consecutive blood counts (in the absence of transfusions).

| | |
|---|---|
| End point type | Primary |

End point timeframe:

by Day +60 from OTL-300 infusion

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 analysis has been specified for this endpoint as it is a single arm study with no comparator.

| **End point values** | OTL-300 | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 9 | | | |
| Units: Percentage | | | | |
| number (confidence interval 95%) | | | | |
| Hematological engraftment (%) | 100 (70.1 to 100) | | | |

## Statistical analyses

No statistical analyses for this end point

## Primary: Exposure to OTL-300 Infusion

| End point title | Exposure to OTL-300 Infusion[3] |
|---|---|

End point description:

Exposure to OTL-300 Infusion was defined by the mean number of CD34+ cells infused, mean transduction efficiency and mean VCN.

| End point type | Primary |
|---|---|

End point timeframe:

0–24 months

Notes:

[3] - 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 analysis has been specified for this endpoint as it is a single arm study with no comparator.

| **End point values** | OTL-300 | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 9 | | | |
| Units: Percent/cells | | | | |
| arithmetic mean (standard deviation) | | | | |
| CD34+ cells [x 10^6/kg] | 18.99 (± 1.182) | | | |
| Transduction efficiency [%] | 59.4 (± 10.74) | | | |
| VCN [copies/cell] | 0.93 (± 0.269) | | | |

## Statistical analyses

No statistical analyses for this end point

## Primary: Polyclonal engraftment

| End point title | Polyclonal engraftment[4] |
|---|---|

End point description:

Polyclonality of hematopoiesis was defined as >1000 unique integration sites retrieved from peripheral blood and/or bone marrow cells when available.

| End point type | Primary |
|---|---|

End point timeframe:

Polyclonal engraftment evaluated by integration analysis at 6, 12, 18, 24 months after OTL-300 infusion.

Notes:

[4] - 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 analysis has been specified for this endpoint as it is a single arm study with no comparator.

| **End point values** | OTL-300 | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 9 | | | |
| Units: Percent | | | | |
| median (confidence interval 95%) | | | | |
| 6 months | 100 (70.1 to 100) | | | |
| 12 months | 88.9 (56.5 to 98.0) | | | |
| 18 months | 77.8 (45.3 to 93.7) | | | |
| 24 months | 100 (70.1 to 100) | | | |
| Any time | 100 (70.1 to 100) | | | |

## Statistical analyses

No statistical analyses for this end point

## Primary: Transfusion Independence

| End point title | Transfusion Independence[5] |
|---|---|

End point description:

Transfusion independence was defined as less than or equal to one transfusion in the previous 6 months.

| End point type | Primary |
|---|---|

End point timeframe:

Transfusion independence at 12 and 24 months after OTL-300 infusion.

Notes:

[5] - 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 analysis has been specified for this endpoint as it is a single arm study with no comparator.

| End point values | OTL-300 | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 9 | | | |
| Units: percent | | | | |
| number (confidence interval 95%) | | | | |
| Transfusion Independence (Overall)/12 months/N=9 | 55.6 (26.7 to 81.1) | | | |
| Transfusion Independence (Overall)/24 months/N=9 | 44.4 (18.9 to 73.3) | | | |
| Transfusion Independence (3–7 yrs)/12 months/N=3 | 66.7 (20.8 to 93.9) | | | |
| Transfusion Independence (3–7 yrs)/24 months/N=3 | 66.7 (20.8 to 93.9) | | | |
| Transfusion Independence (8–17 yrs)/12 months/N=3 | 66.7 (20.8 to 93.9) | | | |
| Transfusion Independence (8–17 yrs)/24 months/N=3 | 66.7 (20.8 to 93.9) | | | |
| Transfusion Independence (≥18 yrs)/12 months/N=3 | 33.3 (6.1 to 79.2) | | | |
| Transfusion Independence (≥18 yrs)/24 months/N=3 | 0 (0 to 56.1) | | | |

### Statistical analyses

No statistical analyses for this end point

### Primary: Achievement of adequate Hb in transfusion independent subjects

| End point title | Achievement of adequate Hb in transfusion independent subjects[6] |
|---|---|

End point description:

Achievement of adequate hemoglobin in transfusion independent subjects defined as Hb >9 g/dL (adult) or >10 g/dL (child).

| End point type | Primary |
|---|---|

End point timeframe:

Achievement of adequate hemoglobin in transfusion independent subjects measured at 9, 12, 18 and 24 months.

Notes:

[6] - 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 analysis has been specified for this endpoint as it is a single arm study with no comparator.

| End point values | OTL-300 | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 9 | | | |
| Units: percent | | | | |
| number (not applicable) | | | | |
| Adequate Hb level (3-7 yrs)/12 months/N=2 | 0 | | | |
| Adequate Hb level (3-7 yrs)/24 months/N=2 | 0 | | | |
| Adequate Hb level (8-17 yrs)/12 months/N=2 | 100 | | | |

| | | | | |
|---|---|---|---|---|
| Adequate Hb level (8-17 yrs)/24 months/N=2 | 100 | | | |
| Adequate Hb level (>=18 yrs)/12 months/N=1 | 0 | | | |
| Adequate Hb level (>=18 yrs)/24 months/N=0 | 0 | | | |

## Statistical analyses

No statistical analyses for this end point

## Primary: Transfusion Frequency

| End point title | Transfusion Frequency[7] |
|---|---|

End point description:

Reduction in transfusion frequency from baseline.

| End point type | Primary |
|---|---|

End point timeframe:

Baseline transfusion frequency is presented for the 6-month period from Month -7 to Month -1. Post-treatment transfusion frequency is presented for the last 6 months of the study (Month 19 to Month 24).

Notes:

[7] - 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: Application of Poisson generalized linear mixed-model repeated measures was used to compare transfusion frequency after OTL-300 infusion with Pre-Treatment. Comparing 19 to 24 months vs. Pre-Treatment for the overall population (N=9), this indicated a significant decrease in Least Squares Mean annualized transfusion frequency (ratio versus Pre-Treatment = 0.13; p<0.001).

| **End point values** | OTL-300 | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 9 | | | |
| Units: Annualized Transfusion Frequency | | | | |
| median (full range (min-max)) | | | | |
| Transfusion Frequency (Overall)/Pre-treatment/N=9 | 19.96 (14.0 to 33.9) | | | |
| Transfusion Frequency (Overall)/19–24 months/N=9 | 10.19 (0 to 24.4) | | | |
| Transfusion Frequency (3–7 yrs)/Pre-treatment/N=3 | 17.96 (14.0 to 25.9) | | | |
| Transfusion Frequency (3–7 yrs)/19–24 months/N=3 | 0 (0 to 12.6) | | | |
| Transfusion Frequency (8–17 yrs)/Pre-treatment/N=3 | 19.96 (18.0 to 22.0) | | | |
| Transfusion Frequency (8–17 yrs)/19–24 months/N=3 | 0 (0 to 20.5) | | | |
| Transfusion Frequency (≥18 yrs)/Pre-treatment/N=3 | 27.94 (18.0 to 33.9) | | | |
| Transfusion Frequency (≥18 yrs)/19–24 months/N=3 | 11.85 (10.2 to 24.4) | | | |

## Statistical analyses

No statistical analyses for this end point

## Primary: Transfusion Volume

| End point title | Transfusion Volume[8] |
|---|---|

End point description:

Reduction in annualised transfusion volume from baseline.

| End point type | Primary |
|---|---|

End point timeframe:

Baseline transfusion volume is presented for the 6-month period from Month -7 to Month -1. Post-treatment transfusion volume is presented for the last 6 months of the study (Month 19 to Month 24).

Notes:

[8] - 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: Application of Poisson generalized linear mixed-model repeated measures was used to compare transfusion volume after OTL-300 infusion with Pre-Treatment. Comparing 19 to 24 months vs. Pre-Treatment for the overall population (N=9), this indicated a significant decrease in Least Squares Mean annualized transfusion volume (ratio versus Pre-Treatment = 0.02; p<0.001).

| **End point values** | OTL-300 | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 9 | | | |
| Units: Annualized Transfusion Volume mL/kg/year | | | | |
| median (full range (min-max)) | | | | |
| Transfusion Volume (Overall)/Pre-treatment/N=9 | 257.41 (190.4 to 346.4) | | | |
| Transfusion Volume (Overall)/ 19–24 months/N=9 | 85.99 (0 to 237.9) | | | |
| Transfusion Volume (3–7 yrs)/Pre-treatment/N=3 | 297.56 (190.4 to 346.4) | | | |
| Transfusion Volume (3–7 yrs)/ 19–24 months/N=3 | 0 (0 to 231.8) | | | |
| Transfusion Volume (8–17 yrs)/Pre-treatment/N=3 | 248.48 (239.6 to 257.4) | | | |
| Transfusion Volume (8–17 yrs)/19–24 months/N=3 | 0 (0 to 234.4) | | | |
| Transfusion Volume (≥18 yrs)/Pre-treatment/N=3 | 266.51 (196.8 to 285.9) | | | |
| Transfusion Volume (≥18 yrs)/19–24 months/N=3 | 93.22 (86.0 to 237.9) | | | |

### Statistical analyses

No statistical analyses for this end point

## Primary: Engraftment of genetically corrected cells in bone marrow

| End point title | Engraftment of genetically corrected cells in bone marrow[9] |
|---|---|

End point description:

Adequate engraftment is defined as a vector copy number (VCN) >= 0.15 assessed on bone marrow erythroid cells (both CD36+ and glycophorin-A+).

| End point type | Primary |
|---|---|

End point timeframe:

From 6 months to 24 months

Notes:

[9] - 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 analysis has been specified for this endpoint as it is a single arm study with no comparator.

| **End point values** | OTL-300 | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 9 | | | |
| Units: percent | | | | |
| number (confidence interval 95%) | | | | |
| Engraftment (Overall)/6 months/N=9 | 100 (70.1 to 100) | | | |
| Engraftment (Overall)/12 months/N=9 | 77.8 (45.3 to 93.7) | | | |
| Engraftment (Overall)/24 months/N=9 | 77.8 (45.3 to 93.7) | | | |
| Engraftment (3-7 yrs)/6 months/N=3 | 100 (43.9 to 100) | | | |
| Engraftment (3-7 yrs)/12 months/N=3 | 66.7 (20.8 to 93.9) | | | |
| Engraftment (3-7 yrs)/24 months/N=3 | 66.7 (20.8 to 93.9) | | | |
| Engraftment (8-17 yrs)/6 months/N=3 | 100 (43.9 to 100) | | | |
| Engraftment (8-17 yrs)/12 months/N=3 | 66.7 (20.8 to 93.9) | | | |
| Engraftment (8-17 yrs)/24 months/N=3 | 66.7 (20.8 to 93.9) | | | |
| Engraftment (>=18 yrs)/6 months/N=3 | 100 (43.9 to 100) | | | |
| Engraftment (>=18 yrs)/12 months/N=3 | 100 (43.9 to 100) | | | |
| Engraftment (>=18 yrs)/18 months/N=3 | 100 (43.9 to 100) | | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the start of mobilization until Month 24.

Adverse event reporting additional description:

All AEs were identified using Medical Dictionary for Regulatory Activities (MedDRA version 21.1) terms and for each event the following parameters were recorded: intensity or severity (see below); onset date; stop date; causality assessment with study drug (related/not related); action taken; outcome.

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 21.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | OTL-300 |

Reporting group description: -

| Serious adverse events | OTL-300 | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 9 (44.44%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Mycobacterium fortuitum infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Device related infection | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 5 %

| **Non-serious adverse events** | OTL-300 | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 9 / 9 (100.00%) | | |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 5 / 9 (55.56%) | | |
| occurrences (all) | 9 | | |
| Asthenia | | | |
| subjects affected / exposed | 4 / 9 (44.44%) | | |
| occurrences (all) | 5 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 2 / 9 (22.22%) | | |
| occurrences (all) | 7 | | |
| Axillary pain | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Catheter site erythema | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Catheter site pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Influenza like illness | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Injection site pain | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Injection site swelling | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Reproductive system and breast disorders | | | |
| Balanoposthitis | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Perineal erythema | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Testicular pain | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 2 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Cough | | | |
| subjects affected / exposed | 3 / 9 (33.33%) | | |
| occurrences (all) | 5 | | |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Hiccups | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Nasal turbinate hypertrophy | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 2 | | |
| Psychiatric disorders | | | |
| Panic attack | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 2 | | |
| Investigations | | | |
| Liver iron concentration increased | | | |
| subjects affected / exposed | 3 / 9 (33.33%) | | |
| occurrences (all) | 3 | | |
| Weight increased | | | |
| subjects affected / exposed | 2 / 9 (22.22%) | | |
| occurrences (all) | 2 | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 2 | | |
| Enterobacter test positive | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Liver iron concentration abnormal | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Staphylococcus test positive | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Urine protein/creatinine ratio increased | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Vitamin B12 decreased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Injury, poisoning and procedural complications | | | |
| Joint injury | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Limb injury | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 2 | | |
| Post procedural fever | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Procedural pain | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Congenital, familial and genetic disorders | | | |
| Phimosis | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Cardiac disorders | | | |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 3 / 9 (33.33%) | | |
| occurrences (all) | 4 | | |
| Dysaesthesia | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Syncope | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 5 / 9 (55.56%) | | |
| occurrences (all) | 5 | | |
| Lymphopenia | | | |
| subjects affected / exposed | 2 / 9 (22.22%) | | |
| occurrences (all) | 2 | | |
| Coagulopathy | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Lymphadenopathy | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Neutropenia | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Gastrointestinal disorders | | | |
| Vomiting | | | |
| subjects affected / exposed | 6 / 9 (66.67%) | | |
| occurrences (all) | 7 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 5 / 9 (55.56%) | | |
| occurrences (all) | 7 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 4 / 9 (44.44%) | | |
| occurrences (all) | 8 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 3 / 9 (33.33%) | | |
| occurrences (all) | 5 | | |
| Nausea | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 9 (33.33%) | | |
| occurrences (all) | 4 | | |
| Constipation | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Gingival bleeding | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Stomatitis | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Hepatitis | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Jaundice | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Skin and subcutaneous tissue disorders | | | |
| Rash erythematous | | | |
| subjects affected / exposed | 2 / 9 (22.22%) | | |
| occurrences (all) | 2 | | |
| Drug eruption | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Erythema | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Nodular rash | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Petechiae | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Pruritus | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Rash | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Rash pruritic | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Urticaria | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 3 / 9 (33.33%) | | |
| occurrences (all) | 9 | | |
| Bone pain | | | |
| subjects affected / exposed | 3 / 9 (33.33%) | | |
| occurrences (all) | 3 | | |
| Arthralgia | | | |
| subjects affected / exposed | 2 / 9 (22.22%) | | |
| occurrences (all) | 2 | | |
| Pain in extremity | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 9 (22.22%) | | |
| occurrences (all) | 2 | | |
| Spinal pain | | | |
| subjects affected / exposed | 2 / 9 (22.22%) | | |
| occurrences (all) | 2 | | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 2 | | |
| Infections and infestations | | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 3 / 9 (33.33%) | | |
| occurrences (all) | 3 | | |
| Influenza | | | |
| subjects affected / exposed | 2 / 9 (22.22%) | | |
| occurrences (all) | 3 | | |
| Pharyngitis | | | |
| subjects affected / exposed | 2 / 9 (22.22%) | | |
| occurrences (all) | 2 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 2 / 9 (22.22%) | | |
| occurrences (all) | 2 | | |
| Conjunctivitis | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Folliculitis | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Helicobacter infection | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Human bocavirus infection | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Nasal herpes | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 3 | | |

| | | | | |
|---|---|---|---|---|
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all) | 1 / 9 (11.11%)<br>1 | | | |
| Oral herpes<br>subjects affected / exposed<br>occurrences (all) | 1 / 9 (11.11%)<br>1 | | | |
| Periorbital infection<br>subjects affected / exposed<br>occurrences (all) | 1 / 9 (11.11%)<br>1 | | | |
| Rhinitis<br>subjects affected / exposed<br>occurrences (all) | 1 / 9 (11.11%)<br>1 | | | |
| Salmonellosis<br>subjects affected / exposed<br>occurrences (all) | 1 / 9 (11.11%)<br>1 | | | |
| Streptococcal infection<br>subjects affected / exposed<br>occurrences (all) | 1 / 9 (11.11%)<br>1 | | | |
| Streptococcal sepsis<br>subjects affected / exposed<br>occurrences (all) | 1 / 9 (11.11%)<br>1 | | | |
| Metabolism and nutrition disorders<br>Vitamin D deficiency<br>subjects affected / exposed<br>occurrences (all) | 4 / 9 (44.44%)<br>4 | | | |
| Folate deficiency<br>subjects affected / exposed<br>occurrences (all) | 2 / 9 (22.22%)<br>2 | | | |
| Diabetes mellitus<br>subjects affected / exposed<br>occurrences (all) | 1 / 9 (11.11%)<br>1 | | | |
| Hyperferritinaemia<br>subjects affected / exposed<br>occurrences (all) | 1 / 9 (11.11%)<br>1 | | | |
| Hypoalbuminaemia | | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 2 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 04 November 2015 | The planned assessment of globin expression by high performance liquid chromatography was removed due to the closure of the bioanalytical laboratory. |
| 10 May 2016 | • The conditioning regimen for Group 3 (aged 3–7 years) was modified to be the same as Group 2 (aged 8–17 years). This change was implemented before any subjects in Group 3 were treated.<br>• Inclusion of two additional research endpoints (#2 and #3 in Section 8.2.3). |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported