# Clinical trial results:
# Title: Open, Prospective, Historic-Controlled, Multicenter Study to Evaluate the Safety and Efficacy of Infusion of Liver Cell Suspension (HHLivC) in Children with Urea Cycle Disorders

## Summary

| | |
|---|---|
| EudraCT number | 2015-000988-14 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 15 July 2015 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 11 March 2017 |
| First version publication date | 11 March 2017 |
| Summary attachment (see zip file) | Synopsis CCD05 (Synopsis CCD05 CSR- 29Jun2016_Final Version.pdf) |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | CCD05 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01195753 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | IND Number: 14316 |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | PROMETHERA Biosciences S.A./N.V. |
| Sponsor organisation address | Watson & Crick Hill, Rue Granbonpré 11, Mont-Saint-Guibert, Belgium, B-1435 |
| Public contact | Dr John Tchelingerian, PROMETHERA Biosciences S.A./N.V., +32 (0)1039 4300, contact@promethera.com |
| Scientific contact | Prof Dr Etienne Sokal, PROMETHERA Biosciences S.A./N.V., +32 (0)1039 4300, contact@promethera.com |

Notes:

### Paediatric regulatory details

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMEA-000067-PIP02-11 |
| 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 | 22 January 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 15 July 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 15 July 2015 |
| Was the trial ended prematurely? | Yes |

Notes:

## General information about the trial

Main objective of the trial:

To investigate the safety and efficacy of multiple HHLivC infusions in children with ornithine transcarbamylase deficiency (OTCD), carbamoylphosphate synthetase I deficiency (CPS1D), or argininosuccinate synthetase deficiency (ASSD or citrullinemia).

Protection of trial subjects:

This study was conducted in accordance with "Good Clinical Practice" (GCP) and all applicable regulatory requirements, including the Declaration of Helsinki or with the laws and regulations of the country in which the research was conducted. The protocol, the ICF, and all other required documents were approved by the IRB/IEC prior to the initiation of the study at each institution.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 13 December 2010 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Canada: 4 |
| Country: Number of subjects enrolled | United States: 6 |
| Worldwide total number of subjects | 10 |
| EEA total number of subjects | 0 |

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) | 7 |
| 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:

A global pre-screening log had 90 patients listed and 10 patients were enrolled.

### Pre-assignment

Screening details:

Inclusion criteria were
- age (neonates and up to 5yo)
- Complete OTCD, CPS1D, or ASSD with neonatal-onset type
- Plasma ammonia level ≤250 µmol/l
- consent

### Period 1

| | |
|---|---|
| Period 1 title | pre-catheter placement period |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Blinding implementation details:

As there was only 1 group in the study, a blinded randomization was not applicable

### Arms

| | |
|---|---|
| **Arm title** | Pediatric patients suffering from UCD |

Arm description:

patients up to ≤5years of age suffering from UCD (CPS1D, OTCD or ASSD)

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | HHLivC |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Dispersion for infusion |
| Routes of administration | Intraportal use |

Dosage and administration details:

Human Heterologous Liver Cells (HHLivC) for infusion, application into the portal vein via a Hickman/Broviac catheter introduced into branches of the inferior or superior mesenteric vein by surgery.Cell dosage (divided into 6 applications) for children who weigh:
≤10 kg: 0.3 x 109 viable liver cells per kilogram of body weight
>10 to 15 kg: 3.0 x 109 viable cells nonadjusted to body weight
>15 kg: 0.2 x 109 viable liver cells per kilogram of body weight

| **Number of subjects in period 1** | Pediatric patients suffering from UCD |
|---|---|
| Started | 10 |
| Completed | 10 |

## Period 2

| | |
|---|---|
| Period 2 title | Study period (catheter placement to OLT) |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Blinding implementation details:

As there was only one group/arm in the study, blinding or randomization was not applicable

## Arms

| | |
|---|---|
| **Arm title** | Pediatric patients suffering from UCD |

Arm description:

patients up to ≤5years of age suffering from UCD (CPS1D, OTCD or ASSD)

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | HHLivC |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Dispersion for infusion |
| Routes of administration | Intraportal use |

Dosage and administration details:

Human Heterologous Liver Cells (HHLivC) for infusion, application into the portal vein via a Hickman/Broviac catheter introduced into branches of the inferior or superior mesenteric vein by surgery.Cell dosage (divided into 6 applications) for children who weigh:
≤10 kg: 0.3 x 109 viable liver cells per kilogram of body weight
>10 to 15 kg: 3.0 x 109 viable cells nonadjusted to body weight
>15 kg: 0.2 x 109 viable liver cells per kilogram of body weight

| **Number of subjects in period 2** | Pediatric patients suffering from UCD |
|---|---|
| Started | 10 |
| Completed | 10 |

## Baseline characteristics

### Reporting groups

| Reporting group title | pre-catheter placement period |
|---|---|

Reporting group description: -

| Reporting group values | pre-catheter placement period | Total | |
|---|---|---|---|
| Number of subjects | 10 | 10 | |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 1 | 1 | |
| Infants and toddlers (28 days-23 months) | 6 | 6 | |
| 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 | |
| Age continuous<br>Units: days | | | |
| median | 120.5 | | |
| full range (min-max) | 23 to 1878 | - | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 5 | 5 | |
| Male | 5 | 5 | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Pediatric patients suffering from UCD |
| Reporting group description: patients up to ≤5years of age suffering from UCD (CPS1D, OTCD or ASSD) | |
| Reporting group title | Pediatric patients suffering from UCD |
| Reporting group description: patients up to ≤5years of age suffering from UCD (CPS1D, OTCD or ASSD) | |

### Primary: Safety of the HHLivC treatment

| | |
|---|---|
| End point title | Safety of the HHLivC treatment[1] |
| End point description: patients up to ≤5years of age suffering from UCD (CPS1D, OTCD or ASSD) | |
| End point type | Primary |
| End point timeframe: Safety was evaluated from (first atempt of ) the catheter placement, during the HHLivC cell infusion and during the follow-up until either orthotopic liver transplantation, or the end of the study 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: In view of the exploratory nature of the study and the limited number of patients, all safety analyses were performed with descriptive statistics only.

| End point values | Pediatric patients suffering from UCD | Pediatric patients suffering from UCD | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 10 | 10 | | |
| Units: % related adverse events | 10 | 10 | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Efficacy of HHLivC treatment

| | |
|---|---|
| End point title | Efficacy of HHLivC treatment |
| End point description: | |
| End point type | Secondary |
| End point timeframe: Changes in 13C urea formation from baseline compared to 2 and 4 months (or earlier, if OLT is performed during listing period) after first liver cell infusion and, if available, up to 24 months after the Final Visit | |

| End point values | Pediatric patients suffering from UCD | Pediatric patients suffering from UCD | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 9 | 9 | | |
| Units: µmol*min/L | | | | |
| number (not applicable) | 9 | 9 | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

there are 3 reporting groups, with the same 12 subjects but subdivided over 3 periods -before first catheter placement (attempt) -between catheter placement and (first) OLT (OLT not included) - after (first ) OLT

Adverse event reporting additional description:

there were 10 subjects, and every single event in every patient was reported, thus the frequency threshold is 10%

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 13.1 or hi |

### Reporting groups

| | |
|---|---|
| Reporting group title | onset before the analysis period in CCD05 |
| Reporting group description: - | |
| Reporting group title | onset in the analysis period in CCD05 |
| Reporting group description: - | |
| Reporting group title | onset after the analysis period in CCD05 |
| Reporting group description: - | |

| Serious adverse events | onset before the analysis period in CCD05 | onset in the analysis period in CCD05 | onset after the analysis period in CCD05 |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 9 / 10 (90.00%) | 1 / 9 (11.11%) |
| number of deaths (all causes) | 0 | 1 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Subdural haematoma | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (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 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |
| Surgery | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (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 |
| General disorders and administration site conditions | | | |
| Device malfunction | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (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 |
| Gastrointestinal disorders | | | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 10 (20.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 10 (20.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia viral | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 10 (20.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral sepsis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal sepsis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 10 (0.00%) | 1 / 9 (11.11%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperammonaemia | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 6 / 10 (60.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 13 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |

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

| **Non-serious adverse events** | onset before the analysis period in CCD05 | onset in the analysis period in CCD05 | onset after the analysis period in CCD05 |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 10 / 10 (100.00%) | 10 / 10 (100.00%) | 9 / 9 (100.00%) |
| Vascular disorders | | | |
| Embolism venous | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Haemorrhage | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 10 (20.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Hypertension | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 3 / 10 (30.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Hypotension | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 3 / 10 (30.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Vena cava thrombosis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Thrombosis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Surgical and medical procedures | | | |
| Gastric tube reconstruction | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gastrointestinal tube insertion | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| General disorders and administration site conditions | | | |
| Device dislocation | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pain | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 10 (20.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |

| | | | |
|---|---|---|---|
| Catheter site necrosis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Developmental delay | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Device occlusion | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 10 (20.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Extravasation | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Medical device complication | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Medical device site erythema | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Oedema | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 4 / 10 (40.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 5 | 0 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 10 (20.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Thrombosis in device | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Immune system disorders | | | |
| Transplant rejection | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Reproductive system and breast disorders | | | |
| Tachypnoea | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|---|---|---|---|
| Cough | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nasal congestion | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Hypocapnia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Increased bronchial secretion | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Respiratory distress | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 10 (20.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 5 | 0 |
| Respiratory tract congestion | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Respiratory tract oedema | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Psychiatric disorders | | | |
| Agitation | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 10 (20.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Irritability | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Investigations | | | |
| Blood glucose fluctuation | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 10 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Amino acid level increased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Ammonia increased | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Blood lactic acid increased | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| C-reactive protein increased | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Electrocardiogram PR shortened | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Electrocardiogram T wave peaked | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Human rhinovirus test positive | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Occult blood positive | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Oxygen saturation decreased | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Portal vein pressure increased | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 10 (20.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Prothrombin time prolonged | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Transaminases increased | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Injury, poisoning and procedural complications | | | |
| Procedural pain | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 3 / 10 (30.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Fascial rupture | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 10 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Laceration | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 10 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Contusion | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 10 (20.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Endotracheal intubation complication | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Venous injury | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Congenital, familial and genetic disorders | | | |
| Microcephaly | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cardiac disorders | | | |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 3 / 10 (30.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Bradycardia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Nodal rhythm | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Left ventricular hypertrophy | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Sinus tachycardia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nervous system disorders | | | |
| Seizure | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 10 (20.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Cerebral atrophy | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 10 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Choreoathetosis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 10 (20.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Coma | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dystonia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hyperammonaemic encephalopathy | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypotonia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 10 (20.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Motor dysfunction | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|---|---|---|---|
| Muscle tone disorder | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 3 / 10 (30.00%) | 7 / 10 (70.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 3 | 11 | 0 |
| Splenomegaly | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 10 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Coagulopathy | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 10 (20.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Disseminated intravascular coagulation | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Leukocytosis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Thrombocytosis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Ear and labyrinth disorders | | | |
| Tympanic membrane hyperaemia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Eye disorders | | | |

| | | | |
|---|---|---|---|
| Eye discharge | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 10 (20.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 2 / 10 (20.00%) | 7 / 10 (70.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 2 | 15 | 0 |
| Nausea | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 10 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Ascites | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Constipation | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gastrointestinal hypomotility | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Ileus | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Infantile spitting up | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hepatobiliary disorders | | | |
| Portal vein thrombosis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 10 (20.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis diaper | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 3 / 10 (30.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 5 | 0 |
| Blister | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 10 (20.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Excessive granulation tissue | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Rash | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 3 / 10 (30.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Rash erythematous | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 10 (20.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Rash maculo-papular | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 10 (20.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Renal and urinary disorders | | | |
| Glycosuria | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Haematuria | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 10 (20.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Renal injury | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Endocrine disorders | | | |

| | | | |
|---|---|---|---|
| Adrenal insufficiency | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Muscle twitching | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Infections and infestations | | | |
| Adenovirus infection | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 3 / 10 (30.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Candida nappy rash | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 10 (20.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Device related infection | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 10 (20.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gastroenteritis enteroviral | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Klebsiella infection | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Oral candidiasis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Otitis media | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 10 (20.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 10 (20.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Urinary tract infection bacterial | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Metabolism and nutrition disorders | | | |
| Hyperammonaemia | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 6 / 10 (60.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 18 | 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 5 / 10 (50.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 6 | 0 |
| Fluid overload | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 2 / 10 (20.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |

| | | | |
|---|---|---|---|
| Hyperkalaemia | | | |
| subjects affected / exposed | 2 / 10 (20.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Acidosis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Electrolyte imbalance | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 10 (20.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Fluid imbalance | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Fluid retention | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 4 / 10 (40.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 6 | 0 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 3 / 10 (30.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 10 (20.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 3 / 10 (30.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Hypovolaemia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 10 (20.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Metabolic acidosis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 3 / 10 (30.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |

| | | | |
|---|---|---|---|
| Obesity | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Overweight | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Vitamin D deficiency | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (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 |
|---|---|
| 19 May 2011 | • Added additional time points of blood sampling following administration of 13C Sodium Acetate of 30, 40, and 50 minutes<br>• Added clarifying language to inclusion criteria #2 allowing those subjects without DNA confirmation but who were diagnosed prenatally or via newborn screen to be reviewed for enrollment if the peak ammonia level at first crisis did not reach 500 µmol/L<br>• Added diabetes and cholesterol screen at V2<br>• Added additional ultrasound at V0<br>• Added additional immunosuppression trough at V0<br>• Added clarification of safety parameters needed prior to catheter placement<br>• Added analysis for all routine laboratory screening to search for trends<br>• Generalized text to allow centers to use own standardized procedures (eg, antibiotic prophylaxis, biopsy, infectious disease screening/prophylaxis)<br>• Added clarifying language and literature references concerning 13C assay<br>• Added exploration analysis of SOC samples<br>• Clarified exclusion criteria #6 regarding coagulopathy<br>• Added stipulation that catheter may only be inserted if the total plasma ammonia is ≤ 250 µmol/L |
| 26 June 2012 | • Introduced anti-HLA-assessments prior to and after cell infusion in order to assess a possible immune reaction of the subject against the liver cells<br>• Added time windows for study visits<br>• Reduced visits between V14-V20 from 7 to 3 visits<br>• Defined study termination more precisely<br>• Corrected FU visit schedule<br>• Specified safety reporting period<br>• Added instructions for handling of portal vein catheter dislocation<br>• Adapted time points and volumes in 13C assay |
| 21 June 2013 | • Added exclusion criteria of portal vein thrombosis and veno-occlusive diseases<br>• Increased window on follow-up visits from +/- 5/6 days to +/-14 days<br>• Reduced selected clinical laboratory parameters sampling time points (unless clinically indicated) to reduce the volume of blood required<br>• Reworded language to match pediatric investigational plan language<br>• Updated study contact information<br>• Added interim analysis |
| 06 October 2013 | • Changed study reference/control group: Removed group-match, control group to be replaced with efficacy and safety comparison with current standard of care to be completed in separate project<br>• Increased total number of subjects from 20 to 21<br>• Added long-term safety data surveillance<br>• Removed secondary efficacy variable of comparison of enzyme active before and after HHLivC infusion<br>• Updated timing and data analysis of interim analysis; removed matched historic controls<br>• Deleted detailed language defining clinical significance of ureagenesis<br>• Added measures and documentation in case of overdose<br>• Updated statistical methods accordingly; including adding time points for 13C urea evaluation, added parameter to monitor protein intake, updated MedDRA version |

| | |
|---|---|
| 26 March 2015 | • Added between-visit parental safety check telephone calls to review AEs, concomitant medications, hospitalization, and other important subject information<br>• Added time points for analysis of anti-HLA antibody formation<br>• Included post-OLT questionnaire to capture complications of OLT due to previous liver cell therapy<br>• Modified safety reporting information for harmonization with other CCD05 study documents<br>• Clarified management of premature discontinuation of treatment/ early study discontinuation, especially subjects who did not receive all infusions<br>• Removed promotional language from benefits summary<br>• Added risks of study measures and LCT previously only described in IB<br>• Expanded study to regions outside the US<br>• Clarified listed cell dosage was targeted cell dosage, allowing deviations up to 15%<br>• Added section describing traceability of cell preparation and administration<br>• Updated study background with current trial data and recent literature<br>• Expanded window between consent and first study visit to 28 days |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|---|---|---|
| 23 April 2013 | Death of subject 15-15-03, and IND did not contain sufficient Information under 21 CFR 312.21 to assess the risks to subjects of the proposed studies | 22 May 2013 |

Notes:

## Limitations and caveats

None reported