



Clinical trial results:

Open, Prospective, Uncontrolled, Multicentre Study to Evaluate The Safety and Efficacy of Multiple Applications of Liver Cell Suspension Into The Portal Vein in Children with Urea Cycle Disorders (UCDs)

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2006-000136-27 |
| Trial protocol | DE |
| Global end of trial date | 12 November 2015 |

Results information

| | |
|-----------------------------------|---|
| Result version number | v1 (current) |
| This version publication date | 10 December 2016 |
| First version publication date | 10 December 2016 |
| Summary attachment (see zip file) | Study Synopsis (CCD02_Clinical Study report Synopsis_ final 1.0 22092016.pdf) |

Trial information

Trial identification

| | |
|-----------------------|-------|
| Sponsor protocol code | CCD02 |
|-----------------------|-------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00718627 |
| WHO universal trial number (UTN) | - |

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 Tchelingierian, PROMETHERA Biosciences S.A./N.V., 32 10 39 43 00, contact@promethera.com |
| Scientific contact | Prof Dr Etienne Sokal, PROMETHERA Biosciences S.A./N.V., 32 10 39 43 00, contact@promethera.com |

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-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 | 12 November 2015 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 12 November 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 12 November 2015 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Objective was to investigate the safety and efficacy of multiple applications of liver cell suspension in children with urea cycle disorders.

The primary variables were:

- Safety of the application of liver cells as measured by oxygen saturation, portal blood pressure and flow during the infusion
- Safety of the placement of an application catheter to the portal vein
- Safety of catheter insertion as determined by the evaluation of all adverse events after liver cell infusion (protocol version 5.0, before amendment dated 21 September 2015)
- Safety of the placement of an application catheter to the portal vein by evaluation of all adverse events judged to be related to the catheter placement (as per amendment dated 21 September 2015)

Protection of trial subjects:

The trial was carried out in accordance with the current legal and regulatory requirements, in particular with the Declaration of Helsinki (World Medical Association General Assembly, Tokyo, Japan, October (1996) with the ICH guidelines for Good Clinical Practice (Consolidated Guideline 1 May 1996, including post step errata July 2002) and with local laws and regulations relevant to the use of new therapeutic agents in Germany.

Background therapy: -

Evidence for comparator: -

| | |
|---|----------------|
| Actual start date of recruitment | 21 August 2009 |
| 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 | Germany: 12 |
| Worldwide total number of subjects | 12 |
| EEA total number of subjects | 12 |

Notes:

Subjects enrolled per age group

| | |
|--|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 | 0 |

| | |
|--|----|
| wk | |
| Newborns (0-27 days) | 2 |
| Infants and toddlers (28 days-23 months) | 10 |
| Children (2-11 years) | 0 |
| 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 screening log had 71 patients listed; 54 met inclusion criteria and 12 patients were enrolled, starting from 21/08/2009.

Pre-assignment

Screening details:

Inclusion criteria were

- age (neonates and up to 5yo)
- diagnosis for CPS1D, OTCD or ASSD to be confirmed; biochemically, prenatally or postnatally, by a DNA analysis that would further confirm diagnosis prior to or after inclusion into the study
- Accessibility of portal vein
- Plasma ammonia level ≤ 250 $\mu\text{mol/l}$
- 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 ≤ 5 years 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: 0.3×10^9 viable liver cells per kilogram of body weight

> 10 to 15 kg: 3.0×10^9 viable cells nonadjusted to body weight

> 15 kg: 0.2×10^9 viable liver cells per kilogram of body weight

| | |
|---------------------------------------|---------------------------------------|
| Number of subjects in period 1 | Pediatric patients suffering from UCD |
| Started | 12 |
| Completed | 12 |

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 ≤ 5 years 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: 0.3×10^9 viable liver cells per kilogram of body weight

> 10 to 15 kg: 3.0×10^9 viable cells nonadjusted to body weight

> 15 kg: 0.2×10^9 viable liver cells per kilogram of body weight

| Number of subjects in period 2 | Pediatric patients suffering from UCD |
|--------------------------------|---------------------------------------|
| Started | 12 |
| Completed | 10 |
| Not completed | 2 |
| Adverse event, non-fatal | 2 |

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 | 12 | 12 | |
| Age categorical Units: Subjects | | | |
| Newborns (0-27 days) | 2 | 2 | |
| Infants and toddlers (28 days-23 months) | 10 | 10 | |
| Age continuous Units: days | | | |
| median | 63 | | |
| full range (min-max) | 1 to 521 | - | |
| Gender categorical Units: Subjects | | | |
| Female | 4 | 4 | |
| Male | 8 | 8 | |

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: Primary safety variables: <ul style="list-style-type: none">• Safety of the application of liver cells as measured by oxygen saturation, portal blood pressure and flow during the infusion• Safety of the placement of an application catheter to the portal vein• Safety of catheter insertion as determined by the evaluation of all adverse events after liver cell infusion (before amendment dated 21 September 2015)• Safety of the placement of an application catheter to the portal vein by evaluation of all adverse events judged to be related to the catheter placement (as per amendment dated 21 September 2015) Secondary safety variables were: <ul style="list-style-type: none">• Vital signs• Laboratory Parameters III to V (haematology, biochemistry, urinalysis, immunoglobulins, serology) to monitor the safety of the procedures and immunosuppression, and• Adverse Events | |

| | |
|--|---------|
| End point type | Primary |
| End point timeframe: Safety was evaluated from (first attempt 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 | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 12 | | | |
| Units: % related adverse events | 12 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy of HHLivC treatment

| | |
|-----------------|------------------------------|
| End point title | Efficacy of HHLivC treatment |
|-----------------|------------------------------|

End point description:

- Changes in 13C urea formation from baseline compared to 2 and 4 months
- Change in the respective enzyme activity in samples from the explanted liver taken after OLT compared to the enzyme activity in the liver biopsy taken prior to the first liver cell application, Detection of donor cell material in samples from the explanted liver taken after OLT compared with the liver biopsy taken prior to first liver cell application,
- Number, duration and severity of metabolic crises (maximal ammonia concentration, duration of coma),
- Laboratory parameters I and II: ammonia and amino acids in plasma and orotic acid in urine (except in CPS1D),
- Growth and protein intake
- Nutritional status
- Use of ammonia scavenging drugs and
- Time to death and survival at 6 month after liver cell infusion (per amendment to protocol version 5.0)

| | |
|----------------|-----------|
| 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 | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 12 | | | |
| Units: $\mu\text{mol} \cdot \text{min} / \text{L}$ | | | | |
| number (not applicable) | 12 | | | |

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 12 subjects, and every single event in every patient was reported, thus the frequency threshold is 8.33%

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

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|----|
| Dictionary version | 18 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | CCD02 study group in the analysis period |
|-----------------------|--|

Reporting group description:

adverse events with onset in the analysis period in CCD02 (between first attempt of catheter placement and first OLT)

| | |
|-----------------------|---|
| Reporting group title | CCD02 study group after analysis period |
|-----------------------|---|

Reporting group description:

adverse events with onset after the analysis period in CCD02, meaning after the start of the first attempt for an orthotopic liver transplant, thus including the liver transplant

| | |
|-----------------------|--|
| Reporting group title | CCD02 study group before the analysis period |
|-----------------------|--|

Reporting group description:

the adverse events with onset before the analysis period in CCD02 (before first attempt of catheter placement)

| Serious adverse events | CCD02 study group in the analysis period | CCD02 study group after analysis period | CCD02 study group before the analysis period |
|---|--|---|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 12 / 12 (100.00%) | 12 / 12 (100.00%) | 12 / 12 (100.00%) |
| number of deaths (all causes) | 0 | 2 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intra-abdominal haematoma | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 12 (8.33%) | 0 / 12 (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 |

| | | | |
|--|-----------------|----------------|----------------|
| peripheral ischaemia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 12 (8.33%) | 0 / 12 (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 | | | |
| Crying | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device dislocation | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fatigue | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 1 / 12 (8.33%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 4 / 4 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| ammonia increased | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (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 |
| c-reactive protein increased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 12 (8.33%) | 0 / 12 (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 |
| Injury, poisoning and procedural complications | | | |
| Procedural vomiting | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (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 |
| Abdominal injury | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 12 (8.33%) | 0 / 12 (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 |
| complications of transplanted liver | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 2 / 12 (16.67%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| Transplant failure | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 12 (8.33%) | 0 / 12 (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 |
| Congenital, familial and genetic disorders | | | |
| Hypertrophic cardiomyopathy | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Seizure | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Somnolence | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| coagulopathy | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (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 | | | |
| Ascites | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| diarrhoea | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| enteritis | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (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 |
| Vomiting | | | |
| subjects affected / exposed | 4 / 12 (33.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 7 / 7 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| cholangitis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 12 (8.33%) | 0 / 12 (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 |
| Hepatic artery occlusion | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 12 (8.33%) | 0 / 12 (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 |
| Hepatic artery stenosis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 12 (8.33%) | 0 / 12 (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 |
| hepatic function abnormal | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 12 (8.33%) | 0 / 12 (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 |

| | | | |
|---|-----------------|----------------|----------------|
| Skin and subcutaneous tissue disorders | | | |
| hyperhidrosis | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| fistula | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 12 (8.33%) | 0 / 12 (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 | | | |
| Device related infection | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 12 (8.33%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| gastroenteritis | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis norovirus | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal viral infection | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumocystis jirovecii pneumonia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rotavirus infection | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 3 / 12 (25.00%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| abscess | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 12 (8.33%) | 0 / 12 (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 |
| infection | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 12 (8.33%) | 0 / 12 (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 | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 12 (8.33%) | 0 / 12 (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 / 12 (0.00%) | 1 / 12 (8.33%) | 0 / 12 (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 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (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 |
| Hyperammonaemia | | | |
| subjects affected / exposed | 8 / 12 (66.67%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 19 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolic disorder | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (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 |

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

| Non-serious adverse events | CCD02 study group in the analysis period | CCD02 study group after analysis period | CCD02 study group before the analysis period |
|---|--|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 12 / 12 (100.00%) | 1 / 12 (8.33%) | 12 / 12 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Haemangioma | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Vascular disorders | | | |
| Haematoma | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Hypertension | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hypotension | | | |
| subjects affected / exposed | 5 / 12 (41.67%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 7 | 0 | 0 |
| Pallor | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| | | | |
|---|----------------------|---------------------|---------------------|
| jugular vein thrombosis subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 12 (8.33%) 1 |
| Surgical and medical procedures | | | |
| Catheter removal subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Endotracheal intubation subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| General disorders and administration site conditions | | | |
| Catheter site discharge subjects affected / exposed occurrences (all) | 2 / 12 (16.67%) 2 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Catheter site haemorrhage subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Crying subjects affected / exposed occurrences (all) | 2 / 12 (16.67%) 2 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Device occlusion subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Face oedema subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Facial pain subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| General physical health deterioration subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Generalised oedema subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| granuloma | | | |

| | | | |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Malaise | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| medical device complication | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| oedema | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| pyrexia | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Device leakage | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| pain | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 2 / 12 (16.67%) |
| occurrences (all) | 0 | 0 | 2 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 3 / 12 (25.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 3 | 0 | 1 |
| Hypoxia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nasal obstruction | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Pharyngeal erythema | | | |

| | | | |
|-----------------------------|-----------------|----------------|----------------|
| subjects affected / exposed | 2 / 12 (16.67%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Pneumothorax | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Respiratory acidosis | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Stridor | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Tachypnoea | | | |
| subjects affected / exposed | 3 / 12 (25.00%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Rales | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Psychiatric disorders | | | |
| Restlessness | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Investigations | | | |
| Amino acid level increased | | | |
| subjects affected / exposed | 3 / 12 (25.00%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 6 | 0 | 0 |
| ammonia increased | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Bacterial test | | | |

| | | | |
|-------------------------------------|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood albumin decreased | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood bicarbonate decreased | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood lactic acid increased | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood pH decreased | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Body temperature increased | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| C-reactive protein increased | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Cardiac murmur | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Culture urine positive | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Cytomegalovirus test positive | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastrointestinal examination | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |

| | | | |
|--|-----------------|----------------|----------------|
| Heart rate increased | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Immunosuppressant drug level decreased | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Immunosuppressant drug level increased | | | |
| subjects affected / exposed | 3 / 12 (25.00%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| pH urine abnormal | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Accidental overdose | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Burns first degree | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Endotracheal intubation complication | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Lip injury | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Mechanical ventilation complication | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Procedural haemorrhage | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Procedural pain | | | |

| | | | |
|--|-----------------|----------------|----------------|
| subjects affected / exposed | 5 / 12 (41.67%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 5 | 0 | 1 |
| wound | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Congenital, familial and genetic disorders | | | |
| hydrocele | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Cardiac disorders | | | |
| Bradycardia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Sinus bradycardia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Tachycardia | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Nervous system disorders | | | |
| Coordination abnormal | | | |
| subjects affected / exposed | 5 / 12 (41.67%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 5 | 0 | 0 |
| Hypotonia | | | |
| subjects affected / exposed | 3 / 12 (25.00%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Somnolence | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Status epilepticus | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Seizure | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Myoclonic epilepsy | | | |

| | | | |
|--------------------------------------|-----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Tremor | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 2 / 12 (16.67%) |
| occurrences (all) | 0 | 0 | 2 |
| Blood and lymphatic system disorders | | | |
| anaemia | | | |
| subjects affected / exposed | 7 / 12 (58.33%) | 0 / 12 (0.00%) | 2 / 12 (16.67%) |
| occurrences (all) | 10 | 0 | 2 |
| Leukocytosis | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Lymphocytosis | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Splenomegaly | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Thrombocytosis | | | |
| subjects affected / exposed | 3 / 12 (25.00%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 5 | 0 | 0 |
| Eye disorders | | | |
| eyelid oedema | | | |
| subjects affected / exposed | 3 / 12 (25.00%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 5 | 0 | 0 |
| Hypermetropia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Strabismus | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Gastrointestinal disorders | | | |
| abdominal distension | | | |
| subjects affected / exposed | 4 / 12 (33.33%) | 0 / 12 (0.00%) | 4 / 12 (33.33%) |
| occurrences (all) | 5 | 0 | 4 |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| abdominal pain upper | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Abdominal tenderness | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| constipation | | | |
| subjects affected / exposed | 6 / 12 (50.00%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 8 | 0 | 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 2 | 0 | 1 |
| Faeces discoloured | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Flatulence | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 0 | 1 |
| gastrointestinal pain | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| ileus paralytic | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Large intestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| | | | |
|---|-----------------------|---------------------|----------------------|
| Obstruction gastric subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Teething subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Umbilical hernia subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Vomiting subjects affected / exposed occurrences (all) | 8 / 12 (66.67%) 12 | 0 / 12 (0.00%) 0 | 4 / 12 (33.33%) 4 |
| Faeces soft subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Dermatitis diaper subjects affected / exposed occurrences (all) | 6 / 12 (50.00%) 8 | 0 / 12 (0.00%) 0 | 3 / 12 (25.00%) 3 |
| Dry skin subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Eczema subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 1 |
| Erythema subjects affected / exposed occurrences (all) | 5 / 12 (41.67%) 8 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Hypertrophic scar subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Itching scar | | | |

| | | | |
|-----------------------------|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Petechiae | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Rash | | | |
| subjects affected / exposed | 5 / 12 (41.67%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 8 | 0 | 0 |
| Rash generalised | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Rash macular | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Telangiectasia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| hirsutism | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 12 (8.33%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| alopecia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Renal and urinary disorders | | | |
| Leukocyturia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Oliguria | | | |
| subjects affected / exposed | 3 / 12 (25.00%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Renal tubular acidosis | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 2 | 0 | 1 |
| Endocrine disorders | | | |
| cushingoid | | | |

| | | | |
|------------------------------|-----------------|----------------|-----------------|
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| hypothyroidism | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Candida infection | | | |
| subjects affected / exposed | 3 / 12 (25.00%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| clostridium diffilie colitis | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Device related infection | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| fungal infection | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| infection | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Oral candidiasis | | | |
| subjects affected / exposed | 3 / 12 (25.00%) | 0 / 12 (0.00%) | 2 / 12 (16.67%) |
| occurrences (all) | 4 | 0 | 2 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Rhinitis | | | |
| subjects affected / exposed | 4 / 12 (33.33%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 4 | 0 | 1 |
| Rotavirus infection | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| | | | |
|---|-----------------------|---------------------|----------------------|
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 5 / 12 (41.67%) 7 | 0 / 12 (0.00%) 0 | 1 / 12 (8.33%) 1 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Conjunctivitis subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Metabolism and nutrition disorders | | | |
| Acidosis subjects affected / exposed occurrences (all) | 4 / 12 (33.33%) 5 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Fluid retention subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Hyperammonaemia subjects affected / exposed occurrences (all) | 7 / 12 (58.33%) 11 | 0 / 12 (0.00%) 0 | 3 / 12 (25.00%) 3 |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Hyperkalaemia subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Hypoalbuminaemia subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Hypokalaemia subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 1 |
| Hypophosphataemia subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Metabolic acidosis | | | |

| | | | |
|-----------------------------|-----------------|----------------|----------------|
| subjects affected / exposed | 5 / 12 (41.67%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 8 | 0 | 0 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|---|
| 20 January 2010 | <p>Protocol version 2.3 (dated April 16, 2009) was amended and replaced by protocol version 2.4 (dated January 20, 2010), 4 patients enrolled</p> <ul style="list-style-type: none"> • Changed first inclusion criterion from "biochemically proven urea cycle disorder" to "prenatally or postnatally confirmed urea cycle disorder" and changed inclusion criterion "Serum ammonia level $\leq 250 \mu\text{mol/l}$" to "Plasma ammonia level $\leq 250 \mu\text{mol/l}$". • Updated the description of the surgical procedure for catheter placement, closure of the Ductus Venosus Arantii and catheter removal. • Changed the tolerable limit of portal vein pressure. • Added allowance for administration of intravenous methylprednisolone, CNIs as immunosuppressants and basically anticoagulants when discontinued before and during surgical interventions in accordance with the standard of care. Deleted "Experimental drugs". • Added Megalotect (Cytotect®) or the site's standard of care for prophylaxis of EBV-infection. • Added the respective SmPC in its current version as reference document for co-medications. • Deleted regularly flushing of the catheter with a solution containing heparin and that heparin was added to the cell suspension. • Added that cell suspension containing >15 million cells/ml may be diluted with Composol PS® to a maximum volume of 15 ml/kg body weight. • Changed the biometric examinations scheduled for every visit to twice weekly, deleted the urine status parameter urine nitrogen, clarified the time of the second blood draw and changed tacrolimus (or cyclosporin) trough level measurement to from V-1 to V1. • Added additional stopping rules for safety reasons. • Updated Chapter 9 "Safety Reporting". • Minor changes |
| 07 August 2010 | <p>Protocol version 2.4 (dated January 20, 2010) was amended and replaced by protocol version 3.0 (dated August 07, 2010), 2 patients enrolled</p> <ul style="list-style-type: none"> • Added a ^{13}C ureagenesis assay using Sodium ^{13}C acetate as new diagnostic method, as an advanced protocol for the direct determination of the capacity of the urea cycle based on the determination of ^{13}C urea in patient's blood, added ^{13}C assay as additional efficacy outcome measure and expanded study duration due to the test implementation. • Added a subgroup of 3 evaluable older children in the age of 15 months up to ≤ 5 years and changed the inclusion criteria and exclusion criteria (added that the body weight should not be ≤ 3.5 kg) accordingly as well as cell dosage adjustment for older children. • Discontinued sequential enrolment process, as the results of the Interim Analysis have not indicated any safety concerns. • Changed SAE reporting procedure and regular updating. • Changed time period for OLT listing stretching the definite moment for OLT listing at V23 in Week 8 to a time period from V23 in Week 8 to V31 (FV) in Week 16 ('listing period') due to differences in age and developmental progress of the patients. • Changed concomitant medication for safety reasons to allow exchange of methylprednisolone by prednisone, to consider detoxification as best medical care, to add valproate to exclusion criteria, to reduce the trough level of tacrolimus and to evaluate immunosuppression trough level during follow-up visits. • Extended enrolment options to encourage referrals of patients to study centres from other hospitals, also from abroad, due to the rareness of UCD patient. • Changed study title due to the addition of a sub-group to the existing patient population. |

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| 09 March 2011 | <p>Protocol version 3.0 (dated August 07, 2010) was amended and replaced by protocol version 3.1 (dated March 09, 2011), 3 patients enrolled</p> <ul style="list-style-type: none"> • Implemented additional time points to 13C assay based on first test results in 1 Patient. |
| 23 May 2012 | <p>Protocol version 3.1 (dated March 09, 2011) was amended and replaced by protocol version 4.0 (dated May 23, 2012), 1 patient enrolled, 3 patients continued</p> <ul style="list-style-type: none"> • Extended the range for age at enrolment to include patients between >3-<15 months of age to make the age range consistent to the US study CCD05. • Added allowance for peripheral lines to be used at physicians discretion as for older patients a central line may not always be needed. • Specified handling of portal vein catheter dislocation. • Included assessment of initial disease diagnosis by requesting confirmation of diagnosis by mutational analyses into the revised study protocol. • Allowed the documentation of additional parameters to be consistent to the US study CCD05. • Introduced time windows for study visits due to patients coming from abroad and not staying at the study sites for the complete study duration. • Added administrative corrections in protocol including the flowchart for consistency reasons. • Clarified the different modalities for performing the 13C assay scheduled at Final Visit if OLT takes place prior to 4 months of study participation. • Changed Patient Information and the Informed Consent Form to collect and evaluate data by ongoing routine procedures/visits to cover additional information on the influence of HHLivC therapy. • Clarified definition of SAE reporting period. • Changed dosing of cefuroxim or any other prophylactic antibiotic treatment according to different sites' standard of care. • Added HLA-assessments to comply with regulatory requirements. • Adapted time points and volumes in 13C assay according to the experience with kinetics of the 13C-urea formation in paediatric UCD patients. • Omitted V15-17, V19 and V31 since no safety concerns occurred after liver cell application in the first 10 patients and V31 caused a discrepancy with the whole study duration described in the study protocol. • An additional amendment, protocol version 3.2, was pla |
| 12 June 2013 | <p>Protocol version 4.0 (dated May 23, 2012) was amended and replaced by protocol version 5.0 (June 12, 2013), no patients enrolled under protocol version 5.0</p> <ul style="list-style-type: none"> • Extended the exclusion criteria for thrombocytopenia and hereditary thrombophilia according to the Pediatric Investigation Plan (PIP). • Extended primary safety variable of placement of an application catheter to the portal vein to consider all safety issues after liver cell infusion. • Adapted the secondary efficacy variables according to the PIP. • Removed haemodynamic and respiratory monitoring from the secondary efficacy variable vital signs, as assessments for respiratory monitoring are not part of the protocol and blood oxygen saturation is a primary safety variable. • Adapted the number of trial sites to reflect the current status. • Adapted the Justification of Study Design. Dosage and Application Schedule section to reflect the current trial status. • Changed continuous recording of concomitant medication to be documented from V-4 until OLT and only for subjects not undergoing OLT to last FU visit, as documentation of medication during and after OLT has no direct benefit for trial evaluation. • Adapted the End of Study and Patient Population description to include all available data into the analysis of the results, as some patients included in the trial were not able to be fully documented due to various reasons. • Added a second Interim Analysis after treatment of 11 patients for submission process to the European Medicines Agency. • Extended the trial duration and schedule to include the follow-up phase. • Corrected mistakes in the Visit Schedule and modified text to limit the documentation of immunosuppression to the phase before the OLT. • Clarified the description of documentation of AEs and of concomitant medication in the Visit Schedule. • Specified determination and documentation of the tacrolimus blood levels during the Follow-up phase of the trial until OLT. • Specified determi |

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| 21 September 2015 | Amendment to protocol version 5.0 (June 12, 2013) dated September 21, 2015 <ul style="list-style-type: none"> • Administrative change of responsibilities for pharmacovigilance and QPPV • Reduction of sample size from 13 patients planned to 12 patients. • Change in wording of the third primary safety endpoint due to the fact that adverse events collected after the liver cell transplantation do not provide meaningful safety information on catheter placement. • Change in definition of age groups for paediatric sub-group Analysis |
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|--------------|------------------------------|--------------|
| 25 June 2014 | temporarily recruitment halt | - |

Notes:

Limitations and caveats

None reported