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 Tchelingerian, 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)	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	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 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	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 ≤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	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:
- 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:
- 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 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			
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: µmol*min/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	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Surgical and medical procedures			
Catheter removal			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Endotracheal intubation			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Catheter site discharge			
subjects affected / exposed	2 / 12 (16.67%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Catheter site haemorrhage			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Crying			
subjects affected / exposed	2 / 12 (16.67%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Device occlusion			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Face oedema			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Facial pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
General physical health deterioration			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Generalised oedema			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	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	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	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	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Teething			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Umbilical hernia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	8 / 12 (66.67%)	0 / 12 (0.00%)	4 / 12 (33.33%)
occurrences (all)	12	0	4
Faeces soft			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Dermatitis diaper			
subjects affected / exposed	6 / 12 (50.00%)	0 / 12 (0.00%)	3 / 12 (25.00%)
occurrences (all)	8	0	3
Dry skin			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Eczema			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	1
Erythema			
subjects affected / exposed	5 / 12 (41.67%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	8	0	0
Hypertrophic scar			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	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	5 / 12 (41.67%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	7	0	1
Urinary tract infection			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Conjunctivitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	4 / 12 (33.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	5	0	0
Fluid retention			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Hyperammonaemia			
subjects affected / exposed	7 / 12 (58.33%)	0 / 12 (0.00%)	3 / 12 (25.00%)
occurrences (all)	11	0	3
Hyperglycaemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Hyperkalaemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Hypoalbuminaemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Hypokalaemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	1
Hypophosphataemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Metabolic acidosis			

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 January 2010	Protocol version 2.3 (dated April 16, 2009) was amended and replaced by protocol version 2.4 (dated January 20, 2010), 4 patients enrolled • 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 ≤250 µmol/l" to "Plasma ammonia level ≤250 µmol/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	Protocol version 2.4 (dated January 20, 2010) was amended and replaced by protocol version 3.0 (dated August 07, 2010), 2 patients enrolled • Added a 13C ureagenesis assay using Sodium 13C 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 13C urea in patient's blood, added 13C 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.

09 March 2011	Protocol version 3.0 (dated August 07, 2010) was amended and replaced by protocol version 3.1 (dated March 09, 2011), 3 patients enrolled • Implemented additional time points to 13C assay based on first test results in 1 Patient.
23 May 2012	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 • 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	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 • 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

21 September 2015	Amendment to protocol version 5.0 (June 12, 2013) dated September 21, 2015 • 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

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