



Clinical trial results:

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

Summary

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

Results information

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

Trial information

Trial identification

Sponsor protocol code	CCD05
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Additional study identifiers

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

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

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

Notes:

Population of trial subjects

Subjects enrolled per country

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

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	7
Children (2-11 years)	3

Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

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

Pre-assignment

Screening details:

Inclusion criteria were

- age (neonates and up to 5yo)
- Complete OTCD, CPS1D, or ASSD with neonatal-onset type
- Plasma ammonia level ≤ 250 $\mu\text{mol/l}$
- 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
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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	10
Completed	10

Period 2

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

Blinding implementation details:

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

Arms

Arm title	Pediatric patients suffering from UCD
Arm description: patients up to ≤5years of age suffering from UCD (CPS1D, OTCD or ASSD)	
Arm type	Experimental
Investigational medicinal product name	HHLivC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Dispersion for infusion
Routes of administration	Intraportal use

Dosage and administration details:

Human Heterologous Liver Cells (HHLivC) for infusion, application into the portal vein via a Hickman/Broviac catheter introduced into branches of the inferior or superior mesenteric vein by surgery. Cell dosage (divided into 6 applications) for children who weigh:

≤10 kg: 0.3 x 10⁹ viable liver cells per kilogram of body weight

>10 to 15 kg: 3.0 x 10⁹ viable cells nonadjusted to body weight

>15 kg: 0.2 x 10⁹ viable liver cells per kilogram of body weight

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

Baseline characteristics

Reporting groups

Reporting group title	pre-catheter placement period
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Reporting group description: -

Reporting group values	pre-catheter placement period	Total	
Number of subjects	10	10	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	1	1	
Infants and toddlers (28 days-23 months)	6	6	
Children (2-11 years)	3	3	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: days			
median	120.5		
full range (min-max)	23 to 1878	-	
Gender categorical			
Units: Subjects			
Female	5	5	
Male	5	5	

End points

End points reporting groups

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

Primary: Safety of the HHLivC treatment

End point title	Safety of the HHLivC treatment ^[1]
End point description: patients up to ≤5years of age suffering from UCD (CPS1D, OTCD or ASSD)	
End point type	Primary
End point timeframe: Safety was evaluated from (first 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	Pediatric patients suffering from UCD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: % related adverse events	10	10		

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy of HHLivC treatment

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

End point values	Pediatric patients suffering from UCD	Pediatric patients suffering from UCD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: $\mu\text{mol}\cdot\text{min}/\text{L}$				
number (not applicable)	9	9		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

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

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	13.1 or hi
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Reporting groups

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Obesity			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Overweight			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Vitamin D deficiency			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 May 2011	<ul style="list-style-type: none"> Added additional time points of blood sampling following administration of 13C Sodium Acetate of 30, 40, and 50 minutes Added clarifying language to inclusion criteria #2 allowing those subjects without DNA confirmation but who were diagnosed prenatally or via newborn screen to be reviewed for enrollment if the peak ammonia level at first crisis did not reach 500 µmol/L Added diabetes and cholesterol screen at V2 Added additional ultrasound at V0 Added additional immunosuppression trough at V0 Added clarification of safety parameters needed prior to catheter placement Added analysis for all routine laboratory screening to search for trends Generalized text to allow centers to use own standardized procedures (eg, antibiotic prophylaxis, biopsy, infectious disease screening/prophylaxis) Added clarifying language and literature references concerning 13C assay Added exploration analysis of SOC samples Clarified exclusion criteria #6 regarding coagulopathy Added stipulation that catheter may only be inserted if the total plasma ammonia is ≤ 250 µmol/L
26 June 2012	<ul style="list-style-type: none"> Introduced anti-HLA-assessments prior to and after cell infusion in order to assess a possible immune reaction of the subject against the liver cells Added time windows for study visits Reduced visits between V14-V20 from 7 to 3 visits Defined study termination more precisely Corrected FU visit schedule Specified safety reporting period Added instructions for handling of portal vein catheter dislocation Adapted time points and volumes in 13C assay
21 June 2013	<ul style="list-style-type: none"> Added exclusion criteria of portal vein thrombosis and veno-occlusive diseases Increased window on follow-up visits from +/- 5/6 days to +/-14 days Reduced selected clinical laboratory parameters sampling time points (unless clinically indicated) to reduce the volume of blood required Reworded language to match pediatric investigational plan language Updated study contact information Added interim analysis
06 October 2013	<ul style="list-style-type: none"> Changed study reference/control group: Removed group-match, control group to be replaced with efficacy and safety comparison with current standard of care to be completed in separate project Increased total number of subjects from 20 to 21 Added long-term safety data surveillance Removed secondary efficacy variable of comparison of enzyme active before and after HHLivC infusion Updated timing and data analysis of interim analysis; removed matched historic controls Deleted detailed language defining clinical significance of ureagenesis Added measures and documentation in case of overdose Updated statistical methods accordingly; including adding time points for 13C urea evaluation, added parameter to monitor protein intake, updated MedDRA version

26 March 2015	<ul style="list-style-type: none"> Added between-visit parental safety check telephone calls to review AEs, concomitant medications, hospitalization, and other important subject information Added time points for analysis of anti-HLA antibody formation Included post-OLT questionnaire to capture complications of OLT due to previous liver cell therapy Modified safety reporting information for harmonization with other CCD05 study documents Clarified management of premature discontinuation of treatment/ early study discontinuation, especially subjects who did not receive all infusions Removed promotional language from benefits summary Added risks of study measures and LCT previously only described in IB Expanded study to regions outside the US Clarified listed cell dosage was targeted cell dosage, allowing deviations up to 15% Added section describing traceability of cell preparation and administration Updated study background with current trial data and recent literature Expanded window between consent and first study visit to 28 days
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

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

Notes:

Limitations and caveats

None reported