Clinical trial results:
A prospective, open label, multicenter, partially randomized, safety study of one cycle of Promethera HepaStem in Urea Cycle Disorders and Crigler-Najjar Syndrome patients

Summary

EudraCT number	2011-004074-28
Trial protocol	GB BE IT
Global end of trial date	04 November 2014

Results information

Result version number	v1 (current)
This version publication date	11 March 2017
First version publication date	11 March 2017

Trial information

Trial identification

Sponsor protocol code	HEP001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01765283
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, 1435
Public contact	John Tchelingerian, Promethera Biosciences, 32 10 39 43 00, contact@promethera.com
Scientific contact	Etienne Sokal, Promethera Biosciences, 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-001155-PIP01-11
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	04 November 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 November 2014
Global end of trial reached?	Yes
Global end of trial date	04 November 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The study was designed to assess the safety of one cycle of HepaStem infusions up to 6 months in pediatric patients suffering from CN or UCD in terms of clinical status, portal-vein hemodynamics, morphology of the liver, de novo detection of circulating anti-human leukocyte antigen (HLA) antibodies, and/or other immune related markers as well as serious adverse events (SAEs) and clinically significant adverse events (AEs) related to infusion.

Protection of trial subjects:

The study was conducted in accordance with the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP) E6(R1) - Step 4 version dated 10 June 1996, the ethical principles that have their origins in the Declaration of Helsinki and local regulations."
The protocol, all amendments and the informed consent forms (ICFs) / patient information sheets (PIS) were reviewed and approved by the competent authorities (CA) and relevant ethics committee (EC) in each participating country.

Background therapy:

Patients included in the trial were provided with best medical care. It was recommended that their UCD or CN treatment was carried out/continued at the discretion of the investigator responsible for the treatment of the patient.
All UCD patients included in the study had chronic limitation in natural protein intake. This reflects the severe disease phenotypes with low tolerance to natural proteins. All patients chronically received at least one ammonium scavenger medication, with half of them receiving both sodium benzoate and sodium phenylbutyrate. All patients, except the arginase deficiency patient, chronically received supplements of citrulline or arginine or both.
All CN patients were treated with long daily overnight phototherapy (10-12h) and had variable but elevated total blood bilirubin values.

Evidence for comparator: -

Actual start date of recruitment	06 March 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Israel: 4
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Belgium: 7

Country: Number of subjects enrolled	Italy: 1
Worldwide total number of subjects	20
EEA total number of subjects	16

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)	3
Children (2-11 years)	11
Adolescents (12-17 years)	6
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited primarily at hospitals with a specialized pediatric metabolic or hepatology center. Patients could be referred for screening, treatment, 3, 6 and 12 month follow-up visits to academic hospitals with a transplant unit (infusion centers).

Pre-assignment

Screening details:

A total of 21 patients were screened between March 2012 and September 2013. There was one screening failure: an UCD patient presented an exclusion criterion (the patient had a thrombosis in the portal vein) and was therefore not included in the study. Hence, 20 patients were enrolled in the study and received the IMP: 14 UCD and 6 CN patients.

Period 1

Period 1 title	HepaStem infusion - Test period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Pediatric patients suffering from CN

Arm description:

Pediatric CN patients presenting Criggler-Najjar type I or type II poorly controlled under phenobarbital treatment, or experiencing serious impairment in QoL.

Arm type	Experimental
Investigational medicinal product name	Hepastem
Investigational medicinal product code	HHALPC
Other name	Heterologous Human Adult Liver-derived Progenitor Cells
Pharmaceutical forms	Suspension for injection
Routes of administration	Intraportal use

Dosage and administration details:

HepaStem (5x10E6 cells/mL) infused through percutaneous transhepatic catheter inserted in portal vein under radio-guidance.
3 doses investigated:
o Low: 12.5x10E6 cells/kg
o Intermediate: 50x10E6 cells/kg
o High: 200x10E6 cells/kg (max. 4x10E9 total cells)
in pooled UCD/CN patients set in 3 weight cohorts: >20kg; ≥10-20 kg; < 10kg

Dose escalation performed both intra- and inter-cohort:
Intra-cohort: lowest dose given first.
Inter-cohort: 1 given dose to be safe in a higher weight cohort first.
Dose allocation partially randomized: intermediate and high doses randomized from patient 4 onwards in cohorts 1 and 2.

Before portal catheter placement, patients received antibiotics. During HepaStem infusion, bivalirudin was administered (for anticoagulation).
Patients received tacrolimus (for immunosuppression) throughout the study. They also received treatments to prevent opportunistic infections according to recommendations of chemoprophylaxis after liver transplantation.

Arm title	Pediatric patients suffering from UCD

Arm description:

UCD Pediatric patients diagnosis with of one of the UCD subtypes (CPSID, OTCD, ASSD, ASLD, ARGD or NAGSD)

Arm type	Experimental

Investigational medicinal product name	Hepastem
Investigational medicinal product code	HHALPC
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Patients received tacrolimus (for immunosuppression) throughout the study. They also received treatments to prevent opportunistic infections according to recommendations of chemoprophylaxis after liver transplantation.

Number of subjects in period 1	Pediatric patients suffering from CN	Pediatric patients suffering from UCD
Started	6	14
Completed	5	13
Not completed	1	1
Consent withdrawn by subject	1	-
patient received a liver transplant	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Pediatric patients suffering from CN
Reporting group description:	
Pediatric CN patients presenting Criggler-Najjar type I or type II poorly controlled under phenobarbital treatment, or experiencing serious impairment in QoL.	
Reporting group title	Pediatric patients suffering from UCD
Reporting group description:	
UCD Pediatric patients diagnosis with of one of the UCD subtypes (CPSID, OTCD, ASSD, ASLD, ARGD or NAGSD)	

Reporting group values	Pediatric patients suffering from CN	Pediatric patients suffering from UCD	Total
Number of subjects	6	14	20
Age categorical			
Diversity was observed in terms of age at baseline. Two female CPSID patients with early onset disease were 4.4 and 7 years old. The OTCD group included 2 male OTCD patients with early onset disease and 4 male OTCD patients with late onset disease, with a large range of age at baseline (5.9 weeks to 17.2 years of age). It included also 3 female adolescent patients (15.2 to 16.7 years of age) with late onset disease. Two ASLD patients with early onset disease were 1.3 and 10.4 years old. One ARGD patient with early onset disease was 7.2 years old. The CN population ranged from 3.5 to 8.8 years			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	3	3
Children (2-11 years)	6	5	11
Adolescents (12-17 years)	0	6	6
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
mean age of the full study (CN + UCD)			
Units: years			
arithmetic mean	7.98	9.12	
standard deviation	± 5.73	± 6.46	-
Gender categorical			
The sex ratio for UCD patients was 6 female and 8 male patients. The sex ratio for CN patients was 4 female and 2 male patients. This makes a total of 10 female and 10 male patients			
Units: Subjects			
Female	4	6	10
Male	2	8	10

End points

End points reporting groups

Reporting group title	Pediatric patients suffering from CN
Reporting group description:	
Pediatric CN patients presenting Criggler-Najjar type I or type II poorly controlled under phenobarbital treatment, or experiencing serious impairment in QoL.	
Reporting group title	Pediatric patients suffering from UCD
Reporting group description:	
UCD Pediatric patients diagnosis with of one of the UCD subtypes (CPSID, OTCD, ASSD, ASLD, ARGD or NAGSD)	

Primary: HepaStem related adverse events of one cycle of HepaStem infusion

End point title	HepaStem related adverse events of one cycle of HepaStem infusion[1]

End point description:

The primary endpoint was the safety assessment of the technical intervention (infusion of HepaStem in portal vein) common to both indications and all cohorts during the active phase of the study (0-6 months post-infusion). The secondary endpoints included safety assessment up to the 12-month FU.
Safety endpoints defined for assessing safety of HepaStem infusion and HepaStem safety FU included a series of investigations: vital signs, physical examinations, clinical laboratory tests (liver and renal function, hematology, coagulation), anti-HLA and auto-immune antibodies, portal vein pressure, echography and Doppler exam of the liver, liver biopsy and also AEs related to HepaStem infusion and concomitant treatments (antibiotic, and chemoprophylactic treatment, anticoagulation and immunosuppressive treatment).
Clinically significant abnormal values were reported as adverse events which are therefore included in the adverse event tables.

End point type	Primary

End point timeframe:

From Day of portal catheter placement and HepaStem infusion until end of the study up to 12 month FU (primary and secondary safety objectives pooled)

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 on an Intent-To-Treat basis on the Total Safety Population including both CN and UCD indications and the 3 cohorts. Descriptive statistics are used to report adverse events up to 6 months (primary endpoint) and up to 12 months FU.

End point values	Pediatric patients suffering from CN	Pediatric patients suffering from UCD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	14		
Units: nr of patients with related events	6	8		

Attachments (see zip file)	safety evaluation HEP001/EudraCt attachment - Safety

Statistical analyses

No statistical analyses for this end point

Secondary: ureagenesis based on 13C tracer method

End point title	ureagenesis based on 13C tracer method[2]

End point description:

For paediatric patients suffering from UCD, the functional test based on a 13C tracer method was used to evaluate ureagenesis in vivo pre- and post-HepaStem infusion. During the test, blood was collected before labelled precursor ingestion and every 30 minutes for 2h after labelled precursor ingestion. In order to integrate plasma [13C] urea concentrations measured over 2h, plasma [13C] urea Area Under the Curve (AUC)-120 min was calculated (µmol*min/L). Some measurements were missing due to tests not performed at a given visit or missing blood samplings during a test.

End point type	Secondary

End point timeframe:

From Day of portal catheter placement and HepaStem infusion until end of the study up to 12 month FU

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The ureagenesis analysis was only performed in the UCD arm of the study as it is disease specific for UCD and not for CN

End point values	Pediatric patients suffering from UCD			
Subject group type	Reporting group			
Number of subjects analysed	14[3]			
Units: µmol*min/L				
number (not applicable)	14			

Notes:

[3] - Tests performed at baseline, 3-, 6-, 12-month visits respectively for 13, 12, 12 and 13 patients

Attachments (see zip file)	HEP001 ureagenesis efficacy/EudraCt attachment - Efficacy

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Day of portal catheter placement and HepaStem infusion until end of the study up to 12 month FU (primary and secondary safety objectives pooled)

Adverse event reporting additional description:

In HEP001, the adverse events were tabulated as 'all adverse events' and 'serious adverse events'.
In the EudraCt table 'serious adverse events', serious adverse events are reported.
In the EudraCt table 'non-serious adverse events' all adverse events, non-serious and serious are included.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10

Reporting groups

Reporting group title	Pediatric patients suffering from UCD or CN

Reporting group description:

Overall trial

Serious adverse events	Pediatric patients suffering from UCD or CN		
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 20 (75.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Coagulation factor decreased			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Portal vein flow decreased			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Transaminases increased			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Mycosis fungoides			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Transfusion reaction			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Portal vein thrombosis	Additional description: 2 events occurred: 1: thrombosis of the left branch of the portal vein 2: partial thrombus in the main portal vein		
subjects affected / exposed	2 / 20 (10.00%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	5 / 20 (25.00%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Laryngitis			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nasopharyngitis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Parainfluenzae virus infection			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rhinovirus infection			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral infection			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyperammonaemia			
subjects affected / exposed	6 / 20 (30.00%)		
occurrences causally related to treatment / all	4 / 15		
deaths causally related to treatment / all	0 / 0		
Metabolic disorder			
subjects affected / exposed	5 / 20 (25.00%)		
occurrences causally related to treatment / all	0 / 13		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Pediatric patients suffering from UCD or CN		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 20 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Mycosis fungoides			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Hot flush			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Hypotension			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Pallor			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Catheter site haemorrhage			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Catheter site pain			
subjects affected / exposed	5 / 20 (25.00%)		
occurrences (all)	7		
Device dislocation			

subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Extravasation			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	4		
Hyperthermia			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Infusion site pain			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	4		
Injection site haematoma			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Injection site pain			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Local swelling			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Malaise			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Pain			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	6		
Immune system disorders			
Food allergy			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		

Hypersensitivity			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
Reproductive system and breast disorders			
Balanitis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Breast swelling			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	4		
Epistaxis			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Laryngeal oedema			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Nasal congestion			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Pleural effusion			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Rales			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Respiratory distress			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Respiratory failure			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Rhinorrhoea			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Tonsillar hypertrophy			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Aggression			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Agitation			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Confusional state			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Depression			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Mood altered			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Mood swings			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		

Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Amino acid level decreased			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Amino acid level increased			
subjects affected / exposed	5 / 20 (25.00%)		
occurrences (all)	7		
Ammonia increased			
subjects affected / exposed	8 / 20 (40.00%)		
occurrences (all)	23		
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Blood bicarbonate decreased			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Blood bilirubin increased			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	5		
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Blood fibrinogen decreased			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Blood homocysteine increased			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Blood potassium decreased			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
C-reactive protein increased			

subjects affected / exposed	2 / 20 (10.00%)			
occurrences (all)	2			
Coagulation factor decreased				
subjects affected / exposed	2 / 20 (10.00%)			
occurrences (all)	2			
Coagulation time prolonged				
subjects affected / exposed	8 / 20 (40.00%)			
occurrences (all)	12			
Culture urine positive				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Fibrin D dimer increased				
subjects affected / exposed	8 / 20 (40.00%)			
occurrences (all)	8			
Gamma-glutamyltransferase increased				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Haematocrit decreased				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Haemoglobin decreased				
subjects affected / exposed	3 / 20 (15.00%)			
occurrences (all)	3			
Hepatic enzyme increased				
subjects affected / exposed	2 / 20 (10.00%)			
occurrences (all)	2			
HLA marker study positive				
subjects affected / exposed	5 / 20 (25.00%)			
occurrences (all)	6			
Immunosuppressant drug level decreased				
subjects affected / exposed	8 / 20 (40.00%)			
occurrences (all)	11			
Immunosuppressant drug level increased				

subjects affected / exposed	6 / 20 (30.00%)		
occurrences (all)	8		
International normalised ratio increased			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Neutrophil count decreased			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Portal vein flow decreased			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		
Red blood cell count decreased			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Streptococcus test positive			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Ultrasound scan abnormal			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Transaminases increased			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Fall			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Head injury			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Ligament sprain			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Procedural pain			
subjects affected / exposed	5 / 20 (25.00%)		
occurrences (all)	5		
Transfusion reaction			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 20 (30.00%)		
occurrences (all)	6		
Hypertonia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Hypotonia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Somnolence			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Speech disorder developmental			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Tremor			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Hypergammaglobulinaemia			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Lymphadenopathy			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		
Thrombocytosis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	3		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	5 / 20 (25.00%)		
occurrences (all)	5		
Abdominal pain upper			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Ascites			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Dental caries			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	8 / 20 (40.00%)		
occurrences (all)	12		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Haematochezia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Nausea			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	9 / 20 (45.00%)		
occurrences (all)	16		
Hepatobiliary disorders			
Hepatic fibrosis			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	4		
Hypertransaminasaemia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Portal vein thrombosis			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Alopecia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Dermatitis atopic			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Eczema			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Granuloma skin			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Petechiae			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Pigmentation disorder			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Skin exfoliation			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Skin hypopigmentation			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Skin irritation			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
Urticaria			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Renal and urinary disorders			
Renal tubular acidosis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Infections and infestations			
Bronchitis			
subjects affected / exposed	6 / 20 (30.00%)		
occurrences (all)	7		
Cystitis			

subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Ear infection				
subjects affected / exposed	3 / 20 (15.00%)			
occurrences (all)	3			
Fungal infection				
subjects affected / exposed	2 / 20 (10.00%)			
occurrences (all)	2			
Gastroenteritis				
subjects affected / exposed	6 / 20 (30.00%)			
occurrences (all)	7			
Gingivitis				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Impetigo				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Nasopharyngitis				
subjects affected / exposed	9 / 20 (45.00%)			
occurrences (all)	20			
Oral herpes				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	2			
Otitis media				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Pharyngitis				
subjects affected / exposed	2 / 20 (10.00%)			
occurrences (all)	2			
Rhinitis				
subjects affected / exposed	5 / 20 (25.00%)			
occurrences (all)	7			
Tonsillitis				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Upper respiratory tract infection				

subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	4		
Urinary tract infection			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Viral infection			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Vulvovaginitis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Infection			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Laryngitis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Parainfluenzae virus infection			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Rhinovirus infection			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hyperammonaemia			
subjects affected / exposed	6 / 20 (30.00%)		
occurrences (all)	16		
Decreased appetite			
subjects affected / exposed	7 / 20 (35.00%)		
occurrences (all)	9		
Hyperglycaemia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Hypoglycaemia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		

Hypokalaemia subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Hypomagnesaemia subjects affected / exposed occurrences (all)	3 / 20 (15.00%) 3		
Iron deficiency subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Metabolic disorder subjects affected / exposed occurrences (all)	5 / 20 (25.00%) 13		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 February 2012	Belgium: • Amendment I: Protocol version 2.1 dated 13-Feb-2012, o The total l amount of cells that could be infused at once was defined. A second HepaStem bag could be infused directly after the first bag for the children who were to receive a high total cell count requiring several cell bags. o Description of the anticoagulation treatment after last infusion/completion of the cycle: once the last infusion was finished, anticoagulation was to be given at a lower concentration for 30 min and stopped. The removal of the catheter was recommended 30 min after bivalirudin stop because the half-life of bivalirudin is +/- 15 min. o Addition of the long term safety FU study (SAF001) upon request of the MHRA during the CTA evaluation. In accordance with ATMP guidance regular collection and review of safety data were to be proposed to the patient and will continue for 5 years after the infusion of HepaStem. o Addition of of oxygen saturation measurement prior to, during and after each infusion. o The guideline on liver biopsy harvest and sample preparation were annexed to the study protocol to reduce the potential risk inherent to liver biopsies, reducing the number of liver biopsies and the requested amount of tissue per biopsy. o 13C-sodium acetate route of administration was changed from IV to oral. o The guideline for the PBMC sub-study was also annexed.
18 June 2012	Belgium: • Amendment II: Two additional sites were added: o UZ Gent, PI Ruth de Bruyne, Pediatry o UZ Leuven, PI Luc Régal, Pediatry
16 July 2012	Belgium: • Amendment III: Additional study documents: o Patient notebook: CN diary_version 1.0_120621 o Patient notebook: UCD diary_ version 1.0_120621 o Patient study card version 1.0_120621

13 September 2012	Belgium: • Amendment IV: Protocol version 3.0 dated 01-Aug-2012, o The minimum flow rate of infusion was decreased in order to allow more flexibility in applying the optimal flow rate for cell infusion especially in small children, o The dose escalation process was clarified, o A random allocation dose from the third patient onwards was described for CN patients, o Appropriate target and way to reach the recommended level were clarified for the immunosuppressive treatment. o ACT values which should be observed at each infusion stage to ensure appropriate anticoagulation at the time of cell infusion were specified in order to increase safety, o The anticoagulation protocol was clarified, o Protocol for D-dimer measurements was clarified, o Use of a patient diary to collect diet/phototherapy, medication and any other relevant events occurring at the patient's home, o Description of some investigational events (tacrolimus blood levels, urine tests, D-dimer, ammonia blood level and general laboratory tests) to be reported as AEs were added, o The fasting requirements for the 13C test were modified to avoid prolonged fasting in patients with a metabolic disorder, o The aim of the PBMC sub-study was clarified and its study design updated.
09 November 2012	UK: • Amendment I: Protocol version 3.0 dated 01-Aug-2012 + change of PI o Protocol amendment: see amendment IV from Belgium. o Change of PI: - Former PI: Dr. Anhil Dhawan – King's College Hospital – London - New PI: Dr. Patrick McKiernan – Birmingham Children's Hospital – Birmingham.
14 December 2012	France: • Amendment II: One additional site o CHU Toulouse, PI Pierre Broué, Pediatric hepatology, gastroenterology, and nutrition unit.
24 January 2013	France: • Amendment I: Protocol version 3.0 dated 01-Aug-2012 + two additional sites o Protocol amendment: see amendment IV from Belgium. o Two additional sites: - CHRU Tours, PI François Labarthe, Pediatric Medecine - CHU Paris-Robert Debré, PI Hélène Ogier, Pediatric neurology and metabolic diseases.
25 May 2013	Israel: • Amendment I: HEP001-IL Protocol version 1.0 dated 20-Mar-2013 o Israel-specific procedures were highlighted to emphasize the responsibility of each physician, and to clearly explain who is responsible for which specific study procedure. o The timeline set for Europe (recruitment ended March 2013) was prolonged for an additional 3 months specifically for Israel due to prolonged study set-up. This was to provide sufficient time to enroll 5 patients. o It was highlighted that the monitoring of the data collected from the Israeli subjects was to be performed by an Israeli CRO, Clinipace Worldwide, representing Promethera Biosciences (PB). o Informed consent procedure was clarified.

05 August 2013	Belgium: • Amendment V: Protocol version 3.1 dated 25-Jul-2013. o The study was opened to centers outside Europe (Israel), o The number of participating patients was increased and the recruitment period was extended, o The location of formulation of the drug product was updated (IMP could be formulated in Promethera Biosciences or in a mobile unit/hospital laboratory with a fully closed formulation system based on SEPAX device), o The collection of a 5 mL blood sample to collect DNA was added to be used as control for the chimerism analysis and for HLA typing, o The laboratory tests were clarified, o The possibility to prolong hospitalization after the 24h following catheter removal was added, o The placement of the catheter was allowed in the left branch of the portal vein to increase feasibility, o The recommendation to perform hepatic US and Doppler one hour after catheter removal was added to increase safety for the patient, o Some corrections to units were made.
11 September 2013	France: • Amendment III : Protocol version 3.1 dated 25-Jul-2013 o See amendment V from Belgium. Belgium: • Amendment V: Protocol version 3.1 dated 25-Jul-2013. o The study was opened to centers outside Europe (Israel), o The number of participating patients was increased and the recruitment period was extended, o The location of formulation of the drug product was updated (IMP could be formulated in Promethera Biosciences or in a mobile unit/hospital laboratory with a fully closed formulation system based on SEPAX device), o The collection of a 5 mL blood sample to collect DNA was added to be used as control for the chimerism analysis and for HLA typing, o The laboratory tests were clarified, o The possibility to prolong hospitalization after the 24h following catheter removal was added, o The placement of the catheter was allowed in the left branch of the portal vein to increase feasibility, o The recommendation to perform hepatic US and Doppler one hour after catheter removal was added to increase safety for the patient, o Some corrections to units were made.
16 September 2013	UK: • Amendment IV: Protocol version 3.1 dated 25-Jul-2013. o same as amendment V from Belgium. Belgium: • Amendment V: Protocol version 3.1 dated 25-Jul-2013. o The study was opened to centers outside Europe (Israel), o The number of participating patients was increased and the recruitment period was extended, o The location of formulation of the drug product was updated (IMP could be formulated in Promethera Biosciences or in a mobile unit/hospital laboratory with a fully closed formulation system based on SEPAX device), o The collection of a 5 mL blood sample to collect DNA was added to be used as control for the chimerism analysis and for HLA typing, o The laboratory tests were clarified, o The possibility to prolong hospitalization after the 24h following catheter removal was added, o The placement of the catheter was allowed in the left branch of the portal vein to increase feasibility, o The recommendation to perform hepatic US and Doppler one hour after catheter removal was added to increase safety for the patient, o Some corrections to units were made.

18 October 2013	UK: • Amendment II: Due to change of PI, the initial approach to surgically insert the catheter changed. BCH's approach to insert the catheter percutaneously was then considered as a national approach. A national review by a Medical Physics expert and a Clinical Radiation Expert was required. PIS were updated accordingly.
10 December 2013	Italy: • Amendment I: Protocol version 3.1 dated 25-Jul-2013 o See amendment V from Belgium. Belgium: • Amendment V: Protocol version 3.1 dated 25-Jul-2013. o The study was opened to centers outside Europe (Israel), o The number of participating patients was increased and the recruitment period was extended, o The location of formulation of the drug product was updated (IMP could be formulated in Promethera Biosciences or in a mobile unit/hospital laboratory with a fully closed formulation system based on SEPAX device), o The collection of a 5 mL blood sample to collect DNA was added to be used as control for the chimerism analysis and for HLA typing, o The laboratory tests were clarified, o The possibility to prolong hospitalization after the 24h following catheter removal was added, o The placement of the catheter was allowed in the left branch of the portal vein to increase feasibility, o The recommendation to perform hepatic US and Doppler one hour after catheter removal was added to increase safety for the patient, o Some corrections to units were made.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported