Clinical trial results:
A prospective, open label, multicountry, efficacy and safety study of several infusions of HepaStem in Urea Cycle Disorders pediatric patients.

Summary

EudraCT number	2014-000650-11
Trial protocol	BE ES FR PL
Global end of trial date	28 September 2017

Results information

Result version number	v1 (current)
This version publication date	27 April 2022
First version publication date	27 April 2022
Summary attachment (see zip file)	Efficacy (HEP002_11_Efficacy conclusions.pdf) Safety (HEP002_12_Safety conclusions.pdf) Conclusion (HEP002_13_Discussion and overall conclusions.pdf)

Trial information

Trial identification

Sponsor protocol code	HEP002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02489292
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Promethera Therapeutics (formerly Promethera Biosciences)
Sponsor organisation address	Rue Granbonpré 11, Mont-Saint-Guibert, Belgium, 1435
Public contact	Welcome Desk, Promethera Therapeutics (formerly Promethera Biosciences), 32 10394300, regulatory@promethera.com
Scientific contact	Welcome Desk, Promethera Therapeutics (formerly Promethera Biosciences), 32 10394300, regulatory@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 February 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 April 2017
Global end of trial reached?	Yes
Global end of trial date	28 September 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the functional efficacy of HepaStem at 6 months after initiation of infusion in terms of ureagenesis improvement based on a functional test (13C tracer method).

Protection of trial subjects:

The study was conducted in accordance with the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP), the ethical principles that have their origins in the revised 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.

Recruitment was to be split into 2 periods. A first period was planned to confirm the benefit risk ratio in 5 patients before resuming recruitment (i.e., a stopping rule was introduced as a particular measure to protect pediatric patients: If the positive benefit risk ratio for the study was confirmed after the first five patients having completed follow-up (FU) visit 3 (6 months post first infusion), the study was to be continued). The decision to prematurely stop the study occurred before the end of the first recruitment period.

All the appropriate measures were taken to minimize the known risks for the patient as well as pain and distress.

A data safety monitoring board (DSMB) was appointed to review safety data periodically and determine whether subjects were exposed to unnecessary risks.

A Data Review Committee (DRC) composed of external experts in metabolic diseases was appointed to evaluate whether there was a clinical improvement or not based on a complete blinded file of each patient after 6 and 12 months of initiation of HepaStem therapy.

Background therapy:

Patients included in the study were pediatric patients with UCD, aged below 12 years prior to infusion, presenting one of the UCDs defined in the protocol (carbamoylphosphate synthetase I [CPS I] deficiency [CPSID], ornithine transcarbamylase [OTC] deficiency [OTCD], argininosuccinic acid synthetase [ASS] deficiency [ASSD], argininosuccinic acid lyase [ASL] deficiency [ASLD], arginase [ARG] deficiency [ARGD]). Patients had severe disease with impaired protein tolerance defined as: chronic protein restricted diet AND chronic treatment with at least one nitrogen scavenger and showed patency of the portal vein and its branches including mesenteric veins, with normal flow velocity as confirmed by Doppler US and accessibility of the portal vein and/ or affluent.

Evidence for comparator: -

Actual start date of recruitment	31 December 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	9 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Spain: 4
Worldwide total number of subjects	6
EEA total number of subjects	6

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)	0
Children (2-11 years)	6
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:

•Pediatric patient < 12 years prior to infusion.
•Presenting with one of the Urea Cycle Disorders: CPSID, OTCD, ASSD, ASLD, ARGD
•Having severe disease with impaired protein tolerance
•Showing patency of the portal vein and its branches with normal flow velocity as confirmed by Doppler US and accessibility of the portal vein and/ or affluent

Pre-assignment

Screening details:

Participation to this study was voluntary.
During the Screening period (1 to 4 weeks maximum), the patient eligibility was assessed and the investigator ensured that the chronic metabolic treatment was optimized for the patient's metabolic condition (confirmed in writing).

Period 1

Period 1 title	Screening period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Arm title	Single arm - Screening Visit

Arm description:

During this period, the patient eligibility was assessed and the investigator ensured that the chronic metabolic treatment was optimised for the patient's metabolic condition (confirmed in writing). The patient's eligibility was thereafter confirmed by the sponsor's medical monitor.

Arm type	Experimental
Investigational medicinal product name	HepaStem
Investigational medicinal product code	
Other name	Heterologous human adult liver-derived progenitor cells (HHALPC)
Pharmaceutical forms	Dispersion for infusion
Routes of administration	Intraportal use

Dosage and administration details:

Planned daily dose: 12.5 x 10^6 cells/kg body weight (4 infusions foreseen).
Planned total target dose: 50 x 10^6 cells/kg body weight.

Number of subjects in period 1	Single arm - Screening Visit
Started	6
Completed	6

Period 2

Period 2 title	Baseline period
Is this the baseline period?	Yes[1]
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Are arms mutually exclusive?	No
Arm title	Single arm - Baseline Visit 1

Arm description:

This period consisted of 3 visits (BL visit 1 to BL visit 3) during which the 13C tracer method tests were performed to assess the metabolic condition.

Arm type	Experimental
Investigational medicinal product name	HepaStem
Investigational medicinal product code	
Other name	Heterologous human adult liver-derived progenitor cells (HHALPC)
Pharmaceutical forms	Dispersion for infusion
Routes of administration	Intraportal use

Dosage and administration details:

Planned daily dose: 12.5 x 10^6 cells/kg body weight (4 infusions foreseen).
Planned total target dose: 50 x 10^6 cells/kg body weight.

Arm title	Single arm - Baseline Visit 2

Arm description: -

Arm type	Experimental
Investigational medicinal product name	HepaStem
Investigational medicinal product code	
Other name	Heterologous human adult liver-derived progenitor cells (HHALPC)
Pharmaceutical forms	Dispersion for infusion
Routes of administration	Intraportal use

Dosage and administration details:

Planned daily dose: 12.5 x 10^6 cells/kg body weight (4 infusions foreseen).
Planned total target dose: 50 x 10^6 cells/kg body weight.

Arm title	Single arm - Baseline Visit 3

Arm description: -

Arm type	Experimental
Investigational medicinal product name	HepaStem
Investigational medicinal product code	
Other name	Heterologous human adult liver-derived progenitor cells (HHALPC)
Pharmaceutical forms	Dispersion for infusion
Routes of administration	Intraportal use

Dosage and administration details:

Planned daily dose: 12.5 x 10^6 cells/kg body weight (4 infusions foreseen).
Planned total target dose: 50 x 10^6 cells/kg body weight.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: before baseline period is a screening period to verify inclusion/exclusion criteria

Number of subjects in period 2	Single arm - Baseline Visit 1	Single arm - Baseline Visit 2	Single arm - Baseline Visit 3
Started	6	6	6
Completed	6	6	6

Period 3

Period 3 title	Active treatment period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Arm title	Single arm - Active treatment period

Arm description:

This period was subdivided in a permanent mesenteric portal access and catheter (PAC) placement period and in an infusion period. During the infusion period, HepaStem was to be administered in addition to the conventional UCD treatment, with a total target dose of 50*10^6 cells/kg body weight (BW). Although 2 potential methods of HepaStem infusion were described in the protocol, HepaStem was administered through a PAC for all patients (therefore only this method is described in the present report). The patients were to receive a daily dose of 12.5*10^6 cells/kg BW of HepaStem on each infusion day. HepaStem was to be administered on 4 infusion days, spread over an 8-week period with an interval of 2 weeks (± 3 days) between infusion days.
During the baseline and active treatment periods, the chronic metabolic treatment of the patient (adjusted to BW) was to remain stable according to medical practice unless changes were needed for safety reason.

Arm type	Experimental
Investigational medicinal product name	HepaStem
Investigational medicinal product code	
Other name	Heterologous human adult liver-derived progenitor cells (HHALPC)
Pharmaceutical forms	Dispersion for infusion
Routes of administration	Intraportal use

Dosage and administration details:

Planned daily dose: 12.5 x 10^6 cells/kg body weight (4 infusions foreseen).
Planned total target dose: 50 x 10^6 cells/kg body weight.

Number of subjects in period 3	Single arm - Active treatment period
Started	6
Completed	3
Not completed	3
Physician decision	1
Comedication (bivalirudine) no longer available	2

Period 4

Period 4 title	Follow-up period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Arm title	Single arm - Follow-up Month 3

Arm description:

Starting approximately 12 weeks after the first HepaStem infusion day, this period was to last about 9 months with study visits taking place every 6 weeks (FU visits 1 to 7).
13C tracer method tests were to be performed every 3 month post first infusion.
After any change, an additional control visit was to be organized at least within 15 days for controlling the metabolic parameters of the patient. At each visit, the reasons for adapting or not the supportive treatment were documented in the eCRF.
For each patient, the maximum duration of the study was foreseen to be ~17 months.

Arm type	Experimental
Investigational medicinal product name	HepaStem
Investigational medicinal product code	
Other name	Heterologous human adult liver-derived progenitor cells (HHALPC)
Pharmaceutical forms	Dispersion for infusion
Routes of administration	Intraportal use

Dosage and administration details:

Planned daily dose: 12.5 x 10^6 cells/kg body weight (4 infusions foreseen).
Planned total target dose: 50 x 10^6 cells/kg body weight.

Number of subjects in period 4	Single arm - Follow-up Month 3
Started	3
Completed	2
Not completed	1
Adverse event, non-fatal	1

Baseline characteristics

Reporting groups

Reporting group title	Baseline period

Reporting group description: -

Reporting group values	Baseline period	Total	
Number of subjects	6	6	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	6	6	
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: years			
arithmetic mean	6.8		
standard deviation	± 3.4	-	
Gender categorical Units: Subjects			
Female	3	3	
Male	3	3	
Weight			
Note: n=5 for Included Set			
Units: kilogram(s)			
arithmetic mean			
standard deviation	±	-	
Height			
Note: n=5 for Included Set			
Units: centimetre			
arithmetic mean			
standard deviation	±	-	
Head circumference			
Note: n=3 for Included Set			
Units: centimetre			
arithmetic mean			
standard deviation	±	-	
AUC 0-120 min for 13C Blood urea concentration			
Units: min*µmol/L			
median			
full range (min-max)		-	
Total protein intake			

Units: mg/kg/day median full range (min-max)		- 	
Natural protein intake Units: mg/kg/day median full range (min-max)		- 	

Subject analysis sets	
Subject analysis set title	Included Set
Subject analysis set type	Full analysis
Subject analysis set description: The included set (IS) consisted of all patients who signed an informed consent and performed at least one baseline (BL) visit.	
Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description: The Safety Set (SS) included all patients from the Included Set (IS) who received at least one infusion of HepaStem.	

Reporting group values	Included Set	Safety Set	
Number of subjects	6	3	
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over	 6 	 3 	
Age continuous Units: years arithmetic mean standard deviation	 6.8 ± 3.4	 5.7 ± 4.1	
Gender categorical Units: Subjects			
Female Male	3 3	0 3	
Weight			
Note: n=5 for Included Set			
Units: kilogram(s) arithmetic mean standard deviation	 21.48 ± 7.64	 21.13 ± 10.36	
Height			
Note: n=5 for Included Set			
Units: centimetre arithmetic mean	 111.2	 107.1	

standard deviation	± 18.5	± 22.7	
Head circumference			
Note: n=3 for Included Set			
Units: centimetre			
arithmetic mean	50.67	50.67	
standard deviation	± 0.58	± 0.58	
AUC 0-120 min for 13C Blood urea concentration			
Units: min*µmol/L			
median		33.39	
full range (min-max)		13.07 to 70.02	
Total protein intake			
Units: mg/kg/day			
median	1010.6	820.0	
full range (min-max)	470 to 1309	470 to 987	
Natural protein intake			
Units: mg/kg/day			
median	743.4	600	
full range (min-max)	0 to 1160	0 to 836	

End points

End points reporting groups

Reporting group title	Single arm - Screening Visit

Reporting group description:

During this period, the patient eligibility was assessed and the investigator ensured that the chronic metabolic treatment was optimised for the patient's metabolic condition (confirmed in writing). The patient's eligibility was thereafter confirmed by the sponsor's medical monitor.

Reporting group title	Single arm - Baseline Visit 1

Reporting group description:

This period consisted of 3 visits (BL visit 1 to BL visit 3) during which the 13C tracer method tests were performed to assess the metabolic condition.

Reporting group title	Single arm - Baseline Visit 2

Reporting group description: -

Reporting group title	Single arm - Baseline Visit 3

Reporting group description: -

Reporting group title	Single arm - Active treatment period

Reporting group description:

This period was subdivided in a permanent mesenteric portal access and catheter (PAC) placement period and in an infusion period. During the infusion period, HepaStem was to be administered in addition to the conventional UCD treatment, with a total target dose of 50*10^6 cells/kg body weight (BW). Although 2 potential methods of HepaStem infusion were described in the protocol, HepaStem was administered through a PAC for all patients (therefore only this method is described in the present report). The patients were to receive a daily dose of 12.5*10^6 cells/kg BW of HepaStem on each infusion day. HepaStem was to be administered on 4 infusion days, spread over an 8-week period with an interval of 2 weeks (± 3 days) between infusion days.
During the baseline and active treatment periods, the chronic metabolic treatment of the patient (adjusted to BW) was to remain stable according to medical practice unless changes were needed for safety reason.

Reporting group title	Single arm - Follow-up Month 3

Reporting group description:

Starting approximately 12 weeks after the first HepaStem infusion day, this period was to last about 9 months with study visits taking place every 6 weeks (FU visits 1 to 7).
13C tracer method tests were to be performed every 3 month post first infusion.
After any change, an additional control visit was to be organized at least within 15 days for controlling the metabolic parameters of the patient. At each visit, the reasons for adapting or not the supportive treatment were documented in the eCRF.
For each patient, the maximum duration of the study was foreseen to be ~17 months.

Subject analysis set title	Included Set
Subject analysis set type	Full analysis

Subject analysis set description:

The included set (IS) consisted of all patients who signed an informed consent and performed at least one baseline (BL) visit.

Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Set (SS) included all patients from the Included Set (IS) who received at least one infusion of HepaStem.

Primary: Ureagenesis improvement at 6 months post first infusion day (follow-up [FU] visit 3)

End point title	Ureagenesis improvement at 6 months post first infusion day (follow-up [FU] visit 3)[1]

End point description:

The primary endpoint was evaluated using the absolute 13C blood urea area under the drug concentration-time curve calculated between 0 and 120 minutes, AUC(0-120 min), quantified with the 13C tracer method at FU visit 3 and comparing it with baseline (BL) evaluations (measurements at the 3 visits occurring during the BL period).

13C blood urea concentration (C) was measured in plasma before and 30, 60, 90 and 120 minutes after ingestion of 27 mg/kg solution of [1-13C] sodium-acetate at each assessment visits.
The AUC(0-120 min) was calculated by linear trapezoidal rule.
AUC was considered as missing for a specific visit if any 13C blood urea concentration was not available at any time point.
The 13C blood urea concentration at each time-point and the AUC(0-120 min) are summarized by study visit.
Individual medians per study period for the AUC(0-120 min) are also summarized by study periods.

End point type	Primary

End point timeframe:

At 6 months post first infusion day (FU visit 3)

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: descriptive analysis only

End point values	Single arm - Baseline Visit 1	Single arm - Baseline Visit 2	Single arm - Baseline Visit 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	3	3	
Units: min*µmol/L				
median (full range (min-max))	20.78 (11.96 to 70.02)	33.39 (13.07 to 80.75)	57.03 (38.78 to 65.37)	

Attachments (see zip file)	Primary efficacy/HEP002_01_Primary efficacy endpoint.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Ureagenesis improvement at 3, 9, and 12 months post first infusion day (FU visits 1, 5, and 7)

End point title	Ureagenesis improvement at 3, 9, and 12 months post first infusion day (FU visits 1, 5, and 7)

End point description:

End point type	Secondary

End point timeframe:

At 3, 9, and 12 months post first infusion day (FU visits 1, 5, and 7)

End point values	Single arm - Baseline Visit 1	Single arm - Baseline Visit 2	Single arm - Baseline Visit 3	Single arm - Follow-up Month 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	2
Units: min*µmol/L				
median (full range (min-max))	20.78 (11.96 to 70.02)	33.39 (13.07 to 80.75)	57.03 (37.78 to 65.37)	68.00 (61.71 to 74.28)

Attachments (see zip file)	Secondary efficacy/HEP002_02_Secondary clinical efficacy

Statistical analyses

No statistical analyses for this end point

Secondary: Chronic protein intake

End point title	Chronic protein intake

End point description:

Chronic (total and natural) protein intake reported as compared to World health organization (WHO) safe level for age.
Global energy balance was evaluated based on a diet evaluation performed at each visit of the baseline period and at each visit of the FU period. For the diet evaluation, parents were requested to fill-in diet sheets for 3 days before the visit, using paper forms.
The dietician (or other qualified health care professional) evaluated the total protein intake and natural protein intake based on the weight of the patient measured at the study visit ("reported diet"). In parallel, the prescribed dose of protein (total protein and natural protein) was collected at each study visit ("prescribed diet") in order to check compliance to treatment.

End point type	Secondary

End point timeframe:

At study visits during BL period and at scheduled study visits during the FU period.

End point values	Single arm - Baseline Visit 1	Single arm - Baseline Visit 2	Single arm - Baseline Visit 3	Single arm - Follow-up Month 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	3
Units: mg/kg/day				
arithmetic mean (standard deviation)				
Total protein intake	758.9 (± 263.8)	762.1 (± 297.4)	752.8 (± 141.7)	616.2 (± 107.8)
Natural protein intake	478.5 (± 430.8)	478.5 (± 430.8)	422.2 (± 367.2)	273.1 (± 386.2)

Statistical analyses

No statistical analyses for this end point

Secondary: Chronic nitrogen scavenger dose

End point title	Chronic nitrogen scavenger dose

End point description:

The dose of each nitrogen scavenger was collected at each study visit (expressed in mg/day).

End point type	Secondary

End point timeframe:

At scheduled study visits during BL period and at scheduled study visits during the FU period

End point values	Single arm - Baseline Visit 1	Single arm - Baseline Visit 2	Single arm - Baseline Visit 3	Single arm - Active treatment period
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	3
Units: mg/kg/day				
number (not applicable)	318	318	318	318

End point values	Single arm - Follow-up Month 3			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: mg/kg/day				
number (not applicable)	318			

Attachments (see zip file)	Nitrogen scavenger/HEP002_03_Endpoint Individual Plots of

Statistical analyses

No statistical analyses for this end point

Secondary: Blood ammonia

End point title	Blood ammonia

End point description:

Blood samples were taken to measure blood ammonia (fasting and 2 hours post-prandial NH3)

End point type	Secondary

End point timeframe:

At scheduled study visits during screening and BL periods and at scheduled study visits during the FU period

End point values	Single arm - Screening Visit	Single arm - Baseline Visit 1	Single arm - Baseline Visit 2	Single arm - Baseline Visit 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	6	6
Units: µmol/L				
number (not applicable)	60.5	55	43.3	45.6

End point values	Single arm - Active treatment period	Single arm - Follow-up Month 3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	3		
Units: µmol/L				
number (not applicable)	46	52.5		

Attachments (see zip file)	Blood ammonia/HEP002_04_Endpoint Individual Profile of

Statistical analyses

No statistical analyses for this end point

Secondary: Blood amino acids

End point title	Blood amino acids

End point description:

Blood samples were taken to measure amino acid values during screening, BL and FU periods. Aminoacidogram was performed in fasting condition.

End point type	Secondary

End point timeframe:

At scheduled study visits during screening and BL periods and at scheduled study visits during the FU period

End point values	Single arm - Screening Visit	Single arm - Baseline Visit 1	Single arm - Baseline Visit 2	Single arm - Baseline Visit 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	3
Units: µmol/L				
number (not applicable)				
Glutamine	715.655	571	490	531
Alanine	225.535	339.5	344.5	302
Citrulline	123.425	403.7	216.9	217.9
Arginine	60.35	71.8	84	94

End point values	Single arm - Active treatment period	Single arm - Follow-up Month 3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	2		
Units: µmol/L				
number (not applicable)				
Glutamine	986	892.55		
Alanine	542.07	329.965		
Citrulline	296.515	229.555		
Arginine	161.415	73.065		

Attachments (see zip file)	Blood amino acids/HEP002_05_Endpoint Individual Profile of

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: Up to one year after initiation of HepaStem infusion	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0

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

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: described in the attachement

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 November 2014	Amendment A • Following the Paediatric Committee within the European Medicines Agency (PDCO) request and available results from the HEP001 study: o The evaluation of the primary objective was based on biochemical parameters rather than functional parameters (ammonia). The primary and secondary objectives and endpoints were updated accordingly as well as the procedures (laboratory assessments), the rationale for sample size and the planned statistical analysis. o The rational for the new schedule of administration (4 infusions spread over a 2-month period) was updated. • Based upon the results from the HEP001 study which suggested a better efficacy in younger patients, the inclusion was restricted to patients aged below 12 years old. • Following the ANSM (French national competent authority) comments, o The total dose to be administered was clarified. o The differences between the 2 possible methods to administer HepaStem (PAC and transient transhepatic catheter) were clarified in term of procedures and study duration. More specifically, the procedures for each method, including the specification of the catheter to be used were provided. o The study population was redefined (inclusion and exclusion criteria). o The laboratory tests to be performed as well as the time points at which they should be performed were have been updated. o The qualification and training to be followed by the investigators were specified. • The importance to accurately document the evolution of the UCD metabolic condition of each patient throughout the study duration, and to standardise documentation of evaluation was emphasised. • The definition of the pre and post-infusion time windows were clarified.

21 September 2015	Amendment B The amendment followed a consultation of the EMA Scientific Advice Committee (CHMP) where Promethera Biosciences was seeking advice on the development of HepaStem for paediatric patients with UCDs. Additionally, several physicians expert in metabolic disease were consulted. Main major changes are summarised below: • Although based on available data, the benefit risk of the study was positive; a stopping rule was introduced to protect the paediatric patients. The DSMB was to review the efficacy and safety data of the first 5 patients treated till FU visit 3 before recruiting the subsequent patients. • The primary and secondary objectives and, primary and secondary endpoints, were updated because ammonia has been shown not to be a robust primary endpoint. o The primary endpoint was thus defined as ureagenesis improvement at 6 months post first infusion and was evaluated using the absolute 13C blood urea AUC0-120 min quantified with the 13C tracer method. o The secondary objectives/endpoints were adapted following the changes in the primary endpoints. • A DRC was appointed in order to get an objective evaluation of the patients. The members of this committee reviewed the clinical and biological parameters related to the secondary objectives. • The study design was adapted and was divided in 4 periods. A screening period was defined to allow for screening of the patients and for optimising their treatment, if needed. A BL period was also defined. • BL procedures were updated. They included 3 visits (therefore 3 evaluation of the BL ureagenesis) and collect data in a prospective way over 3 months in order to assess intra-patient variability and get a robust BL evaluation. • The request to increase the daily total protein dose adjusted to BW at each visit as of FU visit 3 and the monitoring of diet was strengthened. This was to allow for assessing if the diet could be improved without worsening of the other clinical parameters.
26 April 2016	Amendment C • Stopping rules were adapted to take into account the possibility that some patients may not be eligible or would not complete the baseline period. • Some procedures were clarified: o Protein electrophoresis (following recurrent question raised by the study centres). o Use of the concomitant treatment related to study procedure (clarification of timepoints for tacrolimus and of procedures for ACT measurement in the context of bivalirudin use). o Time window for PAC placement and update regarding the choice of the catheter to be used. • The laboratory performing the 13C analyses was specified, included its localisation, in order to be compliant with ethical practice and EU directive on data privacy.
04 April 2017	This amendment was only submitted in Spain as study recruitment was stopped and only Spain still had patients participating in the study at that date. • The investigational product shipment procedure was updated. • The pharmacovigilance activities had been outsourced and the contact details for AE reporting were then updated. • A long-term safety registry had replaced the foreseen long-term FU study (SAF001) in the aim of unifying data collection with standardised outcome data across all indications targeted by HepaStem therapy. The protocol was updated accordingly.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

01 December 2016	In December 2016, the sponsor decided to prematurely stop the study in order to find a partner before resuming in the best conditions the development of HepaStem as indication for UCD. The decision to prematurely stop the study occurred before the end of the first recruitment period. A total of only 6 patients were enrolled in the study and 3 patients received HepaStem infusion. Of the 3 patients included in the Safety Set, 2 completed the infusion protocol Follow-Up period and one was prematurely discontinued. The planned interim analysis was cancelled following the premature stop of the study.	-

Notes:

Limitations and caveats

None reported