



## Clinical trial results:

**SAF 001: A long-term safety follow-up study of patients suffering from Urea Cycle disorders (UCD) or Crigler-Najjar Syndrome (CN) having received infusions of HepaStem.**

### Summary

EudraCT number	2013-001045-14
Trial protocol	BE PT IT GB
Global end of trial date	20 June 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)	SAF001_Synopsis (SAF001_Clinical Study Report_Final_20190204_Synopsis.pdf)

### Trial information

#### Trial identification

Sponsor protocol code	SAF001
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02051049
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)	EMA-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:

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## 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	20 June 2017
Global end of trial reached?	Yes
Global end of trial date	20 June 2017
Was the trial ended prematurely?	No

Notes:

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## General information about the trial

Main objective of the trial:

The primary objective is to document the safety of HepaStem therapy during a period up to a maximum of 48 months (4 years (Y)) in the SAF001 study (SAF001 Y1+Y2+Y3+Y4).

This long term safety follow-up study will start when the patient is ending the period of active surveillance post infusion of Hepastem in any former interventional study (Study A) conducted by Promethera Biosciences (PB). The safety will be assessed in terms of clinical status, biochemical parameters and morphology of the liver, detection of circulating anti-HLA antibodies specific for donor cells or other immune markers related to liver diseases as well as Serious Adverse Events (SAEs) and AEs of Special Interest (AESI) related to HepaStem therapy.

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.

The safety monitoring was planned to last for a maximum of 4 years for each patient.

However, for different reasons, patients could have been removed from this study:

- In case of organ transplantation, if it was a liver transplantation, liver samples were to be collected from the exograft. An additional visit after orthotopic liver transplantation (OLT) including examinations and OLT questionnaire completion were also requested
- In case of intake of other investigational treatments

Nevertheless, whenever possible, Promethera Biosciences was to continue to collect safety data of these patients once a year in collaboration with the center where the patient was followed.

If the patient terminated their participation prematurely, they were asked to have a last visit including the evaluation of all the study parameters, similar to those at 24- or 48-months, depending on the case.

Background therapy:

No investigational medicinal product was administered during this trial.

All UCD and CN patients included in the trial continued their disease-specific treatment based on usual metabolic monitoring under the responsibility of the investigator/treating physician.

A low level of immunosuppression was maintained after a HepaStem infusion (in the initial investigational HEP001 study) to avoid a potential risk of developing an immunization against HepaStem, which would be detrimental for HepaStem or any other future treatment with cells or organ transplant (Kaneku 2013, O`Leary 2011). Thus, in the SAF001 study, a close monitoring was set up to follow the level of immunosuppression of the patients.

Patients might have been maintained under immunosuppressive treatment based on investigator's judgement and in some cases based on the results of functional <sup>13</sup>C tests. For patients who received HepaStem 12 months ago, the recommended target through blood level for tacrolimus was 4 ± 2 ng/mL.

However, immunosuppression could have been terminated at any time following the decision taken by the investigator/treating physician.

Any termination was to be carefully documented.

Evidence for comparator:

Not applicable

Actual start date of recruitment	17 April 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

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### Population of trial subjects

#### Subjects enrolled per country

Country: Number of subjects enrolled	Portugal: 1
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Israel: 4
Worldwide total number of subjects	17
EEA total number of subjects	11

Notes:

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#### 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)	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:

Ten centers were active in 5 countries (Belgium, France, the UK, Italy and Israel).  
Date of first patient screened: 17-APR-2013; date of first patient enrolled: 17-APR-2013.

### Pre-assignment

Screening details:

A total of 17 patients (12 UCD and 5 CN) were enrolled. All received infusions of HepaStem during the former interventional clinical HEP001 study and had terminated their participation in that study. All signed an informed consent form. None received mature liver cell or stem cell transplantation other than HepaStem, or organ liver transplantation.

### Period 1

Period 1 title	Visit 0 Month
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Pediatric patients suffering from CN

Arm description:

CN pediatric patients presenting with Crigler-Najjar syndrome type I or type II (poorly controlled under phenobarbital treatment or experiencing serious impairment in QoL) in the former interventional clinical HEP001 study

Arm type	Crigler-Najjar
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:

HepaStem was administrated in the previous interventional trial HEP001

<b>Arm title</b>	Pediatric patients suffering from UCD
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Arm description:

UCD pediatric patients diagnosed with of one of the UCD subtypes (CPSID, OTCD, ASSD, ASLD, ARGD or NAGSD) in the former interventional clinical HEP001 study

Arm type	UCD
No investigational medicinal product assigned in this arm	

<b>Number of subjects in period 1</b>	Pediatric patients suffering from CN	Pediatric patients suffering from UCD
Started	5	12
Completed	5	12

<b>Period 2</b>	
Period 2 title	Visit 6 Months
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded
<b>Arms</b>	
Are arms mutually exclusive?	Yes
<b>Arm title</b>	Pediatric patients suffering from CN
Arm description:	
CN pediatric patients presenting with Crigler-Najjar syndrome type I or type II (poorly controlled under phenobarbital treatment or experiencing serious impairment in QoL) in the former interventional clinical HEP001 study	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
<b>Arm title</b>	Pediatric patients suffering from UCD
Arm description:	
UCD pediatric patients diagnosed with of one of the UCD subtypes (CPSID, OTCD, ASSD, ASLD, ARGD or NAGSD) in the former interventional clinical HEP001 study	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

<b>Number of subjects in period 2</b>	Pediatric patients suffering from CN	Pediatric patients suffering from UCD
Started	5	12
Completed	5	12

<b>Period 3</b>	
Period 3 title	Visit 12 Months
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded
<b>Arms</b>	
Are arms mutually exclusive?	Yes

<b>Arm title</b>	Pediatric patients suffering from CN
Arm description: CN pediatric patients presenting with Crigler-Najjar syndrome type I or type II (poorly controlled under phenobarbital treatment or experiencing serious impairment in QoL) in the former interventional clinical HEP001 study	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
<b>Arm title</b>	Pediatric patients suffering from UCD
Arm description: UCD pediatric patients diagnosed with of one of the UCD subtypes (CPSID, OTCD, ASSD, ASLD, ARGD or NAGSD) in the former interventional clinical HEP001 study	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

<b>Number of subjects in period 3</b>	Pediatric patients suffering from CN	Pediatric patients suffering from UCD
Started	5	12
Completed	5	12

<b>Period 4</b>	
Period 4 title	Visit 18 Months
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded
<b>Arms</b>	
Are arms mutually exclusive?	Yes
<b>Arm title</b>	Pediatric patients suffering from CN
Arm description: CN pediatric patients presenting with Crigler-Najjar syndrome type I or type II (poorly controlled under phenobarbital treatment or experiencing serious impairment in QoL) in the former interventional clinical HEP001 study	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
<b>Arm title</b>	Pediatric patients suffering from UCD
Arm description: UCD pediatric patients diagnosed with of one of the UCD subtypes (CPSID, OTCD, ASSD, ASLD, ARGD or NAGSD) in the former interventional clinical HEP001 study	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

<b>Number of subjects in period 4</b>	Pediatric patients suffering from CN	Pediatric patients suffering from UCD
Started	5	12
Completed	3	12
Not completed	2	0
Lost to follow-up	1	-
Discovery of exclusion criteria	1	-

## Period 5

Period 5 title	Visit 24 Months
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	Pediatric patients suffering from UCD
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Arm description:

UCD pediatric patients diagnosed with of one of the UCD subtypes (CPSID, OTCD, ASSD, ASLD, ARGD or NAGSD) in the former interventional clinical HEP001 study

Arm type	No intervention
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No investigational medicinal product assigned in this arm

<b>Arm title</b>	Pediatric patients suffering from CN
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Arm description:

CN pediatric patients presenting with Crigler-Najjar syndrome type I or type II (poorly controlled under phenobarbital treatment or experiencing serious impairment in QoL) in the former interventional clinical HEP001 study

Arm type	No intervention
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No investigational medicinal product assigned in this arm

<b>Number of subjects in period 5</b>	Pediatric patients suffering from UCD	Pediatric patients suffering from CN
Started	12	3
Completed	9	3
Not completed	3	0
Physician decision	1	-
Lost to follow-up	2	-

**Period 6**

Period 6 title	Visit 30 Months
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

**Arms**

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Pediatric patients suffering from CN

Arm description:

CN pediatric patients presenting with Crigler-Najjar syndrome type I or type II (poorly controlled under phenobarbital treatment or experiencing serious impairment in QoL) in the former interventional clinical HEP001 study

Arm type	No intervention
No investigational medicinal product assigned in this arm	
<b>Arm title</b>	Pediatric patients suffering from UCD

Arm description:

UCD pediatric patients diagnosed with of one of the UCD subtypes (CPSID, OTCD, ASSD, ASLD, ARGD or NAGSD) in the former interventional clinical HEP001 study

Arm type	No intervention
No investigational medicinal product assigned in this arm	

<b>Number of subjects in period 6</b>	Pediatric patients suffering from CN	Pediatric patients suffering from UCD
Started	3	9
Completed	1	9
Not completed	2	0
Discovery of exclusion criteria	1	-
Sponsor decision	1	-

**Period 7**

Period 7 title	Visit 36 Months
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

**Arms**

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Pediatric patients suffering from UCD

Arm description:

UCD pediatric patients diagnosed with of one of the UCD subtypes (CPSID, OTCD, ASSD, ASLD, ARGD or NAGSD) in the former interventional clinical HEP001 study

Arm type	No intervention
No investigational medicinal product assigned in this arm	
<b>Arm title</b>	Pediatric patients suffering from CN

Arm description:

CN pediatric patients presenting with Crigler-Najjar syndrome type I or type II (poorly controlled under phenobarbital treatment or experiencing serious impairment in QoL) in the former interventional clinical HEP001 study

Arm type | No intervention

No investigational medicinal product assigned in this arm

<b>Number of subjects in period 7</b>	Pediatric patients suffering from UCD	Pediatric patients suffering from CN
Started	9	1
Completed	7	1
Not completed	2	0
Sponsor decision	2	-

### Period 8

Period 8 title | Visit 42 Months

Is this the baseline period? | No

Allocation method | Not applicable

Blinding used | Not blinded

### Arms

Are arms mutually exclusive? | Yes

**Arm title** | Pediatric patients suffering from UCD

Arm description:

UCD pediatric patients diagnosed with of one of the UCD subtypes (CPSID, OTCD, ASSD, ASLD, ARGD or NAGSD) in the former interventional clinical HEP001 study

Arm type | No intervention

No investigational medicinal product assigned in this arm

**Arm title** | Pediatric patients suffering from CN

Arm description:

CN pediatric patients presenting with Crigler-Najjar syndrome type I or type II (poorly controlled under phenobarbital treatment or experiencing serious impairment in QoL) in the former interventional clinical HEP001 study

Arm type | No intervention

No investigational medicinal product assigned in this arm

<b>Number of subjects in period 8</b>	Pediatric patients suffering from UCD	Pediatric patients suffering from CN
Started	7	1
Completed	2	0
Not completed	5	1
Sponsor decision	5	1

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### Period 9

Period 9 title	Visit 48 Months
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

<b>Arm title</b>	Pediatric patients suffering from UCD
Arm description:	
UCD pediatric patients diagnosed with of one of the UCD subtypes (CPSID, OTCD, ASSD, ASLD, ARGD or NAGSD) in the former interventional clinical HEP001 study	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

<b>Number of subjects in period 9</b>	Pediatric patients suffering from UCD
Started	2
Completed	1
Not completed	1
Sponsor decision	1

## Baseline characteristics

### Reporting groups

Reporting group title	Pediatric patients suffering from CN
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Reporting group description:

CN pediatric patients presenting with Crigler-Najjar syndrome type I or type II (poorly controlled under phenobarbital treatment or experiencing serious impairment in QoL) in the former interventional clinical HEP001 study

Reporting group title	Pediatric patients suffering from UCD
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Reporting group description:

UCD pediatric patients diagnosed with of one of the UCD subtypes (CPSID, OTCD, ASSD, ASLD, ARGD or NAGSD) in the former interventional clinical HEP001 study

Reporting group values	Pediatric patients suffering from CN	Pediatric patients suffering from UCD	Total
Number of subjects	5	12	17
Age categorical			
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	0	0
Children (2-11 years)	5	6	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			
Units: years			
arithmetic mean	6.7	11.5	
standard deviation	± 2.0	± 6.1	-
Gender categorical			
Units: Subjects			
Female	3	6	9
Male	2	6	8
Cognitive assessment (Wechsler scores)			
Units: Subjects			
WPPSI	1	1	2
WISC	1	1	2
WAIS	3	10	13
Weight			
Units: kilogram(s)			
arithmetic mean	22.64	40.02	
standard deviation	± 6.16	± 23.85	-
Height			
Units: centimetre			
arithmetic mean	116.40	134.21	
standard deviation	± 10.53	± 30.35	-
Head circumference			

Units: centimetre			
arithmetic mean	49.70	49.00	
standard deviation	±	± 3.92	-

### Subject analysis sets

Subject analysis set title	Pediatric patients suffering from CN
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety analysis set: All patients included in this follow-up study were analyzed.

The following subgroups have been considered for the analysis:

- The study population includes 2 types of indication:
  - o patients suffering from UCD with specific associated subtypes being UCD NAGS, UCD CPS I, UCD OTC, UCD ASS, UCD ASL and UCD Arginase
  - o patients suffering from CN with specific associated subtypes being CN I and CN II

Analyses were reported separately for each indication and some analyses were reported per indication (sub)type.

Some analyses were performed according to cohorts that were defined in the previous HEP001 study and based on:

- Theoretical assigned dose group: low dose cohort (12.5x10<sup>6</sup> cells/kg), intermediate dose (50x10<sup>6</sup> cells/kg) and high dose (200x10<sup>6</sup> cells/kg).
- Weight: cohort > 20 kg, cohort ≥ 10 kg-20 kg and cohort < 10 kg.
- Age at the time of the first treatment infusion: Age cohort ≤ 12 years and age cohort > 12 years

Subject analysis set title	Pediatric patients suffering from UCD
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety analysis set: All patients included in this follow-up study were analyzed.

The following subgroups have been considered for the analysis:

- The study population includes 2 types of indication:
  - o patients suffering from UCD with specific associated subtypes being UCD NAGS, UCD CPS I, UCD OTC, UCD ASS, UCD ASL and UCD Arginase
  - o patients suffering from CN with specific associated subtypes being CN I and CN II

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- Weight: cohort > 20 kg, cohort ≥ 10 kg-20 kg and cohort < 10 kg.
- Age at the time of the first treatment infusion: Age cohort ≤ 12 years and age cohort > 12 years

Reporting group values	Pediatric patients suffering from CN	Pediatric patients suffering from UCD	
Number of subjects	5	12	
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)	11		
Adolescents (12-17 years)	6		
Adults (18-64 years)			
From 65-84 years			
85 years and over			

Age continuous Units: years arithmetic mean standard deviation	10.1 ± 5.6	±	
Gender categorical Units: Subjects			
Female Male	9 8		
Cognitive assessment (Wechsler scores) Units: Subjects			
WPPSI WISC WAIS	1 1 0	1 1 2	
Weight Units: kilogram(s) arithmetic mean standard deviation	34.91 ± 21.62	±	
Height Units: centimetre arithmetic mean standard deviation	128.97 ± 27.03	±	
Head circumference Units: centimetre arithmetic mean standard deviation	49.14 ± 3.41	±	

## End points

### End points reporting groups

Reporting group title	Pediatric patients suffering from CN
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Reporting group description:

CN pediatric patients presenting with Crigler-Najjar syndrome type I or type II (poorly controlled under phenobarbital treatment or experiencing serious impairment in QoL) in the former interventional clinical HEP001 study

Reporting group title	Pediatric patients suffering from UCD
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Reporting group description:

UCD pediatric patients diagnosed with of one of the UCD subtypes (CPSID, OTCD, ASSD, ASLD, ARGD or NAGSD) in the former interventional clinical HEP001 study

Reporting group title	Pediatric patients suffering from CN
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Reporting group description:

CN pediatric patients presenting with Crigler-Najjar syndrome type I or type II (poorly controlled under phenobarbital treatment or experiencing serious impairment in QoL) in the former interventional clinical HEP001 study

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UCD pediatric patients diagnosed with of one of the UCD subtypes (CPSID, OTCD, ASSD, ASLD, ARGD or NAGSD) in the former interventional clinical HEP001 study

Reporting group title	Pediatric patients suffering from CN
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Reporting group description:

CN pediatric patients presenting with Crigler-Najjar syndrome type I or type II (poorly controlled under phenobarbital treatment or experiencing serious impairment in QoL) in the former interventional clinical HEP001 study

Reporting group title	Pediatric patients suffering from UCD
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Reporting group description:

UCD pediatric patients diagnosed with of one of the UCD subtypes (CPSID, OTCD, ASSD, ASLD, ARGD or NAGSD) in the former interventional clinical HEP001 study

Reporting group title	Pediatric patients suffering from CN
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Reporting group description:

CN pediatric patients presenting with Crigler-Najjar syndrome type I or type II (poorly controlled under phenobarbital treatment or experiencing serious impairment in QoL) in the former interventional clinical HEP001 study

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UCD pediatric patients diagnosed with of one of the UCD subtypes (CPSID, OTCD, ASSD, ASLD, ARGD or NAGSD) in the former interventional clinical HEP001 study

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Reporting group description:

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Reporting group title	Pediatric patients suffering from UCD
-----------------------	---------------------------------------

Reporting group description:

UCD pediatric patients diagnosed with of one of the UCD subtypes (CPSID, OTCD, ASSD, ASLD, ARGD or

NAGSD) in the former interventional clinical HEP001 study

Reporting group title	Pediatric patients suffering from UCD
-----------------------	---------------------------------------

Reporting group description:

UCD pediatric patients diagnosed with of one of the UCD subtypes (CPSID, OTCD, ASSD, ASLD, ARGD or NAGSD) in the former interventional clinical HEP001 study

Reporting group title	Pediatric patients suffering from CN
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Reporting group description:

CN pediatric patients presenting with Crigler-Najjar syndrome type I or type II (poorly controlled under phenobarbital treatment or experiencing serious impairment in QoL) in the former interventional clinical HEP001 study

Reporting group title	Pediatric patients suffering from UCD
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Reporting group description:

UCD pediatric patients diagnosed with of one of the UCD subtypes (CPSID, OTCD, ASSD, ASLD, ARGD or NAGSD) in the former interventional clinical HEP001 study

Reporting group title	Pediatric patients suffering from CN
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Reporting group description:

CN pediatric patients presenting with Crigler-Najjar syndrome type I or type II (poorly controlled under phenobarbital treatment or experiencing serious impairment in QoL) in the former interventional clinical HEP001 study

Reporting group title	Pediatric patients suffering from UCD
-----------------------	---------------------------------------

Reporting group description:

UCD pediatric patients diagnosed with of one of the UCD subtypes (CPSID, OTCD, ASSD, ASLD, ARGD or NAGSD) in the former interventional clinical HEP001 study

Subject analysis set title	Pediatric patients suffering from CN
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Safety analysis set: All patients included in this follow-up study were analyzed.

The following subgroups have been considered for the analysis:

- The study population includes 2 types of indication:
    - o patients suffering from UCD with specific associated subtypes being UCD NAGS, UCD CPS I, UCD OTC, UCD ASS, UCD ASL and UCD Arginase
    - o patients suffering from CN with specific associated subtypes being CN I and CN II
- Analyses were reported separately for each indication and some analyses were reported per indication (sub)type.

Some analyses were performed according to cohorts that were defined in the previous HEP001 study and based on:

- Theoretical assigned dose group: low dose cohort ( $12.5 \times 10^6$  cells/kg), intermediate dose ( $50 \times 10^6$  cells/kg) and high dose ( $200 \times 10^6$  cells/kg).
- Weight: cohort > 20 kg, cohort  $\geq$  10 kg-20 kg and cohort < 10 kg.
- Age at the time of the first treatment infusion: Age cohort  $\leq$  12 years and age cohort > 12 years

Subject analysis set title	Pediatric patients suffering from UCD
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Safety analysis set: All patients included in this follow-up study were analyzed.

The following subgroups have been considered for the analysis:

- The study population includes 2 types of indication:
    - o patients suffering from UCD with specific associated subtypes being UCD NAGS, UCD CPS I, UCD OTC, UCD ASS, UCD ASL and UCD Arginase
    - o patients suffering from CN with specific associated subtypes being CN I and CN II
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Some analyses were performed according to cohorts that were defined in the previous HEP001 study and based on:

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- Weight: cohort > 20 kg, cohort  $\geq$  10 kg-20 kg and cohort < 10 kg.
- Age at the time of the first treatment infusion: Age cohort  $\leq$  12 years and age cohort > 12 years

## Primary: Long-term safety profile of HepaStem

End point title	Long-term safety profile of HepaStem <sup>[1]</sup>
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End point description:

The primary endpoint was to characterize the long-term safety profile of HepaStem. Safety was assessed by evaluating the following parameters:

- Physical examination
- Vital signs
- Laboratory tests
- Liver tumor marker
- Autoimmune markers related to liver pathology
- Anti-human leucocyte antigen (HLA) antibodies specific for donor cell haplotypes
- Morphology of liver, bile ducts and portal system by ultrasound
- Morphology of the kidneys by ultrasound
- Non-serious or serious adverse events of special interest (AESI) and serious adverse events (SAEs) related to HepaStem therapy

End point type	Primary
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End point timeframe:

During a period up to a maximum of 48 months (4 years) in the SAF001 study (SAF001 Year 1 + Year 2 + Year 3 + Year 4)

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: Only descriptive analysis has been done, not possible to enter descriptive analysis in system

End point values	Pediatric patients suffering from CN	Pediatric patients suffering from UCD		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5	12		
Units: Absolute (n) and relative (%) frequency	5	12		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Long-term disease evolution and general safety after having received HepaStem

End point title	Long-term disease evolution and general safety after having received HepaStem
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End point description:

The secondary endpoints were to characterize the disease evolution and the general safety post HepaStem infusion through the evaluation of the report on cognitive skills, behavior, and health-related QoL indicators, and the frequency and severity of metabolic decompensation reported as AESI.

The general safety was also evaluated based on the following parameters:

For CN patients:

- Metabolic parameters: serum total and unconjugated bilirubin levels
- Report on supportive treatment and any adjustment of phototherapy and medication

For UCD patients:

- Metabolic parameters: ammonia values, amino acids in plasma (alanine, arginine, citrulline, glutamine and argininosuccinate acid for UCD ASL patients only), orotic acid in urine (for UCD OTC patients only), argininosuccinate acid in urine (for UCD ASL patients only)
- Report on supportive treatment and any adjustment of diet (natural protein intake, total protein intake, amino acid supplements) and medication (e.g., nitrogen scavengers)

End point type	Secondary
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End point timeframe:

During a period up to a maximum of 60 months post HepaStem infusion (HEP001 study + SAF001 year 1 + year 2 + year 3 + year 4)

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<b>End point values</b>	Pediatric patients suffering from CN			
Subject group type	Subject analysis set			
Number of subjects analysed	17 <sup>[2]</sup>			
Units: Absolute (n) and relative (%) frequency	17			

Notes:

[2] - Descriptive analysis

### **Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Each patient was to be followed up for a maximum of 48 months.

For each patient, the entire period of follow-up post HepaStem infusion could then be up to a maximum of 60 months (HEP001 study + 4 years in SAF001).

Adverse event reporting additional description:

Only SAEs or AESIs were reported in this study.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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### Reporting groups

Reporting group title	Pediatric patients suffering from UCD or CN
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Reporting group description: -

<b>Serious adverse events</b>	Pediatric patients suffering from UCD or CN		
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 17 (70.59%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Mycosis fungoides			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Loss of consciousness			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			

Pyrexia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Influenza like illness			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastritis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorder			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tonsillitis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	5 / 17 (29.41%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

<p>Infections and infestations</p> <p>Beta haemolytic streptococcal infection</p> <p>subjects affected / exposed</p> <p>occurrences causally related to treatment / all</p> <p>deaths causally related to treatment / all</p>	<p>1 / 17 (5.88%)</p> <p>0 / 1</p> <p>0 / 0</p>		
<p>Gastroenteritis</p> <p>subjects affected / exposed</p> <p>occurrences causally related to treatment / all</p> <p>deaths causally related to treatment / all</p>	<p>1 / 17 (5.88%)</p> <p>0 / 1</p> <p>0 / 0</p>		
<p>Gastroenteritis rotavirus</p> <p>subjects affected / exposed</p> <p>occurrences causally related to treatment / all</p> <p>deaths causally related to treatment / all</p>	<p>1 / 17 (5.88%)</p> <p>0 / 1</p> <p>0 / 0</p>		
<p>Otitis externa</p> <p>subjects affected / exposed</p> <p>occurrences causally related to treatment / all</p> <p>deaths causally related to treatment / all</p>	<p>1 / 17 (5.88%)</p> <p>0 / 1</p> <p>0 / 0</p>		
<p>Pharyngitis streptococcal</p> <p>subjects affected / exposed</p> <p>occurrences causally related to treatment / all</p> <p>deaths causally related to treatment / all</p>	<p>1 / 17 (5.88%)</p> <p>0 / 1</p> <p>0 / 0</p>		
<p>Viral infection</p> <p>subjects affected / exposed</p> <p>occurrences causally related to treatment / all</p> <p>deaths causally related to treatment / all</p>	<p>2 / 17 (11.76%)</p> <p>0 / 4</p> <p>0 / 0</p>		
<p>Tonsillitis</p> <p>subjects affected / exposed</p> <p>occurrences causally related to treatment / all</p> <p>deaths causally related to treatment / all</p>	<p>1 / 17 (5.88%)</p> <p>0 / 1</p> <p>0 / 0</p>		
<p>Metabolism and nutrition disorders</p> <p>Hyperammonaemia</p> <p>subjects affected / exposed</p> <p>occurrences causally related to treatment / all</p> <p>deaths causally related to treatment / all</p>	<p>4 / 17 (23.53%)</p> <p>0 / 16</p> <p>0 / 0</p>		

Metabolic disorder			
subjects affected / exposed	5 / 17 (29.41%)		
occurrences causally related to treatment / all	0 / 12		
deaths causally related to treatment / all	0 / 0		

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

<b>Non-serious adverse events</b>	Pediatric patients suffering from UCD or CN		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 17 (70.59%)		
Investigations			
Amino acid level increased			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
HLA marker study positive			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Mycosis fungoides			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Nervous system disorders			
Loss of consciousness			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Gastritis			

subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Gastrointestinal disorder subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Vomiting subjects affected / exposed occurrences (all)	4 / 17 (23.53%) 5		
Hepatobiliary disorders Hyperbilirubinaemia subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Skin and subcutaneous tissue disorders Eczema subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Infections and infestations Beta haemolytic streptococcal infection subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Gastroenteritis subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Gastroenteritis rotavirus subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Otitis externa subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Pharyngitis streptococcal subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Staphylococcal infection subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Tonsillitis			

subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Viral infection			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	4		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 December 2013	<p>Amendment A (Protocol version 2.0 dated 05-Dec-2013):</p> <ul style="list-style-type: none"><li>• To allow all patients who received HepaStem infusion to be included in the study (modification of study title, primary objective, inclusion criteria)</li><li>• To justify more precisely the maintenance of a low level of immunosuppression following HepaStem therapy, and to define, on the request of ANSM (French regulatory authority), rules to stop or adapt the immunosuppressive regimen rules</li><li>• To adapt the procedures:<ul style="list-style-type: none"><li>o use of a notebook to record relevant information in between visits in order to detect AE of special interest</li><li>o specifications of physical examination and vital signs measurements</li><li>o addition of 2 psychological assessments (WAIS for patients who turned 18 years old and the Leiter International Performance Scale for children and adult patients who are cognitively delayed, non-English speaking, hearing impaired, speech impaired, or autistic) and a behavioral psychological assessments for patients who turned 18 years old,</li><li>o addition of a statement to allow collection of essential information in terms of cell engraftment (collection of liver samples from the exograft in case of premature discontinuation because of a liver transplantation)</li><li>o addition of definitions for metabolic decompensation to clarify AESI</li><li>o deletion of some information about efficacy parameters</li></ul></li><li>• To described in more details the primary objective in order to be in alignment with the assessments previously approved by the EC/Health Authority</li><li>• To clarify the frequency of interim analyses</li><li>• To update the number of pediatric patients (from 18 to 20 patients)</li></ul>
14 July 2016	<p>Amendment B (Protocol version 3.0 dated 14-Jul-2016):</p> <ul style="list-style-type: none"><li>• To clarify the procedure of consent for minors or adults legally incapable</li><li>• To specify how the decision to maintain the immunosuppressive treatment should be taken (by the investigator, in agreement with the patient's family, based on the clinical condition / evolution of the patient)</li><li>• To clarify some procedures (identity of the proteins measured by serum protein electrophoresis was clarified; precision on the baseline visit in case of the patient was not enrolled within 4 weeks after the last visit of the former study)</li><li>• To ensure that previous infusions of HepaStem do not impact in any way the outcome of OLT, a last visit after OLT including examinations and OLT questionnaire completion was added</li><li>• To specify the outsourcing of monitoring activities</li></ul>

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported