1 TITLE PAGE

SAF001: A long-term safety follow-up study of patients having received infusions of HepaStem. Clinical study report – Full version for regulatory submission	
Investigational product:	HepaStem (Heterologous Human Adult liver-derived progenitor cells [HHALPC])
Indication studied:	1/ Crigler-Najjar syndrome (CN) 2/ Urea cycle disorders (UCD)
Protocol identification number:	SAF001
Phase:	I/II
Eudract number:	2013-001045-14
Study initiation date:	17-Apr-2013 (first patient, first visit)
Study completion date:	20-Jun-2017 (last patient, last visit)
Date of the report (version):	04-Feb-2019 (Final)
Coordinating investigator	Prof. Françoise SMETS Cliniques Universitaires St Luc Paediatric Avenue Hippocrate, 10/1301 1200 Brussels – Belgium
Sponsor:	Promethera Biosciences Rue Granbonpré, 11 1435 Mont Saint Guibert Belgium
Sponsor signatory:	Prof. Etienne SOKAL, Chief Scientific and Medical Officer
This study was performed in compliance with the current version of the declaration of Helsinki and with the ICH note for guidance on GCP (CPMP/ICH/135/95), including the archiving of essential documents.	

2 SYNOPSIS

Name of sponsor/Company: Promethera Biosciences	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use only)**
Name of finished product: Not applicable		
Name of active ingredient: HepaStem (Heterologous Human Adult liver-derived progenitor cells)		

Title of the study:
SAF001: A long-term safety follow-up study of patients having received infusions of HepaStem.

Coordinating Investigator: Prof. Françoise SMETS – Cliniques Universitaires St Luc - Belgium

Study centres: 2 centres in Belgium (Cliniques Universitaires St Luc Brussels, Universitair Ziekenhuis Antwerp), 2 centres in France (Centre Hospitalier Régional Universitaire Lille, Centre Hospitalier Universitaire Toulouse), one centre in United Kingdom ([UK], Great Ormond Street Hospital London), one centre in Italy (Ospedale Pediatrico Bambina Gesù di Roma) one centre in Portugal (Pediatrico Hospital of Coimbra), 3 centres in Israel (Rambam Medical Centre - Meyer Children's Hospital, Hadassah Ein-Kerem Medical Centre, Schneider Children's Medical Centre of Israel).

Publication (reference): None as of 04-Feb-2019

Study period: From to 17-Apr-2013 to 20-Jun-2017	**Phase of development:** I/II

Objectives:

Primary:

The primary objective of the SAF001 long-term safety follow-up study in patients having received infusions of HepaSteam in the former HEP001 study was to document the safety of HepaStem 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).

Secondary:

The secondary objectives were:

- To document the long-term disease evolution after having received HepaStem up to a maximum of :
  - 24 months in the SAF study (SAF001 Year 1 + Year 2)
  - 36 months post infusion (HEP001 study + SAF001 Year 1 + Year 2)
  - 60 months post infusion (HEP001 study + SAF001 Year 1 + Year 2 + Year 3 + Year 4)
- To document the general safety during a period up to a maximum 60 months post infusion (HEP001 study + SAF001 Year 1 + Year 2 + Year 3 + Year 4).

Study design:

The SAF001 study was a prospective, open-label, multicentre, long-term safety follow-up study of patients having received infusions of HepaStem. All patients having received HepaStem in the former interventional HEP001 study were invited to enter the study and have been diagnosed with Urea Cycle Disorders (UCD) or Crigler Najjar syndrome (CN).

Patients were enrolled at the end of their participation in the HEP001 study if the eligibility criteria were met and if a written informed consent was given. Data collected at the last visit of the HEP001 study (± 4 weeks) were considered as the SAF001 baseline data. The planned follow-up of each patient in the SAF001 study was maximum 48 months (4 years).

A 2-year assessment of both safety and disease evolution was carried out by scheduling visits every 6 months for 2 years (Year 1 + Year 2) with the first follow-up visit scheduled 6 months after the last follow-up visit of the HEP001 study. An additional 2-year assessment was carried out by scheduling yearly visits for 2 additional

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years and a mid-year interview during Year 3 and during Year 4 (phone call or physical visit).

Therefore, as each patient has been followed actively in the former study, the complete period of follow-up post infusion of HepaStem could then be up to a maximum of 60 months (5 years).

Number of patients:

Previously enrolled in and completing the HEP001 study: 18 patients

Follow-up in the SAF001 study (Safety analysis set): 17 patients (12 patients with UCD and 5 with CN)

Diagnosis and main criteria for inclusion:

Paediatric and young adult patients with CN and UCD who received infusions of HepaStem during the former HEP001 interventional study and who have terminated their participation in that study, who signed an informed consent* and have not received mature liver cell or stem cell transplantation other than HepaStem, or organ liver transplant.

** For patients under 18 years of age (16 years in UK) and for adult patients legally incapable: parents or a legal representative should have provided a written informed consent before enrolment and an assent should have been signed by the patient.*

Test product: HepaStem

Dose, mode of administration and batch/lot number: Not applicable as the study product was administered in the HEP001 study of which this study is the safety follow-up.

Reference product: Not applicable.

Duration of the study:

Each patient was to be followed 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).

Criteria for evaluation:

Safety:

The safety was assessed in terms of:

- Serious Adverse Events (SAEs) and Adverse Events of Special Interest (AESI) related to HepaStem.
- Vital signs and physical examination.
- Laboratory tests (haematology, anti-HLA antibodies, liver tumour marker, autoimmune markers related to liver pathology).
- Morphology of liver and kidneys (ultrasound).

Disease evolution:

- Cognitive skills, behaviour, and health-related quality of life (QoL) indicators.
- Frequency and severity of metabolic decompensation reported as AESI.
- Metabolic parameters (serum total bilirubin and unconjugated bilirubin levels for CN patients and plasma ammonia, plasma amino acids, orotic acid or argininosuccinate acid in urine when relevant for UCD patients).
- Supportive treatment in adjustment of medication (all patients), phototherapy (CN patients) or diet (UCD patients).

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Statistical methods:

The performed analyses were based on descriptive statistics. For continuous variables, descriptive statistics consisted of number of subjects, mean, median, standard deviation (SD), minimum, and maximum. Categorical endpoints were summarised using absolute (number of subjects) and relative (percentages) frequencies.

Summary of results:

Of the 18 patients who completed the HEP001 study, 17 entered the long-term follow-up:

- 12 UCD patients: 7 with ornithine carbamoyltranferase (OTC) deficiency (UCD OTC), 2 with carbamoyl phosphate synthase I (CPS I) deficiency (UCD CPS I), 2 with argininosuccinate lyase (ASL) deficiency (UCD ASL) and one with arginase deficiency (UCD Arginase),
- 5 CN patients, 4 with CN Type I and one with CN Type II.

During the HEP001 study, 8 patients received a high dose of HepaStem ($200x10^6$ cells/kg), 5 patients received an intermediate dose ($50x10^6$ cells/kg) and 4 patients received a low dose ($12.5x10^6$ cells/kg).

All patients but one prematurely discontinued the study mainly on sponsor's decision. Indeed, the sponsor decided to prematurely end the SAF001 follow-up study and to follow-up patients receiving HepaStem in the clinical trials conducted during its development in a new registry.

CN patients were aged 5-10 years old and 2 patients out of 5 were male. UCD patients were aged 2-18 years old and half of them were male.

Safety:

Only SAEs or AESI were reported in this study.

A total of 62 AEs were reported by 13 patients over the 48-month follow-up. Among these, 55 (reported by 12 patients) were of special interest, of which 49 were also reported as SAEs. Seven (7) additional SAEs were reported (in total 56 SAEs were reported by 12 patients).

None of the AEs were considered as causally related to HepaStem. Events were generally related to pre-existing conditions (39 SAEs reported by 9 patients and 4 non serious AESI reported by 3 patients) and/or to at least another cause (49 SAEs reported by 11 patients and 6 non serious AESI reported by 3 patients).

The most common AEs (preferred term) were hyperammonaemia (18 events, 4 patients), metabolic disorder (12 events, 5 patients), vomiting (6 events, 5 patients) and viral infection (5 events, 2 patients).

Five (5) patients experienced a total of 12 episodes of metabolic decompensation (among which one patient with UCD OTC had 3 episodes and one patient with UCD CPS I had 6 episodes). Eighteen (18) episodes of hyperammonaemia were reported for 4 patients. During the first year of follow-up in the SAF study, 3 episodes of hyperammonaemia occurred in 2 patients and 7 events of metabolic decompensation occurred in 3 patients. This was comparable or slightly higher than that observed during the HEP001 study (4 patients experienced 7 episodes of metabolic disorder and one patient experienced 5 episodes of hyperammonaemia over one year of follow-up). Incidence per year of hyperammonaemia tended to increase in year 2 and 3 (8 and 6 episodes reported by 4 and 3 patients, respectively) while incidence of metabolic disorder tended to decrease (3 and 2 events reported by 3 and 2 patients, respectively). Overall, metabolic disorders seemed to occur more frequently in patients aged > 12 year at HepaStem infusion (4 patients versus one in age cohort ≤ 12) while hyperammonaemia occurred in the same proportion of patients in each age cohort.

No deaths and no pregnancies were reported during this long-term follow-up.

No particular safety signals were detected in vital signs, growth parameters, physical examination or immunological assessments.

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Disease evolution:

Overall, the course of the diseases was in line with the HEP001 study observations.

Globally, assessed laboratory values were in line with the patient pathologies and the guidelines for their management:

- High levels of unconjugated bilirubin remaining close to the recommended upper limit (350 µmol/L) for CN patients.
- High values of ammonia and glutamine for UCD patients.
- High values of alanine for patient with UCD OTC.
- Normal range values of citrulline for patients with UCD CPS I and UCD Arginase, low values for patients with UCD OTC and high values for patients with UCD ASL.
- Normal range values of arginine for patients with UCD CPS I, UCD OTC and UCD ASL and high value for patients with UCD Arginase.

High values of unconjugated bilirubin (> 350 µm) were reported for one CN patient at 6-month follow-up which resolved after appropriate action was taken (phototherapy).

Furthermore, episodes of high ammonia were documented in patients with UCD OTC and UCD CPS I (4 and one, respectively). Some of these episodes were reported as serious AESI, and one was considered to be related to a fading effect of the cell transplantation.

Twelve (12) events of metabolic decompensation were reported by 4 patients with UCD OTC and one patient with UCD CPS I over the 48-month follow-up.

Conclusion:

In conclusion, the long-term safety follow-up of HepaStem evidenced no safety signal up to 4-years after HepaStem infusion. All patients maintained their supportive treatment and the incidence of metabolic decompensation and hyperammonaemia remained in line with that observed in the one-year follow-up after HepaStem infusion in the HEP001 study. The incidence and nature of the reported SAEs and AESI reflect the intrinsic fragility of the study population. Laboratory results remained in line with the patient's pathologies and the guidelines for their management. Consequently, the study brings evidence of good long-term tolerance of HepaStem (up to 5 years after infusion) in a paediatric population of patients with UCD and CN.

Date of report: 04-Feb-2019 (Final)