EU Clinical Trials Register

Clinical trial results:
Multicenter Phase II Safety and Preliminary Efficacy Study of 2 dose regimens of HepaStem in Patients with Acute on Chronic Liver Failure

Summary

EudraCT number	2016-001177-32
Trial protocol	BE FR ES BG
Global end of trial date	21 August 2020

Results information

Result version number	v1 (current)
This version publication date	01 June 2022
First version publication date	01 June 2022
Summary attachment (see zip file)	Safety (HEP101_Safety summary.pdf)
	Efficacy (HEP101_Preliminary efficacy summary.pdf)

Trial information

Trial identification

Sponsor protocol code	HEP101

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02946554
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)	No
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	15 September 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 August 2019
Global end of trial reached?	Yes
Global end of trial date	21 August 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the safety of different dose regimens of HepaStem in cirrhotic patients presenting with acute-on-chronic liver failure (ACLF) or with acute decompensation (AD) at risk of developing ACLF up to Day 28 of the active study period.

Protection of trial subjects:

The study was conducted in accordance with the ICH Guideline for GCP (specific to ATMP), the guiding principles of the "Declaration of Helsinki", the local data protection and all other applicable regulatory requirements.

Several study procedures were added or updated during the study conduct through amendments to protect trial subjects.
•Participants were hospitalized during the screening and treatment periods to allow continuous monitoring; vital signs were continuously monitored
•Hepatic ultrasonography and US Doppler of the portal vein were performed before and/or during and after each HepaStem, as well as at during the last study visit
•Infusion criteria were updated in order to ensure that participants with a significant pre-existing coagulation imbalance would not receive HepaStem and specify the action to be taken in case of major changes in the coagulation factors
•Additional monitoring blood tests were performed to ensure a close follow-up of the participants before, during and after the infusions
•The volume of HepaStem to be administered and the frequency of administration were reduced in the amended protocols
•In order to prevent transfusion-like reaction, a bolus of 100 mg hydrocortisone or equivalent glucocorticoid was given 15 to 30 minutes before each HepaStem infusion.
•The frequency of SMC meetings was increased
•The sample size was updated
•Adequate medical care was provided to the study participants in case of an adverse event (AE) or a serious AE, which were to be followed up by the investigator until resolution or until the degree of persistent disability could be assessed.
Some procedures, such as the optional transjugular biopsy, were no longer required to limit any further risk of bleeding for the participant.
After completion of the study, all participants who received at least 1 infusion of HepaStem were invited to participate in the long-term follow-up PROLONGSTEM study for 5 additional years (EudraCT: 2017-003989-27)

Background therapy:

All participants were recruited at hospitals with specialized hepatology and intensive care units.
Cirrhotic patients with ACLF/AD at risk of developing ACLF at first evaluation post-admission and/or developing ACLF during hospitalization were assessed for inclusion.
The study was designed to administer HepaStem in subsequent cohorts of participants hospitalized for ACLF/AD and/or who developed ACLF during hospitalization.

Evidence for comparator:

Not applicable

Actual start date of recruitment	05 December 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	Belgium: 15
Country: Number of subjects enrolled	Bulgaria: 5
Worldwide total number of subjects	24
EEA total number of subjects	24

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	24
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

21 centers in hospitals with specialized hepatology and intensive care units opened in 4 countries; 10 centers were active in 3 countries (Spain, Belgium and Bulgaria).
Date of first patient screened: 05-DEC-2016; date of first patient enrolled: 16-DEC-2016.

Pre-assignment

Screening details:

The screening period lasted up to 7 days following informed consent signature and allowed assessing participant's eligibility.
Participants were hospitalized during the screening period.
34 patients were screened, 25 were eligible and included in the FAS, 24 received HepaStem infusion and were included in the SAF.

Pre-assignment period milestones

Number of subjects started	24
Number of subjects completed	24

Period 1

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

Blinding implementation details:

All participants included in the study were adults suffering from cirrhosis as diagnosed by liver histology or clinical and imaging examination.
There was no blinding in this study.

Arms

Arm title	Single arm - Screening period

Arm description: -

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Single arm - Screening period
Started	24
Completed	24

Period 2

Period 2 title	Infusion day (Day 1)
Is this the baseline period?	Yes[1]
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

All participants enrolled in the study were administered 1 or 2 doses (one week apart) of HepaStem. There was no blinding in this study.

Arms

Arm title	Single arm - Infusion day (Day 1)

Arm description: -

Arm type	Experimental
Investigational medicinal product name	HepaStem
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Dispersion for infusion
Routes of administration	Intravenous use

Dosage and administration details:

- Cohort 1, first participants enrolled (4.2×10^6 cells/kg BW/infusion, twice or 5.3×10^6 cells/kg BW/infusion, once): N=3, initial Cohort 1a.
- Cohort 2 (0.6-0.8×10^6 cells/kg BW/infusion): N=6, all participants from initial Cohort 1b and 2a.
- Cohort 3 (0.6×10^6 cells/kg BW/infusion, twice): N=3, 3 participants from initial Cohort 2b.
- Cohort 4 (1.2×10^6 cells/kg BW/infusion): N=4, all 3 participants from initial Cohort 2c plus one participant from initial Cohort 2b.
- Cohort 5 (1.2×10^6 cells/kg BW/infusion, twice): N=8, all 5 participants from initial Cohort 2d plus 3 participants from initial Cohort 2b.

Notes:

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

Justification: Baseline characteristics included the assessments performed on Day 1 prior to the first infusion when data were available (vital signs, blood tests). Changes from screening to Day 1 prior to infusion or shift tables are provided for quantitative and qualitative parameters, respectively.

Number of subjects in period 2	Single arm - Infusion day (Day 1)
Started	24
Completed	24

Period 3

Period 3 title	Active treatment period D14
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

All participants enrolled in the study were administered 1 or 2 doses (one week apart) of HepaStem. There was no blinding in this study.

Arms

Arm title	Single arm - Active treatment period D14
Arm description: -	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 3	Single arm - Active treatment period D14
Started	24
Completed	22
Not completed	2
Adverse event, serious fatal	2

Period 4

Period 4 title	Active surveillance period D28
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Single arm - Active surveillance period D28
Arm description: -	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 4	Single arm - Active surveillance period D28
Started	22
Completed	20
Not completed	2
Adverse event, serious fatal	1
Physician decision	1

Period 5

Period 5 title	Long-term follow-up period M3
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Single arm - Long-term follow-up period M3

Arm description: -

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 5	Single arm - Long-term follow-up period M3
Started	20
Completed	17
Not completed	3
Adverse event, serious fatal	3

Period 6

Period 6 title	Long-term follow-up period Y1
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Single arm - Long-term follow-up period Y1

Arm description: -

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 6	Single arm - Long-term follow-up period Y1
Started	17
Completed	15
Not completed	2
Adverse event, serious fatal	1
Lost to follow-up	1

Baseline characteristics

Reporting groups

Reporting group title	Infusion day (Day 1)

Reporting group description: -

Reporting group values	Infusion day (Day 1)	Total	
Number of subjects	24	24	
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)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	24	24	
From 65-84 years	0	0	
85 years and over	0	0	
Adults	0	0	
Age continuous			
Units: years			
arithmetic mean	50.51		
standard deviation	± 9.22	-	
Gender categorical			
Units: Subjects			
Female	7	7	
Male	17	17	
ACLF at Time of admission in current hospital			
Units: Subjects			
No	8	8	
Yes	16	16	
ACLF at Time of admission in current department			
Units: Subjects			
No	1	1	
Yes	23	23	
West Haven criteria			
Units: Subjects			
Grade 0	13	13	
Grade 1	9	9	
Grade 2	2	2	
Grade 3	0	0	
Etiology of cirrhosis			
Units: Subjects			
Alcoholic liver disease	23	23	
Autoimmune disease	1	1	

Previous episode(s) of ACLF Units: Subjects			
Yes	4	4	
No	20	20	
CLIF ACLF grade Units: Subjects			
No ACLF/ACLF Grade 0	9	9	
ACLF Grade 1	10	10	
ACLF Grade 2	5	5	
ACLF Grade 3	0	0	
Time Since admission in current hospital Units: Days			
arithmetic mean	17.0		
standard deviation	± 17.4	-	
Time Since admission in current department Units: Days			
arithmetic mean	13.3		
standard deviation	± 14.2	-	
New MELD score Units: score			
arithmetic mean	27.18		
standard deviation	± 4.22	-	
CLIF-C AD Score Units: Score			
arithmetic mean	58.36		
standard deviation	± 9.74	-	
Bilirubin Units: mg/dL			
arithmetic mean	20.48		
standard deviation	± 10.04	-	
Platelets Units: 10^9/L			
arithmetic mean	134.67		
standard deviation	± 81.52	-	
Prothrombin Intl. Normalized Ratio Units: Ratio			
arithmetic mean	2.05		
standard deviation	± 0.49	-	
Time since the diagnosis of cirrhosis Units: month			
arithmetic mean	36.3		
standard deviation	± 55.6	-	
Height Units: centimetre			
arithmetic mean	171.9		
standard deviation	± 8.8	-	
Weight Units: kilogram(s)			
arithmetic mean	78.3		
standard deviation	± 17.5	-	

Body Mass Index			
Units: mg/m²			
arithmetic mean	26.4		
standard deviation	± 4.8	-	
CLIF-OF score			
Units: Disease score			
arithmetic mean	9.21		
standard deviation	± 1.41	-	
CLIF-C ACLF score			
Observed values for 15 patients (missing for 9 patients)			
Units: Disease score			
arithmetic mean	49.02		
standard deviation	± 6.85	-	
Child Pugh score			
Units: Disease score			
arithmetic mean	10.83		
standard deviation	± 1.46	-	
Creatinine			
Serum creatinine			
Units: mg/dL			
arithmetic mean	1.04		
standard deviation	± 0.47	-	
Albumin			
Serum albumin			
Units: g/dL			
arithmetic mean	3.02		
standard deviation	± 0.49	-	

Subject analysis sets

Subject analysis set title	SAF
Subject analysis set type	Safety analysis

Subject analysis set description:

Of the 25 participants who were eligible and included in the FAS, only 24 who received 1 or 2 doses of HepaStem infusion were included in the SAF. Six participants for whom a major protocol deviation was recorded were excluded from the PP, which was constituted of 18 participants.

Reporting group values	SAF		
Number of subjects	24		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	24		
From 65-84 years	0		
85 years and over	0		
Adults	0		

Age continuous Units: years			
arithmetic mean	50.51		
standard deviation	± 9.22		
Gender categorical Units: Subjects			
Female	7		
Male	17		
ACLF at Time of admission in current hospital Units: Subjects			
No	8		
Yes	16		
ACLF at Time of admission in current department Units: Subjects			
No	1		
Yes	23		
West Haven criteria Units: Subjects			
Grade 0	13		
Grade 1	9		
Grade 2	2		
Grade 3	0		
Etiology of cirrhosis Units: Subjects			
Alcoholic liver disease	23		
Autoimmune disease	1		
Previous episode(s) of ACLF Units: Subjects			
Yes	4		
No	20		
CLIF ACLF grade Units: Subjects			
No ACLF/ACLF Grade 0	9		
ACLF Grade 1	10		
ACLF Grade 2	5		
ACLF Grade 3	0		
Time Since admission in current hospital Units: Days			
arithmetic mean	17.0		
standard deviation	± 17.4		
Time Since admission in current department Units: Days			
arithmetic mean	13.3		
standard deviation	± 14.2		
New MELD score Units: score			
arithmetic mean	27.18		
standard deviation	± 4.22		
CLIF-C AD Score			

Units: Score			
arithmetic mean	58.36		
standard deviation	± 9.74		
Bilirubin			
Units: mg/dL			
arithmetic mean	20.48		
standard deviation	± 10.04		
Platelets			
Units: 10^9/L			
arithmetic mean	134.67		
standard deviation	± 81.52		
Prothrombin Intl. Normalized Ratio			
Units: Ratio			
arithmetic mean	2.05		
standard deviation	± 0.49		
Time since the diagnosis of cirrhosis			
Units: month			
arithmetic mean	36.3		
standard deviation	± 55.6		
Height			
Units: centimetre			
arithmetic mean	171.9		
standard deviation	± 8.8		
Weight			
Units: kilogram(s)			
arithmetic mean	78.3		
standard deviation	± 17.5		
Body Mass Index			
Units: mg/m²			
arithmetic mean	26.4		
standard deviation	± 4.8		
CLIF-OF score			
Units: Disease score			
arithmetic mean	9.21		
standard deviation	± 1.41		
CLIF-C ACLF score			
Observed values for 15 patients (missing for 9 patients)			
Units: Disease score			
arithmetic mean	49.02		
standard deviation	± 6.85		
Child Pugh score			
Units: Disease score			
arithmetic mean	10.83		
standard deviation	± 1.46		
Creatinine			
Serum creatinine			
Units: mg/dL			
arithmetic mean	1.04		
standard deviation	± 0.47		
Albumin			
Serum albumin			
Units: g/dL			

arithmetic mean	3.02		
standard deviation	± 0.49		

End points

End points reporting groups

Reporting group title	Single arm - Screening period
Reporting group description: -	
Reporting group title	Single arm - Infusion day (Day 1)
Reporting group description: -	
Reporting group title	Single arm - Active treatment period D14
Reporting group description: -	
Reporting group title	Single arm - Active surveillance period D28
Reporting group description: -	
Reporting group title	Single arm - Long-term follow-up period M3
Reporting group description: -	
Reporting group title	Single arm - Long-term follow-up period Y1
Reporting group description: -	
Subject analysis set title	SAF
Subject analysis set type	Safety analysis

Subject analysis set description:

Of the 25 participants who were eligible and included in the FAS, only 24 who received 1 or 2 doses of HepaStem infusion were included in the SAF. Six participants for whom a major protocol deviation was recorded were excluded from the PP, which was constituted of 18 participants.

Primary: Adverse events reported up to Day 28 of the active study period

End point title	Adverse events reported up to Day 28 of the active study period[1]

End point description:

Adverse events (AEs) assessed for seriousness, severity, relationship to HepaStem and/or HepaStem administration procedure (including clinically significant changes in clinical examinations, vital signs, laboratory tests, abdominal echography and Doppler).
The relationship will be assessed based on investigator assessment and in addition by the SMC and the sponsor's pharmacovigilance in line with the ATMP guideline.

End point type	Primary

End point timeframe:

Up to Day 28 (end of active study period)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypotheses were assessed.
Standard descriptive statistics were used for quantitative and categorical variables.

End point values	Single arm - Active treatment period D14	Single arm - Active surveillance period D28	SAF	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	24	22[2]	24	
Units: Number of cases				
Gastrointestinal disorders	13	13	13	
Infections and infestations	10	10	10	
General disorders and administration site condit.	9	9	9	
Respiratory, thoracic and mediastinal disorders	8	8	8	
Metabolism and nutrition disorders	7	7	7	
Vascular disorders	6	6	6	

Nervous system disorders	5	5	5	
Renal and urinary disorders	5	5	5	
Hepatobiliary disorders	4	4	4	
Surgical and medical procedure	3	3	3	
Blood and lymphatic system disorders	2	2	2	
Injury, poisoning and procedural complications	2	2	2	
Skin and subcutaneous tissue disorders	2	2	2	
Cardiac disorders	1	1	1	
Musculoskeletal and connective tissue disorders	1	1	1	
Psychiatric disorders	1	1	1	
Reproductive system and breast disorders	1	1	1	

Notes:

[2] - The number/percentage of participants having at least one adverse event were measured from D1 to D28

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical efficacy parameters assessed on Day 28, Month 3 and Year 1 - Mortality and liver transplantation

End point title	Clinical efficacy parameters assessed on Day 28, Month 3 and Year 1 - Mortality and liver transplantation

End point description:

No formal statistical hypotheses were assessed.
Standard descriptive statistics were used for quantitative and categorical variables.

End point type	Secondary

End point timeframe:

On Day 28 (end of the active study period), Month3, and Year 1 (end of the long-term follow-up and of the study)

End point values	Single arm - Infusion day (Day 1)	Single arm - Active surveillance period D28	Single arm - Long-term follow-up period M3	SAF
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	24	19	16	24
Units: Number of cases				
Mortality	4	3	1	8
Liver transplantation	3	1	0	4

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical efficacy parameter assessed on Day 28, Month 3 and Year 1 - CLIF-OF score

End point title	Clinical efficacy parameter assessed on Day 28, Month 3 and Year 1 - CLIF-OF score

End point description:

No formal statistical hypotheses were assessed.
Standard descriptive statistics were used for quantitative and categorical variables.

End point type	Secondary

End point timeframe:

On Day 28 (end of the active study period), Month3, and Year 1 (end of the long-term follow-up and of the study)

End point values	Single arm - Active surveillance period D28	Single arm - Long-term follow-up period M3	Single arm - Long-term follow-up period Y1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	13	15	
Units: Disease score				
arithmetic mean (standard deviation)				
CLIF-OF score	7.53 (± 1.7)	6.15 (± 0.38)	6.27 (± 0.59)	

Statistical analyses

No statistical analyses for this end point

Secondary: Biological efficacy parameter at Day 28, Month 3 and Year 1 – Bilirubin

End point title	Biological efficacy parameter at Day 28, Month 3 and Year 1 – Bilirubin

End point description:

Serum total bilirubin.
No formal statistical hypotheses were assessed.
Standard descriptive statistics were used for quantitative and categorical variables.

End point type	Secondary

End point timeframe:

On Day 28 (end of the active study period), Month3, and Year 1 (end of the long-term follow-up and of the study)

End point values	Single arm - Active surveillance period D28	Single arm - Long-term follow-up period M3	Single arm - Long-term follow-up period Y1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	19	17	15	
Units: mg/dL				
arithmetic mean (standard deviation)				
Bilirubin	9.63 (± 10.89)	2.36 (± 1.99)	2.58 (± 2.47)	

Statistical analyses

No statistical analyses for this end point

Secondary: Biological efficacy parameter at Day 28, Month 3 and Year 1 - Creatinine

End point title	Biological efficacy parameter at Day 28, Month 3 and Year 1 - Creatinine

End point description:

Serum creatinine.
No formal statistical hypotheses were assessed.
Standard descriptive statistics were used for quantitative and categorical variables.

End point type	Secondary

End point timeframe:

On Day 28 (end of the active study period), Month3, and Year 1 (end of the long-term follow-up and of the study)

End point values	Single arm - Active surveillance period D28	Single arm - Long-term follow-up period M3	Single arm - Long-term follow-up period Y1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	19	17	15	
Units: mg/dL				
arithmetic mean (standard deviation)				
Creatinine	0.89 (± 0.36)	0.95 (± 0.34)	0.85 (± 0.29)	

Statistical analyses

No statistical analyses for this end point

Secondary: Biological efficacy parameter at Day 28, Month 3 and Year 1 - INR

End point title	Biological efficacy parameter at Day 28, Month 3 and Year 1 - INR

End point description:

Prothrombin International Normalized Ratio.
No formal statistical hypotheses were assessed.
Standard descriptive statistics were used for quantitative and categorical variables.

End point type	Secondary

End point timeframe:

On Day 28 (end of the active study period), Month3, and Year 1 (end of the long-term follow-up and of the study)

End point values	Single arm - Active surveillance period D28	Single arm - Long-term follow-up period M3	Single arm - Long-term follow-up period Y1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	19	17	15	
Units: ratio				
arithmetic mean (standard deviation)				
INR	1.69 (± 0.93)	1.32 (± 0.28)	1.28 (± 0.28)	

Statistical analyses

No statistical analyses for this end point

Secondary: Biological efficacy parameter at Day 28, Month 3 and Year 1 - Albumin

End point title	Biological efficacy parameter at Day 28, Month 3 and Year 1 - Albumin

End point description:

Serum Albumin.
No formal statistical hypotheses were assessed.
Standard descriptive statistics were used for quantitative and categorical variables.

End point type	Secondary

End point timeframe:

On Day 28 (end of the active study period), Month3, and Year 1 (end of the long-term follow-up and of the study)

End point values	Single arm - Active surveillance period D28	Single arm - Long-term follow-up period M3	Single arm - Long-term follow-up period Y1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	17	15	
Units: g/dL				
arithmetic mean (standard deviation)				
Albumin	3.46 (± 0.82)	3.69 (± 0.60)	3.91 (± 0.76)	

Statistical analyses

No statistical analyses for this end point

Secondary: Adverse Events of Special Interest

End point title	Adverse Events of Special Interest

End point description:

Serious adverse event with fatal outcome, malignancies, adverse events assessed by the investigator as possibly related to HepaStem, liver transplantation and outcome of liver transplantation.
No formal statistical hypotheses were assessed.
Standard descriptive statistics were used for quantitative and categorical variables.

End point type	Secondary

End point timeframe:

Between Day 28 and Month 3, and between Month 3 and Year 1

End point values	Single arm - Long-term follow-up period M3	Single arm - Long-term follow-up period Y1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	17		
Units: Number of cases				
Serious adverse event with fatal outcome	3	0		
Malignancy	0	0		
AE assessed as possibly related to HepaStem	0	0		
Liver transplantation and outcome	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: New ACLF episode

End point title	New ACLF episode

End point description:

New ACLF episode.
No formal statistical hypotheses were assessed.
Standard descriptive statistics were used for quantitative and categorical variables.

End point type	Secondary

End point timeframe:

Between Day 28 and Month 3, and between Month 3 and Year 1

End point values	Single arm - Long-term follow-up period M3	Single arm - Long-term follow-up period Y1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	17		
Units: Number of cases				
New ACLF episode	0	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical efficacy parameter assessed up to Day 28 - CLIF-C ACLF score

End point title	Clinical efficacy parameter assessed up to Day 28 - CLIF-C ACLF score
End point description:	
No formal statistical hypotheses were assessed. Standard descriptive statistics were used for quantitative and categorical variables.	
End point type	Secondary
End point timeframe:	
On Day 28 (end of the active study period)	

End point values	Single arm - Active surveillance period D28			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: Disease score				
arithmetic mean (standard deviation)				
CLIF-C ACLF score	49.60 (± 5.67)			

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical efficacy parameter assessed on Day 28, Month 3 and Year 1 - CLIF ACLF grade

End point title	Clinical efficacy parameter assessed on Day 28, Month 3 and Year 1 - CLIF ACLF grade
End point description:	
No formal statistical hypotheses were assessed. Standard descriptive statistics were used for quantitative and categorical variables.	
End point type	Secondary
End point timeframe:	
On Day 28 (end of the active study period), Month3, and Year 1 (end of the long-term follow-up and of the study)	

End point values	Single arm - Active surveillance period D28	Single arm - Long-term follow-up period M3	Single arm - Long-term follow-up period Y1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	13	15	
Units: Number				
No ACLF/ACLF Grade 0	13	13	15	
ACLF Grade 1	2	0	0	
ACLF Grade 2	2	0	0	
ACLF Grade 3	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical efficacy parameter assessed on Day 28, Month 3 and Year 1 - CLIF-C AD

End point title	Clinical efficacy parameter assessed on Day 28, Month 3 and Year 1 - CLIF-C AD

End point description:

No formal statistical hypotheses were assessed.
Standard descriptive statistics were used for quantitative and categorical variables.

End point type	Secondary

End point timeframe:

On Day 28 (end of the active study period), Month3, and Year 1 (end of the long-term follow-up and of the study)

End point values	Single arm - Active surveillance period D28	Single arm - Long-term follow-up period M3	Single arm - Long-term follow-up period Y1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	19	17	15	
Units: Disease score				
arithmetic mean (standard deviation)				
CLIF-C AD	51.60 (± 9.30)	44.91 (± 6.49)	44.86 (± 6.56)	

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical efficacy parameter assessed on Day 28, Month 3 and Year 1 - MELD score

End point title	Clinical efficacy parameter assessed on Day 28, Month 3 and Year 1 - MELD score

End point description:

No formal statistical hypotheses were assessed.
Standard descriptive statistics were used for quantitative and categorical variables.

End point type	Secondary

End point timeframe:

On Day 28 (end of the active study period), Month3, and Year 1 (end of the long-term follow-up and of the study)

End point values	Single arm - Active surveillance period D28	Single arm - Long-term follow-up period M3	Single arm - Long-term follow-up period Y1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	19	17	15	
Units: Disease score				
arithmetic mean (standard deviation)				
MELD score	20.88 (± 7.99)	13.13 (± 5.24)	12.26 (± 4.63)	

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical efficacy parameter assessed on Day 28, Month 3 and Year 1 - Child Pugh score

End point title	Clinical efficacy parameter assessed on Day 28, Month 3 and Year 1 - Child Pugh score

End point description:

No formal statistical hypotheses were assessed.
Standard descriptive statistics were used for quantitative and categorical variables.

End point type	Secondary

End point timeframe:

On Day 28 (end of the active study period), Month3, and Year 1 (end of the long-term follow-up and of the study)

End point values	Single arm - Active surveillance period D28	Single arm - Long-term follow-up period M3	Single arm - Long-term follow-up period Y1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	16	15	
Units: Disease score				
arithmetic mean (standard deviation)				
Child Pugh score	8.94 (± 2.08)	6.44 (± 1.55)	6.27 (± 1.79)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:	
AEs up to Day 28, AESIs between Day 28 and Year 1	
Adverse event reporting additional description:	
Up to Day 28, all AEs were collected and assessed for seriousness, severity, relationship to HepaStem and/or HepaStem administration procedure (including clinically significant changes in clinical examinations, vital signs, laboratory tests, abdominal echography and Doppler). Between Day 28 and Year 1, only AESIs were collected.	
Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

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: Information relative to non-serious adverse events is provided in the endpoint section: Primary endpoint (Adverse events reported up to Day 28) and secondary endpoint (Adverse Events of Special Interest reported between Day 28 and Year 1)

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 December 2016	v2.0 • Inclusion/exclusion criteria were updated: o as HepaStem might have a procoagulant effect, inclusion and treatment discontinuation criteria were further specified o the delay between corticosteroid treatment and screening visit was updated • The organ failure criteria were clarified to take into account patients treated with terlipressin.
21 March 2017	v3.0 (only submitted to Belgian competent authorities; not approved) dated 21 Mar-2017 v3.2 (submitted to Belgium IEC) dated 11-May-2017, v 3.1 and v3.3 (approved) submitted to the French competent authorities Following the occurrence for the 2 severe SAEs of bleeding and the temporary halt of the study, the study protocol was amended: • To decrease the dose and their frequency of administration (refer to Sections 9.1.1 and 9.4 for further details). Consequently, the volume to be administered was also adapted • To enroll participants who were at a less severe stage of ACLF, i.e., patients with AD and INR < 2 • To increase the safety monitoring of the participants before, during and after HepaStem infusion: o by increasing the monitoring of coagulation parameters (addition of monitoring parameters and repetition of some assessments during and after the treatment period) o by allowing the collection of a sample for TEG/TGT to be analyzed centrally o by repeating the imagery examination at the last participant visit to have a complete status of the participant at the end of study comparable to the evaluations done at screening o in addition, to limit any further risk of bleeding for the participant, transjugular liver biopsy was no longer required and an exclusion criterion (if performed, sufficient time in-between procedure and dosing was to be allowed) • To update criteria for infusion in order to ensure that participants with a significant pre-existing coagulation imbalance would not receive HepaStem and specify the action to be taken in case of major changes in the coagulation factors (refer to Section 9.3.1 for further details) • To increase the frequency of SMC meetings • To update the sample size • For participants who underwent a major surgery, at least 4 weeks have to pass before cells infusion • To ensure the independency of the SMC, all members are to be external and independent to PROMETHERA THERAPEUTICS
15 February 2018	v 4.0 (only submitted in Spain and Bulgaria) • The screening period was extended to ensure the delivery of HepaStem on site within the screening period.

26 June 2018	v 5.0 and v5.1
	• Two additional cohorts (2c and 2d), including each 3 participants, were planned in order to assess the safety of higher dose (1.0x10^6 cells/kg BW/infusion).
	• The recruitment of 3 additional participants (more severe ACLF) to be included in the cohort considered as safe by the SMC (Cohort 2b) has been added.
	• To be in line with the inclusion of patients at a more severe stage of the disease, exclusion criteria were redefined to exclude participants with circulatory and/or respiratory failure according to the CLIF C OF consortium.
	• Following the conclusion raised by the SMC members on 25-Jun-2018, the patients with a suspicion of hepatocellular carcinoma were to be excluded. All exams were to be performed to confirm or not the diagnosis.
	• Screening procedures were revised in order to include the monitoring of fibrinogen.
14 December 2018	v 6.0 and v6.1
	• The total sample size was revised based upon SMC's recommendations to approximately 21 evaluable participants.
	• A third and fourth analyses were planned on Day 28 and Month 3, respectively, on all participants, including enrolled participants in Cohort 2b having an INR > 2 and participants enrolled in Cohorts 2c and 2d.
	• Before HepaStem infusion, an equivalent of hydrocortisone (in equivalent dose) could be given instead of hydrocortisone.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

 None reported

Online references

 http://www.ncbi.nlm.nih.gov/pubmed/34169246