Clinical trial results:
Multicenter, open-label, safety and tolerability study of ascending doses of HepaStem in patients with cirrhotic and pre-cirrhotic non-alcoholic steato-hepatitis (NASH).

Summary

EudraCT number	2018-004449-18
Trial protocol	FR BE BG PL ES RO
Global end of trial date	31 August 2020

Results information

Result version number	v1 (current)
This version publication date	28 April 2024
First version publication date	28 April 2024

Trial information

Trial identification

Sponsor protocol code	HEP201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03963921
WHO universal trial number (UTN)	-
Other trial identifiers	PANASH: HEP201

Notes:

Sponsors

Sponsor organisation name	Cellaïon
Sponsor organisation address	Rue Granbonpré 11, Mont-Saint-Guibert, Belgium, 1435
Public contact	Welcome desk, Cellaïon, 32 10 394300, info@cellaion.com
Scientific contact	Welcome desk, Cellaïon, 32 10 394300, info@cellaion.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	21 November 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 August 2020
Global end of trial reached?	Yes
Global end of trial date	31 August 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial is to determine the safety and tolerability of ascending single and repeated doses of HepaStem up to Day 28 administered to patients with cirrhotic and pre cirrhotic NASH.

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.
All patients received HepaStem at the study site under the surveillance of appropriate study personnel. The patients were to stay hospitalized for a minimum duration of 24 hours after the infusion of HepaStem to ensure their continuous monitoring.
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.
Successive dose cohorts received progressively larger doses through a stepwise approach evaluated by the Safety Monitoring Committee.
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, EU-CTR 2022-500251-22-00).

Background therapy:

The participants were recruited at hospitals with specialized hepatology and intensive care units. The patients' profile consisted of NASH with stage F3 or (compensated/early decompensated) F4 fibrosis with proven diagnosis of NASH demonstrated by liver biopsy before screening, available within 6 months for F3 patients or 2 years for F4 patients. If biopsy was not available within these time windows, a biopsy was to be performed at screening. F4 patients for whom the biopsy did not confirm the diagnosis of NASH could be included, provided that any other causes of underlying liver diseases were excluded.
Decompensated F4 patients had to present one of the following clinical signs of decompensation:
- Total bilirubin > 2 mg/dL (direct bilirubin > 1.5 mg/dL in case of suspected Gilbert's syndrome), and/or
- Clinical signs of ascites, and/or
- Clinical or electroencephalography evidence of HE up to grade II

Evidence for comparator:

Not applicable

Actual start date of recruitment	15 March 2019
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Romania: 2
Country: Number of subjects enrolled	Spain: 7
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Bulgaria: 8
Country: Number of subjects enrolled	France: 1
Worldwide total number of subjects	23
EEA total number of subjects	23

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)	17
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Ten investigational sites in 6 countries recruited 23 participants: 2 in Bulgaria, 2 in Belgium, 1 in France, 1 in Poland, 3 in Spain, and 1 in Romania.
The recruitment period lasted approximately 10 months (FPFV 19-APR-2019 - LPFV 20-FEB-20120).

Pre-assignment

Screening details:

The screening period lasted up to 14 days following informed consent signature and allowed assessing participant's eligibility.
Participants were hospitalized during the screening period.
31 participants were screened, 23 were eligible and included in the safety analysis set (SAF).

Period 1

Period 1 title	Infusion Day 1
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

All participants enrolled in the study were administered a single or 3 repeated weekly infusions of 0.5 or 1.0 x 10^6 cells of HepaStem/kg body weight (BW).
There was no blinding in this study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Single arm - Dose Cohort 1

Arm description:

Dose Cohort 1

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:

- Dose Cohort 1: 0.5 x 10^6 cells of HepaStem/kg body weight (BW), administered as single intravenous infusion.

Arm title	Single arm - Dose Cohort 2

Arm description:

Dose Cohort 2

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:

- Dose Cohort 2: 1.0 x 10^6 cells of HepaStem/kg BW, administered as single intravenous infusion.

Arm title	Single arm - Dose Cohort 3

Arm description:	
Dose Cohort 3	
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:

- Dose Cohort 3: 0.5 x 10^6 cells of HepaStem/kg BW, administered as 3 repeated weekly intravenous infusions for a total dose of 1.5 x 10^6 cells of HepaStem/kg BW.

Arm title	Single arm - Dose Cohort 4
Arm description:	
Dose Cohort 4	
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:

- Dose Cohort 4: 1.0 x 10^6 cells of HepaStem/kg BW, administered as 3 repeated weekly intravenous infusions for a total dose of 3.0 x 10^6 cells of HepaStem/kg BW.

Number of subjects in period 1	Single arm - Dose Cohort 1	Single arm - Dose Cohort 2	Single arm - Dose Cohort 3
Started	6	6	7
Completed	6	6	7

Number of subjects in period 1	Single arm - Dose Cohort 4
Started	4
Completed	4

Period 2

Period 2 title	Infusion Day 1 (post infusion)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes

Arm title	Single arm - Dose Cohort 1
Arm description: Dose Cohort 1	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Single arm - Dose Cohort 2
Arm description: Dose Cohort 2	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Single arm - Dose Cohort 3
Arm description: Dose Cohort 3	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Single arm - Dose Cohort 4
Arm description: Dose Cohort 4	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 2	Single arm - Dose Cohort 1	Single arm - Dose Cohort 2	Single arm - Dose Cohort 3
Started	6	6	7
Completed	6	6	7

Number of subjects in period 2	Single arm - Dose Cohort 4
Started	4
Completed	4

Period 3	
Period 3 title	Infusion Day 8
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded
Arms	
Are arms mutually exclusive?	Yes

Arm title	Single arm - Dose Cohort 1
Arm description: Dose Cohort 1	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Arm title	Single arm - Dose Cohort 2
Arm description: Dose Cohort 2	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Arm title	Single arm - Dose Cohort 3
Arm description: Dose Cohort 3	
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:

- Dose Cohort 3: 0.5 x 10^6 cells of HepaStem/kg BW, administered as 3 repeated weekly intravenous infusions for a total dose of 1.5 x 10^6 cells of HepaStem/kg BW.

Arm title	Single arm - Dose Cohort 4
Arm description: Dose Cohort 4	
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:

- Dose Cohort 4: 1.0 x 10^6 cells of HepaStem/kg BW, administered as 3 repeated weekly intravenous infusions for a total dose of 3.0 x 10^6 cells of HepaStem/kg BW.

Number of subjects in period 3	Single arm - Dose Cohort 1	Single arm - Dose Cohort 2	Single arm - Dose Cohort 3
Started	6	6	7
Completed	6	6	7

Number of subjects in period 3	Single arm - Dose Cohort 4
Started	4
Completed	4

Period 4	
Period 4 title	Infusion Day 8 (post infusion)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded
Arms	
Are arms mutually exclusive?	Yes
Arm title	Single arm - Dose Cohort 1
Arm description: Dose Cohort 1	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Single arm - Dose Cohort 2
Arm description: Dose Cohort 2	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Single arm - Dose Cohort 3
Arm description: Dose Cohort 3	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Single arm - Dose Cohort 4
Arm description: Dose Cohort 4	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 4	Single arm - Dose Cohort 1	Single arm - Dose Cohort 2	Single arm - Dose Cohort 3
Started	6	6	7
Completed	6	6	7

Number of subjects in period 4	Single arm - Dose Cohort 4
Started	4
Completed	4

Period 5

Period 5 title	Infusion Day 15
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Single arm - Dose Cohort 1

Arm description:

Dose Cohort 1

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Single arm - Dose Cohort 2

Arm description:

Dose Cohort 2

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Single arm - Dose Cohort 3

Arm description:

Dose Cohort 3

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:

- Dose Cohort 3: 0.5 x 10^6 cells of HepaStem/kg BW, administered as 3 repeated weekly intravenous infusions for a total dose of 1.5 x 10^6 cells of HepaStem/kg BW.

Arm title	Single arm - Dose Cohort 4

Arm description:

Dose Cohort 4

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:

- Dose Cohort 4: 1.0 x 10^6 cells of HepaStem/kg BW, administered as 3 repeated weekly intravenous infusions for a total dose of 3.0 x 10^6 cells of HepaStem/kg BW.

Number of subjects in period 5	Single arm - Dose Cohort 1	Single arm - Dose Cohort 2	Single arm - Dose Cohort 3
Started	6	6	7
Completed	6	6	7

Number of subjects in period 5	Single arm - Dose Cohort 4
Started	4
Completed	4

Period 6	
Period 6 title	Infusion Day 15 (post infusion)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded
Arms	
Are arms mutually exclusive?	Yes
Arm title	Single arm - Dose Cohort 1
Arm description: Dose Cohort 1	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Single arm - Dose Cohort 2
Arm description: Dose Cohort 2	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Single arm - Dose Cohort 3
Arm description: Dose Cohort 3	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Single arm - Dose Cohort 4
Arm description: Dose Cohort 4	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 6	Single arm - Dose Cohort 1	Single arm - Dose Cohort 2	Single arm - Dose Cohort 3
Started	6	6	7
Completed	6	6	7

Number of subjects in period 6	Single arm - Dose Cohort 4
Started	4
Completed	4

Period 7	
Period 7 title	Follow-up period (up to Day 28)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded
Arms	
Are arms mutually exclusive?	Yes
Arm title	Single arm - Dose Cohort 1
Arm description: Dose Cohort 1	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Single arm - Dose Cohort 2
Arm description: Dose Cohort 2	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Single arm - Dose Cohort 3
Arm description: Dose Cohort 3	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Single arm - Dose Cohort 4
Arm description: Dose Cohort 4	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 7	Single arm - Dose Cohort 1	Single arm - Dose Cohort 2	Single arm - Dose Cohort 3
Started	6	6	7
Completed	6	6	7

Number of subjects in period 7	Single arm - Dose Cohort 4
Started	4
Completed	4

Period 8	
Period 8 title	Follow-up period (up to Month 6)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded
Arms	
Are arms mutually exclusive?	Yes
Arm title	Single arm - Dose Cohort 1
Arm description: Dose Cohort 1	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Single arm - Dose Cohort 2
Arm description: Dose Cohort 2	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Single arm - Dose Cohort 3
Arm description: Dose Cohort 3	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Single arm - Dose Cohort 4
Arm description: Dose Cohort 4	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 8	Single arm - Dose Cohort 1	Single arm - Dose Cohort 2	Single arm - Dose Cohort 3
Started	6	6	7
Completed	6	4	7
Not completed	0	2	0
Consent withdrawn by subject	-	2	-

Number of subjects in period 8	Single arm - Dose Cohort 4
Started	4
Completed	3
Not completed	1
Consent withdrawn by subject	1

Baseline characteristics

Reporting groups	
Reporting group title	Single arm - Dose Cohort 1
Reporting group description: Dose Cohort 1	
Reporting group title	Single arm - Dose Cohort 2
Reporting group description: Dose Cohort 2	
Reporting group title	Single arm - Dose Cohort 3
Reporting group description: Dose Cohort 3	
Reporting group title	Single arm - Dose Cohort 4
Reporting group description: Dose Cohort 4	

Reporting group values	Single arm - Dose Cohort 1	Single arm - Dose Cohort 2	Single arm - Dose Cohort 3
Number of subjects	6	6	7
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)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	4	6	5
From 65-84 years	2	0	2
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	55.0	52.2	61.7
standard deviation	± 11.6	± 10.1	± 4.0
Gender categorical Units: Subjects			
Female	4	3	2
Male	2	3	5
Fibrosis stage Units: Subjects			
F3	3	3	3
F4	3	3	4
Height Units: centimetre			
arithmetic mean	169.5	168.3	164.4
standard deviation	± 12.1	± 13.0	± 10.9
Weight Units: kilogram(s)			

arithmetic mean	102.0	95.0	86.7
standard deviation	± 21.3	± 21.8	± 12.3
BMI			
Units: kilogram(s)/square metre			
arithmetic mean	35.2	33.4	32.2
standard deviation	± 4.4	± 5.9	± 4.2
Waist circumference			
Units: centimetre			
arithmetic mean	109.2	110.2	108.3
standard deviation	± 10.9	± 9.1	± 11.6
NAS			
Non-alcoholic fatty liver disease (NAFLD) activity score			
Units: unit(s)			
arithmetic mean	6.17	5.83	4.00
standard deviation	± 1.60	± 1.17	± 1.63
SAF steatosis score			
Units: unit(s)			
arithmetic mean	2.50	2.60	1.43
standard deviation	± 0.84	± 0.55	± 0.79
SAF activity score			
Units: unit(s)			
arithmetic mean	3.17	2.33	2.14
standard deviation	± 0.98	± 1.37	± 1.57
Liver stiffness measurement			
Units: kPa			
arithmetic mean	7.77	14.29	14.43
standard deviation	± 0.88	± 7.97	± 4.21
Controlled attenuation parameter			
Units: dB/m			
arithmetic mean	348.0	348.4	309.9
standard deviation	± 40.4	± 46.7	± 72.9
White blood cell count			
Units: 10/L			
arithmetic mean	7.51	8.15	6.55
standard deviation	± 2.08	± 2.01	± 0.77
Creatinine			
Units: mg/dL			
arithmetic mean	0.97	0.78	0.65
standard deviation	± 0.21	± 0.22	± 0.10
Urea			
Units: mmol/L			
arithmetic mean	5.27	4.73	5.27
standard deviation	± 2.16	± 1.86	± 0.65
D-dimers			
Units: mg/L			
arithmetic mean	0.37	0.35	0.26
standard deviation	± 0.17	± 0.15	± 0.15
Fibrinogen			
Units: mg/dL			
arithmetic mean	375.3	369.8	409.7
standard deviation	± 58.1	± 145.5	± 57.3
INR			

Units: ratio			
arithmetic mean	1.01	1.10	1.02
standard deviation	± 0.05	± 0.11	± 0.10
Platelets			
Units: 10/L			
arithmetic mean	189.0	174.7	206.3
standard deviation	± 65.8	± 63.0	± 45.9
Protein C			
Units: percentage			
arithmetic mean	113.8	89.4	105.8
standard deviation	± 27.0	± 25.1	± 6.4
Protein S			
Units: percentage			
arithmetic mean	97.3	101.4	92.0
standard deviation	± 27.4	± 13.0	± 20.2
Thrombin time			
Units: second			
arithmetic mean	18.2	17.4	14.9
standard deviation	± 2.6	± 3.7	± 3.0
Plasminogen activator inhibitor-1 activity			
Units: UA/mL			
arithmetic mean	26.0	18.8	25.8
standard deviation	± 5.7	± 7.7	± 11.3
Total bilirubin			
Units: mg/dL			
arithmetic mean	0.66	1.17	0.71
standard deviation	± 0.26	± 0.59	± 0.42
Alkaline phosphatase			
Units: U/L			
arithmetic mean	76.0	83.3	97.4
standard deviation	± 18.0	± 22.9	± 39.4
Alanine aminotransferase			
Units: U/L			
arithmetic mean	64.5	44.8	63.4
standard deviation	± 29.9	± 34.4	± 26.9
Aspartate aminotransferase			
Units: U/L			
arithmetic mean	50.5	38.9	41.4
standard deviation	± 23.0	± 15.6	± 12.3
γ-glutamyl transferase			
Units: U/L			
arithmetic mean	72.4	84.9	64.1
standard deviation	± 35.1	± 47.7	± 57.9
Fasting glucose			
Units: mmol/L			
arithmetic mean	7.15	8.51	7.20
standard deviation	± 1.76	± 2.67	± 1.48
Hemoglobin A1c			
Units: L/L			
arithmetic mean	6.52	5.80	6.42
standard deviation	± 1.16	± 1.12	± 1.10

High density lipoprotein			
Units: mmol/L			
arithmetic mean	1.08	0.94	1.10
standard deviation	± 0.22	± 0.24	± 0.22
Low density lipoprotein			
Units: mmol/L			
arithmetic mean	3.26	1.98	2.46
standard deviation	± 0.87	± 0.80	± 1.18
Triglyceride			
Units: mmol/L			
arithmetic mean	3.23	2.58	2.52
standard deviation	± 2.23	± 1.03	± 0.57
Total cholesterol			
Units: mmol/L			
arithmetic mean	5.48	3.72	4.06
standard deviation	± 1.06	± 0.85	± 1.23
Uric acid			
Units: µmol/L			
arithmetic mean	393.5	323.3	304.0
standard deviation	± 109.4	± 69.2	± 59.2
Hyaluronic acid			
Units: µg/L			
median	22.5	53.5	83.0
full range (min-max)	12.0 to 329.0	28.0 to 294.0	13.0 to 152.5
Tissue inhibitor of metalloproteinase-1			
Units: ng/L			
median	129.4	142.9	116.4
full range (min-max)	105.2 to 199.2	97.9 to 243.3	80.3 to 194.4
N-terminal propeptide of Type III collagen			
Units: U/mL			
median	1.01	1.04	0.91
full range (min-max)	0.60 to 1.30	0.63 to 1.47	0.59 to 1.14
C-reactive protein			
Units: mg/L			
median	3.65	4.50	2.80
full range (min-max)	0.90 to 11.00	2.20 to 21.10	0.00 to 15.60
Interleukin-6			
Units: pg/mL			
median	1.79	4.75	2.88
full range (min-max)	1.14 to 4.32	1.51 to 7.88	0.93 to 3.44
Adiponectin			
Units: µg/mL			
median	5.18	5.24	7.43
full range (min-max)	3.20 to 10.47	2.52 to 7.04	3.46 to 8.83
MELD-Na			
Units: score			
arithmetic mean	7.33	8.33	7.00
standard deviation	± 0.82	± 1.97	± 1.15
Child-Pugh			
Units: score			
arithmetic mean	5.00	5.17	5.14

standard deviation	± 0.00	± 0.41	± 0.38
CLIF-C AD			
Units: score			
arithmetic mean	43.2	43.7	42.3
standard deviation	± 6.4	± 3.1	± 3.0
APRI			
Aspartate aminotransferase to platelet ratio index			
Units: score			
arithmetic mean	0.73	0.63	0.56
standard deviation	± 0.50	± 0.26	± 0.17
FIB-4			
Fibrosis-4 (score)			
Units: score			
arithmetic mean	-0.12	0.10	-0.43
standard deviation	± 1.35	± 1.26	± 0.60

Reporting group values	Single arm - Dose Cohort 4	Total	
Number of subjects	4	23	
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)	2	17	
From 65-84 years	2	6	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	56.0		
standard deviation	± 14.0	-	
Gender categorical			
Units: Subjects			
Female	1	10	
Male	3	13	
Fibrosis stage			
Units: Subjects			
F3	2	11	
F4	2	12	
Height			
Units: centimetre			
arithmetic mean	164.5		
standard deviation	± 11.1	-	
Weight			
Units: kilogram(s)			
arithmetic mean	94.3		
standard deviation	± 11.0	-	
BMI			

Units: kilogram(s)/square metre			
arithmetic mean	34.9		
standard deviation	± 2.7	-	
Waist circumference			
Units: centimetre			
arithmetic mean	115.5		
standard deviation	± 11.3	-	
NAS			
Non-alcoholic fatty liver disease (NAFLD) activity score			
Units: unit(s)			
arithmetic mean	4.50		
standard deviation	± 1.29	-	
SAF steatosis score			
Units: unit(s)			
arithmetic mean	1.50		
standard deviation	± 0.58	-	
SAF activity score			
Units: unit(s)			
arithmetic mean	3.50		
standard deviation	± 0.58	-	
Liver stiffness measurement			
Units: kPa			
arithmetic mean	25.63		
standard deviation	± 20.87	-	
Controlled attenuation parameter			
Units: dB/m			
arithmetic mean	325.8		
standard deviation	± 71.0	-	
White blood cell count			
Units: 10/L			
arithmetic mean	5.81		
standard deviation	± 0.33	-	
Creatinine			
Units: mg/dL			
arithmetic mean	0.76		
standard deviation	± 0.09	-	
Urea			
Units: mmol/L			
arithmetic mean	5.13		
standard deviation	± 1.28	-	
D-dimers			
Units: mg/L			
arithmetic mean	0.34		
standard deviation	± 0.38	-	
Fibrinogen			
Units: mg/dL			
arithmetic mean	316.1		
standard deviation	± 75.2	-	
INR			
Units: ratio			
arithmetic mean	1.17		
standard deviation	± 0.08	-	

Platelets Units: 10/L arithmetic mean standard deviation	 174.6 ± 70.8	 -	
Protein C Units: percentage arithmetic mean standard deviation	 105.8 ± 41.1	 -	
Protein S Units: percentage arithmetic mean standard deviation	 90.4 ± 15.3	 -	
Thrombin time Units: second arithmetic mean standard deviation	 15.9 ± 1.2	 -	
Plasminogen activator inhibitor-1 activity Units: UA/mL arithmetic mean standard deviation	 24.7 ± 7.0	 -	
Total bilirubin Units: mg/dL arithmetic mean standard deviation	 1.09 ± 0.87	 -	
Alkaline phosphatase Units: U/L arithmetic mean standard deviation	 87.5 ± 35.1	 -	
Alanine aminotransferase Units: U/L arithmetic mean standard deviation	 47.3 ± 28.6	 -	
Aspartate aminotransferase Units: U/L arithmetic mean standard deviation	 35.8 ± 15.5	 -	
γ-glutamyl transferase Units: U/L arithmetic mean standard deviation	 76.0 ± 48.4	 -	
Fasting glucose Units: mmol/L arithmetic mean standard deviation	 7.38 ± 1.36	 -	
Hemoglobin A1c Units: L/L arithmetic mean standard deviation	 6.73 ± 0.95	 -	
High density lipoprotein Units: mmol/L arithmetic mean	 1.16	 	

standard deviation	± 0.24	-	
Low density lipoprotein			
Units: mmol/L			
arithmetic mean	4.28		
standard deviation	± 1.18	-	
Triglyceride			
Units: mmol/L			
arithmetic mean	4.10		
standard deviation	± 3.36	-	
Total cholesterol			
Units: mmol/L			
arithmetic mean	5.96		
standard deviation	± 1.16	-	
Uric acid			
Units: µmol/L			
arithmetic mean	393.3		
standard deviation	± 87.8	-	
Hyaluronic acid			
Units: µg/L			
median	81.0		
full range (min-max)	21.6 to 128.5	-	
Tissue inhibitor of metalloproteinase-1			
Units: ng/L			
median	148.0		
full range (min-max)	63.7 to 172.3	-	
N-terminal propeptide of Type III collagen			
Units: U/mL			
median	0.91		
full range (min-max)	0.51 to 1.09	-	
C-reactive protein			
Units: mg/L			
median	2.56		
full range (min-max)	0.00 to 7.70	-	
Interleukin-6			
Units: pg/mL			
median	2.44		
full range (min-max)	1.58 to 4.30	-	
Adiponectin			
Units: µg/mL			
median	4.59		
full range (min-max)	3.87 to 5.20	-	
MELD-Na			
Units: score			
arithmetic mean	9.00		
standard deviation	± 2.16	-	
Child-Pugh			
Units: score			
arithmetic mean	5.25		
standard deviation	± 0.50	-	
CLIF-C AD			
Units: score			

arithmetic mean	43.3		
standard deviation	± 5.4	-	
APRI			
Aspartate aminotransferase to platelet ratio index			
Units: score			
arithmetic mean	0.65		
standard deviation	± 0.30	-	
FIB-4			
Fibrosis-4 (score)			
Units: score			
arithmetic mean	0.23		
standard deviation	± 2.02	-	

Subject analysis sets

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

Subject analysis set description:

The Safety analysis set (SAF) included all patients entered in the study who received at least one dose of the IMP.

Reporting group values	Safety analysis set		
Number of subjects	23		
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)	17		
From 65-84 years	6		
85 years and over	0		
Age continuous Units: years			
arithmetic mean	56.5		
standard deviation	± 10.0		
Gender categorical Units: Subjects			
Female	10		
Male	13		
Fibrosis stage Units: Subjects			
F3	11		
F4	12		
Height Units: centimetre			
arithmetic mean	166.8		
standard deviation	± 11.2		

Weight			
Units: kilogram(s)			
arithmetic mean	94.2		
standard deviation	± 17.4		
BMI			
Units: kilogram(s)/square metre			
arithmetic mean	33.7		
standard deviation	± 4.4		
Waist circumference			
Units: centimetre			
arithmetic mean	110.3		
standard deviation	± 10.3		
NAS			
Non-alcoholic fatty liver disease (NAFLD) activity score			
Units: unit(s)			
arithmetic mean	5.13		
standard deviation	± 1.66		
SAF steatosis score			
Units: unit(s)			
arithmetic mean	2.00		
standard deviation	± 0.87		
SAF activity score			
Units: unit(s)			
arithmetic mean	2.70		
standard deviation	± 1.29		
Liver stiffness measurement			
Units: kPa			
arithmetic mean	14.60		
standard deviation	± 10.66		
Controlled attenuation parameter			
Units: dB/m			
arithmetic mean	332.6		
standard deviation	± 57.5		
White blood cell count			
Units: 10/L			
arithmetic mean	7.09		
standard deviation	± 1.68		
Creatinine			
Units: mg/dL			
arithmetic mean	0.79		
standard deviation	± 0.20		
Urea			
Units: mmol/L			
arithmetic mean	5.10		
standard deviation	± 1.52		
D-dimers			
Units: mg/L			
arithmetic mean	0.33		
standard deviation	± 0.20		
Fibrinogen			
Units: mg/dL			
arithmetic mean	374.1		

standard deviation	± 90.9		
INR			
Units: ratio			
arithmetic mean	1.06		
standard deviation	± 0.10		
Platelets			
Units: 10/L			
arithmetic mean	188.0		
standard deviation	± 57.7		
Protein C			
Units: percentage			
arithmetic mean	104.2		
standard deviation	± 25.6		
Protein S			
Units: percentage			
arithmetic mean	95.5		
standard deviation	± 19.4		
Thrombin time			
Units: second			
arithmetic mean	17.0		
standard deviation	± 2.9		
Plasminogen activator inhibitor-1 activity			
Units: UA/mL			
arithmetic mean	23.8		
standard deviation	± 8.5		
Total bilirubin			
Units: mg/dL			
arithmetic mean	0.89		
standard deviation	± 0.55		
Alkaline phosphatase			
Units: U/L			
arithmetic mean	86.4		
standard deviation	± 29.2		
Alanine aminotransferase			
Units: U/L			
arithmetic mean	56.0		
standard deviation	± 29.5		
Aspartate aminotransferase			
Units: U/L			
arithmetic mean	42.2		
standard deviation	± 16.7		
γ-glutamyl transferase			
Units: U/L			
arithmetic mean	73.8		
standard deviation	± 45.8		
Fasting glucose			
Units: mmol/L			
arithmetic mean	7.57		
standard deviation	± 1.89		
Hemoglobin A1c			
Units: L/L			

arithmetic mean	6.39		
standard deviation	± 1.05		
High density lipoprotein			
Units: mmol/L			
arithmetic mean	1.06		
standard deviation	± 0.23		
Low density lipoprotein			
Units: mmol/L			
arithmetic mean	2.86		
standard deviation	± 1.25		
Triglyceride			
Units: mmol/L			
arithmetic mean	3.00		
standard deviation	± 1.83		
Total cholesterol			
Units: mmol/L			
arithmetic mean	4.67		
standard deviation	± 1.36		
Uric acid			
Units: µmol/L			
arithmetic mean	347.9		
standard deviation	± 86.8		
Hyaluronic acid			
Units: µg/L			
median	64.0		
full range (min-max)	12.0 to 329.0		
Tissue inhibitor of metalloproteinase-1			
Units: ng/L			
median	139.3		
full range (min-max)	63.7 to 243.3		
N-terminal propeptide of Type III collagen			
Units: U/mL			
median	0.94		
full range (min-max)	0.51 to 1.47		
C-reactive protein			
Units: mg/L			
median	2.80		
full range (min-max)	0.00 to 21.10		
Interleukin-6			
Units: pg/mL			
median	2.70		
full range (min-max)	0.93 to 7.88		
Adiponectin			
Units: µg/mL			
median	5.20		
full range (min-max)	2.52 to 10.47		
MELD-Na			
Units: score			
arithmetic mean	7.78		
standard deviation	± 1.62		
Child-Pugh			

Units: score			
arithmetic mean	5.13		
standard deviation	± 0.34		
CLIF-C AD			
Units: score			
arithmetic mean	43.0		
standard deviation	± 4.3		
APRI			
Aspartate aminotransferase to platelet ratio index			
Units: score			
arithmetic mean	0.64		
standard deviation	± 0.31		
FIB-4			
Fibrosis-4 (score)			
Units: score			
arithmetic mean	-0.10		
standard deviation	± 1.22		

End points

End points reporting groups

Reporting group title	Single arm - Dose Cohort 1
Reporting group description: Dose Cohort 1	
Reporting group title	Single arm - Dose Cohort 2
Reporting group description: Dose Cohort 2	
Reporting group title	Single arm - Dose Cohort 3
Reporting group description: Dose Cohort 3	
Reporting group title	Single arm - Dose Cohort 4
Reporting group description: Dose Cohort 4	
Reporting group title	Single arm - Dose Cohort 1
Reporting group description: Dose Cohort 1	
Reporting group title	Single arm - Dose Cohort 2
Reporting group description: Dose Cohort 2	
Reporting group title	Single arm - Dose Cohort 3
Reporting group description: Dose Cohort 3	
Reporting group title	Single arm - Dose Cohort 4
Reporting group description: Dose Cohort 4	
Reporting group title	Single arm - Dose Cohort 1
Reporting group description: Dose Cohort 1	
Reporting group title	Single arm - Dose Cohort 2
Reporting group description: Dose Cohort 2	
Reporting group title	Single arm - Dose Cohort 3
Reporting group description: Dose Cohort 3	
Reporting group title	Single arm - Dose Cohort 4
Reporting group description: Dose Cohort 4	
Reporting group title	Single arm - Dose Cohort 1
Reporting group description: Dose Cohort 1	
Reporting group title	Single arm - Dose Cohort 2
Reporting group description: Dose Cohort 2	
Reporting group title	Single arm - Dose Cohort 3
Reporting group description: Dose Cohort 3	
Reporting group title	Single arm - Dose Cohort 4

Reporting group description:
Dose Cohort 4

Reporting group title	Single arm - Dose Cohort 1

Reporting group description:
Dose Cohort 1

Reporting group title	Single arm - Dose Cohort 2

Reporting group description:
Dose Cohort 2

Reporting group title	Single arm - Dose Cohort 3

Reporting group description:
Dose Cohort 3

Reporting group title	Single arm - Dose Cohort 4

Reporting group description:
Dose Cohort 4

Reporting group title	Single arm - Dose Cohort 1

Reporting group description:
Dose Cohort 1

Reporting group title	Single arm - Dose Cohort 2

Reporting group description:
Dose Cohort 2

Reporting group title	Single arm - Dose Cohort 3

Reporting group description:
Dose Cohort 3

Reporting group title	Single arm - Dose Cohort 4

Reporting group description:
Dose Cohort 4

Reporting group title	Single arm - Dose Cohort 1

Reporting group description:
Dose Cohort 1

Reporting group title	Single arm - Dose Cohort 2

Reporting group description:
Dose Cohort 2

Reporting group title	Single arm - Dose Cohort 3

Reporting group description:
Dose Cohort 3

Reporting group title	Single arm - Dose Cohort 4

Reporting group description:
Dose Cohort 4

Reporting group title	Single arm - Dose Cohort 1

Reporting group description:
Dose Cohort 1

Reporting group title	Single arm - Dose Cohort 2

Reporting group description:
Dose Cohort 2

Reporting group title	Single arm - Dose Cohort 3

Reporting group description:
Dose Cohort 3

Reporting group title	Single arm - Dose Cohort 4

Reporting group description:
Dose Cohort 4

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

Subject analysis set description:

The Safety analysis set (SAF) included all patients entered in the study who received at least one dose of the IMP.

Primary: Adverse events reported up to Day 28 assessed for seriousness, severity, relationship to the IMP and/or IMP administration procedure

End point title	Adverse events reported up to Day 28 assessed for seriousness, severity, relationship to the IMP and/or IMP administration procedure[1]

End point description:

Safety assessments from the time of signing the ICF through the Day 28 Visit included:
- Adverse events/Treatment-emergent adverse events
- Physical examination
- Imaging
- Vital signs
- Local laboratory measurements

End point type	Primary

End point timeframe:

Up to Day 28

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 statistics.
The study was not powered with respect to any specific hypothesis.
Incidence of specific AEs and SAEs are tabulated as count and percentage, broken down by dose level.

End point values	Safety analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: Number of cases	28			

Attachments (see zip file)	HEP201_Primary Safety Endpoint_20231121_AEs up to D28. HEP201_Primary Safety Endpoint_20231121_AEs up to D28_T.

Statistical analyses

No statistical analyses for this end point

Secondary: AEs reported up to Month 6 assessed for seriousness, severity, relationship to the IMP and/or IMP administration procedure

End point title	AEs reported up to Month 6 assessed for seriousness, severity, relationship to the IMP and/or IMP administration procedure

End point description:

Secondary safety assessments included:
- AEs reported up to Month 6 post infusion assessed for seriousness, severity, relationship to the IMP and/or IMP administration procedure

End point type	Secondary

End point timeframe:

Up to Month 6

End point values	Safety analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: Number of cases	48			

Attachments (see zip file)	HEP201_Secondary Safety Endpoint_20231121_3_TEAEs up to HEP201_Secondary Safety Endpoint_20231121_3_TEAEs up to

Statistical analyses

No statistical analyses for this end point

Secondary: Presence of anti-HLA antibodies (Abs) and identification of donor HLA specificity

End point title	Presence of anti-HLA antibodies (Abs) and identification of donor HLA specificity

End point description:

To understand better the effects HepaStem on immunogenicity development, anti-HLA Abs (class I and II) were assessed (specificity identification and quantification) in serum samples collected before infusion as well as on Day 28, Month 3, and Month 6 by Luminex method in a Central laboratory. The threshold for detection was set at a mean Fluorescence intensity (MFI) > 1500. MFI > 5000 was considered as clinically significant level.

End point type	Secondary

End point timeframe:

Up to Month 6

End point values	Safety analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: Number of patients with anti-HLA Abs	7			

Attachments (see zip file)	HEP201_Secondary Safety Endpoint_20231121_1_HLA.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Coagulation tests up to 24 hours post infusion

End point title	Coagulation tests up to 24 hours post infusion

End point description:

Local laboratory measurements included platelet counts, and levels of fibrinogen, INR, aPTT, D-dimer, TT, protein C, and protein S.
Central laboratory measurements included plasminogen activator inhibitor-1 (PAI-1) activity.
Laboratory measurements were carried out by standard, validated, and widely used methods.
All blood samples for the safety laboratory tests had to be taken in a fasting state.
Concentrations are expressed in mg/L (D-dimers), mg/dL (fibrinogen). G/L (platelet counts), % (Protein C and Protein S), seconds (TT and aPTT), UA/mL (PAI-1).
INR has no unit.

End point type	Secondary

End point timeframe:

Up to 24 hours post infusion

End point values	Single arm - Dose Cohort 1	Single arm - Dose Cohort 2	Single arm - Dose Cohort 3	Single arm - Dose Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	7	4
Units: concentration or ratio				
arithmetic mean (standard deviation)				
D-dimers	0.37 (± 0.17)	0.35 (± 0.15)	0.26 (± 0.15)	0.34 (± 0.38)
Fibrinogen	375.3 (± 58.1)	369.8 (± 145.5)	409.7 (± 57.3)	316.1 (± 75.2)
INR	1.01 (± 0.05)	1.10 (± 0.11)	1.02 (± 0.10)	1.17 (± 0.08)
Platelet count	189.0 (± 65.8)	174.7 (± 63.0)	206.3 (± 45.9)	174.6 (± 70.8)
Protein C	113.8 (± 27.0)	89.4 (± 25.1)	105.8 (± 6.4)	105.8 (± 41.1)
Protein S	97.3 (± 27.4)	101.4 (± 13.0)	92.0 (± 20.2)	90.4 (± 15.3)
TT	18.2 (± 2.6)	17.4 (± 3.7)	14.9 (± 3.0)	15.9 (± 1.2)
PAI-1	26.0 (± 5.7)	18.8 (± 7.7)	25.8 (± 11.3)	24.7 (± 7.0)
aPTT	28.5 (± 2.1)	28.9 (± 3.8)	27.2 (± 13.0)	27.8 (± 3.5)

End point values	Single arm - Dose Cohort 1	Single arm - Dose Cohort 2	Single arm - Dose Cohort 3	Single arm - Dose Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	7	4
Units: concentration or ratio				
arithmetic mean (standard deviation)				
D-dimers	0.43 (± 0.17)	0.67 (± 0.49)	0.45 (± 0.32)	0.63 (± 0.53)
Fibrinogen	334.3 (± 61.5)	359.5 (± 125.1)	392.1 (± 57.7)	323.7 (± 80.1)
INR	1.05 (± 0.06)	1.10 (± 0.13)	1.03 (± 0.06)	1.18 (± 0.08)
Platelet count	183.2 (± 66.2)	172.8 (± 64.9)	212.6 (± 53.7)	174.7 (± 81.0)
Protein C	113.2 (± 25.7)	83.6 (± 18.3)	106.5 (± 8.6)	104.5 (± 50.9)
Protein S	98.0 (± 22.1)	96.2 (± 6.5)	87.6 (± 21.2)	88.9 (± 17.9)
TT	18.6 (± 2.4)	16.7 (± 2.5)	16.7 (± 4.5)	17.1 (± 1.2)
PAI-1	19.8 (± 7.6)	17.2 (± 9.5)	22.1 (± 7.5)	21.1 (± 14.3)
aPTT	27.9 (± 2.1)	27.5 (± 3.2)	25.8 (± 12.0)	26.6 (± 2.8)

End point values	Single arm - Dose Cohort 3	Single arm - Dose Cohort 4	Single arm - Dose Cohort 3	Single arm - Dose Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	4	6	4
Units: concentration or ratio				
arithmetic mean (standard deviation)				
D-dimers	0.40 (± 0.32)	0.36 (± 0.32)	0.63 (± 0.61)	0.90 (± 0.48)
Fibrinogen	423.6 (± 86.2)	349.0 (± 92.3)	398.3 (± 80.2)	360.9 (± 131.0)
INR	1.02 (± 0.08)	1.015 (± 0.13)	1.05 (± 0.10)	1.15 (± 0.09)
Platelet count	220.1 (± 44.1)	175.3 (± 90.1)	194.0 (± 49.4)	149.0 (± 56.7)
Protein C	104.6 (± 14.2)	107.2 (± 37.0)	103.2 (± 14.7)	107.0 (± 35.1)
Protein S	94.0 (± 37.6)	90.2 (± 19.0)	78.1 (± 18.9)	88.8 (± 24.5)
TT	15.7 (± 3.3)	18.3 (± 3.4)	13.1 (± 4.2)	17.4 (± 1.8)
PAI-1	25.8 (± 11.0)	26.0 (± 7.0)	17.3 (± 4.5)	20.7 (± 6.4)
aPTT	25.3 (± 12.1)	28.5 (± 2.7)	25.8 (± 13.0)	26.9 (± 4.0)

End point values	Single arm - Dose Cohort 3	Single arm - Dose Cohort 4	Single arm - Dose Cohort 3	Single arm - Dose Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	4	7	3
Units: concentration or ratio				
arithmetic mean (standard deviation)				
D-dimers	2.06 (± 4.53)	0.57 (± 0.40)	2.18 (± 3.73)	1.06 (± 0.82)
Fibrinogen	407.1 (± 71.3)	344.9 (± 73.3)	413.0 (± 46.1)	369.0 (± 140.1)
INR	1.00 (± 0.07)	1.15 (± 0.14)	1.05 (± 0.06)	1.15 (± 0.11)
Platelet count	242.4 (± 49.3)	174.5 (± 93.1)	219.0 (± 52.6)	204.7 (± 112.6)
Protein C	107.0 (± 13.5)	107.1 (± 33.5)	101.6 (± 11.6)	107.9 (± 39.2)
Protein S	98.1 (± 11.2)	81.3 (± 6.9)	92.3 (± 12.5)	91.6 (± 18.1)
TT	17.8 (± 4.7)	16.8 (± 1.0)	18.0 (± 4.4)	16.4 (± 1.7)
PAI-1	25.7 (± 10.0)	24.5 (± 7.4)	21.4 (± 5.9)	20.1 (± 5.8)
aPTT	26.7 (± 12.9)	27.8 (± 2.9)	24.7 (± 11.8)	27.2 (± 4.3)

Attachments (see zip file)	HEP201_Secondary Safety Endpoint_20231121_2_Coagulation.

Statistical analyses

No statistical analyses for this end point

Secondary: Composite scores for disease stage: MELD, Child-Pugh and CLIF-C AD (for F4 decompensated) scores

End point title	Composite scores for disease stage: MELD, Child-Pugh and CLIF-C AD (for F4 decompensated) scores

End point description:

Original and new MELD(-Na) scores, Child-Pugh score, and chronic liver failure consortium acute decompensation (CLIF-C AD) score (for F4 decompensated) were calculated based on the various exams performed.

End point type	Secondary

End point timeframe:

Up to Month 6

End point values	Single arm - Dose Cohort 1	Single arm - Dose Cohort 2	Single arm - Dose Cohort 3	Single arm - Dose Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	7	4
Units: score				
arithmetic mean (standard deviation)				
New MELD (MELD-Na)	7.3 (± 0.8)	8.3 (± 2.0)	7.0 (± 1.2)	9.0 (± 2.2)
Child-Pugh	5.0 (± 0.0)	5.2 (± 0.4)	5.1 (± 0.4)	5.3 (± 0.5)
CLIF-C AD	43.2 (± 6.4)	43.7 (± 3.1)	42.3 (± 3.0)	43.3 (± 5.4)

End point values	Single arm - Dose Cohort 1	Single arm - Dose Cohort 2	Single arm - Dose Cohort 3	Single arm - Dose Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	5	7	3
Units: score				
arithmetic mean (standard deviation)				
New MELD (MELD-Na)	7.7 (± 1.2)	8.4 (± 1.1)	6.9 (± 0.7)	7.3 (± 0.6)
Child-Pugh	5.0 (± 0.0)	5.0 (± 0.0)	5.0 (± 0.0)	5.0 (± 0.0)
CLIF-C AD	43.5 (± 4.8)	43.0 (± 3.1)	42.4 (± 2.6)	41.0 (± 5.3)

End point values	Single arm - Dose Cohort 1	Single arm - Dose Cohort 2	Single arm - Dose Cohort 3	Single arm - Dose Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	4	6	3
Units: score				
arithmetic mean (standard deviation)				
New MELD (MELD-Na)	7.3 (± 0.8)	6.8 (± 0.5)	6.7 (± 0.5)	7.3 (± 1.2)
Child-Pugh	5.0 (± 0.0)	5.0 (± 0.0)	5.0 (± 0.0)	5.0 (± 0.0)
CLIF-C AD	45.5 (± 4.5)	43.8 (± 1.5)	43.0 (± 2.4)	39.3 (± 5.1)

Attachments (see zip file)	HEP201_Secondary Efficacy Endpoint_20231121_1_Scores.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Quantitative assessment of liver function

End point title	Quantitative assessment of liver function

End point description:

Local laboratory measurements for liver function included levels of bilirubin, ALT, AST, GGT, ALP, and albumin.
Laboratory measurements were carried out by standard, validated, and widely used methods.
Total bilirubin is expressed in mg/dL, liver enzymes in U/L, albumin in g/L.

End point type	Secondary

End point timeframe:

Up to Month 6

End point values	Single arm - Dose Cohort 1	Single arm - Dose Cohort 2	Single arm - Dose Cohort 3	Single arm - Dose Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	7	4
Units: concentration				
arithmetic mean (standard deviation)				
Total bilirubin	0.66 (± 0.26)	1.17 (± 0.59)	0.71 (± 0.42)	1.09 (± 0.87)
ALP	76.0 (± 18.0)	83.3 (± 22.9)	97.4 (± 39.4)	87.5 (± 35.1)
ALT	64.5 (± 29.9)	44.8 (± 34.4)	63.4 (± 26.9)	47.3 (± 28.6)
AST	50.5 (± 23.0)	38.9 (± 15.6)	41.4 (± 12.3)	35.8 (± 15.5)
GGT	72.4 (± 35.1)	84.9 (± 47.7)	64.1 (± 57.9)	76.0 (± 48.4)

End point values	Single arm - Dose Cohort 1	Single arm - Dose Cohort 2	Single arm - Dose Cohort 3	Single arm - Dose Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	7	3
Units: concentration				
arithmetic mean (standard deviation)				
Total bilirubin	0.69 (± 0.31)	0.90 (± 0.39)	0.69 (± 0.35)	0.67 (± 0.15)
ALP	75.7 (± 22.2)	93.5 (± 21.7)	92.6 (± 35.9)	70.0 (± 10.6)
ALT	62.3 (± 23.7)	41.7 (± 33.3)	50.7 (± 22.1)	45.0 (± 21.6)
AST	48.4 (± 13.8)	36.7 (± 14.7)	43.6 (± 22.6)	38.3 (± 16.9)
GGT	69.7 (± 31.1)	89.3 (± 48.0)	59.6 (± 51.3)	46.3 (± 17.1)

End point values	Single arm - Dose Cohort 1	Single arm - Dose Cohort 2	Single arm - Dose Cohort 3	Single arm - Dose Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	4	7	3
Units: concentration				
arithmetic mean (standard deviation)				
Total bilirubin	0.61 (± 0.16)	0.78 (± 0.15)	0.72 (± 0.30)	0.26 (± 0.13)
ALP	85.0 (± 20.5)	85.8 (± 7.4)	92.6 (± 36.4)	82.3 (± 19.9)

ALT	57.2 (± 38.4)	36.0 (± 14.7)	54.0 (± 31.6)	33.7 (± 1.5)
AST	43.3 (± 20.0)	37.5 (± 8.7)	43.4 (± 23.6)	32.3 (± 8.1)
GGT	74.5 (± 39.1)	74.0 (± 60.8)	62.0 (± 65.5)	92.7 (± 88.6)

Attachments (see zip file)	HEP201_Secondary Efficacy Endpoint_20231121_2_Liver

Statistical analyses

No statistical analyses for this end point

Secondary: Quantitative assessment of metabolic biomarkers and clinical signs

End point title	Quantitative assessment of metabolic biomarkers and clinical signs

End point description:

Local laboratory measurements for metabolic biomarkers included levels of glucose, insulin, total cholesterol, LDL, HDL, triglycerides, uric acid, and HbA1C.
Waist circumference and BMI (except in decompensated patients with ascites) were also measured or calculated.
Laboratory measurements were carried out by standard, validated, and widely used methods.
Fasting glucose is expressed in mmol/L, fasting insulin in pmol/L, HDL, LDL, total cholesterol and triglycerides in mmol/L, uric acid in µmol/L, creatinine in mg.dL.

End point type	Secondary

End point timeframe:

Up to Month 6

End point values	Single arm - Dose Cohort 1	Single arm - Dose Cohort 2	Single arm - Dose Cohort 3	Single arm - Dose Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	7	4
Units: concentration or length				
arithmetic mean (standard deviation)				
Fasting glucose	7.15 (± 1.76)	8.51 (± 2.67)	7.20 (± 1.48)	7.38 (± 1.36)
Fasting insulin	349 (± 315)	201 (± 135)	153 (± 45)	338 (± 297)
HDL	1.08 (± 0.22)	0.94 (± 0.24)	1.10 (± 0.22)	1.16 (± 0.24)
LDL	3.26 (± 0.87)	1.98 (± 0.80)	2.46 (± 1.18)	4.28 (± 1.18)
Total cholesterol	5.48 (± 1.06)	3.72 (± 0.85)	4.06 (± 1.23)	5.96 (± 1.16)
Triglycerides	3.23 (± 2.23)	1.75 (± 0.84)	1.27 (± 0.44)	1.98 (± 1.3)
Uric acid	394 (± 109)	323 (± 69)	304 (± 59)	393 (± 88)
Creatinine	0.97 (± 0.21)	0.78 (± 0.22)	0.65 (± 0.10)	0.76 (± 0.09)

End point values	Single arm - Dose Cohort 1	Single arm - Dose Cohort 2	Single arm - Dose Cohort 3	Single arm - Dose Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	7	3
Units: concentration or length				
arithmetic mean (standard deviation)				

Fasting glucose	6.67 (± 1.70)	7.22 (± 1.62)	7.06 (± 2.93)	6.14 (± 1.21)
Fasting insulin	274 (± 156)	142 (± 59)	233 (± 154)	301 (± 329)
HDL	1.16 (± 0.18)	0.98 (± 0.26)	1.12 (± 0.21)	1.11 (± 0.24)
LDL	2.89 (± 0.59)	2.06 (± 0.78)	2.51 (± 1.11)	3.89 (± 0.97)
Total cholesterol	5.11 (± 1.20)	3.71 (± 0.82)	4.26 (± 1.15)	5.41 (± 0.34)
Triglycerides	2.45 (± 1.96)	1.47 (± 0.56)	1.48 (± 0.33)	1.74 (± 0.77)
Uric acid	376 (± 103)	302 (± 48)	315 (± 46)	408 (± 87)
Creatinine	1.02 (± 0.22)	0.77 (± 0.26)	0.69 (± 0.09)	0.73 (± 0.13)

End point values	Single arm - Dose Cohort 1	Single arm - Dose Cohort 2	Single arm - Dose Cohort 3	Single arm - Dose Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	4	7	3
Units: concentration or length				
arithmetic mean (standard deviation)				
Fasting glucose	6.32 (± 1.09)	7.69 (± 2.25)	6.64 (± 0.87)	6.84 (± 1.68)
Fasting insulin	214 (± 150)	313 (± 295)	246 (± 240)	277 (± 273)
HDL	1.30 (± 0.29)	1.17 (± 0.22)	1.05 (± 0.18)	1.24 (± 0.23)
LDL	3.51 (± 0.73)	2.55 (± 0.84)	2.55 (± 1.22)	3.67 (± 1.40)
Total cholesterol	5.90 (± 1.14)	4.36 (± 0.82)	4.10 (± 1.18)	5.43 (± 1.31)
Triglycerides	2.32 (± 1.09)	1.37 (± 0.34)	1.27 (± 0.28)	1.28 (± 0.18)
Uric acid	346 (± 106)	322 (± 71)	308 (± 77)	352 (± 25)
Creatinine	0.99 (± 0.14)	0.68 (± 0.09)	0.67 (± 0.10)	0.67 (± 0.17)

Attachments (see zip file)	HEP201_Secondary Efficacy Endpoint_20231121_3_Metabolism

Statistical analyses

No statistical analyses for this end point

Secondary: Quantitative assessment of liver fibrosis biomarkers and stiffness

End point title	Quantitative assessment of liver fibrosis biomarkers and stiffness

End point description:

Liver stiffness and liver steatosis were simultaneously evaluated using non-invasive ultrasound imaging Fibroscan® 530 Compact or 502 Touch (Echosens, Paris, France) or with the Logiq S8 XDclear 2.0 ultrasound system with Integrated Liver Package (GE Healthcare and Echosens).
Liver stiffness measurement (LSM) was evaluated by vibration-controlled transient elastography (TE).
Fibrosis scores as non-invasive tests based on serum markers have limited value for definitive diagnosis of liver fibrosis; however, they help to rule-in or rule-out advanced fibrosis especially iin combination with TE.
Simple non-patented fibrosis scores were calculated.

End point type	Secondary

End point timeframe:

Up to Month 6

End point values	Single arm - Dose Cohort 1	Single arm - Dose Cohort 2	Single arm - Dose Cohort 3	Single arm - Dose Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	7	4
Units: unit(s)				
arithmetic mean (standard deviation)				
NAFLD score	-0.12 (± 1.35)	0.10 (± 1.26)	-0.43 (± 0.60)	0.23 (± 2.02)
FIB-4	2.03 (± 1.24)	2.01 (± 0.76)	1.60 (± 0.30)	2.16 (± 1.34)
APRI	0.73 (± 0.50)	0.63 (± 0.26)	0.56 (± 0.17)	0.65 (± 0.30)

End point values	Single arm - Dose Cohort 1	Single arm - Dose Cohort 2	Single arm - Dose Cohort 3	Single arm - Dose Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	7	3
Units: unit(s)				
arithmetic mean (standard deviation)				
NAFLD score	-0.34 (± 1.62)	0.22 (± 1.14)	-0.61 (± 0.59)	-0.60 (± 2.19)
FIB-4	1.83 (± 0.87)	1.95 (± 0.93)	1.70 (± 0.61)	1.65 (± 1.34)
APRI	0.60 (± 0.36)	0.58 (± 0.21)	0.55 (± 0.30)	0.54 (± 0.27)

End point values	Single arm - Dose Cohort 1	Single arm - Dose Cohort 2	Single arm - Dose Cohort 3	Single arm - Dose Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	4	7	3
Units: unit(s)				
arithmetic mean (standard deviation)				
NAFLD score	-0.37 (± 1.48)	0.04 (± 0.90)	-0.23 (± 0.64)	0.50 (± 2.60)
FIB-4	1.74 (± 0.69)	1.81 (± 0.82)	1.83 (± 0.56)	3.06 (± 2.14)
APRI	0.55 (± 0.34)	0.53 (± 0.20)	0.60 (± 0.33)	0.74 (± 0.43)

Attachments (see zip file)	HEP201_Secondary Efficacy Endpoint_20231121_4_Fibrosis

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Month 6 post infusion

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Safety analysis set (SAF)

Reporting group description: -

Serious adverse events	Safety analysis set (SAF)		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 23 (17.39%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatic mass	Additional description: Since a lesion of undetermined nature was already present at the same location and with the same size in repeated ultrasound images before study participation, the Sponsor assessed the event as not related to the IMP.		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Prostate cancer	Additional description: The event of prostatic adenocarcinoma occurred 223 days after the single administration of the study drug. The temporal relationship regarding the IMP was considered implausible. The event was assessed as unlikely related to the IMP.		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Ischaemic stroke	Additional description: Five days after the 2nd infusion, the patient experienced an ischemic stroke of mild severity that completely resolved 6 days after the event onset and that was assessed as possibly related to the pre-existing condition of arterial hypertension & T2D		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			

Renal colic	Additional description: Forty-three days after the first infusion, the patient experienced reno-ureteral colic of mild severity that resolved with analgesic treatment on the day after the event onset. The temporal relationship with the IMP was considered implausible.		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Safety analysis set (SAF)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 23 (78.26%)		
Investigations			
Fibrin D dimer increased			
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	2		
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 23 (13.04%)		
occurrences (all)	3		
Tremor			
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	2		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	6 / 23 (26.09%)		
occurrences (all)	7		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	3 / 23 (13.04%)		
occurrences (all)	3		
Diarrhoea			
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	2		
Toothache			
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 August 2019	Study protocol v2.0 dated 29-AUG-2019: • The denomination of the IMP was updated from Heterologous Human Adult Liver-Derived Progenitor Cells (HHALPC) to Human Allogenic Liver-Derived Progenitor Cells (HALPC) • The exclusion criterion relative to the use (rather than the refusal to use) of highly effective (rather than reliable) contraceptive methods (Exclusion criterion #30) was updated. • The total volume of blood collected during the study procedures was added • A summary of potential risks and benefits was added • The DLT definition was updated not to limit it to 2 identical serious events • A 4-day safety period between each patient was added for Dose Cohorts 1 and 2 • A safety period between each patient for sequential management was defined for Dose Cohorts 3 and 4 • A negative pregnancy test for female patients of childbearing potential was added as eligibility infusion criterion • It was clarified that the laboratory urine pregnancy test was only applicable for female patients of childbearing potential
10 December 2019	Study protocol v3.0 dated 10-DEC-2019: • Additional patients with more advanced cirrhotic F4 NASH were envisaged and 2 additional dose cohorts (5 and 6) were added; other sections in the protocol were adapted accordingly • Some exploratory endpoints were removed because they were already described elsewhere • Exclusion criterion #2 relative to alcohol consumption was updated • Exclusion criterion #17 and #18 were merged and the numbering of subsequent exclusion criteria was adapted accordingly • Exclusion criterion #29 relative to known hypersensitivity to some antibiotics was added • Switzerland was added as participating country • The recommendation to consult the Summary of product characteristics (SmPCs) of corticosteroids used as preventive pre-medication was added • A sub-section relative to the notification of new facts was added in Section 12.2.10 • The sub-section relative to interim analysis was clarified

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported