Clinical trial results:
Human Liver Stem Cells (HLSCs) in patients suffering from liver-based inborn metabolic diseases causing life-threatening neonatal onset of hyperammonemic encephalopathy

Summary

EudraCT number	2012-002120-33
Trial protocol	IT
Global end of trial date	18 July 2017

Results information

Result version number	v1 (current)
This version publication date	14 August 2021
First version publication date	14 August 2021
Summary attachment (see zip file)	Intrahepatic Administration of Human Liver Stem Cells in Infants with Inherited Neonatal-Onset Hyperammonemia: A Phase I Study (Stem Cell Rev Rep. 2020 Feb16(1)-186-197..pdf)

Trial information

Trial identification

Sponsor protocol code	HLSCS01-11

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino
Sponsor organisation address	Corso Bramante 88, Torino, Italy, 10126
Public contact	Dr. Marco Spada, Centro Malattie Metaboliche/ Presidio Ospedaliero Regina Margherita, 39 0113135857, marco.spada@unito.it
Scientific contact	Dr. Marco Spada, Centro Malattie Metaboliche/ Presidio Ospedaliero Regina Margherita, 39 0113135857, marco.spada@unito.it

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	18 July 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 July 2017
Global end of trial reached?	Yes
Global end of trial date	18 July 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate hepatic and extra-hepatic complications after liver intraparenchymal HLSC injection in neonates suffering from inborn liver metabolic diseases causing life-threatening neonatal-onset of hyperammonemic encephalopathy

Protection of trial subjects:

a total of two injections was administered, the first one as soon as the patient entered the study. The second admnistration had to be performed one week after the first, only in the absence of adverse events related to the first treatment. Each patient was regularly followed for clinical and laboratory aspects. Treatment was to be terminated in the following events: completion of 2 injections, unacceptable toxicity or withdrawal of consent.

Background therapy:

Standard of care

Evidence for comparator: -

Actual start date of recruitment	05 October 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Ethical reason, Regulatory reason, Scientific research
Long term follow-up duration	1 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 3
Worldwide total number of subjects	3
EEA total number of subjects	3

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)	3
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

start date 10 Feb 2014; end date 18 Jan 2017

Pre-assignment

Screening details:

Inclusion criteria: neonatal-onset hyperammonemic encephalopathy; formal biochemical diagnosis of one inborn metabolic disease (CPS1-, OTC-, ASS-, PCC-, MCM-, ASL-deficiency); formal evaluation for early OLT; be referred to OIRM, Centro Malattie Metaboliche, TO;
Exclusion criteria: refusal of signing informed consent; uncontrolled coagulopathy.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Baseline to dose level 1

Arm description:

baseline to subjects treated with 125,000 HLSC cells x gram of liver

Arm type	Experimental
Investigational medicinal product name	HLSC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intrahepatic use

Dosage and administration details:

two doses of 125,000 HLSC cells x gram of liver administered at two weeks interval

Arm title	Baseline to dose level 2

Arm description:

baseline to subjects treated with 250,000 HLSC cells x gram of liver

Arm type	Experimental
Investigational medicinal product name	HLSC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intrahepatic use

Dosage and administration details:

two doses of 250,000 HLSC cells x gram of liver administered at two weeks interval

Number of subjects in period 1	Baseline to dose level 1	Baseline to dose level 2
Started	1	2
Completed	1	2

Period 2	
Period 2 title	treatment
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms	
Are arms mutually exclusive?	Yes
Arm title	dose level 1

Arm description:
subjects treated with 125,000 HLSC cells x gram of liver

Arm type	Experimental
Investigational medicinal product name	HLSC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intrahepatic use

Dosage and administration details:
two doses of 125,000 HLSC cells x gram of liver administered at two weeks interval

Arm title	dose level 2

Arm description:
subjects treated with 250,000 HLSC cells x gram of liver

Arm type	Experimental
Investigational medicinal product name	HLSC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intrahepatic use

Dosage and administration details:
two doses of 250,000 HLSC cells x gram of liver administered at two weeks interval

Number of subjects in period 2	dose level 1	dose level 2
Started	1	2
Completed	1	2

Baseline characteristics

Reporting groups	
Reporting group title	baseline

Reporting group description:

A total of 3 subjects were screened and entered into the study. No significant differences between subjects of the two treatment groups were observed with respect to age, height and body weight. Subjects underwent a physical examination, instrumental examinations and measurement of vital signs at the screening visit. Moreover a series of pathological values were examined in order to perform the diagnosis for metabolic disease.
Of note, at physical examination all patients presented hypotonia. All reported positive history for at least one abnormality at the Hematological system (anemia) and at the Neurological system (commonly hyperammonemia / hyperammonemic comas). All abnormalities were continuing at the time of the study entry, except for the neonatal hyperammonemia / hyperammonemic comas, which were resolved before the signature of the informed consent.

Reporting group values	baseline	Total	
Number of subjects	3	3	
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)	3	3	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
A total of 3 subjects were screened. All entered into the study			
Units: months			
arithmetic mean	2.90		
standard deviation	± 1.62	-	
Gender categorical Units: Subjects			
Female	2	2	
Male	1	1	

End points

End points reporting groups

Reporting group title	Baseline to dose level 1
Reporting group description: baseline to subjects treated with 125,000 HLSC cells x gram of liver	
Reporting group title	Baseline to dose level 2
Reporting group description: baseline to subjects treated with 250,000 HLSC cells x gram of liver	
Reporting group title	dose level 1
Reporting group description: subjects treated with 125,000 HLSC cells x gram of liver	
Reporting group title	dose level 2
Reporting group description: subjects treated with 250,000 HLSC cells x gram of liver	

Primary: Hepatic complications

End point title	Hepatic complications[1]
End point description: portal vein thrombosis, intrahepatic hematoma, injury of the hepatic artery, arterio-portal, portal-biliary and arterio-biliary fistula, acute hepatic cytolysis > 20 times normal, clinical and biochemical signs of liver failure (ascites, development of jaundice with conjugated bilirubin above 3 mg/dL, alterations in INR > 2.5), appearance of cancer-like liver nodular lesions	
End point type	Primary
End point timeframe: from the administration of the first dose (V1) to 4 weeks after the administration of the second dose (V4).	

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: The total study population was 3 subjects.
Descriptive statistics (e.g., mean, standard deviation, minimum, maximum for continuous data; frequency tables for categorical data) are provided per dose level and overall.
Summary statistics were provided per dose level and overall.
Summary statistics: quantitative parameters were summarized using descriptive statistics: N, Mean, Median, STD,Minimum, Maximum; qualitative parameters were summarized using frequency tables: N and percentage (%).

End point values	dose level 1	dose level 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	2		
Units: number of events	1	2		

Attachments (see zip file)	Overall summary of Adverse Events.pdf Summary of Adverse Events, by patient and overall.pdf Category of Adverse Events, by patient and overall.pdf

Statistical analyses

No statistical analyses for this end point

Primary: Extra-hepatic complications

End point title	Extra-hepatic complications[2]

End point description:

pulmonary embolism, significant extra-hepatic (abdominal and/or chest) haemorrhage (requiring blood transfusion and / or specific treatment), documented sepsis with bacteremia, adverse reactions to sedative drugs administered for interventional radiological procedure

End point type	Primary

End point timeframe:

from the administration of the first dose (V1) to 4 weeks after the administration of the second dose (V4).

Notes:

[2] - 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: The total study population was 3 subjects.
Descriptive statistics (e.g., mean, standard deviation, minimum, maximum for continuous data; frequency tables for categorical data) are provided per dose level and overall.
Summary statistics were provided per dose level and overall.
Summary statistics: quantitative parameters were summarized using descriptive statistics: N, Mean, Median, STD,Minimum, Maximum; qualitative parameters were summarized using frequency tables: N and percentage (%).

End point values	dose level 1	dose level 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	2		
Units: number of events	1	2		

Attachments (see zip file)	Overall summary of Adverse Events/Overall summary of Summary of Adverse Events, by patient and overall/Summary Category of Adverse Events, by patient and overall/Category of

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: adverse events assessment started at baseline (signature of Informed Consent) and ended at the last visit (V4), 4 weeks after the administration of last dose.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20

Reporting groups	
Reporting group title	dose level 1
Reporting group description: subjects with two doses of 125,000 HLSC cells x gram of liver, administered at 2 weeks interval	
Reporting group title	dose level 2
Reporting group description: subjects with two doses of 250,000 HLSC cells x gram of liver, administered at 2 weeks interval	

Serious adverse events	dose level 1	dose level 2	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)	0 / 2 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	dose level 1	dose level 2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)	2 / 2 (100.00%)	
Nervous system disorders			
Agitation neonatal			
subjects affected / exposed	1 / 1 (100.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Tremor			
subjects affected / exposed	0 / 1 (0.00%)	1 / 2 (50.00%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			

Thrombocytosis			
subjects affected / exposed	1 / 1 (100.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Eyelid oedema			
subjects affected / exposed	1 / 1 (100.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 1 (100.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	0 / 1 (0.00%)	1 / 2 (50.00%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	1 / 1 (100.00%)	1 / 2 (50.00%)	
occurrences (all)	1	1	
Rash			
subjects affected / exposed	0 / 1 (0.00%)	1 / 2 (50.00%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Leukocyturia			
subjects affected / exposed	1 / 1 (100.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	0 / 1 (0.00%)	2 / 2 (100.00%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 September 2014	n. 1 : to include into the study patients affected by Deficiency of argininosuccinate lyase (ASL) (protocol Version 1.2 26 aug 2014)
08 June 2016	n. 2: to extend product expiration date to 36 months (IMPD Quality Report HLSCs_Drug substance and drug product", Vers. Final 1.1_17.02.16)

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/31792768