Clinical trial results:
Combined drug Approach to Prevent Ischemia-reperfusion injury during Transplantation of Livers (CAPITL): a first-in-men study

Summary

EudraCT number	2012-001960-31
Trial protocol	BE
Global end of trial date	14 February 2019

Results information

Result version number	v1 (current)
This version publication date	28 March 2023
First version publication date	28 March 2023

Trial information

Trial identification

Sponsor protocol code	S54348

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02251041
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UZLeuven
Sponsor organisation address	Herestraat 49, Leuven, Belgium,
Public contact	Diethard Monbaliu, UZ Leuven, +32 (0)16342361, diethard.monbaliu@uzleuven.be
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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	14 February 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 February 2019
Global end of trial reached?	Yes
Global end of trial date	14 February 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate
- the safety of the drug combination/multifactorial modulation
- the effectiveness of the drug combination/multifactorial modulation in reducing the peak of aspartate amino transferase (AST) – a surrogate marker of ischemia-reperfusion injury (IRI) - after liver transplantation.

Protection of trial subjects:

Trial subjects were monitored closely in the first days after intervention.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 August 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 72
Worldwide total number of subjects	72
EEA total number of subjects	72

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)	45
From 65 to 84 years	27
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Adults waitlisted for a first solitary full-size liver transplantation were considered for enrollment at the time of liver offer. Each patient participating in the trial gave his/her informed consent prior to entry into the trial.

Pre-assignment

Screening details:

Out of 310 screened subjects, 93 were found eligible, enrolled and randomized; 21 subjects were excluded (1 screen failure, 20 technical failures), resulting in 36 subjects per study arm.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	combined drug approach

Arm description:

In the study arm, a combined-drug approach was given in addition to standard-of-care: following static cold preservation, donor livers were infused with epoprostenol (ex-situ, portal vein); recipients were given oral α-tocopherol and melatonin prior to anesthesia, and intravenous anti-thrombin-III, infliximab, apotransferrin, recombinant erythropoietin-β, c1-inhibitor and glutathione during the anhepatic and reperfusion phase.

Arm type	Experimental
Investigational medicinal product name	C1-inhibitor
Investigational medicinal product code	
Other name	Cetor, Cinryze®
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dosage: 1000 U
Way and duration of administration: IV – 5 minutes
Timing of administration: 10 minutes before reperfusion

Investigational medicinal product name	Antithrombin III
Investigational medicinal product code	
Other name	Atenativ®
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dose: 3000 IU
Way and duration of administration: IV – 15 minutes
Timing of administration: Start of anhepatic phase

Investigational medicinal product name	EPO-β
Investigational medicinal product code	
Other name	Neorecormon®
Pharmaceutical forms	Solution for injection/infusion in pre-filled syringe
Routes of administration	Intravenous use

Dosage and administration details:

Dosage: 30.000 IU + 30.000 IU

Way and duration of administration: IV – 2 minutes
Timing of administration: 13-15 minutes before reperfusion + 6 hours after reperfusion

Investigational medicinal product name	Melatonin
Investigational medicinal product code	
Other name	Circadin®
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Dosage: 6 mg
Way of administration: orally
Timing of administration: on the ward before the transplantation

Investigational medicinal product name	Epoprostenol
Investigational medicinal product code	
Other name	Flolan®
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intrahepatic use

Dosage and administration details:

Dose: 500 µg
Way of administration: Flush through the vena porta during the bench table
Timing of administration: Ex-situ during the bench table before the implantation

Investigational medicinal product name	Glutathione
Investigational medicinal product code	
Other name	Tationil 600®
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dose: 3 g
Way and duration of administration: IV – 2 minutes
Timing of administration: 2-4 minutes before reperfusion

Investigational medicinal product name	Infliximab
Investigational medicinal product code	
Other name	Remicade®
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dose: 3 mg/Kg
Way and duration of administration: IV – 3 hours
Timing of administration: Start of anhepatic phase after infusion of Antihrombin III; Interruption of the infusion during the administration of Glutathione; Restarted 15 minutes after reperfusion

Investigational medicinal product name	Vitamin E suspension
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Dose: 500 mg
Way of administration: Orally
Timing of administration: On the ward before the transplantation

Investigational medicinal product name	Apotransferrin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dose: 170 mg/kg
Way and duration of administration: IV – 3 hours

Timing of administration: Start of anhepatic phase; Interruption for sequential administration of erythropoietin, C1-inhibitor and Glutathione; Restarted 15 minutes after reperfusion

Arm title	Control group
Arm description: Standard of Care	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	combined drug approach	Control group
Started	36	36
Completed	32	33
Not completed	4	3
Adverse event, serious fatal	4	3

Baseline characteristics

Reporting groups	
Reporting group title	combined drug approach
Reporting group description:	
In the study arm, a combined-drug approach was given in addition to standard-of-care: following static cold preservation, donor livers were infused with epoprostenol (ex-situ, portal vein); recipients were given oral α-tocopherol and melatonin prior to anesthesia, and intravenous anti-thrombin-III, infliximab, apotransferrin, recombinant erythropoietin-β, c1-inhibitor and glutathione during the anhepatic and reperfusion phase.	
Reporting group title	Control group
Reporting group description:	
Standard of Care	

Reporting group values	combined drug approach	Control group	Total
Number of subjects	36	36	72
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)	28	28	56
From 65-84 years	8	8	16
85 years and over	0	0	0
Age continuous			
Adults aged 18 years or older, who were waitlisted for a first solitary full-size liver transplantation and who consented in writing to the study when entering the waiting list, were screened for eligibility at the time of liver offer.			
Units: years			
median	57	59	
inter-quartile range (Q1-Q3)	45.5 to 70	48 to 67.5	-
Gender categorical Units: Subjects			
Female	9	11	20
Male	27	25	52

End points

End points reporting groups

Reporting group title	combined drug approach
Reporting group description:	
In the study arm, a combined-drug approach was given in addition to standard-of-care: following static cold preservation, donor livers were infused with epoprostenol (ex-situ, portal vein); recipients were given oral α-tocopherol and melatonin prior to anesthesia, and intravenous anti-thrombin-III, infliximab, apotransferrin, recombinant erythropoietin-β, c1-inhibitor and glutathione during the anhepatic and reperfusion phase.	
Reporting group title	Control group
Reporting group description:	
Standard of Care	

Primary: Peak AST

End point title	Peak AST
End point description:	
End point type	Primary
End point timeframe:	
Peak AST within the first 72 hours following reperfusion	

End point values	combined drug approach	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	36		
Units: U/L				
geometric mean (confidence interval 95%)	1262.9 (946.3 to 1685.4)	1451.2 (1097.4 to 1936.7)		

Statistical analyses

Statistical analysis title	Linear regression model
Comparison groups	combined drug approach v Control group
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Regression, Linear

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Within 1 year post transplantation	
Assessment type	Systematic

Dictionary used	
Dictionary name	Physician's wording
Dictionary version	0

Reporting groups	
Reporting group title	combined drug approach
Reporting group description: -	
Reporting group title	Control group
Reporting group description: -	

Serious adverse events	combined drug approach	Control group	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 36 (16.67%)	4 / 36 (11.11%)	
number of deaths (all causes)	4	3	
number of deaths resulting from adverse events	4	3	
Injury, poisoning and procedural complications			
Bleeding time abnormal			
subjects affected / exposed	1 / 36 (2.78%)	2 / 36 (5.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical failure			
subjects affected / exposed	1 / 36 (2.78%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	1 / 36 (2.78%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Renal failure			

subjects affected / exposed	1 / 36 (2.78%)	2 / 36 (5.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Respiratory failure			
subjects affected / exposed	1 / 36 (2.78%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Portal vein thrombosis			
subjects affected / exposed	0 / 36 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			
subjects affected / exposed	1 / 36 (2.78%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

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

Non-serious adverse events	combined drug approach	Control group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 36 (100.00%)	36 / 36 (100.00%)	
Injury, poisoning and procedural complications			
Bleeding			
subjects affected / exposed	1 / 36 (2.78%)	2 / 36 (5.56%)	
occurrences (all)	1	2	
other surgical complications			
subjects affected / exposed	7 / 36 (19.44%)	3 / 36 (8.33%)	
occurrences (all)	7	3	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 36 (0.00%)	1 / 36 (2.78%)	
occurrences (all)	0	1	
Arrhythmia			

subjects affected / exposed	5 / 36 (13.89%)	4 / 36 (11.11%)	
occurrences (all)	5	4	
General disorders and administration site conditions			
Renal impairment			
subjects affected / exposed	9 / 36 (25.00%)	10 / 36 (27.78%)	
occurrences (all)	9	10	
Pleural effusion			
subjects affected / exposed	3 / 36 (8.33%)	4 / 36 (11.11%)	
occurrences (all)	3	4	
Urinary tract infection			
subjects affected / exposed	3 / 36 (8.33%)	2 / 36 (5.56%)	
occurrences (all)	3	2	
Respiratory insufficiency			
subjects affected / exposed	1 / 36 (2.78%)	2 / 36 (5.56%)	
occurrences (all)	1	2	
Portal vein thrombosis			
subjects affected / exposed	0 / 36 (0.00%)	1 / 36 (2.78%)	
occurrences (all)	0	1	
Infections and infestations			
Pneumonia bacterial			
subjects affected / exposed	2 / 36 (5.56%)	2 / 36 (5.56%)	
occurrences (all)	2	2	
Sepsis			
subjects affected / exposed	1 / 36 (2.78%)	0 / 36 (0.00%)	
occurrences (all)	1	0	
Bacterial infection			
subjects affected / exposed	2 / 36 (5.56%)	0 / 36 (0.00%)	
occurrences (all)	2	0	
Fungal infection			
subjects affected / exposed	1 / 36 (2.78%)	0 / 36 (0.00%)	
occurrences (all)	1	0	
donor preservation solution infection			
subjects affected / exposed	10 / 36 (27.78%)	6 / 36 (16.67%)	
occurrences (all)	10	6	
donor aorta patch infection			

subjects affected / exposed	8 / 36 (22.22%)	9 / 36 (25.00%)	
occurrences (all)	8	9	
Wound infection			
subjects affected / exposed	0 / 36 (0.00%)	1 / 36 (2.78%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 October 2014	Change in randomisation Ancillary studies : secondary use of biopsies and blood samples
04 December 2014	Addition of informed consent in German
10 June 2015	Grammar changes in French IC Cetor replaced by Cinryze
31 July 2015	Changes in reporting of medication post transplantation during follow-up
08 March 2016	Adding 'acute liver failure' to the exclusion criteria

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported