



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 |
| Scientific contact | Diethard Monbaliu, UZ Leuven, +32 (0)16342361, diethard.monbaliu@uzleuven.be |

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 occurrences (all) | 5 / 36 (13.89%) 5 | 4 / 36 (11.11%) 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