



## 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                    |
| <b>Arm title</b>             | 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  $\alpha$ -tocopherol and melatonin prior to anesthesia, and intravenous anti-thrombin-III, infliximab, apotransferrin, recombinant erythropoietin- $\beta$ , 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- $\beta$                                          |
| 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

|                                                           |                 |
|-----------------------------------------------------------|-----------------|
| <b>Arm title</b>                                          | Control group   |
| Arm description:<br>Standard of Care                      |                 |
| Arm type                                                  | No intervention |
| No investigational medicinal product assigned in this arm |                 |

| <b>Number of subjects in period 1</b> | 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 $\alpha$ -tocopherol and melatonin prior to anesthesia, and intravenous anti-thrombin-III, infliximab, apotransferrin, recombinant erythropoietin- $\beta$ , 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:<br>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 $\alpha$ -tocopherol and melatonin prior to anesthesia, and intravenous anti-thrombin-III, infliximab, apotransferrin, recombinant erythropoietin- $\beta$ , c1-inhibitor and glutathione during the anhepatic and reperfusion phase. |                        |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Control group          |
| Reporting group description:<br>Standard of Care                                                                                                                                                                                                                                                                                                                                                                                                                                               |                        |

### Primary: Peak AST

|                                                                                  |          |
|----------------------------------------------------------------------------------|----------|
| End point title                                                                  | Peak AST |
| End point description:                                                           |          |
| End point type                                                                   | Primary  |
| End point timeframe:<br>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 %

| <b>Non-serious adverse events</b>                     | 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<br>occurrences (all)        | 5 / 36 (13.89%)<br>5 | 4 / 36 (11.11%)<br>4 |  |
| General disorders and administration<br>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<br>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<br>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