



## Clinical trial results:

### Therapeutic Equivalence Study of Propofol Using Target-Controlled Infusion of Propofol 2% (20 mg/mL) MCT Fresenius Compared with Diprivan 20 mg/mL (AstraZeneca) in Patients Undergoing Elective Surgery

#### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2012-005701-43   |
| Trial protocol           | FR               |
| Global end of trial date | 13 February 2014 |

#### Results information

|                                |                |
|--------------------------------|----------------|
| Result version number          | v1 (current)   |
| This version publication date  | 08 April 2016  |
| First version publication date | 01 August 2015 |

#### Trial information

##### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | PROP-001-CP3 |
|-----------------------|--------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01856998 |
| WHO universal trial number (UTN)   | -           |

Notes:

##### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Fresenius Kabi Deutschland GmbH   |
| Sponsor organisation address | Else-Kröner-Str. 1, Bad Homburg, Germany, 61352   |
| Public contact               | Division Medical & Clinical Affairs Generics & Standard Solutions, Volume Therapy, Fresenius Kabi Deutschland GmbH, scientific-contact@fresenius-kabi.com |
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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                       | 26 March 2014    |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 31 January 2014  |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 13 February 2014 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the therapeutic equivalence, based on pharmacodynamic parameters, of Propofol 2% (20 mg/mL) MCT Fresenius and Diprivan 20 mg/mL (AstraZeneca) administered by target-controlled infusion (TCI)

Protection of trial subjects:

It was the responsibility of the Investigator to obtain a signed informed consent form from all patients prior to inclusion in the study.

After administration of propofol, the patient was observed for an appropriate period of time. Circulatory and respiratory functions were constantly monitored (e.g. electrocardiogram [ECG], pulse oximetry) and facilities for maintenance of patient airways, artificial ventilation, and other resuscitation facilities were immediately available at all times.

For sedation during surgical and diagnostic procedures, propofol was not administered by the same person conducting the surgical or diagnostic procedure. Infusion of colloids was to replace estimated blood loss in a 1:1 ratio with continuous infusion of iso-oncotic colloid. The type of colloid product used was selected as per standard of care.

Suspected hypovolaemia could have been treated with boluses of colloid solution in increments of 100 to 250 mL. If hypovolaemia was not a threat to the welfare of the patient, colloid administration was to be kept to  $\leq 500$  mL.

Prior to emergence from anaesthesia the patient could have been administered medication for post operative nausea and vomiting as per local standard of care.

The patient was monitored and received post-anaesthesia care as per local standard of care.

Patients were determined eligible for discharge from the peri-procedural setting as per local standard of care, but were not allowed to go home unaccompanied.

If discharged home, the patient was instructed not to consume alcohol, to drive, to operate machinery, or to work in potentially hazardous situations for a suitable period following recovery from anaesthesia as per local standard of care.

Background therapy: -

Evidence for comparator:

Propofol was first developed and patented by ICI (now AstraZeneca), marketed under the proprietary name Diprivan

|   |             |
|---|-------------|
| Actual start date of recruitment                          | 28 May 2013 |
| Long term follow-up planned                               | No          |
| Independent data monitoring committee (IDMC) involvement? | No          |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |            |
|--------------------------------------|------------|
| Country: Number of subjects enrolled | France: 71 |
| Worldwide total number of subjects   | 71         |
| EEA total number of subjects         | 71         |

Notes:

| <b>Subjects enrolled per age group</b>    |    |
|---|----|
| 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)                      | 70 |
| From 65 to 84 years                       | 1  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

The trial was monocentric and conducted in France. 1st patient was enrolled on 28 May 2013 and last patient completed the study on 13 Feb 2014. A total of 71 patients were enrolled of whom 70 were randomised: 35 to Propofol MCT Fresenius and 35 to Diprivan. All randomised patients received treatment as per the protocol and all completed the study.

### Pre-assignment

Screening details:

Included were male and female patients,  $\geq 18$  to  $< 65$  years of age, with ASA physical status 1 or 2 and undergoing elective, minor orthopaedic, vascular, urological, and gynaecological surgery. One patient was enrolled but not randomised to treatment; patient was deemed a screening failure due to violation of an exclusion criterion.

### Period 1

|                              |   |
|------------------------------|---|
| Period 1 title               | Overall Trial (overall period)                      |
| Is this the baseline period? | Yes   |
| Allocation method            | Randomised - controlled                             |
| Blinding used                | Double blind  |
| Roles blinded                | Subject, Investigator, Monitor, Data analyst, Carer |

Blinding implementation details:

All study procedures in the surgery room were performed by a blinded anaesthetist and a blinded nurse. Randomisation and blinding procedures (preparation of syringes) were performed by another unblinded nurse, in another room. The empty used study drug vials were packed and carried back to the pharmacy for storage before the unblinded monitoring visit, performed by an unblinded monitor.

### Arms

|  |                                      |
|--|--------------------------------------|
| Are arms mutually exclusive?           | Yes                                  |
| <b>Arm title</b>                       | Propofol 2% (20 mg/mL) MCT Fresenius |
| Arm description: -                     |                                      |
| Arm type                               | Experimental                         |
| Investigational medicinal product name | Propofol 2% (20 mg/mL) MCT Fresenius |
| Investigational medicinal product code |                                      |
| Other name                             | Propofol 20 mg/ml                    |
| Pharmaceutical forms                   | Emulsion for injection/infusion      |
| Routes of administration               | Intravenous use                      |

Dosage and administration details:

Dosage: Initial effect-site target concentration: 5  $\mu\text{g/mL}$ , if necessary increased by 1  $\mu\text{g/mL}$  every 60 seconds until Loss of Eyelash Reflex (LOER).

Frequency: Continuously (was adjusted to keep Bispectral Index (BIS) between 40 and 60, however maintenance target concentration could have been increased if a patient needs a BIS  $< 40$  with regard to individual condition and the respective surgery).

Duration: Until end of surgery

|  |   |
|--|---|
| <b>Arm title</b>                       | Diprivan 20 mg/mL (AstraZeneca)                       |
| Arm description: -                     |   |
| Arm type                               | Active comparator                                     |
| Investigational medicinal product name | Diprivan 20 mg/mL (AstraZeneca)                       |
| Investigational medicinal product code |   |
| Other name                             | Propofol 20 mg/ml                                     |
| Pharmaceutical forms                   | Emulsion for injection/infusion in pre-filled syringe |
| Routes of administration               | Intravenous use                                       |

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Dosage and administration details:

Dosage: Initial effect-site target concentration: 5 µg/mL; if necessary increased by 1 µg/mL every 60 seconds until Loss of Eyelash Reflex (LOER).

Frequency: Continuously (was adjusted to keep Bispectral Index (BIS) between 40 and 60, however maintenance target concentration could have been increased if a patient needed a BIS <40 with regard to individual condition and the respective surgery).

Duration: Until end of surgery

| <b>Number of subjects in period 1</b> <sup>[1]</sup> | Propofol 2% (20 mg/mL) MCT Fresenius | Diprivan 20 mg/mL (AstraZeneca) |
|--|--------------------------------------|---------------------------------|
| Started  | 35                                   | 35                              |
| Completed  | 35                                   | 35                              |

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Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: In this study 'enrolled patients' defines all patients who had provided informed consent for this study (N=71). One of the 71 enrolled patients was not randomised to treatment and thus has not entered the baseline period. Therefore only 70 patients entered the baseline period.

## Baseline characteristics

### Reporting groups

|                                |                                      |
|--------------------------------|--------------------------------------|
| Reporting group title          | Propofol 2% (20 mg/mL) MCT Fresenius |
| Reporting group description: - |                                      |
| Reporting group title          | Diprivan 20 mg/mL (AstraZeneca)      |
| Reporting group description: - |                                      |

| Reporting group values                | Propofol 2% (20 mg/mL) MCT Fresenius | Diprivan 20 mg/mL (AstraZeneca) | Total |
|---------------------------------------|--------------------------------------|---------------------------------|-------|
| Number of subjects                    | 35                                   | 35                              | 70    |
| Age categorical<br>Units: Subjects    |                                      |                                 |       |
| Adults (18-64 years)                  | 35                                   | 34                              | 69    |
| From 65-84 years                      | 0                                    | 1                               | 1     |
| Age continuous<br>Units: years        |                                      |                                 |       |
| arithmetic mean                       | 44.6                                 | 48                              |       |
| standard deviation                    | ± 10.54                              | ± 9.39                          | -     |
| Gender categorical<br>Units: Subjects |                                      |                                 |       |
| Female                                | 12                                   | 17                              | 29    |
| Male                                  | 23                                   | 18                              | 41    |

## End points

### End points reporting groups

|                              |                                      |
|------------------------------|--------------------------------------|
| Reporting group title        | Propofol 2% (20 mg/mL) MCT Fresenius |
| Reporting group description: | -                                    |
| Reporting group title        | Diprivan 20 mg/mL (AstraZeneca)      |
| Reporting group description: | -                                    |

### Primary: Time to Loss of Eyelash Reflex (LOER)

|                 |                                       |
|-----------------|---------------------------------------|
| End point title | Time to Loss of Eyelash Reflex (LOER) |
|-----------------|---------------------------------------|

End point description:

The study drug infusion was administered beginning at an initial effect-site target propofol concentration of 5 µg/mL.

LOER was to be assessed by gently touching the patient's eyelashes. If LOER had not occurred within 150 seconds of starting study drug infusion, target propofol effect-site concentration was to be increased by 1 µg/mL every 60 seconds until LOER was observed.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

LOER was to be assessed every 10 seconds from the initiation of TCI anaesthesia (device mediated study drug infusion) until LOER occurred up to 150 seconds.

The overall timeframe until LOER is observed varies from patient to patient.

| End point values                     | Propofol 2%<br>(20 mg/mL)<br>MCT Fresenius | Diprivan 20<br>mg/mL<br>(AstraZeneca) |  |  |
|--------------------------------------|--|---------------------------------------|--|--|
| Subject group type                   | Reporting group                            | Reporting group                       |  |  |
| Number of subjects analysed          | 34 <sup>[1]</sup>                          | 35 <sup>[2]</sup>                     |  |  |
| Units: Minutes                       |  |                                       |  |  |
| arithmetic mean (standard deviation) | 2.602 (±<br>1.49412)                       | 2.5096 (±<br>1.40146)                 |  |  |

Notes:

[1] - Intention-to-treat (ITT) analysis set

[2] - Intention-to-treat (ITT) analysis set

### Statistical analyses

|                            |                         |
|----------------------------|-------------------------|
| Statistical analysis title | Therapeutic Equivalence |
|----------------------------|-------------------------|

Statistical analysis description:

No formal statistical inference was required by the ANSM (French Health Authority). But a descriptive comparison of the primary endpoint (time to LOER) between the test and reference treatment was performed using analysis of variance (ANOVA) with a single fixed effect for treatment. This analysis was specified as descriptive since the study was not powered for the comparison. Treatment difference (test – reference) with 90% confidence intervals (CI) are presented for the ITT population.

|                   |  |
|-------------------|--|
| Comparison groups | Propofol 2% (20 mg/mL) MCT Fresenius v Diprivan 20 mg/mL (AstraZeneca) |
|-------------------|--|

|   |                                |
|---|--------------------------------|
| Number of subjects included in analysis | 69                             |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | equivalence                    |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 0.092                          |
| Confidence interval                     |                                |
| level                                   | 90 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -0.489                         |
| upper limit                             | 0.674                          |

### Secondary: Time to Bispectral Index 50

|                 |                             |
|-----------------|-----------------------------|
| End point title | Time to Bispectral Index 50 |
|-----------------|-----------------------------|

End point description:

Throughout the surgical procedure, the propofol target effect-site concentration was to be adjusted to maintain the Bispectral Index (BIS) at 40 to 60. A lower BIS was permissible if the Investigator providing anaesthesia considered it as clinically required for maintenance of adequate anaesthesia.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

A stopwatch was used to assess the time to BIS 50. The start of the stopwatch coincided directly with initiation of infusion of the study drug. The time to BIS 50 was taken at the first occasion BIS 50 was recorded on the BIS monitor.

| End point values                     | Propofol 2%<br>(20 mg/mL)<br>MCT Fresenius | Diprivan 20<br>mg/mL<br>(AstraZeneca) |  |  |
|--------------------------------------|--|---------------------------------------|--|--|
| Subject group type                   | Reporting group                            | Reporting group                       |  |  |
| Number of subjects analysed          | 34   | 35                                    |  |  |
| Units: Minutes                       |  |                                       |  |  |
| arithmetic mean (standard deviation) | 3.6089 (±<br>1.95474)                      | 4.5033 (±<br>2.72717)                 |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Predicted Effect-site Propofol Concentrations at Time of LOER

|                 |   |
|-----------------|---|
| End point title | Predicted Effect-site Propofol Concentrations at Time of LOER |
|-----------------|---|

End point description:

Patient-level predicted effect-site propofol concentrations were extracted from the infusion pump data.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Measured after initiation of infusion of the study drug at the timepoint where the LOER occurred.

| <b>End point values</b>              | Propofol 2%<br>(20 mg/mL)<br>MCT Fresenius | Diprivan 20<br>mg/mL<br>(AstraZeneca) |  |  |
|--------------------------------------|--|---------------------------------------|--|--|
| Subject group type                   | Reporting group                            | Reporting group                       |  |  |
| Number of subjects analysed          | 33   | 34                                    |  |  |
| Units: µg/ml                         |  |                                       |  |  |
| arithmetic mean (standard deviation) | 5.088 (±<br>0.4568)                        | 5.143 (±<br>0.6714)                   |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Predicted Effect-site Propofol Concentrations at Time of BIS 50

|                        |   |
|------------------------|---|
| End point title        | Predicted Effect-site Propofol Concentrations at Time of BIS 50   |
| End point description: | Patient-level predicted effect-site propofol concentrations were extracted from the infusion pump data.   |
| End point type         | Secondary   |
| End point timeframe:   | Measured at the timepoint where the BIS 50 value was recorded on the BIS monitor for the 1st occasion after initiation of infusion of the study drug. |

| <b>End point values</b>              | Propofol 2%<br>(20 mg/mL)<br>MCT Fresenius | Diprivan 20<br>mg/mL<br>(AstraZeneca) |  |  |
|--------------------------------------|--|---------------------------------------|--|--|
| Subject group type                   | Reporting group                            | Reporting group                       |  |  |
| Number of subjects analysed          | 33   | 33                                    |  |  |
| Units: µg/ml                         |  |                                       |  |  |
| arithmetic mean (standard deviation) | 5.122 (±<br>0.4547)                        | 5.454 (±<br>0.857)                    |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Plasma Propofol Concentration 2 (+/- 1) minutes after infusion start

|                        |  |
|------------------------|--|
| End point title        | Plasma Propofol Concentration 2 (+/- 1) minutes after infusion start |
| End point description: | Secondary Pharmacokinetic (PK) outcome variables                     |
| End point type         | Secondary  |

End point timeframe:  
2 (+/- 1) minutes after infusion start

| <b>End point values</b>               | Propofol 2%<br>(20 mg/mL)<br>MCT Fresenius | Diprivan 20<br>mg/mL<br>(AstraZeneca) |  |  |
|---------------------------------------|--|---------------------------------------|--|--|
| Subject group type                    | Reporting group                            | Reporting group                       |  |  |
| Number of subjects analysed           | 30 <sup>[3]</sup>                          | 26 <sup>[4]</sup>                     |  |  |
| Units: µg/ml                          |  |                                       |  |  |
| median (inter-quartile range (Q1-Q3)) | 3.4 (2.3 to 4.7)                           | 3.4 (2.6 to 4.3)                      |  |  |

Notes:

[3] - PK analysis set

[4] - PK analysis set

### Statistical analyses

No statistical analyses for this end point

### Secondary: Plasma Propofol Concentration 10 (+/- 2) minutes after infusion start

|                 |   |
|-----------------|---|
| End point title | Plasma Propofol Concentration 10 (+/- 2) minutes after infusion start |
|-----------------|---|

End point description:

Secondary PK outcome variables

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

10 (+/- 2) minutes after infusion start

| <b>End point values</b>               | Propofol 2%<br>(20 mg/mL)<br>MCT Fresenius | Diprivan 20<br>mg/mL<br>(AstraZeneca) |  |  |
|---------------------------------------|--|---------------------------------------|--|--|
| Subject group type                    | Reporting group                            | Reporting group                       |  |  |
| Number of subjects analysed           | 20   | 17                                    |  |  |
| Units: µg/ml                          |  |                                       |  |  |
| median (inter-quartile range (Q1-Q3)) | 4.05 (2.75 to 5)                           | 5.5 (4.2 to 6.1)                      |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Plasma Propofol Concentration 10 minutes after achieving target concentration

|                 |   |
|-----------------|---|
| End point title | Plasma Propofol Concentration 10 minutes after achieving target concentration |
|-----------------|---|

End point description:

Secondary PK outcome variables

|   |           |
|---|-----------|
| End point type                                  | Secondary |
| End point timeframe:                            |           |
| 10 minutes after achieving target concentration |           |

|                                       |  |                                       |  |  |
|---------------------------------------|--|---------------------------------------|--|--|
| <b>End point values</b>               | Propofol 2%<br>(20 mg/mL)<br>MCT Fresenius | Diprivan 20<br>mg/mL<br>(AstraZeneca) |  |  |
| Subject group type                    | Reporting group                            | Reporting group                       |  |  |
| Number of subjects analysed           | 22   | 22                                    |  |  |
| Units: µg/ml                          |  |                                       |  |  |
| median (inter-quartile range (Q1-Q3)) | 4.45 (3.5 to 5.6)                          | 4.3 (3.5 to 6.4)                      |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Plasma Propofol Concentration 30 minutes after achieving target concentration

|   |   |
|---|---|
| End point title                                 | Plasma Propofol Concentration 30 minutes after achieving target concentration |
| End point description:                          |   |
| Secondary PK outcome variables                  |   |
| End point type                                  | Secondary   |
| End point timeframe:                            |   |
| 30 minutes after achieving target concentration |   |

|                                       |  |                                       |  |  |
|---------------------------------------|--|---------------------------------------|--|--|
| <b>End point values</b>               | Propofol 2%<br>(20 mg/mL)<br>MCT Fresenius | Diprivan 20<br>mg/mL<br>(AstraZeneca) |  |  |
| Subject group type                    | Reporting group                            | Reporting group                       |  |  |
| Number of subjects analysed           | 14   | 14                                    |  |  |
| Units: µg/ml                          |  |                                       |  |  |
| median (inter-quartile range (Q1-Q3)) | 4.45 (3.3 to 5.8)                          | 4.35 (3.4 to 5.3)                     |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Maximum percent change in mean arterial pressure (MAP) from Baseline to Time of LOER

|                 |  |
|-----------------|--|
| End point title | Maximum percent change in mean arterial pressure (MAP) from Baseline to Time of LOER |
|-----------------|--|

End point description:

MAP = DBP + (SBP - DBP)/3 rounded to the nearest integer, where SBP = systolic blood pressure and DBP = diastolic blood pressure.

Baseline is defined as the last non-missing measurement taken prior to the initiation of study drug infusion.

The first MAP measurement after LOER was considered as the value at LOER.

|                      |                               |
|----------------------|-------------------------------|
| End point type       | Secondary                     |
| End point timeframe: | From baseline to time of LOER |

| <b>End point values</b>              | Propofol 2%<br>(20 mg/mL)<br>MCT Fresenius | Diprivan 20<br>mg/mL<br>(AstraZeneca) |  |  |
|--------------------------------------|--|---------------------------------------|--|--|
| Subject group type                   | Reporting group                            | Reporting group                       |  |  |
| Number of subjects analysed          | 33 <sup>[5]</sup>                          | 35 <sup>[6]</sup>                     |  |  |
| Units: Percent                       |  |                                       |  |  |
| arithmetic mean (standard deviation) | -9.39 (±<br>14.622)                        | -7.09 (±<br>17.167)                   |  |  |

Notes:

[5] - Safety analysis set

[6] - Safety analysis set

### Statistical analyses

No statistical analyses for this end point

### Secondary: Maximum percent change in heart rate from Baseline to Time of LOER

|                        |   |  |  |  |
|------------------------|---|--|--|--|
| End point title        | Maximum percent change in heart rate from Baseline to Time of LOER  |  |  |  |
| End point description: | Baseline is defined as the last non-missing measurement taken prior to the initiation of study drug infusion. Heart rate (beats/minute) was based on the measurement of pulse rate.<br>The first pulse rate measurement after LOER was considered as the value of heart rate at time of LOER. |  |  |  |
| End point type         | Secondary   |  |  |  |
| End point timeframe:   | From baseline to time of LOER   |  |  |  |

| <b>End point values</b>              | Propofol 2%<br>(20 mg/mL)<br>MCT Fresenius | Diprivan 20<br>mg/mL<br>(AstraZeneca) |  |  |
|--------------------------------------|--|---------------------------------------|--|--|
| Subject group type                   | Reporting group                            | Reporting group                       |  |  |
| Number of subjects analysed          | 33   | 35                                    |  |  |
| Units: Percent                       |  |                                       |  |  |
| arithmetic mean (standard deviation) | -4.99 (±<br>13.434)                        | -3.62 (±<br>15.95)                    |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Pain Score for Facial Expression 1 min after start of infusion

End point title | Pain Score for Facial Expression 1 min after start of infusion

End point description:

Pain score of facial expression: Score 0 - if the subject has a relaxed face, makes eye contact, shows interest in surroundings; Score 1 - if the subject has a worried facial expression, with eyebrows lowered, eyes partially closed, cheeks raised, mouth pursed; Score 2 - if the subject has deep furrows in the forehead, closed eyes, an open mouth, deep lines around nose and lips.

End point type | Secondary

End point timeframe:

1 min after start of infusion

| End point values                                | Propofol 2%<br>(20 mg/mL)<br>MCT Fresenius | Diprivan 20<br>mg/mL<br>(AstraZeneca) |  |  |
|---|--|---------------------------------------|--|--|
| Subject group type                              | Reporting group                            | Reporting group                       |  |  |
| Number of subjects analysed                     | 35   | 35                                    |  |  |
| Units: Number of subjects with available result |  |                                       |  |  |
| Score 0   | 22   | 16                                    |  |  |
| Score 1   | 9  | 7                                     |  |  |
| Score 2   | 3  | 12                                    |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Pain Score for Facial Expression 6 min after start of infusion

End point title | Pain Score for Facial Expression 6 min after start of infusion

End point description:

Pain score of facial expression: Score 0 - if the subject has a relaxed face, makes eye contact, shows interest in surroundings; Score 1 - if the subject has a worried facial expression, with eyebrows lowered, eyes partially closed, cheeks raised, mouth pursed; Score 2 - if the subject has deep furrows in the forehead, closed eyes, an open mouth, deep lines around nose and lips.

End point type | Secondary

End point timeframe:

6 min after start of infusion

| End point values                                | Propofol 2%<br>(20 mg/mL)<br>MCT Fresenius | Diprivan 20<br>mg/mL<br>(AstraZeneca) |  |  |
|---|--|---------------------------------------|--|--|
| Subject group type                              | Reporting group                            | Reporting group                       |  |  |
| Number of subjects analysed                     | 35   | 35                                    |  |  |
| Units: Number of subjects with available result |  |                                       |  |  |

|         |   |   |  |  |
|---------|---|---|--|--|
| Score 0 | 1 | 1 |  |  |
| Score 1 | 0 | 0 |  |  |
| Score 2 | 0 | 0 |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Pain Score for Motor Response to Light Pressure 1 min after start of infusion

|                 |   |
|-----------------|---|
| End point title | Pain Score for Motor Response to Light Pressure 1 min after start of infusion |
|-----------------|---|

End point description:

Pain score of motor response to light pressure at site of or proximal to venous cannula where the study drug was infused: Score 0 - if there is no response; Score 1 - if the subject withdraws or guards the infusion site; Score 2 - if spontaneous motor response (withdraws or guards the injection without light pressure).

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

1 min after start of infusion

| End point values                                | Propofol 2%<br>(20 mg/mL)<br>MCT Fresenius | Diprivan 20<br>mg/mL<br>(AstraZeneca) |  |  |
|---|--|---------------------------------------|--|--|
| Subject group type                              | Reporting group                            | Reporting group                       |  |  |
| Number of subjects analysed                     | 35   | 35                                    |  |  |
| Units: Number of subjects with available result |  |                                       |  |  |
| Score 0   | 23   | 13                                    |  |  |
| Score 1   | 4  | 11                                    |  |  |
| Score 2   | 7  | 11                                    |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Pain Score for Motor Response to Light Pressure 6 min after start of infusion

|                 |   |
|-----------------|---|
| End point title | Pain Score for Motor Response to Light Pressure 6 min after start of infusion |
|-----------------|---|

End point description:

Pain score of motor response to light pressure at site of or proximal to venous cannula where the study drug was infused: Score 0 - if there is no response; Score 1 - if the subject withdraws or guards the infusion site; Score 2 - if spontaneous motor response (withdraws or guards the injection without light pressure).

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:  
6 min after start of infusion

| <b>End point values</b>                         | Propofol 2%<br>(20 mg/mL)<br>MCT Fresenius | Diprivan 20<br>mg/mL<br>(AstraZeneca) |  |  |
|---|--|---------------------------------------|--|--|
| Subject group type                              | Reporting group                            | Reporting group                       |  |  |
| Number of subjects analysed                     | 35   | 35                                    |  |  |
| Units: Number of subjects with available result |  |                                       |  |  |
| Score 0   | 0  | 1                                     |  |  |
| Score 1   | 1  | 0                                     |  |  |
| Score 2   | 0  | 0                                     |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Pain Score for Verbal Response 1 min after start of infusion

End point title | Pain Score for Verbal Response 1 min after start of infusion

End point description:

Pain score of verbal response to light pressure at site of or proximal to venous cannula where the study drug was infused : Score 0 - if there is no verbal response; Score 1 - if the subject makes any sound or verbalisation; Score 2 - if spontaneous verbal expression of pain (without light pressure).

End point type | Secondary

End point timeframe:

1 min after start of infusion

| <b>End point values</b>                         | Propofol 2%<br>(20 mg/mL)<br>MCT Fresenius | Diprivan 20<br>mg/mL<br>(AstraZeneca) |  |  |
|---|--|---------------------------------------|--|--|
| Subject group type                              | Reporting group                            | Reporting group                       |  |  |
| Number of subjects analysed                     | 35   | 35                                    |  |  |
| Units: Number of subjects with available result |  |                                       |  |  |
| Score 0   | 16   | 13                                    |  |  |
| Score 1   | 7  | 6                                     |  |  |
| Score 2   | 11   | 16                                    |  |  |

### Statistical analyses

No statistical analyses for this end point

**Secondary: Pain Score for Verbal Response 6 min after start of infusion**

|                 |  |
|-----------------|--|
| End point title | Pain Score for Verbal Response 6 min after start of infusion |
|-----------------|--|

End point description:

Pain score of verbal response to light pressure at site of or proximal to venous cannula where the study drug was infused: Score 0 - if there is no verbal response; Score 1 - if the subject makes any sound or verbalisation; Score 2 - if spontaneous verbal expression of pain (without light pressure).

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

6 min after start of infusion

| <b>End point values</b>                         | Propofol 2%<br>(20 mg/mL)<br>MCT Fresenius | Diprivan 20<br>mg/mL<br>(AstraZeneca) |  |  |
|---|--|---------------------------------------|--|--|
| Subject group type                              | Reporting group                            | Reporting group                       |  |  |
| Number of subjects analysed                     | 35   | 35                                    |  |  |
| Units: Number of subjects with available result |  |                                       |  |  |
| Score 0   | 1  | 1                                     |  |  |
| Score 1   | 0  | 0                                     |  |  |
| Score 2   | 0  | 0                                     |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Time to Spontaneous Eye Opening**

|                 |                                 |
|-----------------|---------------------------------|
| End point title | Time to Spontaneous Eye Opening |
|-----------------|---------------------------------|

End point description:

Time to eye opening (minutes) was derived based on the time of eye opening relative to termination time of study drug infusion. Time to spontaneous eye opening (minutes) = (date/time of spontaneous eye opening - date/time of termination of study drug infusion).

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From termination of study drug infusion until spontaneous eye opening

| <b>End point values</b>              | Propofol 2%<br>(20 mg/mL)<br>MCT Fresenius | Diprivan 20<br>mg/mL<br>(AstraZeneca) |  |  |
|--------------------------------------|--|---------------------------------------|--|--|
| Subject group type                   | Reporting group                            | Reporting group                       |  |  |
| Number of subjects analysed          | 35   | 35                                    |  |  |
| Units: Minutes                       |  |                                       |  |  |
| arithmetic mean (standard deviation) | 24.7 (± 11.87)                             | 19.7 (± 12.84)                        |  |  |

## Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

The period of observation lasted from the day the patient signed the Informed Consent until the last follow-up visit. The Investigator had to report any SAE without undue delay within 24 hours following first awareness of the event.

Adverse event reporting additional description:

In this study, all AEs/SAEs were documented, but only treatment-emergent adverse events (TEAEs), i.e. AEs that started or worsened in severity at or after the initiation of study drug infusion till the end of the study, including the Follow-up Visit, were reported and summarized in tables.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 16.1   |

### Reporting groups

|                       |                                      |
|-----------------------|--------------------------------------|
| Reporting group title | Propofol 2% (20 mg/mL) MCT Fresenius |
|-----------------------|--------------------------------------|

Reporting group description: -

|                       |                                 |
|-----------------------|---------------------------------|
| Reporting group title | Diprivan 20 mg/mL (AstraZeneca) |
|-----------------------|---------------------------------|

Reporting group description: -

| <b>Serious adverse events</b>                     | Propofol 2% (20 mg/mL) MCT Fresenius | Diprivan 20 mg/mL (AstraZeneca) |  |
|---|--------------------------------------|---------------------------------|--|
| Total subjects affected by serious adverse events |                                      |                                 |  |
| subjects affected / exposed                       | 1 / 35 (2.86%)                       | 1 / 35 (2.86%)                  |  |
| number of deaths (all causes)                     | 0                                    | 0                               |  |
| number of deaths resulting from adverse events    | 0                                    | 0                               |  |
| Injury, poisoning and procedural complications    |                                      |                                 |  |
| Post procedural haemorrhage                       |                                      |                                 |  |
| subjects affected / exposed                       | 1 / 35 (2.86%)                       | 0 / 35 (0.00%)                  |  |
| occurrences causally related to treatment / all   | 0 / 1                                | 0 / 0                           |  |
| deaths causally related to treatment / all        | 0 / 0                                | 0 / 0                           |  |
| Nervous system disorders                          |                                      |                                 |  |
| Syncope   |                                      |                                 |  |
| subjects affected / exposed                       | 0 / 35 (0.00%)                       | 1 / 35 (2.86%)                  |  |
| occurrences causally related to treatment / all   | 0 / 0                                | 0 / 1                           |  |
| deaths causally related to treatment / all        | 0 / 0                                | 0 / 0                           |  |

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

| <b>Non-serious adverse events</b>  | Propofol 2% (20 mg/mL) MCT Fresenius | Diprivan 20 mg/mL (AstraZeneca) |  |
|--|--------------------------------------|---------------------------------|--|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed | 31 / 35 (88.57%)                     | 31 / 35 (88.57%)                |  |
| Vascular disorders   |                                      |                                 |  |
| Hypotension  |                                      |                                 |  |
| subjects affected / exposed  | 9 / 35 (25.71%)                      | 4 / 35 (11.43%)                 |  |
| occurrences (all)  | 9                                    | 4                               |  |
| Haematoma  |                                      |                                 |  |
| subjects affected / exposed  | 0 / 35 (0.00%)                       | 1 / 35 (2.86%)                  |  |
| occurrences (all)  | 0                                    | 1                               |  |
| General disorders and administration site conditions                                 |                                      |                                 |  |
| Hyperthermia   |                                      |                                 |  |
| subjects affected / exposed  | 3 / 35 (8.57%)                       | 4 / 35 (11.43%)                 |  |
| occurrences (all)  | 3                                    | 4                               |  |
| Fatigue  |                                      |                                 |  |
| subjects affected / exposed  | 4 / 35 (11.43%)                      | 1 / 35 (2.86%)                  |  |
| occurrences (all)  | 4                                    | 1                               |  |
| Infusion site pain   |                                      |                                 |  |
| subjects affected / exposed  | 2 / 35 (5.71%)                       | 2 / 35 (5.71%)                  |  |
| occurrences (all)  | 2                                    | 2                               |  |
| Injection site pain  |                                      |                                 |  |
| subjects affected / exposed  | 1 / 35 (2.86%)                       | 3 / 35 (8.57%)                  |  |
| occurrences (all)  | 1                                    | 3                               |  |
| Malaise  |                                      |                                 |  |
| subjects affected / exposed  | 1 / 35 (2.86%)                       | 3 / 35 (8.57%)                  |  |
| occurrences (all)  | 1                                    | 3                               |  |
| Pyrexia  |                                      |                                 |  |
| subjects affected / exposed  | 0 / 35 (0.00%)                       | 2 / 35 (5.71%)                  |  |
| occurrences (all)  | 0                                    | 2                               |  |
| Asthenia   |                                      |                                 |  |
| subjects affected / exposed  | 0 / 35 (0.00%)                       | 1 / 35 (2.86%)                  |  |
| occurrences (all)  | 0                                    | 1                               |  |
| Chills   |                                      |                                 |  |
| subjects affected / exposed  | 0 / 35 (0.00%)                       | 1 / 35 (2.86%)                  |  |
| occurrences (all)  | 0                                    | 1                               |  |
| Hypothermia  |                                      |                                 |  |

|   |                     |                     |  |
|---|---------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all)  | 0 / 35 (0.00%)<br>0 | 1 / 35 (2.86%)<br>1 |  |
| Injection site haematoma<br>subjects affected / exposed<br>occurrences (all)                                    | 0 / 35 (0.00%)<br>0 | 1 / 35 (2.86%)<br>1 |  |
| Immune system disorders<br>Iodine allergy<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 35 (2.86%)<br>1 | 0 / 35 (0.00%)<br>0 |  |
| Reproductive system and breast<br>disorders<br>Penile pain<br>subjects affected / exposed<br>occurrences (all)  | 1 / 35 (2.86%)<br>1 | 0 / 35 (0.00%)<br>0 |  |
| Respiratory, thoracic and mediastinal<br>disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all) | 1 / 35 (2.86%)<br>1 | 0 / 35 (0.00%)<br>0 |  |
|   |                     |                     |  |
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)  | 1 / 35 (2.86%)<br>1 | 0 / 35 (0.00%)<br>0 |  |
| Psychiatric disorders<br>Anxiety<br>subjects affected / exposed<br>occurrences (all)                            | 1 / 35 (2.86%)<br>1 | 2 / 35 (5.71%)<br>2 |  |
| Agitation<br>subjects affected / exposed<br>occurrences (all)   | 1 / 35 (2.86%)<br>1 | 1 / 35 (2.86%)<br>1 |  |
| Depression<br>subjects affected / exposed<br>occurrences (all)  | 1 / 35 (2.86%)<br>1 | 0 / 35 (0.00%)<br>0 |  |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)  | 1 / 35 (2.86%)<br>1 | 0 / 35 (0.00%)<br>0 |  |
| Investigations<br>C-reactive protein increased  |                     |                     |  |

|  |                        |                        |  |
|--|------------------------|------------------------|--|
| subjects affected / exposed<br>occurrences (all)   | 0 / 35 (0.00%)<br>0    | 2 / 35 (5.71%)<br>2    |  |
| Blood pressure increased<br>subjects affected / exposed<br>occurrences (all)               | 0 / 35 (0.00%)<br>0    | 1 / 35 (2.86%)<br>1    |  |
| Blood urine<br>subjects affected / exposed<br>occurrences (all)                            | 1 / 35 (2.86%)<br>1    | 0 / 35 (0.00%)<br>0    |  |
| Blood urine present<br>subjects affected / exposed<br>occurrences (all)                    | 1 / 35 (2.86%)<br>1    | 0 / 35 (0.00%)<br>0    |  |
| Gamma-glutamyltransferase<br>increased<br>subjects affected / exposed<br>occurrences (all) | 1 / 35 (2.86%)<br>1    | 0 / 35 (0.00%)<br>0    |  |
| Oxygen saturation decreased<br>subjects affected / exposed<br>occurrences (all)            | 1 / 35 (2.86%)<br>1    | 0 / 35 (0.00%)<br>0    |  |
| Respiratory rate decreased<br>subjects affected / exposed<br>occurrences (all)             | 0 / 35 (0.00%)<br>0    | 1 / 35 (2.86%)<br>1    |  |
| Transaminases increased<br>subjects affected / exposed<br>occurrences (all)                | 1 / 35 (2.86%)<br>1    | 0 / 35 (0.00%)<br>0    |  |
| Injury, poisoning and procedural<br>complications  |                        |                        |  |
| Procedural pain<br>subjects affected / exposed<br>occurrences (all)                        | 10 / 35 (28.57%)<br>10 | 13 / 35 (37.14%)<br>13 |  |
| Post procedural swelling<br>subjects affected / exposed<br>occurrences (all)               | 0 / 35 (0.00%)<br>0    | 1 / 35 (2.86%)<br>1    |  |
| Wound complication<br>subjects affected / exposed<br>occurrences (all)                     | 1 / 35 (2.86%)<br>1    | 0 / 35 (0.00%)<br>0    |  |
| Cardiac disorders  |                        |                        |  |

|   |                      |                      |  |
|---|----------------------|----------------------|--|
| Bradycardia<br>subjects affected / exposed<br>occurrences (all)                             | 0 / 35 (0.00%)<br>0  | 1 / 35 (2.86%)<br>1  |  |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)    | 1 / 35 (2.86%)<br>1  | 1 / 35 (2.86%)<br>1  |  |
| Syncope<br>subjects affected / exposed<br>occurrences (all)                                 | 1 / 35 (2.86%)<br>1  | 0 / 35 (0.00%)<br>0  |  |
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)                            | 1 / 35 (2.86%)<br>1  | 0 / 35 (0.00%)<br>0  |  |
| Presyncope<br>subjects affected / exposed<br>occurrences (all)                              | 0 / 35 (0.00%)<br>0  | 1 / 35 (2.86%)<br>1  |  |
| Ear and labyrinth disorders<br>Vertigo<br>subjects affected / exposed<br>occurrences (all)  | 2 / 35 (5.71%)<br>2  | 3 / 35 (8.57%)<br>3  |  |
| Gastrointestinal disorders<br>Dysphagia<br>subjects affected / exposed<br>occurrences (all) | 8 / 35 (22.86%)<br>8 | 8 / 35 (22.86%)<br>8 |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)                                  | 7 / 35 (20.00%)<br>7 | 6 / 35 (17.14%)<br>6 |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)                                | 5 / 35 (14.29%)<br>5 | 5 / 35 (14.29%)<br>5 |  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)                            | 2 / 35 (5.71%)<br>2  | 3 / 35 (8.57%)<br>3  |  |
| Abdominal Pain<br>subjects affected / exposed<br>occurrences (all)                          | 1 / 35 (2.86%)<br>1  | 1 / 35 (2.86%)<br>1  |  |
| Diarrhoea   |                      |                      |  |

|  |                |                |  |
|--|----------------|----------------|--|
| subjects affected / exposed            | 2 / 35 (5.71%) | 0 / 35 (0.00%) |  |
| occurrences (all)                      | 2              | 0              |  |
| Abdominal distension                   |                |                |  |
| subjects affected / exposed            | 0 / 35 (0.00%) | 1 / 35 (2.86%) |  |
| occurrences (all)                      | 0              | 1              |  |
| Abdominal hernia                       |                |                |  |
| subjects affected / exposed            | 1 / 35 (2.86%) | 0 / 35 (0.00%) |  |
| occurrences (all)                      | 1              | 0              |  |
| Abdominal pain upper                   |                |                |  |
| subjects affected / exposed            | 0 / 35 (0.00%) | 1 / 35 (2.86%) |  |
| occurrences (all)                      | 0              | 1              |  |
| Dyspepsia                              |                |                |  |
| subjects affected / exposed            | 0 / 35 (0.00%) | 1 / 35 (2.86%) |  |
| occurrences (all)                      | 0              | 1              |  |
| Gastrointestinal disorder              |                |                |  |
| subjects affected / exposed            | 0 / 35 (0.00%) | 1 / 35 (2.86%) |  |
| occurrences (all)                      | 0              | 1              |  |
| Skin and subcutaneous tissue disorders |                |                |  |
| Pruritus                               |                |                |  |
| subjects affected / exposed            | 1 / 35 (2.86%) | 1 / 35 (2.86%) |  |
| occurrences (all)                      | 1              | 1              |  |
| Cold sweat                             |                |                |  |
| subjects affected / exposed            | 0 / 35 (0.00%) | 1 / 35 (2.86%) |  |
| occurrences (all)                      | 0              | 1              |  |
| Erythema                               |                |                |  |
| subjects affected / exposed            | 0 / 35 (0.00%) | 1 / 35 (2.86%) |  |
| occurrences (all)                      | 0              | 1              |  |
| Hyperhidrosis                          |                |                |  |
| subjects affected / exposed            | 0 / 35 (0.00%) | 1 / 35 (2.86%) |  |
| occurrences (all)                      | 0              | 1              |  |
| Urticaria                              |                |                |  |
| subjects affected / exposed            | 0 / 35 (0.00%) | 1 / 35 (2.86%) |  |
| occurrences (all)                      | 0              | 1              |  |
| Renal and urinary disorders            |                |                |  |
| Urinary retention                      |                |                |  |

|  |                     |                      |  |
|--|---------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all)                         | 1 / 35 (2.86%)<br>1 | 1 / 35 (2.86%)<br>1  |  |
| Dysuria<br>subjects affected / exposed<br>occurrences (all)              | 0 / 35 (0.00%)<br>0 | 1 / 35 (2.86%)<br>1  |  |
| Haematuria<br>subjects affected / exposed<br>occurrences (all)           | 1 / 35 (2.86%)<br>1 | 0 / 35 (0.00%)<br>0  |  |
| Musculoskeletal and connective tissue disorders                          |                     |                      |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)            | 2 / 35 (5.71%)<br>2 | 3 / 35 (8.57%)<br>3  |  |
| Neck pain<br>subjects affected / exposed<br>occurrences (all)            | 1 / 35 (2.86%)<br>1 | 4 / 35 (11.43%)<br>4 |  |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)    | 1 / 35 (2.86%)<br>1 | 3 / 35 (8.57%)<br>3  |  |
| Musculoskeletal pain<br>subjects affected / exposed<br>occurrences (all) | 2 / 35 (5.71%)<br>2 | 1 / 35 (2.86%)<br>1  |  |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)           | 0 / 35 (0.00%)<br>0 | 2 / 35 (5.71%)<br>2  |  |
| Myalgia<br>subjects affected / exposed<br>occurrences (all)              | 1 / 35 (2.86%)<br>1 | 0 / 35 (0.00%)<br>0  |  |
| Metabolism and nutrition disorders                                       |                     |                      |  |
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all)   | 0 / 35 (0.00%)<br>0 | 1 / 35 (2.86%)<br>1  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Only a descriptive comparison of the primary endpoint (time to LOER) between test and reference treatment was performed. Therefore, no statistical inference was taken.

Notes: