# Clinical trial results:
# The Effect of Morphine on the Human Central Nervous System
## Summary

| | |
|---|---|
| EudraCT number | 2016-002623-29 |
| Trial protocol | DK |
| Global end of trial date | 22 August 2017 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 21 July 2018 |
| First version publication date | 21 July 2018 |
| Summary attachment (see zip file) | EudraCT Results Report (EudraCT_report.pdf) |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | Lundbeckstudy2016 |

**Additional study identifiers**

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

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Aalborg University Hospital |
| Sponsor organisation address | Mølleparkvej 4, Aalborg, Denmark, 9000 |
| Public contact | Mech-Sense, Mech-Sense, Aalborg University Hospital, dilelic@gmail.com |
| Scientific contact | Mech-Sense, Mech-Sense, Aalborg University Hospital, dilelic@gmail.com |

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 | 31 May 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 22 August 2017 |
| Global end of trial reached? | Yes |
| Global end of trial date | 22 August 2017 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The project aims to investigate the effect of I.V. morphine on the central nervous system (including spinal cord and the brain) and to observe whether these effects are reversed by an opioid-receptor blocker (naloxone).

Protection of trial subjects:

A doctor was available during every experimental visit for immediate assistance if needed. Moreover, heart rate, noninvasive blood pressure, and peripheral oxygen saturation were continuously monitored and documented every 15 minutes. Additionally, 3 L of oxygen was continuously supplied by a nasal cannula. The infusion would be stopped if the oxygen saturation decreased to less than 92%. If the morphine side effects were too intolerable for the subjects, the morphine IV infusion would immediately be stopped and naloxone would be given. Furthermore, metoloperamide was present in the laboratory and administered to the subjects in case these asked for it. Metoloperamide treats nausea and vomiting. The volunteers were instructed to contact us if there are any issues/side effects/adverse events after the experiment. Moreover, the volunteers were monitored for at least one hour after the experiment until the medical personnel deems they were ready to leave the lab.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 01 August 2016 |
| 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 | Denmark: 20 |
| Worldwide total number of subjects | 20 |
| EEA total number of subjects | 20 |

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) | 20 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

The subjects were recruited in Denmark from website www.forsoegsperson.dk website between December 1, 2016 and July 3, 2017.

### Pre-assignment

Screening details:

27 subjects were screened.

Each healthy volunteer was asked to meet at The Department of Gastroenterology, Aalborg Hospital for all visits (provided that a healthy volunteer fulfills the criteria to participate and wishes to take part in the study). The initial visit was the screening visit where the volunteers were explained what the study is

### Period 1

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

Blinding implementation details:

The treatment medication was mixed by someone on the research staff not otherwise involved in the study. All study medications were similarly mixed in the same amount of saline solution so that the subject and the experimenter were blinded to study drug.

### Arms

| | |
|---|---|
| **Arm title** | Placebo |
| Arm description: - | |
| Arm type | Placebo |
| Investigational medicinal product name | Saline Solution |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion in pre-filled syringe |
| Routes of administration | Intravenous use |

Dosage and administration details:

Route of administration: intravenous
Dosage: 10ml saline over ten minutes followed by 50 ml saline for the next hour and 45 minutes (to mimic the morphine infusion)
Dosage: 10ml saline bolus followed by 50 ml saline infusion for 45 minutes (to mimic the naloxone infusion)
Administered once, on first or second experimental day (the placebo day)

| **Number of subjects in period 1** | Placebo |
|---|---|
| Started | 20 |
| Completed | 20 |

## Period 2

| | |
|---|---|
| Period 2 title | Morphine |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst |

Blinding implementation details:

The treatment medication was mixed by someone on the research staff not otherwise involved in the study. All study medications were similarly mixed in the same amount of saline solution so that the subject and the experimenter were blinded to study drug.

## Arms

| | |
|---|---|
| **Arm title** | Morphine and Naloxone |

Arm description: -

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Morphine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion in pre-filled syringe |
| Routes of administration | Intravenous use |

Dosage and administration details:

Route of administration: intravenous
Dosage: 0.15mg/kg mixed with 10ml saline over ten minutes in the first 7 subjects and 0.12mg/kg mixed with 10ml saline over ten minutes in the last 13 subjects. Thereafter 0.05mg/kg/hr mixed with 50ml saline for the next hour and 45 minutes
Administered once, on the first or second experimental visit on the morphine day

| | |
|---|---|
| Investigational medicinal product name | Naloxone |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion in pre-filled syringe |
| Routes of administration | Intravenous use |

Dosage and administration details:

Route of administration: intravenous

Dosage: 2mg mixed with 10ml saline bolus in the first 7 volunteers and 1mg mixed with 10ml saline bolus in the remaining 13 volunteers. This was followed by 4mg/hr mixed with 50ml saline infusion for 45 minutes.
Naloxone infusion was initiated 60 minutes after morphine infusion was initiated. When naloxone was given, both morphine and naloxone were infused simultaneously.

| **Number of subjects in period 2** | Morphine and Naloxone |
|---|---|
| Started | 20 |
| Completed | 20 |

## Baseline characteristics

### Reporting groups

| | |
|---|---|
| Reporting group title | Placebo |

Reporting group description: -

| Reporting group values | Placebo | Total | |
|---|---|---|---|
| Number of subjects | 20 | 20 | |
| Age categorical<br>Units: Subjects | | | |
| In utero | | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | | 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) | | 0 | |
| From 65-84 years | | 0 | |
| 85 years and over | | 0 | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 23 | | |
| standard deviation | ± 2 | - | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 0 | 0 | |
| Male | 20 | 20 | |

### Subject analysis sets

| | |
|---|---|
| Subject analysis set title | Placebo Group - placebo |
| Subject analysis set type | Full analysis |

Subject analysis set description:

This is placebo treatment in placebo period. This was a cross-over study, so each subject participated in period 1 and period 2. Data between the two periods were compared.

| | |
|---|---|
| Subject analysis set title | Morphine Group - morphine |
| Subject analysis set type | Full analysis |

Subject analysis set description:

This is morphine treatment in the morphine period. This was a cross-over study so all subjects participated in Period 1 and Period 2. Data from the two periods were compared.

| | |
|---|---|
| Subject analysis set title | Placebo Group - baseline |
| Subject analysis set type | Full analysis |

Subject analysis set description:

THis is baseline for placebo period in this cross-over study.

| | |
|---|---|
| Subject analysis set title | Placebo group - placebo + placebo |
| Subject analysis set type | Full analysis |

Subject analysis set description:

This is double placebo infusion during placebo period. This is to mimic the moprhine + naloxone infusion

in the morphine period.

| | |
|---|---|
| Subject analysis set title | Morphine Group - baseline |
| Subject analysis set type | Full analysis |

Subject analysis set description:

This is baseline in the morphine period.

| | |
|---|---|
| Subject analysis set title | Morphine Group - morphine + naloxone |
| Subject analysis set type | Full analysis |

Subject analysis set description:

This is morphine and naloxone simultaneous administration during the morphine visit.

| **Reporting group values** | Placebo Group - placebo | Morphine Group - morphine | Placebo Group - baseline |
|---|---|---|---|
| Number of subjects | 20 | 20 | 20 |
| Age categorical<br>Units: Subjects | | | |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over | | | |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | ± | ± | ± |
| Gender categorical<br>Units: Subjects | | | |
| Female | 0 | 0 | 0 |
| Male | 20 | 20 | 20 |

| **Reporting group values** | Placebo group - placebo + placebo | Morphine Group - baseline | Morphine Group - morphine + naloxone |
|---|---|---|---|
| Number of subjects | 20 | 20 | 20 |
| Age categorical<br>Units: Subjects | | | |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over | | | |

| | | | |
|---|---|---|---|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | ±<br> | ±<br> | ±<br> |
| Gender categorical<br>Units: Subjects | | | |
| Female | 0 | 0 | 0 |
| Male | 20 | 20 | 20 |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Placebo |
| Reporting group description: - | |
| Reporting group title | Morphine and Naloxone |
| Reporting group description: - | |
| Subject analysis set title | Placebo Group - placebo |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| This is placebo treatment in placebo period. This was a cross-over study, so each subject participated in period 1 and period 2. Data between the two periods were compared. | |
| Subject analysis set title | Morphine Group - morphine |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| This is morphine treatment in the morphine period. This was a cross-over study so all subjects participated in Period 1 and Period 2. Data from the two periods were compared. | |
| Subject analysis set title | Placebo Group - baseline |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| THis is baseline for placebo period in this cross-over study. | |
| Subject analysis set title | Placebo group - placebo + placebo |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| This is double placebo infusion during placebo period. This is to mimic the moprhine + naloxone infusion in the morphine period. | |
| Subject analysis set title | Morphine Group - baseline |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| This is baseline in the morphine period. | |
| Subject analysis set title | Morphine Group - morphine + naloxone |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| This is morphine and naloxone simultaneous administration during the morphine visit. | |

### Primary: Reflex EMG

| | |
|---|---|
| End point title | Reflex EMG |
| End point description: | |
| | |
| End point type | Primary |
| End point timeframe: | |
| Period 1 and Period 2 | |

| End point values | Placebo Group - placebo | Morphine Group - morphine | Placebo Group - baseline | Placebo group - placebo + placebo |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 19 | 19 | 19 | 19 |
| Units: AUC | | | | |
| arithmetic mean (standard error) | 34.1 (± 7.3) | 28.1 (± 6.4) | 31.9 (± 7.1) | 34.8 (± 8.7) |

| End point values | Morphine Group - baseline | Morphine Group - morphine + naloxone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 19 | 19 | | |
| Units: AUC | | | | |
| arithmetic mean (standard error) | 40.7 (± 8.1) | 43.4 (± 9.3) | | |

**Statistical analyses**

| Statistical analysis title | Reflex EMG |
|---|---|
| Comparison groups | Placebo Group - placebo v Morphine Group - morphine v Placebo Group - baseline v Placebo group - placebo + placebo v Morphine Group - baseline v Morphine Group - morphine + naloxone |
| Number of subjects included in analysis | 114 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | < 0.05 |
| Method | ANOVA |

**Primary: Reflex EEG latency peak 1**

| End point title | Reflex EEG latency peak 1 |
|---|---|

End point description:

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

End point timeframe:

Period 1 and Period 2

| End point values | Placebo Group - placebo | Morphine Group - morphine | Placebo Group - baseline | Placebo group - placebo + placebo |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 20 | 20 | 20 | 20 |
| Units: uV | | | | |
| arithmetic mean (standard error) | 111.8 (± 3.7) | 111 (± 4.0) | 115.4 (± 3.3) | 113.5 (± 4) |

| End point values | Morphine Group - baseline | Morphine Group - morphine + naloxone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 20 | 20 | | |
| Units: uV | | | | |
| arithmetic mean (standard error) | 113.2 (± 3.4) | 113.8 (± 4.4) | | |

**Statistical analyses**

| Statistical analysis title | Reflex EEG latency peak 1 |
|---|---|
| Comparison groups | Morphine Group - morphine v Placebo Group - baseline v Placebo group - placebo + placebo v Morphine Group - baseline v Morphine Group - morphine + naloxone v Placebo Group - placebo |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | > 0.05 |
| Method | ANOVA |

**Primary: Reflex EEG latency peak 2**

| End point title | Reflex EEG latency peak 2 |
|---|---|

End point description:

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

End point timeframe:

Period 1 and Period 2

| End point values | Placebo Group - placebo | Morphine Group - morphine | Placebo Group - baseline | Placebo group - placebo + placebo |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 20 | 20 | 20 | 20 |
| Units: ms | | | | |
| arithmetic mean (standard error) | 253.4 (± 7.6) | 258.8 (± 8.6) | 257.7 (± 8.4) | 251.9 (± 8.1) |

| End point values | Morphine Group - baseline | Morphine Group - morphine + naloxone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 20 | 20 | | |
| Units: ms | | | | |
| arithmetic mean (standard error) | 261.1 (± 8.1) | 258.1 (± 8.3) | | |

**Statistical analyses**

| Statistical analysis title | Reflex EEG latency peak 2 |
|---|---|
| Comparison groups | Placebo Group - placebo v Morphine Group - morphine v Placebo Group - baseline v Placebo group - placebo + placebo v Morphine Group - baseline v Morphine Group - morphine + naloxone |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | > 0.05 |
| Method | ANOVA |

**Primary: Reflex EEG amplitude peak 1**

| End point title | Reflex EEG amplitude peak 1 |
|---|---|

End point description:

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

End point timeframe:

Period 1 and Period 2

| End point values | Placebo Group - placebo | Morphine Group - morphine | Placebo Group - baseline | Placebo group - placebo + placebo |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 20 | 20 | 20 | 20 |
| Units: uV | | | | |
| arithmetic mean (standard error) | 19.2 (± 1.7) | 19.9 (± 2.0) | 20.9 (± 1.8) | 19.5 (± 1.9) |

| End point values | Morphine Group - baseline | Morphine Group - morphine + naloxone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 20 | 20 | | |
| Units: uV | | | | |
| arithmetic mean (standard error) | 21.3 (± 1.8) | 20.0 (± 1.8) | | |

**Statistical analyses**

| Statistical analysis title | Reflex EEG amplitude peak 1 |
|---|---|
| Comparison groups | Placebo Group - placebo v Morphine Group - morphine v Placebo Group - baseline v Placebo group - placebo + placebo v Morphine Group - baseline v Morphine Group - morphine + naloxone |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | > 0.05 |
| Method | ANOVA |

**Primary: Reflex EEG amplitude peak 2**

| End point title | Reflex EEG amplitude peak 2 |
|---|---|

End point description:

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

End point timeframe:

Period 1 and Period 2

| End point values | Placebo Group - placebo | Morphine Group - morphine | Placebo Group - baseline | Placebo group - placebo + placebo |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 20 | 20 | 20 | 20 |
| Units: uV | | | | |
| arithmetic mean (standard error) | 26.2 (± 1.7) | 24.6 (± 2.1) | 27.1 (± 1.7) | 25.3 (± 2.1) |

| End point values | Morphine Group - baseline | Morphine Group - morphine + naloxone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 20 | 20 | | |
| Units: uV | | | | |
| arithmetic mean (standard error) | 27.4 (± 1.8) | 26.2 (± 2) | | |

**Statistical analyses**

| Statistical analysis title | Reflex EEG amplitude peak 2 |
|---|---|
| Comparison groups | Placebo Group - placebo v Morphine Group - morphine v Placebo Group - baseline v Placebo group - placebo + placebo v Morphine Group - baseline v Morphine Group - morphine + naloxone |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | < 0.05 |
| Method | ANOVA |

**Primary: Spinal EEG peak 1 latency**

| End point title | Spinal EEG peak 1 latency |
|---|---|
| End point description: | |

| End point type | Primary |
|---|---|
| End point timeframe: | |
| Period 1 and Period 2 | |

| End point values | Placebo Group - placebo | Morphine Group - morphine | Placebo Group - baseline | Placebo group - placebo + placebo |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 19 | 19 | 19 | 19 |
| Units: ms | | | | |
| arithmetic mean (standard error) | 11.3 (± 0.8) | 11.1 (± 0.7) | 11.2 (± 0.8) | 11.1 (± 0.7) |

| End point values | Morphine Group - baseline | Morphine Group - morphine + naloxone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 19 | 19 | | |
| Units: ms | | | | |
| arithmetic mean (standard error) | 11 (± 0.6) | 11.1 (± 0.7) | | |

**Statistical analyses**

| Statistical analysis title | Spinal EEG peak 1 latency |
|---|---|
| Comparison groups | Placebo Group - placebo v Morphine Group - morphine v Placebo Group - baseline v Placebo group - placebo + placebo v Morphine Group - baseline v Morphine Group - morphine + naloxone |
| Number of subjects included in analysis | 114 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | > 0.05 |
| Method | ANOVA |

**Primary: Spinal EEG peak 2 latency**

| End point title | Spinal EEG peak 2 latency |
|---|---|

End point description:

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

End point timeframe:

Period 1 and Period 2

| End point values | Placebo Group - placebo | Morphine Group - morphine | Placebo Group - baseline | Placebo group - placebo + placebo |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 19 | 19 | 19 | 19 |
| Units: ms | | | | |
| arithmetic mean (standard error) | 13.9 (± 1.1) | 14.1 (± 0.8) | 14.2 (± 1) | 13.9 (± 1) |

| End point values | Morphine Group - baseline | Morphine Group - morphine + naloxone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 19 | 19 | | |
| Units: ms | | | | |
| arithmetic mean (standard error) | 13.8 (± 0.7) | 14 (± 0.8) | | |

**Statistical analyses**

| Statistical analysis title | Spinal peak 2 latency |
|---|---|
| Comparison groups | Placebo Group - placebo v Morphine Group - morphine v Placebo Group - baseline v Placebo group - placebo + placebo v Morphine Group - baseline v Morphine Group - morphine + naloxone |
| Number of subjects included in analysis | 114 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | > 0.05 |
| Method | ANOVA |

**Primary: Spinal EEG amplitude peak 1**

| End point title | Spinal EEG amplitude peak 1 |
|---|---|

End point description:

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

End point timeframe:

Period 1 and Period 2

| End point values | Placebo Group - placebo | Morphine Group - morphine | Placebo Group - baseline | Placebo group - placebo + placebo |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 19 | 19 | 19 | 19 |
| Units: uV | | | | |
| arithmetic mean (standard deviation) | 11.3 (± 0.8) | 11.2 (± 0.8) | 11.1 (± 0.7) | 11.1 (± 0.7) |

| End point values | Morphine Group - baseline | Morphine Group - morphine + naloxone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 19 | 19 | | |
| Units: uV | | | | |
| arithmetic mean (standard deviation) | 11 (± 0.6) | 11.1 (± 0.7) | | |

**Statistical analyses**

| Statistical analysis title | spinal peak 1 amplitude |
|---|---|
| Comparison groups | Morphine Group - morphine v Placebo Group - baseline v Placebo group - placebo + placebo v Morphine Group - baseline v Morphine Group - morphine + naloxone v Placebo Group - placebo |
| Number of subjects included in analysis | 114 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | > 0.05 |
| Method | ANOVA |

**Primary: Spinal EEG amplitude peak 2**

| End point title | Spinal EEG amplitude peak 2 |
|---|---|
| End point description: | |

| End point type | Primary |
|---|---|
| End point timeframe: | |
| Period 1 and Period 2 | |

| End point values | Placebo Group - placebo | Morphine Group - morphine | Placebo Group - baseline | Placebo group - placebo + placebo |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 19 | 19 | 19 | 19 |
| Units: uV | | | | |
| arithmetic mean (standard error) | 2.2 (± 0.7) | 2.4 (± 0.6) | 2.2 (± 0.9) | 2.2 (± 1.2) |

| End point values | Morphine Group - baseline | Morphine Group - morphine + naloxone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 19 | 19 | | |
| Units: uV | | | | |
| arithmetic mean (standard error) | 2.3 (± 0.9) | 2.2 (± 0.6) | | |

**Statistical analyses**

| Statistical analysis title | Spinal EEG peak 2 amplitude |
|---|---|
| Comparison groups | Placebo Group - placebo v Morphine Group - morphine v Placebo Group - baseline v Placebo group - placebo + placebo v Morphine Group - baseline v Morphine Group - morphine + naloxone |
| Number of subjects included in analysis | 114 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | > 0.05 |
| Method | ANOVA |

**Primary: Somatosensory Evoked Potentials p14 latency**

| End point title | Somatosensory Evoked Potentials p14 latency |
|---|---|
| End point description: | |

| End point type | Primary |
|---|---|
| End point timeframe: | |
| Period 1 and Period 2 | |

| End point values | Placebo Group - placebo | Morphine Group - morphine | Placebo Group - baseline | Placebo group - placebo + placebo |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 19 | 19 | 19 | 19 |
| Units: ms | | | | |
| arithmetic mean (standard error) | 15.5 (± 0.9) | 15.3 (± 0.8) | 15.4 (± 0.7) | 15.3 (± 0.8) |

| End point values | Morphine Group - baseline | Morphine Group - morphine + naloxone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 19 | 19 | | |
| Units: ms | | | | |
| arithmetic mean (standard error) | 15.5 (± 0.6) | 15.6 (± 0.7) | | |

**Statistical analyses**

| Statistical analysis title | P14 latency |
|---|---|
| Comparison groups | Placebo Group - placebo v Morphine Group - morphine v Placebo Group - baseline v Placebo group - placebo + placebo v Morphine Group - baseline v Morphine Group - morphine + naloxone |
| Number of subjects included in analysis | 114 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | > 0.05 |
| Method | ANOVA |

**Primary: somatosensory evoked potentials N20 latency**

| End point title | somatosensory evoked potentials N20 latency |
|---|---|

End point description:

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

End point timeframe:

Period 1 and Period 2

| End point values | Placebo Group - placebo | Morphine Group - morphine | Placebo Group - baseline | Placebo group - placebo + placebo |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 19 | 19 | 19 | 19 |
| Units: ms | | | | |
| arithmetic mean (standard error) | 20.6 (± 0.9) | 20.9 (± 1.1) | 20.7 (± 1.1) | 20.6 (± 1) |

| End point values | Morphine Group - baseline | Morphine Group - morphine + naloxone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 19 | 19 | | |
| Units: ms | | | | |
| arithmetic mean (standard error) | 20.8 (± 0.8) | 20.7 (± 0.8) | | |

**Statistical analyses**

| Statistical analysis title | N20 latency |
|---|---|
| Comparison groups | Placebo Group - placebo v Morphine Group - morphine v Placebo Group - baseline v Placebo group - placebo + placebo v Morphine Group - baseline v Morphine Group - morphine + naloxone |
| Number of subjects included in analysis | 114 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | > 0.05 |
| Method | ANOVA |

**Primary: Somatosensory evoked potentials P14 amplitude**

| End point title | Somatosensory evoked potentials P14 amplitude |
|---|---|

End point description:

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

End point timeframe:

Period 1 and Period 2

| End point values | Placebo Group - placebo | Morphine Group - morphine | Placebo Group - baseline | Placebo group - placebo + placebo |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 19 | 19 | 19 | 19 |
| Units: uV | | | | |
| arithmetic mean (standard deviation) | 0.6 (± 0.3) | 0.7 (± 0.3) | 0.6 (± 0.2) | 0.7 (± 0.2) |

| End point values | Morphine Group - baseline | Morphine Group - morphine + naloxone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 19 | 19 | | |
| Units: uV | | | | |
| arithmetic mean (standard deviation) | 0.6 (± 0.3) | 0.7 (± 0.2) | | |

**Statistical analyses**

| Statistical analysis title | P14 amplitude |
|---|---|
| Comparison groups | Placebo Group - placebo v Morphine Group - morphine v Placebo Group - baseline v Placebo group - placebo + placebo v Morphine Group - baseline v Morphine Group - morphine + naloxone |
| Number of subjects included in analysis | 114 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | > 0.05 |
| Method | ANOVA |

**Primary: Somatosensory evoked potentials N20 amplitude**

| End point title | Somatosensory evoked potentials N20 amplitude |
|---|---|

End point description:

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

End point timeframe:

Period 1 and Period 2

| End point values | Placebo Group - placebo | Morphine Group - morphine | Placebo Group - baseline | Placebo group - placebo + placebo |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 19 | 19 | 19 | 19 |
| Units: uV | | | | |
| arithmetic mean (standard error) | 1.2 (± 0.6) | 1.2 (± 0.6) | 1.1 (± 0.5) | 1.2 (± 0.6) |

| End point values | Morphine Group - baseline | Morphine Group - morphine + naloxone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 19 | 19 | | |
| Units: uV | | | | |
| arithmetic mean (standard error) | 1.2 (± 0.4) | 1.2 (± 0.6) | | |

**Statistical analyses**

| Statistical analysis title | N20 amplitude |
|---|---|
| Comparison groups | Placebo Group - placebo v Morphine Group - morphine v Placebo Group - baseline v Placebo group - placebo + placebo v Morphine Group - baseline v Morphine Group - morphine + naloxone |
| Number of subjects included in analysis | 114 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | > 0.05 |
| Method | ANOVA |

**Primary: Resting EEG Delta**

| End point title | Resting EEG Delta |
|---|---|

End point description:

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

End point timeframe:

Period 1 and Period 2

| End point values | Placebo Group - placebo | Morphine Group - morphine | Placebo Group - baseline | Placebo group - placebo + placebo |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 20 | 20 | 20 | 20 |
| Units: uV | | | | |
| arithmetic mean (standard error) | 17.5 (± 1.1) | 16.9 (± 0.8) | 17.7 (± 1.2) | 17.4 (± 1) |

| End point values | Morphine Group - baseline | Morphine Group - morphine + naloxone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 20 | 20 | | |
| Units: uV | | | | |
| arithmetic mean (standard error) | 17.9 (± 1) | 16.9 (± 0.8) | | |

**Statistical analyses**

| Statistical analysis title | Resting EEG Delta |
|---|---|
| Comparison groups | Placebo Group - placebo v Morphine Group - morphine v Placebo Group - baseline v Placebo group - placebo + placebo v Morphine Group - baseline v Morphine Group - morphine + naloxone |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | > 0.05 |
| Method | ANOVA |

**Primary: Resting EEG Theta**

| End point title | Resting EEG Theta |
|---|---|

End point description:

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

End point timeframe:

Period 1 and Period 2

| End point values | Placebo Group - placebo | Morphine Group - morphine | Placebo Group - baseline | Placebo group - placebo + placebo |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 20 | 20 | 20 | 20 |
| Units: uV | | | | |
| arithmetic mean (standard deviation) | 16.9 (± 0.7) | 17 (± 0.7) | 17.5 (± 0.8) | 16.6 (± 0.7) |

| End point values | Morphine Group - baseline | Morphine Group - morphine + naloxone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 20 | 20 | | |
| Units: uV | | | | |
| arithmetic mean (standard deviation) | 17 (± 0.6) | 17.4 (± 0.8) | | |

**Statistical analyses**

| Statistical analysis title | Resting EEG Theta |
|---|---|
| Comparison groups | Placebo Group - placebo v Morphine Group - morphine v Placebo Group - baseline v Placebo group - placebo + placebo v Morphine Group - baseline v Morphine Group - morphine + naloxone |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | > 0.05 |
| Method | ANOVA |

**Primary: Resting EEG Alpha**

| End point title | Resting EEG Alpha |
|---|---|

End point description:

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

End point timeframe:

Period 1 and Period 2

| End point values | Placebo Group - placebo | Morphine Group - morphine | Placebo Group - baseline | Placebo group - placebo + placebo |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 20 | 20 | 20 | 20 |
| Units: uV | | | | |
| arithmetic mean (standard error) | 29.6 (± 1.6) | 29.5 (± 1.5) | 29.3 (± 1.6) | 30.2 (± 1.6) |

| End point values | Morphine Group - baseline | Morphine Group - morphine + naloxone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 20 | 20 | | |
| Units: uV | | | | |
| arithmetic mean (standard error) | 29 (± 1.4) | 30.2 (± 1.4) | | |

**Statistical analyses**

| Statistical analysis title | Resting EEG Alpha |
|---|---|
| Comparison groups | Placebo Group - placebo v Morphine Group - morphine v Placebo Group - baseline v Placebo group - placebo + placebo v Morphine Group - baseline v Morphine Group - morphine + naloxone |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | > 0.05 |
| Method | ANOVA |

**Primary: Resting EEG Beta**

| End point title | Resting EEG Beta |
|---|---|

End point description:

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

End point timeframe:

Period 1 and Period 2

| End point values | Placebo Group - placebo | Morphine Group - morphine | Placebo Group - baseline | Placebo group - placebo + placebo |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 20 | 20 | 20 | 20 |
| Units: uV | | | | |
| arithmetic mean (standard error) | 16 (± 0.4) | 16.3 (± 0.5) | 16.1 (± 0.4) | 15.9 (± 0.4) |

| End point values | Morphine Group - baseline | Morphine Group - morphine + naloxone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 20 | 20 | | |
| Units: uV | | | | |
| arithmetic mean (standard error) | 16.2 (± 0.5) | 16 (± 0.4) | | |

**Statistical analyses**

| Statistical analysis title | Resting EEG Beta |
|---|---|
| Comparison groups | Placebo Group - placebo v Morphine Group - morphine v Placebo Group - baseline v Placebo group - placebo + placebo v Morphine Group - baseline v Morphine Group - morphine + naloxone |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | > 0.05 |
| Method | ANOVA |

**Primary: Tonic Pain EEG Delta**

| End point title | Tonic Pain EEG Delta |
|---|---|

End point description:

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

End point timeframe:

Period 1 and Period 2

| End point values | Placebo Group - placebo | Morphine Group - morphine | Placebo Group - baseline | Placebo group - placebo + placebo |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 19 | 19 | 19 | 19 |
| Units: uV | | | | |
| arithmetic mean (standard error) | 25.7 (± 1.4) | 23.5 (± 1.1) | 26.3 (± 1.2) | 25.2 (± 1.4) |

| End point values | Morphine Group - baseline | Morphine Group - morphine + naloxone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 19 | 19 | | |
| Units: uV | | | | |
| arithmetic mean (standard error) | 25.6 (± 1.1) | 25.4 (± 1.4) | | |

**Statistical analyses**

| Statistical analysis title | Tonic Pain EEG Delta |
|---|---|
| Comparison groups | Placebo Group - placebo v Morphine Group - morphine v Placebo Group - baseline v Placebo group - placebo + placebo v Morphine Group - baseline v Morphine Group - morphine + naloxone |
| Number of subjects included in analysis | 114 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | < 0.05 |
| Method | ANOVA |

**Primary: Tonic Pain EEG Theta**

| End point title | Tonic Pain EEG Theta |
|---|---|

End point description:

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

End point timeframe:

Period 1 and Period 2

| End point values | Placebo Group - placebo | Morphine Group - morphine | Placebo Group - baseline | Placebo group - placebo + placebo |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 19 | 19 | 19 | 19 |
| Units: uV | | | | |
| arithmetic mean (standard error) | 17.4 (± 0.7) | 16.6 (± 0.6) | 17.5 (± 0.7) | 17.8 (± 0.8) |

| End point values | Morphine Group - baseline | Morphine Group - morphine + naloxone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 19 | 19 | | |
| Units: uV | | | | |
| arithmetic mean (standard error) | 17.6 (± 0.6) | 17.6 (± 0.8) | | |

**Statistical analyses**

| Statistical analysis title | Tonic Pain EEG Theta |
|---|---|
| Comparison groups | Placebo Group - placebo v Morphine Group - morphine v Placebo Group - baseline v Placebo group - placebo + placebo v Morphine Group - baseline v Morphine Group - morphine + naloxone |
| Number of subjects included in analysis | 114 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | < 0.05 |
| Method | ANOVA |

**Primary: Tonic Pain EEG Alpha**

| End point title | Tonic Pain EEG Alpha |
|---|---|
| End point description: | |

| End point type | Primary |
|---|---|
| End point timeframe: | |
| Period 1 and Period 2 | |

| End point values | Placebo Group - placebo | Morphine Group - morphine | Placebo Group - baseline | Placebo group - placebo + placebo |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 19 | 19 | 19 | 19 |
| Units: uV | | | | |
| arithmetic mean (standard error) | 21.9 (± 1.9) | 22.8 (± 1.6) | 21.4 (± 1.7) | 22 (± 1.8) |

| End point values | Morphine Group - baseline | Morphine Group - morphine + naloxone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 19 | 19 | | |
| Units: uV | | | | |
| arithmetic mean (standard error) | 21.1 (± 1.4) | 21.8 (± 1.9) | | |

**Statistical analyses**

| Statistical analysis title | Tonic Pain EEG Alpha |
|---|---|
| Comparison groups | Placebo Group - placebo v Morphine Group - morphine v Placebo Group - baseline v Placebo group - placebo + placebo v Morphine Group - baseline v Morphine Group - morphine + naloxone |
| Number of subjects included in analysis | 114 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | < 0.05 |
| Method | ANOVA |

**Primary: Tonic Pain EEG Beta**

| End point title | Tonic Pain EEG Beta |
|---|---|

End point description:

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

End point timeframe:

Period 1 and Period 2

| End point values | Placebo Group - placebo | Morphine Group - morphine | Placebo Group - baseline | Placebo group - placebo + placebo |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 19 | 19 | 19 | 19 |
| Units: uV | | | | |
| arithmetic mean (standard error) | 15.2 (± 0.5) | 14.8 (± 0.3) | 15.2 (± 0.4) | 15.4 (± 0.4) |

| End point values | Morphine Group - baseline | Morphine Group - morphine + naloxone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 19 | 19 | | |
| Units: uV | | | | |
| arithmetic mean (standard error) | 15.0 (± 0.5) | 15.1 (± 0.5) | | |

**Statistical analyses**

| Statistical analysis title | Tonic Pain EEG Beta |
|---|---|
| Comparison groups | Placebo Group - placebo v Morphine Group - morphine v Placebo Group - baseline v Placebo group - placebo + placebo v Morphine Group - baseline v Morphine Group - morphine + naloxone |
| Number of subjects included in analysis | 114 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | > 0.05 |
| Method | ANOVA |

**Secondary: Reflex Pain Rating**

| End point title | Reflex Pain Rating |
|---|---|

End point description:

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

End point timeframe:

Period 1 and Period 2

| End point values | Placebo Group - placebo | Morphine Group - morphine | Placebo Group - baseline | Placebo group - placebo + placebo |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 20 | 20 | 20 | 20 |
| Units: cm | | | | |
| arithmetic mean (standard error) | 2.7 (± 0.4) | 2.5 (± 0.4) | 2.5 (± 0.4) | 3.0 (± 0.4) |

| End point values | Morphine Group - baseline | Morphine Group - morphine + naloxone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 20 | 20 | | |
| Units: cm | | | | |
| arithmetic mean (standard error) | 3 (± 0.5) | 3.2 (± 0.5) | | |

**Statistical analyses**

| Statistical analysis title | Reflex Pain Scores |
|---|---|
| Comparison groups | Placebo Group - placebo v Morphine Group - morphine v Placebo Group - baseline v Placebo group - placebo + placebo v Morphine Group - baseline v Morphine Group - morphine + naloxone |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | < 0.05 |
| Method | ANOVA |

**Secondary: Reflex Unpleasantness Rating**

| End point title | Reflex Unpleasantness Rating |
|---|---|

End point description:

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

End point timeframe:

Period 1 and Period 2

| End point values | Placebo Group - placebo | Morphine Group - morphine | Placebo Group - baseline | Placebo group - placebo + placebo |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 20 | 20 | 20 | 20 |
| Units: cm | | | | |
| arithmetic mean (standard error) | 4.6 (± 0.4) | 3.6 (± 0.5) | 4.6 (± 0.4) | 4.5 (± 0.4) |

| End point values | Morphine Group - baseline | Morphine Group - morphine + naloxone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 20 | 20 | | |
| Units: cm | | | | |
| arithmetic mean (standard error) | 4.6 (± 0.5) | 4.7 (± 0.4) | | |

**Statistical analyses**

| Statistical analysis title | Reflex Unpleasantness Scores |
|---|---|
| Comparison groups | Placebo Group - placebo v Morphine Group - morphine v Placebo Group - baseline v Placebo group - placebo + placebo v Morphine Group - baseline v Morphine Group - morphine + naloxone |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | < 0.05 |
| Method | ANOVA |

**Secondary: Cold-Pressor Pain Rating**

| End point title | Cold-Pressor Pain Rating |
|---|---|

End point description:

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

End point timeframe:

Period 1 and Period 2

| End point values | Placebo Group - placebo | Morphine Group - morphine | Placebo Group - baseline | Placebo group - placebo + placebo |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 20 | 20 | 20 | 20 |
| Units: cm | | | | |
| arithmetic mean (standard error) | 6.7 (± 0.4) | 5.4 (± 0.5) | 6.5 (± 0.3) | 7 (± 0.3) |

| End point values | Morphine Group - baseline | Morphine Group - morphine + naloxone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 20 | 20 | | |
| Units: cm | | | | |
| arithmetic mean (standard error) | 6.4 (± 0.3) | 6.7 (± 0.3) | | |

**Statistical analyses**

| Statistical analysis title | Cold-Pressor Pain Scores |
|---|---|
| Comparison groups | Placebo Group - placebo v Morphine Group - morphine v Placebo Group - baseline v Placebo group - placebo + placebo v Morphine Group - baseline v Morphine Group - morphine + naloxone |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | < 0.05 |
| Method | ANOVA |

**Secondary: Cold-Pressor Unpleasantness Rating**

| End point title | Cold-Pressor Unpleasantness Rating |
|---|---|

End point description:

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

End point timeframe:

Period 1 and Period 2

| End point values | Placebo Group - placebo | Morphine Group - morphine | Placebo Group - baseline | Placebo group - placebo + placebo |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 20 | 20 | 20 | 20 |
| Units: cm | | | | |
| arithmetic mean (standard error) | 8 (± 0.4) | 6.3 (± 0.4) | 7.9 (± 0.3) | 8.2 (± 0.3) |

| End point values | Morphine Group - baseline | Morphine Group - morphine + naloxone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 20 | 20 | | |
| Units: cm | | | | |
| arithmetic mean (standard error) | 7.7 (± 0.3) | 8.1 (± 0.3) | | |

**Statistical analyses**

| Statistical analysis title | Cold-Pressor Unpleasantness Scores |
|---|---|
| Comparison groups | Placebo Group - placebo v Morphine Group - morphine v Placebo Group - baseline v Placebo group - placebo + placebo v Morphine Group - baseline v Morphine Group - morphine + naloxone |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | < 0.05 |
| Method | ANOVA |

**Secondary: Heat Pain Tolerance Threshold**

| End point title | Heat Pain Tolerance Threshold |
|---|---|
| End point description: | |

| End point type | Secondary |
|---|---|
| End point timeframe: | |
| Period 1 and Period 2 | |

| End point values | Placebo Group - placebo | Morphine Group - morphine | Placebo Group - baseline | Placebo group - placebo + placebo |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 20 | 20 | 20 | 20 |
| Units: Celcius | | | | |
| arithmetic mean (standard error) | 48 (± 0.5) | 48.4 (± 0.4) | 48.4 (± 0.4) | 48.5 (± 0.4) |

| End point values | Morphine Group - baseline | Morphine Group - morphine + naloxone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 20 | 20 | | |
| Units: Celcius | | | | |
| arithmetic mean (standard error) | 48.5 (± 0.3) | 47.7 (± 0.4) | | |

**Statistical analyses**

| Statistical analysis title | Heat pain tolerance threshold |
|---|---|
| Comparison groups | Placebo Group - placebo v Morphine Group - morphine v Placebo Group - baseline v Placebo group - placebo + placebo v Morphine Group - baseline v Morphine Group - morphine + naloxone |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | > 0.05 |
| Method | ANOVA |

**Secondary: Electrical Pain Tolerance Threshold**

| End point title | Electrical Pain Tolerance Threshold |
|---|---|

End point description:

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

End point timeframe:

Period 1 and Period 2

| End point values | Placebo Group - placebo | Morphine Group - morphine | Placebo Group - baseline | Placebo group - placebo + placebo |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 20 | 20 | 20 | 20 |
| Units: mA | | | | |
| arithmetic mean (standard error) | 19.1 (± 2.3) | 23.4 (± 3) | 18.8 (± 2.1) | 18.8 (± 2.3) |

| End point values | Morphine Group - baseline | Morphine Group - morphine + naloxone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 20 | 20 | | |
| Units: mA | | | | |
| arithmetic mean (standard error) | 17.7 (± 1.9) | 18.7 (± 2.2) | | |

**Statistical analyses**

| Statistical analysis title | Electrical Pain Tolerance Threshold |
|---|---|
| Comparison groups | Placebo Group - placebo v Morphine Group - morphine v Placebo Group - baseline v Placebo group - placebo + placebo v Morphine Group - baseline v Morphine Group - morphine + naloxone |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | < 0.05 |
| Method | ANOVA |

**Secondary: Bone Pressure Pain Tolerance Threshold**

| End point title | Bone Pressure Pain Tolerance Threshold |
|---|---|

End point description:

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

End point timeframe:

Period 1 and Period 2

| End point values | Placebo Group - placebo | Morphine Group - morphine | Placebo Group - baseline | Placebo group - placebo + placebo |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 20 | 20 | 20 | 20 |
| Units: kPa | | | | |
| arithmetic mean (standard error) | 6735 (± 435) | 8678 (± 843) | 7504 (± 506) | 6434 (± 407) |

| End point values | Morphine Group - baseline | Morphine Group - morphine + naloxone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 20 | 20 | | |
| Units: kPa | | | | |
| arithmetic mean (standard error) | 7506 (± 445) | 6572 (± 416) | | |

## Statistical analyses

| Statistical analysis title | Bone Pressure Pain Tolerance Threshold |
|---|---|
| Comparison groups | Placebo Group - placebo v Morphine Group - morphine v Placebo Group - baseline v Placebo group - placebo + placebo v Morphine Group - baseline v Morphine Group - morphine + naloxone |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | < 0.05 |
| Method | ANOVA |

## Adverse events

| Adverse events information[1] | |
|---|---|
| Timeframe for reporting adverse events: | |
| Period 1 and Period 2 | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 19 |

| Reporting groups | |
|---|---|
| Reporting group title | Placebo |
| Reporting group description: - | |
| Reporting group title | Morphine |
| Reporting group description: - | |

| Serious adverse events | Placebo | Morphine | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 20 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | Placebo | Morphine | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 20 (0.00%) | |

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: There were no adverse events.

There were side effects such as drowsiness, nausea and vomitting.

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported