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 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 Units: years			
arithmetic mean	23		
standard deviation	± 2	-	
Gender categorical 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 Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years arithmetic mean standard deviation	±	±	±
Gender categorical 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 Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			

Age continuous Units: years arithmetic mean standard deviation	± 	± 	±
Gender categorical 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