Clinical trial results:
The study comprises two sub-studies:

Study 1 (TME). Effect of High-dose Target-controlled Naloxone Infusion on Pain and Hyperalgesia in Patients following Recovery from Impacted Mandibular Third Molar Extraction. A Randomized, Placebo-controlled, Double-blind Crossover Study (n = 22)

Study 2 (BI): Highdose naloxone: Effects by late administration on pain and hyperalgesia following a human heat injury model. A randomized, double-blind, placebo-controlled, crossover trial with an enriched enrollment design (n = 80)

Study 1 has not been published yet, however, study 2 was published 2020, containing all the data in a supplemental file.

Study 1 included a main part (TME; n = 14) and a validation part (n = 8)

Please, cf. attached paper: Springborg AD, Jensen EK, Kreilgaard M, Petersen MA, Papathanasiou T, Lund TM, Taylor BK, Werner MU. High-dose naloxone: Effects by late administration on pain and hyperalgesia following a human heat injury model. A randomized, double-blind, placebo-controlled, crossover trial with an enriched enrollment design. PLoS One. 2020 Nov 12;15(11):e0242169. doi: 10.1371/journal.pone. 0242169. PMID: 33180816; PMCID: PMC7660513.)

Summary

EudraCT number	2015-005426-19
Trial protocol	DK
Global end of trial date	27 November 2023
Results information	
Result version number	v1 (current)
This version publication date	15 May 2025
First version publication date	15 May 2025
Summary attachment (see zip file)	Springborg et al. 2020 (Burn injury) (Springbord (2020) High-dose naloxone- Effects by late administration on pain and hyperalgesia following a human heat injury model. A randomized, double-blind, placebo- controlled, crossover trial with an enriched enrollment design.pdf) TME summary (Abstract_TME_final.pdf) Springborg et al. 2020 Adverse events (Springborg_BI_2020_Adverse_events.pdf) Study_1_full_dataset (Study_1_data.xlsx.pdf)

Trial information

Trial identification

Sponsor protocol code	51237

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02976337
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Rigshospitalet, Copenhagen University Hospitals
Sponsor organisation address	Blegdamsvej 9, Copenhagen, Denmark,
Public contact	Multidisciplinary Pain Center 7612,, Rigshospitalet, Copenhagen University Hospitals, +45 35457618,
Scientific contact	Multidisciplinary Pain Center 7612,, Rigshospitalet, Copenhagen University Hospitals, +45 35457618,

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	20 March 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 November 2023
Global end of trial reached?	Yes
Global end of trial date	27 November 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Study 1: The principal aim of the study is to investigate whether the administration of high-dose naloxone (3.25 mg/kg), a selective mu-opioid receptor (MOR) antagonist, can re-introduce pain (at rest, during mastication and during pressure-evoked condition) and hyperalgesia four to five weeks after unilateral, uncomplicated, impacted mandibular, third molar extraction.

Study 2: Please, cf. attached paper: Springborg AD, Jensen EK, Kreilgaard M, Petersen MA, Papathanasiou T, Lund TM, Taylor BK, Werner MU. High-dose naloxone: Effects by late administration on pain and hyperalgesia following a human heat injury model. A randomized, double-blind, placebo-controlled, crossover trial with an enriched enrollment design. PLoS One. 2020 Nov 12;15(11):e0242169. doi: 10.1371/journal.pone.0242169. PMID: 33180816; PMCID: PMC7660513.)

Protection of trial subjects:

In previous studies, naloxone given in doses of 2-4 mg/kg i.v. only caused mild side-effects in a minority of volunteers or patients (30%). These side-effects include: nausea, vomiting, weakness, fatigue, tremor, elevations of blood pressure and respiratory rate. During infusion of the drug, participants were monitored with ECG and measurements of pulse oximetry, blood pressure and respiratory rate. During the study a physician and a nurse were present to diagnose and manage development of adverse effects.

Background therapy: -

Evidence for comparator:

An inactive i.v. comparator (0.9% NaCl solution) was used.

Actual start date of recruitment	01 February 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 102
Worldwide total number of subjects	102
EEA total number of subjects	102

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)	102
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study 1: Male participants with unilateral, primary, uncomplicated, impacted mandibular third molar extraction were included between 16-NOV-2017 and 28-NOV-2023

Study 2: Please, cf. attached paper: Springborg et. al. PLoS One. 2020 Nov 12;15(11):e0242169. doi: 10.1371/journal.pone.0242169.

Pre-assignment

Screening details:

Inclusion criteria:
Healthy male
Age above 18 yrs and below 65 yrs
Signed informed consent
Participants submitted to unilateral, primary, impacted, uncomplicated mandibular third molar extraction 4 weeks (+/-3 days) prior to examination Day 1
Standardized surgical procedure
Urin-sample without traces of opioids
ASA I-II
BMI: >18 +<30 kg/m2

Period 1

Period 1 title	Study 1: Main part (TME)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst

Blinding implementation details:

This is a cross-over, block-randomized, double-blind study. Randomization (computer generated using Randomization.com; sequence-randomization in blocks of 4 subjects). Manufacturing, packaging and labelling of drugs were be performed by Skanderborg Hospital Pharmacy, Denmark. Two sets of non-transparent sealed envelopes with the complete randomization list were stored (one by the sponsor and one by the investigator).

Arms

Are arms mutually exclusive?	No
Arm title	Placebo

Arm description:

Placebo was normal saline (0.9% NaCl) delivered in vials of 100 ml.

Arm type	Placebo
Investigational medicinal product name	Saline (0.9% NaCl)
Investigational medicinal product code	
Other name	Normal saline
Pharmaceutical forms	Infusion
Routes of administration	Infusion , Intravenous use, Intravenous bolus use

Dosage and administration details:

Normal saline (0.9% NaCl) delivered by a target-controlled infusion.

Arm title	Naloxone

Arm description:

Naloxone 4 mg/ml, dissolved in a 0.9% NaCl solution, was delivered in vials of 100 ml (manufactured by Skanderborg Hospital Pharmacy, Denmark).

Arm type	Experimental

Investigational medicinal product name	Naloxone 4 mg/ml
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion , Intravenous bolus use , Intravenous use

Dosage and administration details:

Naloxone 4 mg/ml, dissolved in a 0.9% NaCl solution (manufactured by Skanderborg Hospital Pharmacy, Denmark), was delivered by a target-controlled infusion.

Number of subjects in period 1	Placebo	Naloxone
Started	14	14
Completed	14	14

Period 2

Period 2 title	Study 1: Test of validity
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

To validate that the assessment methods used in determining the primary and secondary outcomes had sufficient power to measure:
* primary outcomes: pain intensity scores (NRS 0-10) during rest, masticatory activities, and pressure algometry (100 kPa)
* secondary outcomes: areas of secondary hyperalgesia/allodynia, online reaction time assessments, and Clinical Opiate Withdrawal Scale scores

Arms

Are arms mutually exclusive?	Yes
Arm title	Study 1: Test of validity (pre-surgery)

Arm description:

To validate that the assessment methods used in determining the primary and secondary outcomes had sufficient power to measure:
* primary outcomes: pain intensity scores (NRS 0-10) during rest, masticatory activities, and pressure algometry (100 kPa)
* secondary outcomes: areas of secondary hyperalgesia/allodynia, online reaction time assessments, and Clinical Opiate Withdrawal Scale scores

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Study 1: Test of validity (post-surgery)

Arm description:

To validate that the assessment methods used in determining the primary and secondary outcomes had sufficient power to measure:
* primary outcomes: pain intensity scores (NRS 0-10) during rest, masticatory activities, and pressure algometry (100 kPa)
* secondary outcomes: areas of secondary hyperalgesia/allodynia, online reaction time assessments, and Clinical Opiate Withdrawal Scale scores

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 2	Study 1: Test of validity (pre-surgery)	Study 1: Test of validity (post-surgery)
Started	8	8
Completed	8	8

Baseline characteristics

Reporting groups[1]	
Reporting group title	Study 1: Main part (TME)
Reporting group description: -	

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.
Justification: The number of subjects in the studies are:
Study 1 (TME + validation): n = 14 (TME) + n = 8 (validation), as reported here.
Study 2 (Burn Injury): n = 80 (Burn injury), as reported in the attached paper (Springborg et al. 2020).

Total subjects in the studies: n = 102

Reporting group values	Study 1: Main part (TME)	Total	
Number of subjects	14	14	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	14	14	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	25.9		
standard deviation	± 4.3	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	14	14	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo was normal saline (0.9% NaCl) delivered in vials of 100 ml.	
Reporting group title	Naloxone
Reporting group description:	
Naloxone 4 mg/ml, dissolved in a 0.9% NaCl solution, was delivered in vials of 100 ml (manufactured by Skanderborg Hospital Pharmacy, Denmark).	
Reporting group title	Study 1: Test of validity (pre-surgery)
Reporting group description:	
To validate that the assessment methods used in determining the primary and secondary outcomes had sufficient power to measure: * primary outcomes: pain intensity scores (NRS 0-10) during rest, masticatory activities, and pressure algometry (100 kPa) * secondary outcomes: areas of secondary hyperalgesia/allodynia, online reaction time assessments, and Clinical Opiate Withdrawal Scale scores	
Reporting group title	Study 1: Test of validity (post-surgery)
Reporting group description:	
To validate that the assessment methods used in determining the primary and secondary outcomes had sufficient power to measure: * primary outcomes: pain intensity scores (NRS 0-10) during rest, masticatory activities, and pressure algometry (100 kPa) * secondary outcomes: areas of secondary hyperalgesia/allodynia, online reaction time assessments, and Clinical Opiate Withdrawal Scale scores	

Primary: Pain intensity score during rest

End point title	Pain intensity score during rest
End point description:	
Pain intensity score using the numerical rating scale (NRS 0-10) during rest	
End point type	Primary
End point timeframe:	
At study day 1+2 (main study): *Baseline: 20-9 min. before infusion (target-controlled infusion (TCI)) *TCI 1:15-25 min. after infusion start *TCI 2: 39-49 min. after infusion start *TCI 3: 65-75 min. after infusion start	

End point values	Placebo	Naloxone	Study 1: Test of validity (pre-surgery)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	14	8	
Units: NRS 0-10	14	14	8	

Statistical analyses

Statistical analysis title	Pain at rest
Comparison groups	Placebo v Naloxone
Number of subjects included in analysis	28
Analysis specification	Post-hoc
Analysis type	superiority[1]
P-value	= 1
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0
Variability estimate	Standard deviation
Dispersion value	0

Notes:

[1] - None of the participants reported pain at rest at any of the measurement time points at any of the study days.

Primary: Pain intensity score during masticatory activities

End point title	Pain intensity score during masticatory activities

End point description:

Pain intensity score using the numerical rating scale (NRS 0-10) during masticatory activities

End point type	Primary

End point timeframe:

At study day 1+2 (main study):
*Baseline: 20-9 min. before infusion (target-controlled infusion (TCI))
*TCI 1:15-25 min. after infusion start
*TCI 2: 39-49 min. after infusion start
*TCI 3: 65-75 min. after infusion start

End point values	Placebo	Naloxone	Study 1: Test of validity (pre-surgery)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	14	8	
Units: NRS 0-10	14	14	8	

Statistical analyses

Statistical analysis title	Pain intensity during masticatory activities
Comparison groups	Placebo v Naloxone

Number of subjects included in analysis	28
Analysis specification	Post-hoc
Analysis type	superiority[2]
P-value	= 0.2021
Method	ANOVA

Notes:

[2] - ANOVA, where the pain intensity during masticatory activities, was the outcome variable and the measurement time points (baseline, TCI1, TCI2, TCI3) and treatment (Naloxone vs. Placebo) were the predictor variables.

Primary: Pain intensity score applying an external algometry (100 kPa)

End point title	Pain intensity score applying an external algometry (100 kPa)

End point description:

Pain intensity score using the numerical rating scale (NRS 0-10) when applying an external algometry (100 kPa) at the skin sites above the surgical area.

End point type	Primary

End point timeframe:

At study day 1+2 (main study):
*Baseline: 20-9 min. before infusion (target-controlled infusion (TCI))
*TCI 1:15-25 min. after infusion start
*TCI 2: 39-49 min. after infusion start
*TCI 3: 65-75 min. after infusion start

End point values	Placebo	Naloxone	Study 1: Test of validity (pre-surgery)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	14	8	
Units: NRS 0-10	14	14	8	

Statistical analyses

Statistical analysis title	Pain intensity when applying external algometry
Comparison groups	Placebo v Naloxone
Number of subjects included in analysis	28
Analysis specification	Post-hoc
Analysis type	superiority[3]
P-value	= 0.3304
Method	ANOVA

Notes:

[3] - ANOVA, where the pain intensity when applying external algometry was the outcome variable and the measurement time points (baseline, TCI1, TCI2, TCI3) and treatment (Naloxone vs. Placebo) were the predictor variables.

Secondary: Area of secondary hyperalgesia/allodynia

End point title	Area of secondary hyperalgesia/allodynia

End point description:

Secondary outcomes included assessment of area of secondary hyperalgesia/allodynia at mandibular skin sites above the surgical area and on the contralateral side (by nylon monofilament testing)

End point type	Secondary

End point timeframe:

At study day 1+2 (main study):
*Baseline: 20-9 min. before infusion (target-controlled infusion (TCI))
*TCI 1:15-25 min. after infusion start
*TCI 2: 39-49 min. after infusion start
*TCI 3: 65-75 min. after infusion start

End point values	Placebo	Naloxone	Study 1: Test of validity (pre-surgery)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	14	8	
Units: 0-1	14	14	8	

Statistical analyses

Statistical analysis title	Area of secondary hyperalgesia/allodynia
Comparison groups	Placebo v Naloxone
Number of subjects included in analysis	28
Analysis specification	Post-hoc
Analysis type	superiority[4]
P-value	= 1 [5]
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0
Variability estimate	Standard deviation
Dispersion value	0

Notes:

[4] - None of the participants reported an area of secondary hyperalgesia/allodynia at any of the measurement time points at any of the study days (1 or 2).
[5] - None of the participants reported an area of secondary hyperalgesia/allodynia at any of the measurement time points at any of the study days (1 or 2).

Secondary: Online reaction time assessment

End point title	Online reaction time assessment

End point description:

Online reaction time assessment

End point type	Secondary

End point timeframe:

At study day 1+2 (main study)
*Baseline: 20-9 min. before infusion (target-controlled infusion (TCI))
*TCI 1:15-25 min. after infusion start
*TCI 2: 39-49 min. after infusion start
*TCI 3: 65-75 min. after infusion start

End point values	Placebo	Naloxone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: ms				
number (not applicable)	14	14		

Statistical analyses

Statistical analysis title	Online reaction time
Comparison groups	Placebo v Naloxone
Number of subjects included in analysis	28
Analysis specification	Post-hoc
Analysis type	superiority[6]
P-value	= 0.6993
Method	ANOVA

Notes:

[6] - Two-way repeated measures ANOVA, where the online reaction time was the outcome variable and the measurement time points (baseline, TCI1, TCI2, TCI3) and treatment (Naloxone vs. Placebo) were the predictor variables.

Secondary: Clinical Opiate Withdrawal Scale (COWS) scores

End point title	Clinical Opiate Withdrawal Scale (COWS) scores

End point description:

Clinical Opiate Withdrawal Scale (COWS) scores

End point type	Secondary

End point timeframe:

At study day 1+2 (main study):
*Baseline: 20-9 min. before infusion (target-controlled infusion (TCI))
*TCI 1:15-25 min. after infusion start
*TCI 2: 39-49 min. after infusion start
*TCI 3: 65-75 min. after infusion start

End point values	Placebo	Naloxone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: 0-48	14	14		

Statistical analyses

Statistical analysis title	Clinical Opiate Withdrawal Scale
Comparison groups	Placebo v Naloxone

Number of subjects included in analysis	28
Analysis specification	Post-hoc
Analysis type	superiority[7]
P-value	= 0.3737
Method	ANOVA

Notes:

[7] - Two-way repeated measures ANOVA, where the COWS was the outcome variable and the measurement time points (baseline, TCI1, TCI2, TCI3) and treatment (Naloxone vs. Placebo) were the predictor variables.

Post-hoc: Validity: pain at rest

End point title	Validity: pain at rest

End point description:

Pain intensity score using the numerical rating scale (NRS 0-10) during rest

End point type	Post-hoc

End point timeframe:

Immediately before and 24 hrs after the TME

End point values	Study 1: Test of validity (pre-surgery)	Study 1: Test of validity (post-surgery)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	8		
Units: NRS 0-10	8	8		

Statistical analyses

Statistical analysis title	Validity: pain at rest

Statistical analysis description:

To validate that the assessment methods used in determining the primary and secondary outcomes had sufficient power to measure:
* primary outcomes: pain intensity scores (NRS 0-10) during rest, masticatory activities, and pressure algometry (100 kPa)
* secondary outcomes: areas of secondary hyperalgesia/allodynia, online reaction time assessments, and Clinical Opiate Withdrawal Scale scores

Comparison groups	Study 1: Test of validity (pre-surgery) v Study 1: Test of validity (post-surgery)
Number of subjects included in analysis	16
Analysis specification	Post-hoc
Analysis type	other[8]
P-value	= 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	3.876
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.741
upper limit	5.009

Notes:

[8] - Paired sample t-test

Post-hoc: Validity: pain during masticatory activities

End point title	Validity: pain during masticatory activities

End point description:

To validate that the assessment methods used in determining the primary and secondary outcomes had sufficient power to measure:
* primary outcomes: pain intensity scores (NRS 0-10) during rest, masticatory activities, and pressure algometry (100 kPa)
* secondary outcomes: areas of secondary hyperalgesia/allodynia, online reaction time assessments, and Clinical Opiate Withdrawal Scale scores

End point type	Post-hoc

End point timeframe:

Immediately before and 24 hours after the TME.

End point values	Study 1: Test of validity (pre-surgery)	Study 1: Test of validity (post-surgery)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	8		
Units: NRS 0-10	8	8		

Statistical analyses

Statistical analysis title	Validity: Pain during masticatory activities

Statistical analysis description:

To ascertain that the assessment methods used in determining the primary and secondary outcome had sufficient power to measure the pain-related issues they intend to measure the validity of the assessment methods the primary outcome measures were tested immediately before and 24 hours after an elective uncomplicated third molar mandibular extraction.

Comparison groups	Study 1: Test of validity (pre-surgery) v Study 1: Test of validity (post-surgery)
Number of subjects included in analysis	16
Analysis specification	Post-hoc
Analysis type	other[9]
P-value	= 0.0008
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	4.974
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.806
upper limit	6.944

Notes:

[9] - Paired sample t-test

Post-hoc: Validity: pain intensity during external algometry

End point title	Validity: pain intensity during external algometry

End point description:

To validate that the assessment methods used in determining the primary and secondary outcomes had sufficient power to measure:
* primary outcomes: pain intensity scores (NRS 0-10) during rest, masticatory activities, and pressure algometry (100 kPa)
* secondary outcomes: areas of secondary hyperalgesia/allodynia, online reaction time assessments, and Clinical Opiate Withdrawal Scale scores

End point type	Post-hoc

End point timeframe:

Immediately before and 24 hours after the TME.

End point values	Study 1: Test of validity (pre-surgery)	Study 1: Test of validity (post-surgery)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	8		
Units: NRS 0-10	8	8		

Statistical analyses

Statistical analysis title	Validity: Pain intensity external algometry

Statistical analysis description:

To ascertain that the assessment methods used in determining the primary and secondary outcome had sufficient power to measure the pain-related issues they intend to measure the validity of the assessment methods the primary outcome measures were tested immediately before and 24 hours after an elective uncomplicated third molar mandibular extraction.

Comparison groups	Study 1: Test of validity (post-surgery) v Study 1: Test of validity (pre-surgery)
Number of subjects included in analysis	16
Analysis specification	Post-hoc
Analysis type	other[10]
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	5.875
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.741
upper limit	7.008

Notes:

[10] - Paired sample t-test

Post-hoc: Validity: area of secondary hyperalgesia/allodynia

End point title	Validity: area of secondary hyperalgesia/allodynia

End point description:

To validate that the assessment methods used in determining the primary and secondary outcomes had sufficient power to measure:
* primary outcomes: pain intensity scores (NRS 0-10) during rest, masticatory activities, and pressure algometry (100 kPa)
* secondary outcomes: areas of secondary hyperalgesia/allodynia, online reaction time assessments, and Clinical Opiate Withdrawal Scale scores

End point type	Post-hoc

End point timeframe:

Immediately before and 24 hours after the TME.

End point values	Study 1: Test of validity (pre-surgery)	Study 1: Test of validity (post-surgery)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	8		
Units: cm2	8	8		

Statistical analyses

Statistical analysis title	Area of secondary hyperalgesia/allodynia

Statistical analysis description:

To ascertain that the assessment methods used in determining the primary and secondary outcome had sufficient power to measure the pain-related issues they intend to measure the validity of the assessment methods the primary outcome measures were tested immediately before and 24 hours after an elective uncomplicated third molar mandibular extraction.

Comparison groups	Study 1: Test of validity (pre-surgery) v Study 1: Test of validity (post-surgery)
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	14.625
Confidence interval	
level	95 %
sides	2-sided
lower limit	12.139
upper limit	17.111
Variability estimate	Standard deviation

Notes:

[11] - Paired sample t-test

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Study1: During main study 15-OCT-2017-31-MAY-2018

Study 2: Please, cf. attached paper: Springborg et al. 2020 BI + Supplemental file: Springborg et al. 2020 Adverse events.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	28.0

Reporting groups

Reporting group title	Naloxone

Reporting group description:

Naloxone 4 mg/ml, dissolved in a 0.9% NaCl solution, was delivered in vials of 100 ml (manufactured by Skanderborg Hospital Pharmacy, Denmark).

Serious adverse events	Naloxone		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 14 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Naloxone		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 14 (28.57%)		
Nervous system disorders			
Anxiety			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Cognitive dysfunction			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		

Hyperacusis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Paraesthesias			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Soreness surgical area			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Tachycardia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Transitory motor dysfunction			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Vertigo			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Xerostomia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 April 2023	To validate that the assessment methods used in determining the primary and secondary outcomes had sufficient power to measure: * primary outcomes: pain intensity scores (NRS 0-10) during rest, masticatory activities, and pressure algometry (100 kPa) * secondary outcomes: areas of secondary hyperalgesia/allodynia, online reaction time assessments, and Clinical Opiate Withdrawal Scale scores

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported