Clinical trial results:
NTNU Intranasal Naloxone Trial
Double blinded, double dummy, randomised controlled trial of intranasal naloxone for pre hospital use

Summary

EudraCT number	2016-004072-22
Trial protocol	NO
Global end of trial date	06 October 2020

Results information

Result version number	v1 (current)
This version publication date	30 April 2022
First version publication date	30 April 2022
Summary attachment (see zip file)	Clinical Study Report (NINA1_Clinical Study Report incl appendix.pdf)

Trial information

Trial identification

Sponsor protocol code	NINA-1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03518021
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Department of Circulation and Imaging, NTNU
Sponsor organisation address	AHL Senteret St. Olavs, Trondheim, Norway,
Public contact	Dept. secretary, Department of Circulation and Imaging, NTNU, 47 73595000, isb-post@medisin.ntnu.no
Scientific contact	Dept. secretary, Department of Circulation and Imaging, NTNU, 47 73595000, isb-post@medisin.ntnu.no

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	30 October 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 October 2020
Global end of trial reached?	Yes
Global end of trial date	06 October 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Measure and evaluate clinical response to nasal naloxone in real opioid overdoses in the pre hospital environment.

Protection of trial subjects:

Patients included in the NINA-1 trial were in several ways vulnerable patients. Opioid users are often considered a vulnerable group in society. The risk of overdose is particularly high for people injecting opioids (heroin), and our inclusion criteria selects out participants with high risk drug use.

Article 20 of the Helsinki Declaration describes research on vulnerable participants. It states that "Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non- vulnerable group". Nasal naloxone is a drug designed especially for the group at risk of opioid overdoses, as emergency treatment of a life threatening condition. Further the declaration states Article 30 regulates the situation of unconscious patients with no legal representative present within the time period research must happen. "Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group". Our inclusion criteria describe exactly such a group- where unconsciousness (low GCS) is an inclusion criterion. This protection was mainly that all other treatment options were unchanged, the only aspect of treatment altered was the dose and route of administration of naloxone. Airway, breathing and follow up was the same for included and not included patients.

Patients were included by trained ambulance personnel, with wide experience in treating opioid intoxicated patients. In addition to the existing professional training they all received study specific training in how to conduct the trial and ensure the well being and safety of participants.

The trial was approved by the Ethics committee and an independent Data Monitoring and Safety Board was in place.

Background therapy:

Patients recruited in this trial were treated by ambulance personnel outside of hospital, and showed signs of opioid intoxication as recognised by coma, respiratory depression and miosis. All such patents were meet with the ABC approach, meaning Airway assessment and management, B breathing: assessment and bag/ mask ventilation if insufficient spontaneous breathing and C Circulation: assessment of circulatory status and management. This was unchanged in the trial protocol, and meant that all included patients received such treatment. The ABC examination and observations were included throughout the trial period, with measurement of blood oxygen saturation, heart rate and blood pressure as warranted. All patients included in the trial received the same care after naloxone treatment as patients not included. This meant follow up in primary or secondary care, or being left at the scene of the overdose; the latter against medical advice.

Evidence for comparator:

Naloxone is a competitive antagonist of μ, δ and κ-opioid receptors and it is most potent at the μ-receptor. It rapidly reverses the effect of morphine and other opioids. The indication for the administration of naloxone in the pre-hospital setting is complete or partial reversal of central nervous

system and/ or respiratory depression, caused by natural or synthetic opioids.

The dose of naloxone needed to treat an opioid overdose varies. Titration, incremental increase in drug dosage to a level of optimal therapeutic effect, is the cornerstone of treatment with this antidote. The medical literature reflects this dosing range and titration principle with recommendations for starting dose ranging all the way between 0.02 and 2.0 mg IV . Pre- trial practice in the participating ambulance services reflected this, with dosing recommendations of 0.4- 0.8 mg intramuscular (IM) naloxone hydrochloride as the primary treatment, with the consideration of intravenous use if feasible. As the inclusion criteria in the trial were severe intoxication the comparator dose was set to 0.8 mg IM naloxone, with additional naloxone given after 10 minutes if nor response, or prior to 10 minutes if patients sate deteriorated.

Actual start date of recruitment	14 June 2018
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	Norway: 286
Worldwide total number of subjects	286
EEA total number of subjects	286

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)	286
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited through the Oslo University Hospital Ambulance Service and Trondheim University Hospital St. Olav's Ambulance Service, both in Norway. Sites opened in June 2018 and closed in august 2020. Patients were included 24 hours a day, by ambulance personnel with study specific training.

Pre-assignment

Screening details:

In the trial period participating sites has a total of n= 97008 callouts, of which n= 965 assessed for eligibility. n=679 was excluded from the trial, but received naloxone according to local guidelines

Period 1

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

Blinding implementation details:

To ensure blinding, a double-dummy design is used. Participants are administered both a nasal spray and an intramuscular injection at the same time, of which one contains naloxone and the other an inactive substance. This ensures that all patients receive naloxone and that both the patient and study workers are blinded for the treatment which the patient is allocated. The blinding assembly, randomisation of kits was performed the pharmacy of the Central Norwegian Regional Health Authority

Arms

Are arms mutually exclusive?	Yes
Arm title	Intranasal naloxone

Arm description:

Active naloxone nasal spray and placebo intramuscular injection

Arm type	Experimental
Investigational medicinal product name	Nasal naloxone 1.4 mg/dose
Investigational medicinal product code	ATC: V03AB15
Other name	Nalokson DnE Nasal Spray 14 mg/mL
Pharmaceutical forms	Nasal spray, solution in single-dose container
Routes of administration	Intranasal use

Dosage and administration details:

The investigational medicinal product (IMP) is a 1.4 mg naloxone hydrochloride nasal spray. This drug is administered as 1.4 mg/0.1 mL nasal spray using the Aptar Unit Dose Device (Louveciennes, France). Spray was produced by Sanivo Pharma, Oslo, Norway. Participants are administered both a nasal spray and an intramuscular injection at the same time, of which one contains naloxone and the other an inactive substance. This ensures that all patients receive naloxone and that both the patient and study workers are blinded for the treatment which the patient is allocated. The drugs will be administered as simultaneously as possible, and within 30 s of each other. The IN spray is administered first if unable to coordinate simultaneous administration on site

Investigational medicinal product name	0,9% Sodium Chloride Injection
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Participants are administered both a nasal spray and an intramuscular injection at the same time, of which one contains naloxone and the other an inactive substance. This ensures that all patients receive naloxone and that both the patient and study workers are blinded for the treatment which the patient is allocated. The drugs will be administered as simultaneously as possible, and within 30 s of each other.

The IN spray is administered first if unable to coordinate simultaneous administration on site. The IM placebo was administered as 2 ml intramuscular injection in the deltoid muscle

Arm title	Intramuscular naloxone

Arm description:

Active intramuscular naloxone and placebo nasal spray

Arm type	Active comparator
Investigational medicinal product name	Naloxone Hydrochloride Injection, USP
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Participants are administered both a nasal spray and an intramuscular injection at the same time, of which one contains naloxone and the other an inactive substance. This ensures that all patients receive naloxone and that both the patient and study workers are blinded for the treatment which the patient is allocated. The drugs will be administered as simultaneously as possible, and within 30 s of each other. The IN spray is administered first if unable to coordinate simultaneous administration on site. The active comparator is 2 mL naloxone hydrochloride (0.4 mg/mL), with a total dose of 0.8 mg. The intramuscular injection should be given in the deltoid muscle.

Investigational medicinal product name	Placebo nasal spray
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray, solution in single-dose container
Routes of administration	Intranasal use

Dosage and administration details:

0.1 ml nasal spray in Aptar Unit Dose container. Produced by Sanivo Pharma. Contained Povidone, Glycerol, Disodium edetate Benzalkonium chloride, Citric acid monohydrate, Sodium citrate, Sodium hydroxide (for pH-adjustment) Hydrochloric acid (for pH-adjustment) Water for injections. Did not contain naloxone

Number of subjects in period 1	Intranasal naloxone	Intramuscular naloxone
Started	139	147
Completed	95	113
Not completed	44	34
Consent withdrawn by subject	14	16
Not received study drug	30	-
Did not receive study drug	-	18

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description:

Please note that due to the trial design 286 participants were randomised to treatment. However, 48 participants woke up or did in other ways not any longer meet inclusion/ exclusion criteria in the short period between randomisation and study drug administration. Only participants being administered study drug (IMP) were asked for consent. Therefor the age/ gender characteristics for these 48 participants are not recorded, and the reported age and gender ratio reflects the Full Analysis Set

Reporting group values	Overall trial	Total	
Number of subjects	286	286	
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)	286	286	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	37.86		
standard deviation	± 10.56	-	
Gender categorical Units: Subjects			
Female	57	57	
Male	229	229	

Subject analysis sets

Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

In EudraCT we report Full analysis set (FAS): All events where the patient received study medicine and where the patient did not refuse or withdrew consent. Please note we report events, not individuals, these 208 events constitute 161 individuals, some included multiple times

Other subject sets analysed were:
- All randomized overdose events: All events that have been randomized whether or not the patient received treatment.
- Safety Set: All events where the patient received study medicine (full or partial adherence to allocated treatment) and including anonymous data on from participants who have not consented
- Per protocol set (PPS): All events where the patient received study medicine fully compliant with the study protocol and where the patient did not refuse or withdrew consent.

Subject analysis set title	Per Protocol set

Subject analysis set type	Per protocol

Subject analysis set description:

Per protocol set (PPS): All events where the patient received study medicine fully compliant with the study protocol and where the patient did not refuse or withdrew consent.

Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety Set: All events where the patient received study medicine (full or partial adherence to allocated treatment) and including anonymous data on from participants who have not consented

Reporting group values	Full Analysis Set (FAS)	Per Protocol set	Safety Set
Number of subjects	208	201	238
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	201	238
From 65-84 years	208		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean	37.86		
standard deviation	± 10.56	±	±
Gender categorical			
Units: Subjects			
Female	37	36	
Male	169	163	

End points

End points reporting groups

Reporting group title	Intranasal naloxone
Reporting group description:	
Active naloxone nasal spray and placebo intramuscular injection	
Reporting group title	Intramuscular naloxone
Reporting group description:	
Active intramuscular naloxone and placebo nasal spray	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
In EudraCT we report Full analysis set (FAS): All events where the patient received study medicine and where the patient did not refuse or withdrew consent. Please note we report events, not individuals, these 208 events constitute 161 individuals, some included multiple times Other subject sets analysed were: • All randomized overdose events: All events that have been randomized whether or not the patient received treatment. • Safety Set: All events where the patient received study medicine (full or partial adherence to allocated treatment) and including anonymous data on from participants who have not consented • Per protocol set (PPS): All events where the patient received study medicine fully compliant with the study protocol and where the patient did not refuse or withdrew consent.	

Subject analysis set title	Per Protocol set
Subject analysis set type	Per protocol
Subject analysis set description:	
Per protocol set (PPS): All events where the patient received study medicine fully compliant with the study protocol and where the patient did not refuse or withdrew consent.	
Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Safety Set: All events where the patient received study medicine (full or partial adherence to allocated treatment) and including anonymous data on from participants who have not consented	

Primary: Proportion of patients with return of spontaneous respiration (above or equal to 10 breaths per minute) within 10 minutes of naloxone administration in pre-hospital opioid overdose.

End point title	Proportion of patients with return of spontaneous respiration (above or equal to 10 breaths per minute) within 10 minutes of naloxone administration in pre-hospital opioid overdose.
End point description:	
Ambulance staff should note the number of minutes from the administration of the study medicine to a spontaneous respiration rate of ≥10 breaths/min.	
End point type	Primary
End point timeframe:	
Within 10 minutes of being administered study drug.	

End point values	Intranasal naloxone	Intramuscular naloxone	Full Analysis Set (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	95	113	208	
Units: number of patients	76	110	208	

Attachments (see zip file)	Primary end-point/primaryOnlyFAS-1.pdf

Statistical analyses

Statistical analysis title	logistic regression

Statistical analysis description:

The dichotomous treatment variable will be adjusted by study site. To account for the the same individual may be included several times the parameters in the model will be estimated by the means of generalized estimating equations (GEE) with exchangeable working correlation. Once the logistic regression model has been fitted to the data, the difference in the marginal predicted probabilities of returning to spontaneous breathing within 10 minutes will be calculated for each group.

Comparison groups	Intranasal naloxone v Intramuscular naloxone
Number of subjects included in analysis	208
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Risk difference (RD)
Point estimate	17.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.9
upper limit	25.6

Notes:

[1] - The primary effect estimate will be the difference in the marginal predicted probabilities of returning to spontaneous breathing within 10 minutes between the groups. This adjusted risk difference will be presented as the risk in the control group minus the risk in the active group If the upper bound of the 95% confidence interval of the risk difference is less than 0.15, then non-inferiority of the active treatment (intranasal naloxone) to the control treatment will be claimed.

Secondary: Changes in Glasgow Coma Scale 0 to 10 minutes

End point title	Changes in Glasgow Coma Scale 0 to 10 minutes

End point description:

Changes in Glasgow Coma Scale from 0 to 10 minutes where 0 is time naloxone is administered

End point type	Secondary

End point timeframe:

0- 10 minutes

End point values	Intranasal naloxone	Intramuscular naloxone	Per Protocol set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	93	108	201	
Units: Glasgow Coma Score	93	108	201	

Statistical analyses

Statistical analysis title	linear regression model

Statistical analysis description:

A linear regression model will be fitted to the data, with the change value (for GCS and oxygen saturation, respectively) as the dependent variable. The dichotomous treatment variable will be adjusted for by study site and the initial measurement before the trial. The model parameters will be fitted using GEE with exchangeable working correlation, to account for the clustering of the data (possibly more than one overdose in each individual).

Comparison groups	Intramuscular naloxone v Intranasal naloxone
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Mean difference (final values)
Point estimate	1.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	3.05

Secondary: Changes in oxygen saturation (SpO2)

End point title	Changes in oxygen saturation (SpO2)

End point description:

Oxygen saturation, SpO2 = oxygen saturation as measured by light absorptionn through a non-invasive pulse oximeter. It is the fraction of oxygen-saturated haemoglobin relative to total haemoglobin (unsaturated + saturated) in the blood. SpO2 is given as a percentage.

The change in SpO2 as measured before the intervention (at baseline), to the SpO2 value measured at the end of the intervention (at 10 minutes). This is a continuous outcome.

End point type	Secondary

End point timeframe:

The change in SpO2 as measured before the intervention (at baseline), to the SpO2 value measured at the end of the intervention (at 10 minutes). This is a continuous outcome.

End point values	Intranasal naloxone	Intramuscular naloxone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93	108		
Units: percent				
number (confidence interval 95%)	22.1 (18.3 to 25.9)	21.8 (14.7 to 28.8)		

Statistical analyses

Statistical analysis title	linear Regression

Statistical analysis description:

A linear regression model will be fitted to the data, with the change value (for GCS and oxygen saturation, respectively) as the dependent variable. The dichotomous treatment variable will be adjusted for by study site and the initial measurement before the trial. The model parameters will be fitted using GEE with exchangeable working correlation, to account for the clustering of the data (possibly more than one overdose in each individual).

Comparison groups	Intranasal naloxone v Intramuscular naloxone
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.1
upper limit	10.4

Secondary: Overdose complications

End point title	Overdose complications

End point description:

Whether or not the patient has an overdose complication. This is recorded during the time of protocol therapy. This is a dichotomous outcome.

End point type	Secondary

End point timeframe:

From Naloxone administered until end of observation time

End point values	Intranasal naloxone	Intramuscular naloxone	Per Protocol set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	93	108	201	
Units: number of patients	93	108	201	

Statistical analyses

Statistical analysis title	logistic regression model.

Statistical analysis description:

The dichotomous treatment variable will be adjusted by study site (the stratification factor used in the randomisation). To account for the possibility that the same individual may be included several times in the trial (i.e. the same person can have several overdoses), the parameters in the logistic regression model will be estimated by the means of generalized estimating equations (GEE) with exchangeable working correlation. Once the logistic regression model has been fitted to the data, the d

Comparison groups	Intranasal naloxone v Intramuscular naloxone
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Mean difference (final values)
Point estimate	0.012
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.053
upper limit	0.077

Secondary: Opioid withdrawal reaction to naloxone reversal

End point title	Opioid withdrawal reaction to naloxone reversal

End point description:

Adverse reactions defined as opioid withdrawal syndromes (MedDra lowest level term (LLT) 10030882). It includes responses subjectively described as abstinence, agitation or aggression. Nausea and vomiting are excluded, and perorated separately as Adverse Events

End point type	Secondary

End point timeframe:

From administration of naloxone to end of observation

End point values	Intranasal naloxone	Intramuscular naloxone	Per Protocol set	Safety Set
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	93	108	201	238
Units: Events with opioid withdrawal	93	108	201	238

Statistical analyses

Statistical analysis title	logistic regression model Per protocol Set

Statistical analysis description:

The will be adjusted by study site . To account for the possibility that the same individual may be included several times in the trial the parameters in the logistic regression model will be estimated by the means of generalized estimating equations (GEE) with exchangeable working correlation. Once the logistic regression model has been fitted to the data, the difference in the marginal predicted will be calculated for each group. There will be no assumption checks performed

Comparison groups	Intranasal naloxone v Intramuscular naloxone

Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Mean difference (final values)
Point estimate	0.012
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.053
upper limit	0.077

Statistical analysis title	logistic regression model safety Set

Statistical analysis description:

The will be adjusted by study site . To account for the possibility that the same individual may be included several times in the trial the parameters in the logistic regression model will be estimated by the means of generalized estimating equations (GEE) with exchangeable working correlation. Once the logistic regression model has been fitted to the data, the difference in the marginal predicted will be calculated for each group. There will be no assumption checks performed

Comparison groups	Intranasal naloxone v Intramuscular naloxone
Number of subjects included in analysis	201
Analysis specification	Post-hoc
Analysis type	non-inferiority[2]
Parameter estimate	Mean difference (final values)
Point estimate	6.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	13

Notes:

[2] - A post hoc analysis was performed on the safety set: All events where the patient received study medicine (full or partial adherence to allocated treatment) and including anonymous data on from participants who have not consented

Secondary: Adverse reactions to naloxone formulation

End point title	Adverse reactions to naloxone formulation

End point description:

Whether or not the patient has an adverse reaction to the naloxone formulation. This is recorded during the time of protocol therapy. This is a dichotomous outcome. An adverse event deemed to have a certain, probable/likely or possible causal relationship to the IMP will be classified as an adverse reaction.

End point type	Secondary

End point timeframe:

From naloxone administration to end of observation

End point values	Intranasal naloxone	Intramuscular naloxone	Per Protocol set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	93	108	201	
Units: Number of events	93	108	201	

Statistical analyses

Statistical analysis title	logistic regression model

Statistical analysis description:

The will be adjusted by study site . To account for the possibility that the same individual may be included several times in the trial the parameters in the logistic regression model will be estimated by the means of generalized estimating equations (GEE) with exchangeable working correlation. Once the logistic regression model has been fitted to the data, the difference in the marginal predicted will be calculated for each group. There will be no assumption checks performed

Comparison groups	Intramuscular naloxone v Intranasal naloxone
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.022
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.116
upper limit	0.071

Secondary: Need for rescue naloxone

End point title	Need for rescue naloxone

End point description:

This is defined as patients treated with non- IMP naloxone in addition to study drug during the study visit, or immediately after transfer to follow up. Some patients will be in clinical need of further naloxone, but not have this given for various reasons. Such reasons not to give rescue naloxone to non-responders will be recorded and listed.

End point type	Secondary

End point timeframe:

From naloxone administration until end of treatment

End point values	Intranasal naloxone	Intramuscular naloxone	Per Protocol set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	93	108	201	
Units: Number of events	93	108	201	

Statistical analyses

Statistical analysis title	logistic regression model

Statistical analysis description:

The will be adjusted by study site . To account for the possibility that the same individual may be included several times in the trial the parameters in the logistic regression model will be estimated by the means of generalized estimating equations (GEE) with exchangeable working correlation. Once the logistic regression model has been fitted to the data, the difference in the marginal predicted will be calculated for each group. There will be no assumption checks performed

Comparison groups	Intranasal naloxone v Intramuscular naloxone
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.194
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.297
upper limit	-0.09

Secondary: Recurrence of opioid overdose

End point title	Recurrence of opioid overdose

End point description:

Recurrence is defined as having received naloxone within 12 hours after discharge from study visit. This includes Take Home Naloxone known to Emergency medical Services, or naloxone administered by the ambulance service. It is assessed by analysing medical records in the Ambulance Service for ambulance callouts to individuals included with known national Identity Number for 12 hours following inclusion in this trial. However, patients who receive Take-Home Naloxone without involving the ambulance service will not be recorded. Patients suffering a fatal overdose in this 12-hour window may not be registered in the trial as the study database will not be linked to the Norwegian National Cause of Death Registry

End point type	Secondary

End point timeframe:

from naloxone administration and 12 hours onwards

End point values	Intranasal naloxone	Intramuscular naloxone	Per Protocol set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	93	108	201	
Units: Numbe of events	93	108	201	

Statistical analyses

Statistical analysis title	logistic regression model

Statistical analysis description:

The will be adjusted by study site . To account for the possibility that the same individual may be included several times in the trial the parameters in the logistic regression model will be estimated by the means of generalized estimating equations (GEE) with exchangeable working correlation. Once the logistic regression model has been fitted to the data, the difference in the marginal predicted will be calculated for each group. There will be no assumption checks performed

Comparison groups	Intramuscular naloxone v Intranasal naloxone
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.002
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.067
upper limit	0.063

Secondary: Follow up after care.

End point title	Follow up after care.

End point description:

Risk of being followed-up at hospital or by primary care as opposed to being left at the scene without further health service follow up.
Defined as the level of health care to which the patient is transferred after treatment by ambulance services, or if left at the scene.
The variable contains the following categories:
1. Left at the scene of treatment. This represent patients who are not transported to further care or follow up after treatment with study drug.
2. Handed over to primary care. In Norway defined as general practitioners and Accident and Emergency Outpatient Clinic (Kommunal legevakt).
3. Handed over to hospital. Patient is transferred to tertiary care, defined as hospitals with facilities for advanced medical investigations and treatment.
4. Others. Some patients are transferred to places not fitting any of these categories, such as drug-user shelters.

End point type	Secondary

End point timeframe:

From naloxone administration until end of obervation

End point values	Intranasal naloxone	Intramuscular naloxone	Per Protocol set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	93	108	201	
Units: number of events	93	108	201	

Statistical analyses

Statistical analysis title	logistic regression model

Statistical analysis description:

The will be adjusted by study site . To account for the possibility that the same individual may be included several times in the trial the parameters in the logistic regression model will be estimated by the means of generalized estimating equations (GEE) with exchangeable working correlation. Once the logistic regression model has been fitted to the data, the difference in the marginal predicted will be calculated for each group. There will be no assumption checks performed

Comparison groups	Intranasal naloxone v Intramuscular naloxone
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.112
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.237
upper limit	0.013

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are reported for the treatment period of 10 minutes with a further observation time of up to 30 minutes. No adverse events are reported after ambulance service has left the patient.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Safety Set

Reporting group description:

Safety Set: All events where the patient received study medicine (full or partial adherence to allocated treatment) and including anonymous data on from participants who have not consented.

Please note this section reports overdose events, not subjects as this trial has some individuals being included on more than one occasion.

Reporting group title	Intranasal naloxone
Reporting group description: -	
Reporting group title	Intramuscular naloxone

Reporting group description: -

Serious adverse events	Safety Set	Intranasal naloxone	Intramuscular naloxone
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 238 (0.42%)	1 / 109 (0.92%)	0 / 129 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
Bradycardia	Additional description: Self limiting and not receiving treatment		
subjects affected / exposed	1 / 238 (0.42%)	1 / 109 (0.92%)	0 / 129 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Safety Set	Intranasal naloxone	Intramuscular naloxone
Total subjects affected by non-serious adverse events			
subjects affected / exposed	61 / 238 (25.63%)	18 / 109 (16.51%)	26 / 129 (20.16%)
Cardiac disorders			

Arrhythmia			
subjects affected / exposed	1 / 238 (0.42%)	1 / 109 (0.92%)	0 / 129 (0.00%)
occurrences (all)	1	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 238 (0.42%)	0 / 109 (0.00%)	1 / 129 (0.78%)
occurrences (all)	1	0	1
Headache			
subjects affected / exposed	9 / 238 (3.78%)	4 / 109 (3.67%)	5 / 129 (3.88%)
occurrences (all)	9	4	9
Hypertonia			
subjects affected / exposed	1 / 238 (0.42%)	1 / 109 (0.92%)	0 / 129 (0.00%)
occurrences (all)	1	1	0
General disorders and administration site conditions			
Drug withdrawal syndrome			
subjects affected / exposed	20 / 238 (8.40%)	5 / 109 (4.59%)	15 / 129 (11.63%)
occurrences (all)	20	5	15
Hypothermia			
subjects affected / exposed	8 / 238 (3.36%)	3 / 109 (2.75%)	5 / 129 (3.88%)
occurrences (all)	8	3	5
Non-cardiac chest pain			
subjects affected / exposed	1 / 238 (0.42%)	0 / 109 (0.00%)	1 / 129 (0.78%)
occurrences (all)	1	0	1
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	12 / 238 (5.04%)	7 / 109 (6.42%)	5 / 129 (3.88%)
occurrences (all)	12	7	5
Vomiting			
subjects affected / exposed	2 / 238 (0.84%)	2 / 109 (1.83%)	0 / 129 (0.00%)
occurrences (all)	2	2	0
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	2 / 238 (0.84%)	0 / 109 (0.00%)	2 / 129 (1.55%)
occurrences (all)	2	0	2
Rhinorrhoea			

subjects affected / exposed	1 / 238 (0.42%)	0 / 109 (0.00%)	1 / 129 (0.78%)
occurrences (all)	1	0	1
Psychiatric disorders			
Aggression			
subjects affected / exposed	1 / 238 (0.42%)	1 / 109 (0.92%)	0 / 129 (0.00%)
occurrences (all)	1	1	0
Agitation			
subjects affected / exposed	1 / 238 (0.42%)	0 / 109 (0.00%)	1 / 129 (0.78%)
occurrences (all)	1	0	1
Musculoskeletal and connective tissue disorders			
Trismus			
subjects affected / exposed	1 / 238 (0.42%)	1 / 109 (0.92%)	0 / 129 (0.00%)
occurrences (all)	1	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 October 2017	version 2.0 (original submission v. 1.0 31st Oct 2016) - Change of producers of comparator active/placebo - Update on pharmacokinetic data in background section - Specifications regarding double dummy design and risk of unintentional unblinding - Changes to consent procedure in accordance with approval from National Ethics Committee
09 January 2018	v. 3.0 - Adding participant in prison/ police custody as exclusion criterium Please note this protocol version was current at first patient inclusion.
31 May 2019	v. 3.1 - Change national coordinating investigator from Ola Dale to Arne Skulberg - Change PI Trondheim from Sindre Mellsemo to Jostein Dale - Change study statistician from Øyvind Salvensen to Morten Valberg - Updated contact information to CI, PI and others. - Align end-date to 31. Dec 2021 between protocol, REC approval and trial registrations
02 September 2019	v. 3.2 - Adding details in protocol section12.9 regarding Safety reporting from participants with withdrawn consent, creating anonymous registration of safety data to expand Full Analysis Set to Safety Set for certain endpoints
06 March 2020	v 3.3 - Change inclusion criteria <8 breaths per minutes to ≤8 breaths per minutes - Further specification relating to 12.9, Safety registration in patients withdrawing consent

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported