



## Clinical trial results:

### Perioperative Methadone for ameliorating postoperative pain and reduction in postoperative opioid consumption in hip fracture patients – Dosage adjusting pilot-study

#### Summary

EudraCT number	2022-001857-22
Trial protocol	DK
Global end of trial date	04 April 2023

#### Results information

Result version number	v1 (current)
This version publication date	24 May 2024
First version publication date	24 May 2024

#### Trial information

##### Trial identification

Sponsor protocol code	Methadone-010922
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05581901
WHO universal trial number (UTN)	-

Notes:

##### Sponsors

Sponsor organisation name	Hospital Sønderjylland
Sponsor organisation address	Kresten Philipsensvej 15, Aabenraa, Denmark, 6200
Public contact	Jesper Ougaard Schønnemann , Department of Orthopaedics, +45 79976170, Jesper.Ougaard.Schoennemann1@rsyd.dk
Scientific contact	Jesper Ougaard Schønnemann , Department of Orthopaedics, +45 79976170, Jesper.Ougaard.Schoennemann1@rsyd.dk

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	18 March 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 April 2023
Global end of trial reached?	Yes
Global end of trial date	04 April 2023
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The objective is to investigate whether doses greater than 0.10 mg/kg are tolerated with no increased risk of respiratory depression, side-effects, or prolonged stay in the post anesthesia care unit (PACU). This is to ensure that the doses used in the literature are tolerated by the elderly and fragile.

Protection of trial subjects:

To minimize any risk regarding Methadone administration a specialist in anesthesiology will be present at administration and will supervise subsequent observation. Medical equipment for emergencies are readily available.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 October 2022
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: 32
Worldwide total number of subjects	32
EEA total number of subjects	32

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)	1
From 65 to 84 years	17
85 years and over	14

## Subject disposition

### Recruitment

Recruitment details:

Patients will be screened for inclusion in the emergency department by the orthopedic resident on duty. The patient and next of kin will receive verbal as well as written information about the study, and should be made aware of the study within the first four hours after arrival. They receive two hours to consider. Consent is written and voluntary.

### Pre-assignment

Screening details:

Every patient presenting with an acute hip fracture in the period of the study will be screened for inclusion by the Orthopedic resident. This will ensure sufficient knowledge regarding 'Good Clinical Practice' and the treatment of hip fractures.

### Period 1

Period 1 title	Treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Blinding implementation details:

Treatment allocation follows the continual reassessment method. The investigator utilizes an adaptive algorithm to assign three patients at a time to one of three dose-groups. An un-blinded nurse prepare the study drug. Carer and subject remain unaware of treatment allocation.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	0.10 mg/kg

Arm description:

Patients in this group has been allocated to receive 0.10 mg/kg of methadone.

Arm type	Active comparator
Investigational medicinal product name	Methadone Streuli
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

The purchased ampoules contain a sterile solution ready for injection. Study medicine is withdrawn by primary caregiver from the emergency department and is administered by the treating certified nurse anesthetist. The Methadone is administered intravenously at the beginning of the hip fracture surgery (10 minutes before knife-to-skin). The medicine is only administered this one time.

<b>Arm title</b>	0.15 mg/kg
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Arm description:

These patients were allocated to receive 0.15 mg/kg methadone

Arm type	Active comparator
Investigational medicinal product name	Methadone Streuli
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

The purchased ampoules contain a sterile solution ready for injection. Study medicine is withdrawn by primary caregiver from the emergency department and is administered by the treating certified nurse anesthetist. The Methadone is administered intravenously at the beginning of the hip fracture surgery

(10 minutes before knife-to-skin). The medicine is only administered this one time.

<b>Arm title</b>	0.20 mg/kg
Arm description: These patients were allocated to receive 0.20 mg/kg methadone perioperatively.	
Arm type	Active comparator
Investigational medicinal product name	Methadone Streuli
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

The purchased ampoules contain a sterile solution ready for injection. Study medicine is withdrawn by primary caregiver from the emergency department and is administered by the treating certified nurse anesthetist. The Methadone is administered intravenously at the beginning of the hip fracture surgery (10 minutes before knife-to-skin). The medicine is only administered this one time.

<b>Number of subjects in period 1</b>	0.10 mg/kg	0.15 mg/kg	0.20 mg/kg
Started	9	22	1
Completed	9	21	0
Not completed	0	1	1
Physician decision	-	1	-
Protocol deviation	-	-	1

## Baseline characteristics

### Reporting groups

Reporting group title	Treatment
Reporting group description: -	

Reporting group values	Treatment	Total	
Number of subjects	32	32	
Age categorical			
Units: Subjects			
Adults (18-64 years)	1	1	
From 65-84 years	17	17	
85 years and over	14	14	
Gender categorical			
Units: Subjects			
Female	20	20	
Male	12	12	
Hip fracture type			
The type of hip fracture			
Units: Subjects			
Collum femoris fracture	22	22	
Pertrochanteric fracture	9	9	
Subtrochanteric fracture	1	1	
ASA classification			
American Society of Anesthesiologists Classification			
Units: Subjects			
ASA 1	0	0	
ASA 2	13	13	
ASA 3	18	18	
ASA 4	1	1	
ASA 5	0	0	
ASA 6	0	0	

### Subject analysis sets

Subject analysis set title	Included patients
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All included patients who have completed the trial	

Reporting group values	Included patients		
Number of subjects	30		
Age categorical			
Units: Subjects			
Adults (18-64 years)	1		
From 65-84 years	16		
85 years and over	13		

Gender categorical			
Units: Subjects			
Female			
Male			
Hip fracture type			
The type of hip fracture			
Units: Subjects			
Collum femoris fracture	21		
Pertrochanteric fracture	8		
Subtrochanteric fracture	1		
ASA classification			
American Society of Anesthesiologists Classification			
Units: Subjects			
ASA 1	0		
ASA 2	13		
ASA 3	16		
ASA 4	1		
ASA 5	0		
ASA 6	0		

## End points

### End points reporting groups

Reporting group title	0.10 mg/kg
Reporting group description:	
Patients in this group has been allocated to receive 0.10 mg/kg of methadone.	
Reporting group title	0.15 mg/kg
Reporting group description:	
These patients were allocated to receive 0.15 mg/kg methadone	
Reporting group title	0.20 mg/kg
Reporting group description:	
These patients were allocated to receive 0.20 mg/kg methadone perioperatively.	
Subject analysis set title	Included patients
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All included patients who have completed the trial	

### Primary: Dose Limiting Toxicity (DLT)

End point title	Dose Limiting Toxicity (DLT)
End point description:	
The primary outcome was respiratory depression, which is a binary parameter defined as a respiratory frequency of <10/min and a peripheral oxygen saturation of <94 % despite 4 liters of oxygen/min. The data source was both the observation chart filled in by the primary caregiver at PACU and observation charts filled in at the ward. The nurse at PACU continuously monitored peripheral oxygen saturation and respiratory frequency until the patient could be discharged to the ward. At the orthopedic ward respiratory depression was registered upon arrival and after 6, 24 and 72 hours after surgery by nurses at the ward.	
End point type	Primary
End point timeframe:	
72 hours post surgery	

End point values	0.10 mg/kg	0.15 mg/kg	0.20 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	21	0 <sup>[1]</sup>	
Units: Respiratory depression				
DLT	0	3		
no DLT	9	18		

Notes:

[1] - No patients in this group included in statistical analysis

### Statistical analyses

Statistical analysis title	Continual Reassessment Method
Statistical analysis description:	
This trial uses the Bayesian continual reassessment method.	
Comparison groups	0.10 mg/kg v 0.15 mg/kg

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	The mean posterior estimate of toxicity
Point estimate	0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	0.17
Variability estimate	Standard deviation
Dispersion value	0.04

## Secondary: Length of stay at the Post Anesthesia Care Unit (PACU)

End point title	Length of stay at the Post Anesthesia Care Unit (PACU)
End point description:	We registered the length of stay at the PACU as hours for each patient. The data source was the observation chart filled in by the primary caregiver at PACU. Discharge from PACU conformed to the national guidelines from the Danish Society for Anesthesiology and Intensive Medicine (DASAIM). Thus, patients had to either meet criteria regarding peripheral oxygen saturation, arousal, and pain level or go through an assessment by an anesthesiologist before discharge.
End point type	Secondary
End point timeframe:	0-12 hours

End point values	0.10 mg/kg	0.15 mg/kg	0.20 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	21	0 <sup>[2]</sup>	
Units: Hours				
number (not applicable)	2.8	2.5		

Notes:

[2] - No patient included in the statistical analysis in this group

## Statistical analyses

Statistical analysis title	Linear regression
Statistical analysis description:	we conducted linear regression analysis. We applied bootstrapped confidence intervals in our linear regression model.
Comparison groups	0.10 mg/kg v 0.15 mg/kg
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.62 <sup>[3]</sup>
Method	Regression, Linear



Notes:

[3] - (CI -1.48; 0.89)

### Secondary: Amount of antidote needed

End point title	Amount of antidote needed
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End point description:

The number of times administration of antidote (Naloxone) was necessary. The limited number of observations precluded the possibility of conducting meaningful statistical analysis. Only one patient received antidote accounting for two out of the 120 possible observations.

End point type	Secondary
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End point timeframe:

72 hours post surgery

End point values	0.10 mg/kg	0.15 mg/kg	0.20 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	21	0 <sup>[4]</sup>	
Units: Binary	1	0		

Notes:

[4] - No patient in this group included in statistical analysis

### Statistical analyses

No statistical analyses for this end point

### Secondary: Opioid consumption

End point title	Opioid consumption
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End point description:

We registered postoperative opioid consumption as a mean consumption of rescue morphine equivalents in each group upon arrival and within the first 6 hours after surgery, within the first 24 hours after surgery, and within the first 72 hours after surgery. We calculated the morphine equivalent dose for different types of opioids. The data source was the medical chart and nurses filled in the amount on the observation chart.

End point type	Secondary
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End point timeframe:

0-72 hours post surgery

End point values	0.10 mg/kg	0.15 mg/kg	0.20 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	21	0 <sup>[5]</sup>	
Units: milligram(s)				
number (not applicable)	9.4	12.6		

Notes:

[5] - No patient included in statistical analysis in this group.

### Statistical analyses

<b>Statistical analysis title</b>	negative binomial regression
Statistical analysis description:	
We used a negative binomial regression due to the integer-like nature of the administered dosage. We applied clustered standard errors on the patient ID level, as we deemed the variation distribution within subjects non-reproducible. We used the mean consumption of rescue morphine equivalents from each group in our calculations.	
Comparison groups	0.10 mg/kg v 0.15 mg/kg
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.34
Method	negative binomial regression
Parameter estimate	Incidence risk ratio (IRR)
Point estimate	1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	2.07
Variability estimate	Standard deviation

## Secondary: Post Operative Nausea or Vomiting (PONV)

End point title	Post Operative Nausea or Vomiting (PONV)
End point description:	
We registered PONV binomial as present or not at 6 and 24 hours after surgery. The data source was the patient's statement at the time, which we entered on the observation chart.	
End point type	Secondary
End point timeframe:	
0-24 hours post surgery	

<b>End point values</b>	0.10 mg/kg	0.15 mg/kg	0.20 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	21	0 <sup>[6]</sup>	
Units: Percentage				
number (not applicable)	9.1	9.8		

Notes:

[6] - Patient not included in statistical analysis

## Statistical analyses

<b>Statistical analysis title</b>	Fisher's exact test
Comparison groups	0.10 mg/kg v 0.15 mg/kg

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 1
Method	Fisher exact

## Secondary: Post Operative Pain Assessment

End point title	Post Operative Pain Assessment
End point description:	
We asked patients to assess their pain intensity at the hip using the VRS as this is a validated scale for hip fracture patients. The scale provides patients with six choices and they must choose the one that best describes their pain. The choices are: 0 (no pain), 1 (slight pain), 2 (moderate pain), 3 (severe pain), 4 (extreme pain), and 5 (unbearable/worst imaginable pain). We asked them to assess pain intensity upon arrival at the ward and at 6, 24, and 72 hours after surgery. The data source was the patient's statement at the time, which we entered on the observation chart.	
End point type	Secondary
End point timeframe:	
0-72 hours post surgery	

End point values	Included patients			
Subject group type	Subject analysis set			
Number of subjects analysed	30			
Units: Verbal Rating Scale				
No pain	59			
Slight pain	36			
Moderate pain	10			
Severe pain	0			
Extreme pain	0			
Unbearable/worst imaginable pain	0			

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

The first 12 days after study drug administration.

Adverse event reporting additional description:

Adverse events were continuously monitored through the hospital stay. After discharge every included patient had a 12-day follow-up phone call where they completed a questionnaire with the investigator.

Assessment type	Systematic
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### Dictionary used

Dictionary name	none
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Dictionary version	0
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### Reporting groups

Reporting group title	All included patients
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Reporting group description:

All of the 31 patients who were exposed to study drug.

Serious adverse events	All included patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 31 (3.23%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Cardiac arrest	Additional description: Circulatory collapse following surgery and general anesthesia.		
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

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

Non-serious adverse events	All included patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 31 (3.23%)		
Nervous system disorders			
Somnolence	Additional description: The patient was observed excessively sleepy and drowsy. Administration of Naloxone had no effect, thus opioid overdose was ruled out. A combination of dehydration and infection was the underlying cause.		
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported