



## Clinical trial results:

### Methoxyflurane and fentanyl in hypovolemia induced by lower body negative pressure in healthy volunteers; A randomized, placebo-controlled crossover study

#### Summary

EudraCT number	2019-004144-29
Trial protocol	NO
Global end of trial date	05 January 2023

#### Results information

Result version number	v1 (current)
This version publication date	01 July 2023
First version publication date	01 July 2023

#### Trial information

##### Trial identification

Sponsor protocol code	lbnp_methoxy_fent_2019
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04641949
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Oslo University Hospital
Sponsor organisation address	Kirkeveien 166, Oslo, Norway, 0450
Public contact	Department of Anesthesiology, Oslo University Hospital, 47 22119690, lars.oivind.hoiseth@hotmail.com
Scientific contact	Department of Anesthesiology, Oslo University Hospital, 90749409 +4722119690, lars.oivind.hoiseth@hotmail.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	05 January 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 January 2023
Global end of trial reached?	Yes
Global end of trial date	05 January 2023
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The objective of the trial is to study if and how the hemodynamic effects of experimental hypovolemia are affected by methoxyflurane and fentanyl compared to placebo. The primary outcome is cardiac stroke volume, and the main secondary outcome is time to time to termination of hypovolemic exposure.

Protection of trial subjects:

The trial was carried out in accordance with the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 February 2020
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	Norway: 15
Worldwide total number of subjects	15
EEA total number of subjects	15

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)	15
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Fifteen healthy volunteers were included in this single-centre study performed at Oslo University Hospital, Aker. First visit of first subject was December 2020, and last visit of last subject was March 2022.

### Pre-assignment

Screening details:

Fifteen subjects were screened for participation, and all screened subjects entered and completed all visits.

### Period 1

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

Blinding implementation details:

The trial was blinded with a crossover design. Three treatments were administered; methoxyflurane, fentanyl or 0.9% saline (placebo). Subjects, investigators present during the visits were blinded. And analysis of primary outcome was performed before unblinding.

### Arms

Are arms mutually exclusive?	No
<b>Arm title</b>	Methoxyflurane

Arm description:

Inhalation Methoxyflurane 3 ml.

Arm type	Experimental
Investigational medicinal product name	Methoxyflurane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

3 ml methoxyflurane 99.9% inhaled without occluding the dilator hole.

<b>Arm title</b>	Fentanyl
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Arm description:

Fentanyl 15µg intravenously.

Arm type	Active comparator
Investigational medicinal product name	Fentanyl
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

Fentanyl 50µg/ml \* 0.5 ml = 25µg injection.

<b>Arm title</b>	Placebo
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Arm description:

Saline (0.9%) intravenously and in inhalator.

Arm type	Placebo
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Investigational medicinal product name	Saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Gastric use, Intravenous bolus use

Dosage and administration details:

3 ml. saline in inhaler and 0.5 ml saline for intravenous injection.

Number of subjects in period 1	Methoxyflurane	Fentanyl	Placebo
Started	15	15	15
Completed	15	15	15

## Period 2

Period 2 title	Visits 1, 2 and 3.
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst

Blinding implementation details:

Inhaler was filled with methoxyflurane or saline. Fentanyl og saline was given intravenously.

## Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Methoxyflurane

Arm description:

Inhalation Methoxyflurane 3 ml.

Arm type	Experimental
Investigational medicinal product name	Methoxyflurane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

3 ml methoxyflurane 99.9% inhaled without occluding the dilator hole.

<b>Arm title</b>	Fentanyl
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Arm description:

Fentanyl 15µg intravenously.

Arm type	Active comparator
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Investigational medicinal product name	Fentanyl
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

Fentanyl 50µg/ml \* 0.5 ml = 25µg injection.

<b>Arm title</b>	Placebo
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Arm description:

Saline (0.9%) intravenously and in inhalator.

Arm type	Placebo
Investigational medicinal product name	Saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Gastric use, Intravenous bolus use

Dosage and administration details:

3 ml. saline in inhaler and 0.5 ml saline for intravenous injection.

<b>Number of subjects in period 2</b>	Methoxyflurane	Fentanyl	Placebo
Started	15	15	15
Completed	15	15	15

## Baseline characteristics

### Reporting groups

Reporting group title	Baseline
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Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	15	15	
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)	15	15	
From 65-84 years	0	0	
85 years and over	0	0	
All subjects	0	0	
Gender categorical			
Units: Subjects			
Female	7	7	
Male	8	8	

### Subject analysis sets

Subject analysis set title	Methoxyflurane
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

Effect of methoxyflurane compared to placebo.

Reporting group values	Methoxyflurane		
Number of subjects	15		
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)	15		
From 65-84 years	0		
85 years and over	0		
All subjects	15		

Gender categorical			
Units: Subjects			
Female	7		
Male	8		

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## End points

### End points reporting groups

Reporting group title	Methoxyflurane
Reporting group description: Inhalation Methoxyflurane 3 ml.	
Reporting group title	Fentanyl
Reporting group description: Fentanyl 15µg intravenously.	
Reporting group title	Placebo
Reporting group description: Saline (0.9%) intravenously and in inhalator.	
Reporting group title	Methoxyflurane
Reporting group description: Inhalation Methoxyflurane 3 ml.	
Reporting group title	Fentanyl
Reporting group description: Fentanyl 15µg intravenously.	
Reporting group title	Placebo
Reporting group description: Saline (0.9%) intravenously and in inhalator.	
Subject analysis set title	Methoxyflurane
Subject analysis set type	Intention-to-treat
Subject analysis set description: Effect of methoxyflurane compared to placebo.	

### Primary: Cardiac output

End point title	Cardiac output
End point description: Effect of treatment on cardiac output during lower body negative pressure.	
End point type	Primary
End point timeframe: During experimental intervention, approximately 30 min.	

End point values	Methoxyflurane	Fentanyl	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15	15	15	
Units: litres per minute				
number (not applicable)	15	15	15	

### Statistical analyses

Statistical analysis title	Effect of methoxyflurane
Statistical analysis description: Effect of methoxyflurane on the effect of LBNP on cardiac output (interaction effect).	



Comparison groups	Methoxyflurane v Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.625 <sup>[1]</sup>
Method	Regression, Linear
Parameter estimate	Mean difference (net)
Point estimate	-0.012
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	0.036

Notes:

[1] - P-value for interaction effect of methoxyflurane compared to placebo.

<b>Statistical analysis title</b>	Effect of fentanyl
Statistical analysis description:	
Effect of fentanyl on the effect of LBNP on cardiac output (interaction effect).	
Comparison groups	Placebo v Fentanyl
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.134 <sup>[2]</sup>
Method	Regression, Linear
Parameter estimate	Mean difference (net)
Point estimate	0.039
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.012
upper limit	0.134

Notes:

[2] - P-value for interaction effect of fentanyl compared to placebo.

## Adverse events

### Adverse events information<sup>[1]</sup>

Timeframe for reporting adverse events:

To end of last visit (one month after last IMP).

Adverse event reporting additional description:

There were no adverse events reported.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.0
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### Reporting groups

Reporting group title	All subjects
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Reporting group description:

All subjects received methoxyflurane 3 ml, fentanyl 25µg and placebo with a crossover design. All subjects received all treatments/ IMPs.

Serious adverse events	All subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	All subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 15 (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 recorded during this trial.

## **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