



Clinical trial results:

PreMeFen

Summary

EudraCT number	2021-000549-42
Trial protocol	NO
Global end of trial date	22 April 2023

Results information

Result version number	v1 (current)
This version publication date	05 June 2026
First version publication date	05 June 2026

Trial information

Trial identification

Sponsor protocol code	PreMeFen
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05137184
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Oslo University Hospital
Sponsor organisation address	Kirkeveien 166, Oslo, Norway, 0450
Public contact	Air Ambulance Department, Oslo University Hospital, frihey@ous-hf.no
Scientific contact	Air Ambulance Department, Oslo University Hospital, +47 91502770, frihey@ous-hf.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	20 March 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 April 2023
Global end of trial reached?	Yes
Global end of trial date	22 April 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective 1a

To determine if a regimen of inhalation of 3 ml methoxyflurane is non-inferior to a regimen of intranasal 50 µ (>70) or 100 µg (>18, <70 years) fentanyl in reduction of moderate to severe pain (NRS ≥ 4) after 10 min in patients >18 years of age. (Repeated dosing allowed)

Primary objective 1b:

To determine if a regimen of inhalation of 3 ml methoxyflurane is non-inferior to a regimen of morphine IV 0.1 mg/kg (0.05 mg/kg from >70 years or fragile patients) in reduction of moderate to severe pain (NRS ≥ 4) after 10 min, in patients >18 years of age. (Repeated dosing allowed)

Primary objective 1c:

To determine if a regimen of intranasal 50 µ (>70 years) or 100 µg (>18, <70 years) fentanyl is non-inferior to a regimen of morphine IV 0.1 mg/kg (or 0.05 mg/kg >70 years old or fragile patients) in reduction of moderate to severe pain (NRS ≥ 4) after 10 min, in patients >18 years of age. (Repeated dosing allowed)

Protection of trial subjects:

Patients with suboptimal effect of study medication was offered rescue medication with other analgesia than the IMP

Background therapy:

NA

Evidence for comparator:

NA

Actual start date of recruitment	08 November 2021
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: 338
Worldwide total number of subjects	338
EEA total number of subjects	338

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)	166
From 65 to 84 years	149
85 years and over	23

Subject disposition

Recruitment

Recruitment details:

Recruitment period was from November 8 2021 to April 22 2023, and the recruitment was performed in the ambulance service at Innlandet Hospital in Norway

Pre-assignment

Screening details:

Patients aged 18 years or older with medical or traumatic acute moderate to severe pain scoring 4 or higher on the Numeric Rating Scale (NRS), normal physiology and ability to provide informed consent. Exclusion criteria included life-threatening or limb-threatening conditions, head injuries with neurological impairment and allergies to IMP.

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Although this is an open-label study and the ambulance personnel were not masked to treatment allocation, the statistician was masked to the allocations in the dataset until the statistical analysis plan was signed and the database was locked.

Arms

Are arms mutually exclusive?	Yes
Arm title	Morphine IV

Arm description:

Patients receiving IV morphine

Arm type	Active comparator
Investigational medicinal product name	Morphine IV
Investigational medicinal product code	N02AA01
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients 18-69 years received 0.1 mg/kg intravenous morphine (Abcur, Helsingborg, Sweden). Patients 70 years or older received 0.05 mg/kg intravenous morphine. Doses were repeated if needed, with interval of 5 minutes, and maximum doses were 0.5 mg/kg morphine

Arm title	Fentanyl IN
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Arm description:

Patients receiving intranasal Fentanyl

Arm type	Experimental
Investigational medicinal product name	Fentanyl IN
Investigational medicinal product code	N02AB03
Other name	
Pharmaceutical forms	Nasal spray, solution
Routes of administration	Intranasal use

Dosage and administration details:

Patients aged 18–69 years received 100 µg intranasal fentanyl (Takeda Pharma, Vallenback Strans, Denmark) Patients 70 years or older received 50 µg intranasal fentanyl Doses were repeated if needed, with interval of 5 minutes, maximum dose was 500 µg intranasal fentanyl.

Arm title	Methoxyflurane inhalation
Arm description:	
Patients receiving methoxyflurane inhalation	
Arm type	Experimental
Investigational medicinal product name	Methoxyflurane
Investigational medicinal product code	N02BG09
Other name	
Pharmaceutical forms	Inhalation vapour, liquid
Routes of administration	Inhalation use

Dosage and administration details:

Patients received 3 mL inhalational methoxyflurane (Medical Developments NED, Amsterdam, Netherlands)

The dose could be repeated, with maximum 6 ml in total.

Number of subjects in period 1	Morphine IV	Fentanyl IN	Methoxyflurane inhalation
Started	111	115	112
Completed	109	112	111
Not completed	2	3	1
Physician decision	2	-	-
Consent withdrawn by subject	-	3	1

Baseline characteristics

Reporting groups

Reporting group title	Morphine IV
Reporting group description:	
Patients receiving IV morphine	
Reporting group title	Fentanyl IN
Reporting group description:	
Patients receiving intranasal Fentanyl	
Reporting group title	Methoxyflurane inhalation
Reporting group description:	
Patients receiving methoxyflurane inhalation	

Reporting group values	Morphine IV	Fentanyl IN	Methoxyflurane inhalation
Number of subjects	111	115	112
Age categorical			
Age groups			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	51	61	64
From 65-84 years	52	48	39
85 years and over	8	6	9
18-69	0	0	0
70 years and over	0	0	0
Gender categorical			
Units: Subjects			
Female	60	57	58
Male	51	58	54

Reporting group values	Total		
Number of subjects	338		
Age categorical			
Age groups			
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)	176		

From 65-84 years	139		
85 years and over	23		
18-69	0		
70 years and over	0		
Gender categorical			
Units: Subjects			
Female	175		
Male	163		

End points

End points reporting groups

Reporting group title	Morphine IV
Reporting group description: Patients receiving IV morphine	
Reporting group title	Fentanyl IN
Reporting group description: Patients receiving intranasal Fentanyl	
Reporting group title	Methoxyflurane inhalation
Reporting group description: Patients receiving methoxyflurane inhalation	

Primary: Change in pain numeric rating scale at 10 minutes

End point title	Change in pain numeric rating scale at 10 minutes
End point description: The primary endpoint was change in pain NRS score from baseline to 10 min after treatment start	
End point type	Primary
End point timeframe: From start administration of study drug, to 10 minutes after start of administration	

End point values	Morphine IV	Fentanyl IN	Methoxyflurane inhalation	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	90	89	102	
Units: Numeric Rating Scale (NRS)				
arithmetic mean (standard deviation)	-2.74 (\pm 2.12)	-1.98 (\pm 2.28)	-3.31 (\pm 2.67)	

Statistical analyses

Statistical analysis title	Linear model methoxyflurane vs IN fentanyl
Statistical analysis description: Linear model comparison of change in NRS for methoxyflurane versus IN fentanyl	
Comparison groups	Methoxyflurane inhalation v Fentanyl IN
Number of subjects included in analysis	191
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Mean difference (final values)
Point estimate	-1.33

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.01
upper limit	-0.64

Statistical analysis title	Linear model methoxyflurane vs IV morphine
Statistical analysis description:	
Linear model comparison of change in NRS for methoxyflurane versus IV morphine	
Comparison groups	Morphine IV v Methoxyflurane inhalation
Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.03
upper limit	0.31

Statistical analysis title	Linear model IN fentanyl vs IV morphine
Statistical analysis description:	
Linear model comparison of change in NRS for IN fentanyl versus IV morphine	
Comparison groups	Morphine IV v Fentanyl IN
Number of subjects included in analysis	179
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Mean difference (final values)
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	1.55

Secondary: Change in pain numeric rating scale at 5 minutes	
End point title	Change in pain numeric rating scale at 5 minutes
End point description:	
This secondary endpoint was change in pain NRS score from baseline to 5 minutes after treatment start	
End point type	Secondary
End point timeframe:	
From start administration of study drug, to 5 minutes after start of administration	

End point values	Morphine IV	Fentanyl IN	Methoxyflurane inhalation	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	90	89	102	
Units: Numeric Rating Scale (NRS)				
arithmetic mean (standard deviation)	-2.17 (± 1.88)	-1.08 (± 1.62)	-2.79 (± 2.60)	

Statistical analyses

Statistical analysis title	Linear model methoxyflurane vs IN fentanyl
Statistical analysis description:	
Linear model comparison of change in NRS for methoxyflurane versus IN fentanyl	
Comparison groups	Methoxyflurane inhalation v Fentanyl IN
Number of subjects included in analysis	191
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Mean difference (final values)
Point estimate	-1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.3
upper limit	-1.1

Statistical analysis title	Linear model methoxyflurane vs IV morphine
Statistical analysis description:	
Linear model comparison of change in NRS for methoxyflurane versus IV morphine	
Comparison groups	Methoxyflurane inhalation v Morphine IV
Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	0.18

Statistical analysis title	Linear model IN fentanyl vs IV morphine
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Statistical analysis description:

Linear model comparison of change in NRS for IN fentanyl versus IV morphine

Comparison groups	Morphine IV v Fentanyl IN
Number of subjects included in analysis	179
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Mean difference (final values)
Point estimate	1.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	1.66

Secondary: Need for rescue medication

End point title	Need for rescue medication
End point description:	
Number of patients receiving rescue medication for pain relief in addition to study drug	
End point type	Secondary
End point timeframe:	
From administration of study drug to end of study	

End point values	Morphine IV	Fentanyl IN	Methoxyflurane inhalation	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	90	89	102	
Units: Patients	14	26	41	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start administration of study drug, to end of study

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	25.E
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Reporting groups

Reporting group title	Morphine IV
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Reporting group description:

Patients receiving IV morphine

Reporting group title	Fentanyl IN
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Reporting group description:

Patients receiving intranasal Fentanyl

Reporting group title	Methoxyflurane inhalation
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Reporting group description:

Patients receiving methoxyflurane inhalation

Serious adverse events	Morphine IV	Fentanyl IN	Methoxyflurane inhalation
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 111 (0.00%)	0 / 115 (0.00%)	1 / 112 (0.89%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Sedation			
subjects affected / exposed	0 / 111 (0.00%)	0 / 115 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory depression			
subjects affected / exposed	0 / 111 (0.00%)	0 / 115 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Morphine IV	Fentanyl IN	Methoxyflurane inhalation
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 111 (23.42%)	27 / 115 (23.48%)	24 / 112 (21.43%)
Vascular disorders			
Hot flush			
subjects affected / exposed	2 / 111 (1.80%)	1 / 115 (0.87%)	1 / 112 (0.89%)
occurrences (all)	2	1	1
Hypotension			
subjects affected / exposed	4 / 111 (3.60%)	1 / 115 (0.87%)	0 / 112 (0.00%)
occurrences (all)	4	1	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 111 (0.00%)	1 / 115 (0.87%)	0 / 112 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 111 (0.00%)	3 / 115 (2.61%)	3 / 112 (2.68%)
occurrences (all)	0	3	3
Headache			
subjects affected / exposed	0 / 111 (0.00%)	2 / 115 (1.74%)	0 / 112 (0.00%)
occurrences (all)	0	2	0
Loss of consciousness			
subjects affected / exposed	0 / 111 (0.00%)	0 / 115 (0.00%)	2 / 112 (1.79%)
occurrences (all)	0	0	2
Nausea			
subjects affected / exposed	7 / 111 (6.31%)	3 / 115 (2.61%)	5 / 112 (4.46%)
occurrences (all)	7	3	5
Sedation			
subjects affected / exposed	0 / 111 (0.00%)	0 / 115 (0.00%)	2 / 112 (1.79%)
occurrences (all)	0	0	2
Somnolence			
subjects affected / exposed	0 / 111 (0.00%)	0 / 115 (0.00%)	1 / 112 (0.89%)
occurrences (all)	0	0	1
Eye disorders			
Eye pruritus			
subjects affected / exposed	0 / 111 (0.00%)	1 / 115 (0.87%)	0 / 112 (0.00%)
occurrences (all)	0	1	0

Gastrointestinal disorders			
	Dry mouth		
	subjects affected / exposed	1 / 111 (0.90%)	0 / 115 (0.00%)
	occurrences (all)	1	0
	Vomiting		
	subjects affected / exposed	14 / 111 (12.61%)	11 / 115 (9.57%)
	occurrences (all)	14	11
Respiratory, thoracic and mediastinal disorders			
	Respiratory depression		
	subjects affected / exposed	3 / 111 (2.70%)	5 / 115 (4.35%)
	occurrences (all)	3	5
Skin and subcutaneous tissue disorders			
	Nasal pruritus		
	subjects affected / exposed	0 / 111 (0.00%)	2 / 115 (1.74%)
	occurrences (all)	0	2
	Pruritus		
	subjects affected / exposed	1 / 111 (0.90%)	1 / 115 (0.87%)
	occurrences (all)	1	1
	Rash		
	subjects affected / exposed	1 / 111 (0.90%)	0 / 115 (0.00%)
	occurrences (all)	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/41275876>