Title page

A randomized controlled, open-label, non-inferiority, three arm clinical study to assess the effectiveness and safety of a regimen with inhalation of low-dose Methoxyflurane compared with a regimen of intranasal Fentanyl and a regimen of intravenous Morphine for the treatment of acute pain with NRS ≥ 4 in patients from 18 years of age carried out by ambulance workers in pre-hospital setting.

Compound: Inhalational Methoxyflurane versus intranasal Fentanyl versus intravenous Morphine.

Brief Title: A comparison of three regimens with inhalational methoxyflurane versus intranasal fentanyl versus intravenous morphine in pre-hospital acute pain management.

Phase: 3
Inhalation of methoxyflurane and intranasal fentanyl will be used outside approved indication. The study intension is to obtain additional information about the efficacy of the investigational products. The PreMeFen is hence a phase 3 study.

Short name: PreMeFen

Sponsor Name: Oslo University Hospital

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Version 3.0, date: 2021.09.02

Regulatory Agency Identifier Number(s)

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World Health Organization (WHO) universal trial number
EudraCT: 2021-000549-42 NO
Approval Date: Not yet approved

Sponsor Signatory: _____ _____
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Coordinating investigator: _____Date:_____
Fridtjof Heyerdahl, MD PhD

Principal investigator (Sykehuset Innlandet): _____Date:_____
Lars Olav Fjose, MD

Protocol Amendment Summary of Changes Table
NA

DOCUMENT HISTORY	
Document	**Date**
Original Protocol: Protocol PreMeFen ver1.0	16-03-2021
PreMeFen Protocol ver 2.0	07-05-2021
PreMeFen Protocol ver 2.1	15.06.2021
PreMeFen Protocol Ver 3.0	02.09.2021

Amendment
NA

Overall Rationale for the Amendment:
NA

Section # and Name	**Description of Change**	**Brief Rationale**
Title page	Added version date and sponsor name	As requested by NoMA
8.3.3	added that the PI is delegated the responsibility for SUSAR reporting from the sponsor	As requested by NoMA
3 and 1.1	secondary endpoint and assessment no 11 are changed so that AE and SAE is registered during study period until end of intervention. Synopsis endpoint description changed accodingly	Harmonize the endpoint description to section 8.3.1, as requested by NoMA
4.4.3	End of study definition changed to reflect last patient last visit	To correspond to section 4.4.2 post-intervention collection of data.

Section # and Name	Description of Change	Brief Rationale
5.2	An exclusion criterion is added, reflecting any condition that in the view of the investigator would suggest that the patient is unable to comply with study protocol and procedures.	As requested by NoMA
2.3.1	Risk of potential adverse reactions and how such adverse events may be comparable between groups are added in the risk table.	As requested by NoMA
5.2	Wording changed from "investigator" to "Study worker"	N.a.
Title	Changed from 12 to 18 years of age	As requested by ethical committee
Sponsor	Changed from Dr Mellesmo to Dr Buskop	New head of division
Whole document	Inclusion changed from 12 to 18 years and older	As requested by ethical committee
Synopsis	Erased "assess for SAE" from 14 days follow-up call in treatment duration paragraph	Study duration is only to ED handover, and 14-days follow up is only to collect clinical information.
4.2, 6th para	The section with paediatric population removed	A consequence of ethical committee decision of only including >18 years of age
8.2 follow-up	Changed last sentence in follow-up section to: Follow-up is to collate data	AE and SAE is only registered during the intervention period, end of intervention is the hand-over in the ED.
10.1 vulnerable groups section and Informed Consent Procedure	The sections are edited with removing text only relevant for paediatric population	A consequence of ethical committee decision of only including >18 years of age
10.1.5	DMC, second bullet point: changed "…provided safety data 14 after IMP administration" to "…provided safety data"	Safety data is only registered during the intervention period, end of intervention is the hand-over in the ED.

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Table of Contents

1. Protocol summary

1.1. Synopsis

Protocol Title:
A randomized controlled, open-label, non-inferiority, three arm, clinical study to assess the effectiveness and safety of a regimen with inhalation of low-dose methoxyflurane compared with a regimen of intranasal fentanyl and a regimen of intravenous morphine for the treatment of acute pain with Numeric Rating Scale (NRS) ≥ 4 in patients from 18 years of age carried out by ambulance workers in pre-hospital setting.

Brief Title: A comparison of three regimens with inhalational methoxyflurane versus intranasal fentanyl versus intravenous morphine in pre-hospital acute pain management.

Rationale: To provide evidence for early, safe, non-invasive and effective pain management in the ambulance service. Pre-hospital pain management is a challenge, but novel administration forms can probably improve treatment and patient satisfaction.

The purpose of this study is to examine whether a) a regimen of low-dose methoxyflurane is non-inferior to a regimen of intranasal fentanyl or b) a regimen of low-dose methoxyflurane is non-inferior to a regimen of intravenous morphine or c) a regimen of intranasal fentanyl is non-inferior to a regimen of intravenous morphine in patients > 18 years of age with acute pain with NRS ≥ 4 in a pre-hospital setting.

Objectives and Endpoints:

Primary Objectives	Primary Endpoints	Assessments
(For each comparison of three arms)		
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 years) or 100 ug (≥ 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)	Changes in pain score from t0 to t10min	ΔNRS t0-t10
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 ug (≥ 18, <70 years) fentanyl is non-inferior to a regimen of morphine IV 0.1 mg/kg in reduction of moderate to severe pain (NRS ≥ 4) after 10 min, in patients ≥ 18 years of age. (Repeated dosing allowed)		

Secondary objectives	Secondary Endpoint	Assessments
To assess the reduction in NRS from baseline to 5, 20, 30 minutes and at end of mission	Changes in pain score from T-0 to T-5, T-20, T-30 and end of mission	ΔNRS t0-t5, ΔNRS t0-t20, ΔNRS t0-t30Δ, ΔNRS t0- t ED-arrival
To assess the need for rescue analgesia in the treatment groups	Need for additional analgesia not in the regimen of the allocated treatment group,	Time of administration, type of medication, dose and route of administration
To determine time difference from scene arrival to IMP administration in the treatment groups	Differences in time arrival to administration of IMP	Δ tx -t0
To determine differences in any adverse events or serious adverse events	Registration of AE and SAE during study period until end of intervention	AE and SAE t0 to end of intervention

Overall Design: This is a randomized, controlled, open label, three-arm, non-inferiority, two-centre, phase 3 drug trial. The randomization is to take place after the screening for eligibility process.
The randomization will be 1:1:1 to the three treatment groups. There will not be treatment blinding but blinding of the statistician.

Main Inclusion Criteria:
Participants are eligible to be included in the study only if all of the following criteria apply:

1. ≥ 18 years of age
2. Acute moderate to severe pain defined by self-reporting pain ≥4 on NRS
3. Capable of giving informed consent
4. Normal physiology

Main exclusion Criteria:
Participants are excluded from the study if any of the following criteria apply:

1. Life-threatening or limb-threatening condition requiring immediate management
2. Pregnancy or breastfeeding
3. Know allergies, hypersensitivity or serious side effects to opioids or methoxyflurane or other excipients
4. Head injury or medical conditions with neurological impairment (GCS<14)
5. Previous malignant hyperthermia or persons with suspect genetic predisposition for malignant hyperthermia
6. Massive facial trauma, visible nasal blockage or on-going nose bleeding
7. History of severe liver disease with jaundice and scleral icterus
8. Dialysis or history of severe renal disease (known chronic kidney failure stage 4 or 5)
9. MAO-inhibitors last 14 days (pharmacological treatment of depression, Mb Parkinson or narcolepsy)
10. Myasthenia gravis
11. Use of IMP analgesics 12 hours prior to inclusion
12. Any condition that in the view of the study worker would suggest that the patient is unable to comply with study protocol and procedures.

Data Monitoring Committee (DMC) will be established prior to study start. See 10.1.4

Brief Summary

Our choice of a non-inferiority trial design is based on the expectation that the non-inferiority of the non-invasive inhalation of low-dose methoxyflurane or intranasal fentanyl to intravenous morphine will contribute to an earlier administration and more practical method in pre-hospital pain management. The primary endpoint in this study is the change in NRS at t0-t10 min, and a non-inferiority margin of Δ1.3 is chosen. The inferiority margin of 1.3 is established and validated as a clinically relevant difference in NRS across different pain conditions.
Condition: participants with acute traumatic and non-traumatic pain with NRS ≥ 4 in pre-hospital setting of non-physician led ambulances in Innlandet Hospital Trust and Oslo University Hospital Ambulance Service who has completed the PreMeFen-training program.

Hypothesis:
null hypothesis (H0) (tested in hierarchic order a-b-c):
a) Methoxyflurane regimen is inferior to intranasal fentanyl regimen or
b) Methoxyflurane regimen is inferior to IV morphine regimen or
c) Intranasal fentanyl regimen is inferior to IV morphine regimen
for treating moderate to severe pain, measured by reduction in Numeric Rating Scale (NRS) 10 minutes after administration.

Alternative hypothesis (H1) (tested in hierarchic order a-b-c):
a) Methoxyflurane regimen is non-inferior to intranasal fentanyl regimen or
b) Methoxyflurane regimen is non-inferior to IV morphine regimen or
c) Intranasal fentanyl regimen is non-inferior to IV morphine regimen
for treating moderate to severe pain, measured by reduction in NRS 10 minutes after administration.
The regimens will be compared in a hierarchic non-inferiority model.

Estimated date of first patient enrolled: 1st September 2021
Anticipated recruitment period: 48 months
Estimated date of last patient completed: 31. December 2025

Treatment Duration:
The study duration for each participant will be from ambulance scene arrival to patient handover in emergency department. The study nurse will undertake a follow up (phone call or review of the medical records) in the 14 days following inclusion.
Number of participants: Patient enrolment until successful inclusion of 270 per protocol patients. See Section 9.2.

Screen failures are defined as subjects who are assessed for selection criteria in the clinical trial but are never subsequently randomised. These will be included in a screening log with a minimum dataset (gender, age and reason not randomised) to ensure transparent reporting of screen failures, see section 5.4

1.2. Flow Chart of trial

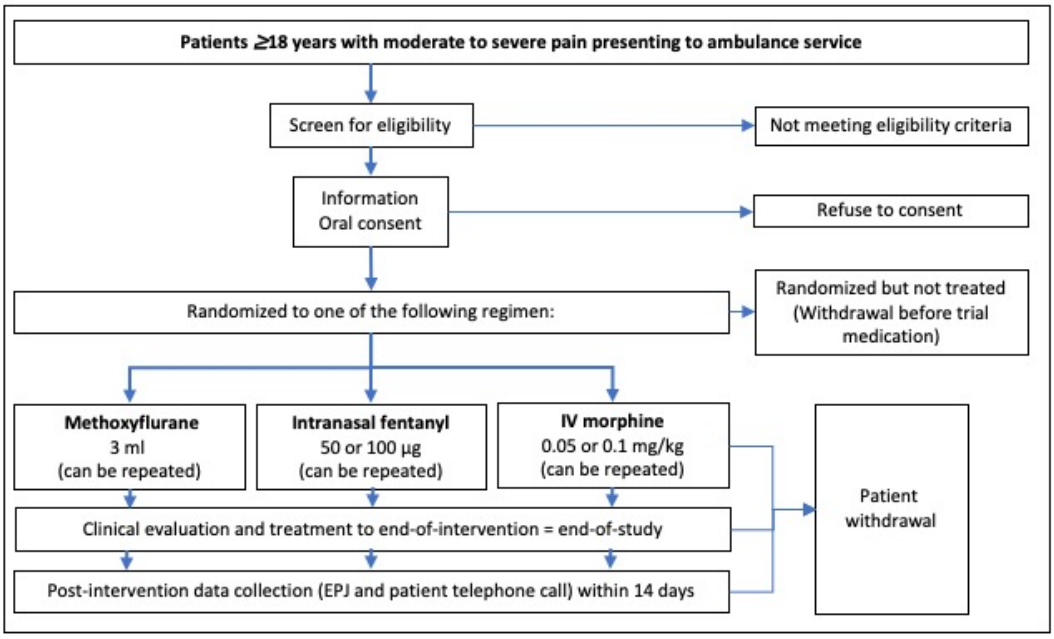


Figure 1 Flow chart inclusion

1.3. Schedule of Activities (SoA)

- T_x : scene arrival
- t_0 : time of IMP administration
- t_5 : 5 minutes after initiation IMP (+/- 1 min)
- t_{10} : 10 minutes after initiation of IMP (+/- 1 min)
- t_{20}: 20 minutes after initiation of IMP (+/- 2 min)
- t_{30} : 30 minutes after initiation of IMP (+/- 2 min)
- t_{ED} : time end of service/ patient handover Emergency Department

1.3.1. Schedule of Activities (SoA)

Timepoint **	Scene arrival T(x) And initial assessment	Administration IMP/ t0	T5 min	T10 min	T20 min	T30 min	T-ED Arrival	Data collection: EPJ or phone call within 14 days	Notes
Arrival by patient*	x								
Inclusion and exclusion criteria	x								Recheck clinical status before randomization and 1st dose of study intervention.]
Informed oral consent	X								
Physical examination including estimation of weight	x								
Medical history	x								Including drugs and alcohol
Allocation	x								
ECG	(x)						(x)		12-lead ECG when suspicious of ACS

Timepoint **	Scene arrival T(x) And initial assessment	Administration IMP/ t0	T5 min	T10 min	T20 min	T30 min	T-ED Arrival	Data collection: EPJ or phone call within 14 days	Notes
									otherwise 3/4 lead monitoring
INTERVENTIONS/observations:									
IV access attempts	x								
-regimen of intranasal fentanyl		x →	→	→	→	→	→		
-regimen of low dose methoxyflurane		x →	→	→	→	→	→		
-regimen of intravenous morphine		x →	→	→	→	→	→		
SpO_2 assessment	X			x	x	x	x		
Blood pressure assessment	X			x		x	x		
Heart rate assessment	X			x	x	x	x		
Respiration rate assessment secondary endpoint	X			x		x	x		
NRS Primary and secondary endpoint	x		x	x primary endpoint	x	x	x		
GCS secondary endpoint	x			x		x	x		
Rescue analgesia secondary endpoint Rescue treatment exploratory endpoint			→	→	→	→	→		According to ambulance service procedure, splinting, reduction, painful evacuation
AE and SAE review		→	→	→	→	→	→		

Timepoint **	Scene arrival T(x) And initial assessment	Administration IMP/ t0	T5 min	T10 min	T20 min	T30 min	T-ED Arrival	Data collection: EPJ or phone call within 14 days	Notes
Patient: assess global medication performance Likert scale							x		
HCP: assess global medication performance Likert scale							x		
Troponin I HS							x		Troponin I HS after hospital admission
Recording final diagnosis								x	After hospital discharge

*Arrival by patient is measured with AMIS arrival at scene but corrected where necessary

**Assessment of NRS and clinical variables at t5 and t10: +/- 1 minute is acceptable, at t20 and t30: +/- 2 minutes is acceptable

2. Introduction

2.1. Study Rationale

The study rationale is to provide evidence for early, safe and effective pain management in the ambulance service with non-invasive and fast acting analgesics in order to increase patient satisfaction.

Examination whether non-invasive inhalation of methoxyflurane is as good as non-invasive intranasal fentanyl or IV morphine in the management of moderate to severe acute pain in patients from 18 years in the ambulance service will contribute to a knowledge gap in the pre-hospital field.

Low-dose methoxyflurane and intranasal fentanyl represent non-invasive and fast acting medications that are well-suited for use by ambulance personnel under difficult pre-hospital settings.

Methoxyflurane is an inhaled analgesic widely used in Australia and New Zealand. It is recently licensed in some European countries as an analgesic for traumatic pain.

The intranasal route provides easy administration with fast peak action time due to the high vascularization of nasal mucosa and absence of first-pass metabolism. Fentanyl is a fast-acting opioid, of which the IV route is well-known among emergency medical practitioners.

2.2. Background

Pre-hospital pain management is a challenge, and several studies have found that pain is frequently undertreated in children and adults in the acute pre-hospital setting(1-3). There are many reasons for this, including challenges with intravenous access; treatment in remote settings without physician present; anxiety for adverse events such as hemodynamic instability, sedation and respiratory depression and difficulties in collaboration with paediatric patients(4). Acute traumatic pain, when treated inadequately, has been found to have both immediate and long-lasting consequences (5). From the patient perspective it is recognized that reduction of pain is an important factor of patient satisfaction(2) and is regarded as a measure of successful treatment (6, 7).

The first attempt of inserting peripheral intravenous catheterization fails in 12-26 % in adults and in 24-54% in children in acute care setting(8). Patients are at risk of inadequate analgesia due to challenges in achieving an intravenous access when the patients are distressed, uncooperative (9) or are in a hostile environment (10). Despite increased awareness of pain management, delay in obtaining an access route encounter delay in administration of pain treatment (11).

Both patients and ambulance personnel are in need of an alternative analgesic that is safe, effective, non-invasive, easily administrable and fast acting. Reviews suggest intranasal fentanyl and inhaled methoxyflurane have these desired properties(12, 13) , but there are no randomized

studies comparing those alternatives neither pre- nor in-hospital settings. Intravenous fentanyl is widely used in patients with chest pain supported by the results from an RCT(14). Intranasal fentanyl is already established as an alternative to invasive analgesia in trauma and visceral pain conditions(15).
High-concentration and low-volume intranasal fentanyl is especially suitable for pain treatment in adolescents and adults due to high bioavailability of about 89% (See Summary of product characteristics SPC). The approved indication for intranasal fentanyl in Europe is the management of breakthrough pain in adults already receiving maintenance opioid therapy for chronic cancer pain. However, intranasal fentanyl is increasingly used in pre-hospital setting for acute pain management in children and adult (9, 13, 15-17).

Methoxyflurane has been extensively used in pre-hospital setting in Australia and New Zealand in both acute visceral and traumatic pain(18-20). The use of methoxyflurane in children appears to be both an efficacious and safe analgesic pre-hospital alternative(20), but more research is needed (21). According to the (SPC) of Penthrox, traumatic pain is the only indication for methoxyflurane in Europe. Methoxyflurane has been used to patients with chest pain and abdominal pain(22, 23) but there are no RCTs comparing methoxyflurane to fentanyl or morphine in this population.

A Cochrane review of the management of acute pain in children concludes that adequately powered studies of high methodological quality are required to determine whether there is any difference in clinical outcomes between intranasal fentanyl and other forms of analgesic treatment of children in acute pain. (24). A change in the European Medicines Agency Paediatric Investigation Plan for methoxyflurane from 2019 includes treatment of acute pain for patients from 6 to less than 18 years (25).

There are no studies comparable to the planed PreMeFen study reportet to the WHO`s International Clinical Registry Platform or in EU Clinical Trial Register.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and expected adverse events of inhalation of low-dose methoxyflurane, intranasal fentanyl and IV morphine may be found in the Summary of Product Characteristics.

2.3.1. Risk Assessment

Summary of Data/Rationale for Risk	Mitigation Strategy
1. Demanding clinical setting with lack of research experience	1. A research assistant provides standardized training for all personnel.
2. Acute medicine setting with transportation of the patient in an ambulance	2. Training involves simulations and particularly focus on safety
Study Interventions: Inhalation of methoxyflurane, intranasal fentanyl and intravenous morphine	

3. The risk of serious adverse events (SAEs) will always be present in pharmacotherapy, See Section 8.3: Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting. Note that these patients would receive opioids also if not included in the study, hence the risk associated with opioids is not study specific. We are not aware of reports of anaphylaxis to intranasal fentanyl or methoxyflurane, but, albeit exceptionally rare, this may in theory occur with almost any drug.	3a. Study workers are medical professionals experienced with opioid therapy. 3b. Training of study personnel is focused on recognizing analgesic toxicity. 3c. Ambulance is equipped with antidote (naloxone) and drugs for handling anaphylaxis (adrenaline, corticosteroids, antihistamines).
4. Adverse reactions related to the study drugs: For all three study drugs, frequent adverse reactions include dizziness, somnolence and nausea, none of which is considered dangerous unless somnolence evolve to coma. The treatment would be to pause the study drug. Antiemetics can be administered. For morphine and fentanyl, additional adverse reactions (for high doses) also include respiratory depression. This can be reversed by antidote Naloxone. The three study drugs have different adverse reaction profiles, but all the frequent or severe reactions are comparable because they are clinical features with acute onset related to the administration. One or more drug/ treatment arms may provide inadequate analgesia at the initial dose, leading to initially inadequate pain relief (oligoanalgesia).	4. all the common adverse reactions are clinical features that study workers are used to deal with as part of everyday tasks. The patients will be observed continuously during study period, as is the routine. Naloxone for reversal of opioid toxicity is a common medical procedure performed by the study workers in their everyday work and is available in the ambulance medical kit. All frequent and expected adverse reactions will be recorded in the eCRF either by checklist or by recording physiology. The training of the study workers focus on the registration of adverse reactions, and training includes online course, tutorial videos and clinical simulation. Additional doses of the IMP may be given if the analgesia is inadequate. Further, rescue medicine (analgesic other

	than the allocated IMP) may be given if inadequate analgesia still persists. Additional analgesic doses are spaced sufficiently to avoid "stacking".
Study Procedures (allocation to non-invasive and invasive pain management)	
5. Intravenous morphine (one of the three study arms) requires intravenous access to be administered which can be difficult to obtain in certain clinical settings	5. Rescue medicine is available as part of the protocol. In case IV access is not obtained, alternatives are available (IN fentanyl or inhalation methoxyflurane)
6. IV is considered necessary in many trauma patients, and cannulation is often triggered by the need for pain treatment. With non-invasive pain treatment, the iv cannulation might be erroneously omitted.	6. The study protocol and instruction shall emphasize to assess the need for an IV line independently of the allocated study procedure.
Other	
7. Exhaled methoxyflurane gas inside the ambulances represents an occupational risk of exposure, causing dizziness and reduced awareness in ambulance workers. Methoxyflurane is not metabolized and could reach clinically significant concentrations without activated carbon filtering. The application device is installed with such filter.	7. Exhalation of methoxyflurane is filtered with activated carbon, and training of the study personnel is focused on this necessity, hence the medication will only be delivered with this device. Resent research suggest that occupational exposure in an ambulance service is clinically unimportant (26)

2.3.2. Benefit Assessment

This study has no placebo arm (which would have been unethical), and the dosing in the three treatment arms are considered to be equipotent. Hence, favourable pharmacodynamic or other effects resulting in faster pain relief will be of significant benefit for the participant.
The aim of the study is to find better and faster analgesics for pre-hospital- treatment without the need of IV access, and with hopefully fewer side effects as this would be an advantage for the 2/3 of patients in the non-invasive groups and the last 1/3 receiving treatment as usual (IV morphine).

Study personnel will receive extra training and will give more focus on patient treatment in general. There are reasons to believe that the result will give better total care for all patients. Patients participating in a clinical study are meticulously selected, closely monitored and the impression from other studies is that patients feel better looked after in a clinical study.

Close measurement of the endpoint NRS will contribute to better care of the specific patient with acute pain. NRS measurement is the basis of effective pain management.

2.3.3. Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimize risk to participants in this study, and weighted with the benefits of the study, the potential risks identified in association with the regimens of inhalational methoxyflurane, intranasal fentanyl or intravenous morphine are justified and acceptable.

3. Objectives and Endpoints

The overall objective of the study is to evaluate if a regimen of low-dose methoxyflurane is non-inferior to a regimen of intranasal fentanyl or if a regimen of low-dose methoxyflurane is non-inferior to a regimen of intravenous morphine or if a regimen of intranasal fentanyl is non-inferior to a regimen of intravenous morphine after 10 minutes in the treatment of moderate to severe acute pain (NRS ≥4) in patients >18 years of age in pre-hospital-setting.

The overall objectives of the study are to be investigated in a hierarchic model, see 9.1.

The primary, secondary and exploratory objectives of this study are listed below, with associated endpoints

	Primary Objectives	Number	Primary Endpoints	Assessment
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 ug (>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)	1.1	Changes in pain score from t0 to t10min	ΔNRS t0-t10
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)	1.2		
1c	To determine if a regimen of intranasal 50 µ(>70 years) or 100 ug (>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)	1.3		
	Secondary Objectives		Secondary endpoint	Assessment
2	To assess the reduction in NRS from baseline at 5, 20, 30 minutes and/or to emergency department (ED) arrival	2.1	Change in pain score from t0-t5	ΔNRS t0-t5
		2.2	Change in pain score from t0-t20	ΔNRS t0-t20
		2.3	Change in pain score from t0-t30	ΔNRS t0-t30Δ
		2.4	Change in pain score from t0-tED-arrival	ΔNRS t0- t ED-arrival
3	To assess the need for rescue analgesia in the treatment groups	3	Need for additional analgesia not in the regimen of the allocated treatment group:	• time of administration • type of medication • dose • route of administration
4	To determine difference in time from scene arrival to IMP administration	4	Difference in time arrival to administration of IMP	Δ tx -t0

5	To determine time difference from scene arrival to pain reduction	5	Time from ambulance personnel arrival to first measure > 2 points reduction in NRS from baseline	Δ tx -to first t with ΔNRS>2
6	To determine any difference in level of sedation	6	Change in level of sedation from t0 to T-10 and T-30	Δ GCS t0 to T-10 and T-30
7	To determine any difference in change in respiratory rate (RR)	7	Change in RR t0 to T-10 and T-30	Δ RR t0 to T-10 and T-30
8	To determine any difference in systolic blood pressure (SBP)	8	Change in SBP t0 to T-10 and T-30	Δ SBP t0 to T-10 and T-30
9	To determine the level of overall health care personnel satisfaction of the treatment	9	Likert scale of HCP satisfaction at end of mission	1–5-point Likert scale
10	To determine the level of overall patient satisfaction of the treatment	10	Likert scale of patient satisfaction at end of mission	1–5-point Likert scale
11	To determine differences in any adverse events or serious adverse events	11	Registration of AE and SAE during study period until end of intervention	AE and SAE t0 to discharge
	Exploratory Objectives		Exploratory endpoints	Assessment
12	To determine efficacy within diagnosis group	12	Analyse Primary and secondary efficacy endpoints stratified by diagnosis or diagnosis groups	ΔNRS t0-t10 stratified by diagnosis group Use of rescue analgesia stratified by diagnosis group ΔNRS t0-t30 stratified by diagnosis group
13	To determine the need for rescue medication in relation to painful procedures (complex evacuation, painful medical procedures)	13	Proportion of patient receiving rescue treatment related to procedures (reposition of fractures, relocation etc)	Use of rescue analgesia stratified by type of procedure
14	To determine any difference in attempts of vascular cannulation with the level of competence of the ambulance worker	14	Attempts of vascular cannulation access	Vascular access attempts from tx to tED and ambulance worker years of experience
15	To determine any difference in NRS reduction or time to pain relief stratified by ambulance worker competence	15	Change in NRS and time to a significant NRS reduction compared to level of competence	ΔNRS from tx to t30mim
16	To determine any difference in patient satisfaction stratified by ambulance personnel competence	16	Ambulance personnel competence and patient satisfaction	Participant Likert scale and ambulance worker years of experience; 1-4, 5-10, 11-20, >21
17	To determine efficacy within ACS groups 1) elevated versus normal Troponin group 2) ACS suspect ECG versus normal ECG	17	Analyze primary and secondary efficacy endpoints stratified by level of troponin after ED admission and sign of ACS on ECG at scene	ΔNRS t0-t10 and/or rescue medication stratified by Troponin groups ΔNRS t0-t10 and/or rescue medication stratified by ECG groups
18	To determine predictors for side effects such as hypotension, reduced GCS and reduced RR with concomitant therapy and other non-IMP variables as possible determinants	18	Analyse AE and SAE in relation to concomitant therapy and other non-IMP determinants	Concomitant therapy and other factors as predictors for hypotension Concomitant therapy and other factors as predictors for reduced GCS

				Concomitant therapy and other factors as predictors for reduced RR

T_{-x}: scene arrival

t_0 : time of IMP administration

t_5 : 5 minutes after IMP administration

t_{10} : 10 minutes after IMP administration

t_{20} : 20 minutes after IMP administration

t_{30} : 30 minutes after IMP administration

t_{ED} : time arrival Emergency Department or end of service

4. Overall Study Design

4.1. Overall Design

This is a randomized, controlled, open label, three-arm, non-inferiority, two-centre, phase 3 drug trial.
The randomization will be 1:1:1 to the three treatment groups. There will not be treatment blinding but blinding of the statistician. A Data Monitoring Committee will be put in place.

Study Period	Estimated date of first patient enrolled: 01. September 2021. Anticipated recruitment period: 48 months. Estimated date of last patient completed: 31. December 2025.
Intervention Duration:	Duration of intervention is defined from scene arrival to handover at hospital or end of ambulance treatment. Duration of intervention is estimated to be between 30 minutes and two hours. Estimated pre-hospital time will differ significantly due to the pre-hospital environment and distance to hospital. End of intervention will be patient hospital handover and end of pre-hospital service engagement.
End of study data collection:	Same as end-of-intervention Data will also be collected from hospital EPJ or phone call to patient within 14 days after end-of-study to collate additional clinical information relevant for endpoint analysis.

4.2. Scientific Rationale for Study Design

Comparison of an active agent against placebo when an existing active substance is available is generally regarded as unethical according to the Declaration of Helsinki Item 33(27). Randomized controlled trials are the accepted gold standard of individual research studies(28). The European Medicines Agency *Guideline on the clinical development of medical products intended for the treatment of pain* state that pain self-assessment is the most valid measure of pain assessment. In addition, they emphasize the need to predefined responder analyses (such as relevant reduction in NRS) and to clearly report the need of rescue medication in pain trials(29).

A non-inferiority trial seeks to determine whether a treatment is not worse than the reference treatment by more than an acceptable amount (the inferiority margin) and is of interest on the premise that the new treatment has some other advantages such as greater availability or less invasiveness(30). Our choice of a non-inferiority trial design is based on the expectation that intranasal fentanyl and inhalation of low-dose methoxyflurane are as good as (non-inferior to) intravenous morphine, and that the first two will contribute to an earlier and more practical administration of the analgesics in the pre-hospital setting. Furthermore, it is of great interest to establish whether the self-administrated inhalation of methoxyflurane is as good as IN fentanyl, because it would ease the pain management in many acute pre-hospital settings.

Numeric Rating Scale (NRS) is a validated research tool for pain assessment (31), and considered to be the optimal scale to evaluate pain among adult patients without cognitive impairment (32). Studies suggests that an NRS-difference of 1,3 is a clinically significant difference (16, 33-35). The primary endpoint in this study is the change in NRS, and a non-inferiority margin of 1.3 is chosen. A non-inferiority is demonstrated ($p < 0.05$ with 1-sided

mean-equivalence t test), if the lower 95 % confidence interval is above the prespecified margin of 1.3, see 9.2

We will use an open label randomized method for two reasons: Methoxyflurane has a distinct smell, and the routes of administration are completely different in the three arms and impossible to blind without the use of dummies. The only way to double-blind the study would be to provide a triple-dummy procedure, which is considered too complex and not feasible in this study context.

We aim to compare *regimens* of the three IMPs, rather than a fixed dose of the medicaments. With *regimen* we mean a flexible dosing of the analgesic using titration to effect, but only using the specific drug in the allocated treatment arm. There are several reasons for comparisons of regimens: 1) The administration of the IMPs differs to a large extent, with the inhalation of methoxyflurane being more or less continuous depending on the patient needs, versus bolus dosing of the others. 2) The pharmacokinetics with bioavailability, Cmax and Tmax are different for all three IMPs. 3) The clinical needs and pain characteristics will be heterogenous with an individual need for titration and redosing that cannot be foreseen, and hence will have to be tailored with redosing within the allocated regimen. 4) Comparison of regimens will address the clinical setting where the interesting objective is to find whether the regimen of non-invasive methods are non-inferior to the existing procedure.

We expect that gender and age will be represented in balance with the normal patient population with acute pain.

4.3. Justification for Dose

Patients will be individually titrated to an analgesic dose that provides adequate analgesia (NRS<4) with tolerable adverse drug reactions. Titration of analgesics is common practice in the pre-hospital setting (36). see also 6.5

Inhalation of low-dose methoxyflurane regimen:
The standard dosing described in the SPC of the product is 3ml for inhalation. The solution is added in the inhalation chamber of the device, and the patient will hold the device and inhale as much as needed. Hence, the inhalation can be continuous, but most often will be intermittent periods with inhalation with or without closing the diluter hole with the finger to increase the amount of drug inhaled. The delivery device is set up in the packaging with a 3 ml bottle. A second bottle with 3 ml can be administered if needed. Continuous inhalation of a bottle containing 3 ml provides analgesic relief for up to 25-30 minutes. Intermittent inhalation may hence provide longer analgesic effect.

The dosing of methoxyflurane in this study will be the standard dosing:

- 3 ml inhalation
- Repeated dosing with addition of 3 ml if needed
- Maximum total dose 6 ml

Intranasal fentanyl regimen:

Intranasal fentanyl is approved for breakthrough pain in cancer patients but is increasingly used in pre-hospital setting (9, 15). Fentanyl 1 µg/kg IN is one of the preferred agents in U.S. EMS systems and offer pain relief along with an acceptable safety profile(13). In a Danish pre-hospital prospective observational study of intranasal fentanyl in adults and children (>8 years old), 903 patients received intranasal fentanyl for severe pain resulting from orthopaedic conditions, abdominal pain, or acute coronary syndrome, the mean cumulative dose was 104µg and maximum dose allowed was 300µg (15).

In an placebo-controlled study from University in Oslo where cold pressor test was used to evaluate pain relief, 3ml methoxyfluran inhalation was considered equipotent with 25µg fentanyl intravenously(37).

Intranasal fentanyl has a bioavailability of 71-89% and both maximal arterial blood concentration and onset of analgesia are reached in approximately 7 minutes in an RCT comparing intravenous and intranasal fentanyl. Both IN and IV administration were generally well tolerated. (38, 39).

Intravenous 1-2 µg/kg fentanyl is a common starting dose in trauma. With a bioavailability of 70-90%, equipotent intranasal fentanyl doses would be 1.25 -2.25 µg/kg. The SPC of intranasal fentanyl describes a starting dose of 50 ug with titration to effect. This is however in a different setting with chronic cancer pain. In our study, we dose according to age as recommended in the SPC (not weight), but with doses adapted to the clinical setting with acute pain with reference to the experiences described above.

Based on this, the dosing of intranasal fentanyl in this study is:

- Patients 18-70 years of age: 100µg intranasal fentanyl
- Patients > 70 years: 50µ intranasal fentanyl
- Repeated dosing allowed with a minimum interval of 5 minutes
- Maximum total dose 500µg

Intravenous morphine regimen:

IV morphine is the most commonly used analgesic globally, and serve as the gold standard for pain management with almost 200 years of experience in the clinical setting. The SOP for morphine dosing in the ambulance service is 0,1 mg/kg for moderate and severe acute pain, with reduction in dose for older or fragile patients. In this study, we follow the same dosing regimen as in the ambulance service:

- Patients <70 years of age: 0.1 mg/kg intravenous morphine
- Patients >70 years of age or fragile patient (as assessed by the ambulance worker): 0.05 mg/kg
- Repeated dosing allowed with a minimum interval of 5 minutes
- Maximum total dose 0.5 mg/kg morphine

4.4. End of Study Definitions

4.4.1. End of Intervention

End of intervention will be patient hospital handover and /or end of pre-hospital service engagement.

4.4.2. Post-intervention collection of data

Each patient will also have data collected in the time from end of intervention within 14 days after end of intervention. This will be done by entering hospital EPJ and a follow-up phone call to the patient.

4.4.3. End of Study

End of study is defined as the last post-intervention collection of data of the last patient last visit.

5. Study Population

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. >18 years of age
2. Acute moderate to severe pain defined by self-reporting pain ≥4 on NRS
3. Capable of giving informed consent
4. Normal physiology defined by the following:

Respiratory Rate/ minute	Heart rate/ minute	Oxygen saturation without supplementary oxygen	Systolic Blood Pressure (mmHg)	Glasgow Coma Score
≥12	55-130	≥95	≥ 100	≥14

SBP: systolic blood pressure.
References (40-42).

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Life-threatening or limb-threatening condition requiring immediate management
2. Pregnancy or breastfeeding
3. Know allergies, hypersensitivity or serious side effects to opioids or methoxyflurane or other excipients
4. Head injury or medical conditions with neurological impairment (GCS<14)
5. Previous malignant hyperthermia or persons with suspect genetic predisposition for malignant hyperthermia
6. Massive facial trauma, visible nasal blockage or on-going nose bleeding
7. History of severe liver disease with jaundice and scleral icterus
8. Dialysis or history of severe renal disease (known chronic kidney failure stage 4 or 5)
9. MAO-inhibitors last 14 days (pharmacological treatment of depression, Mb Parkinson or narcolepsy)
10. Myasthenia gravis
11. Use of IMP analgesics 12 hours prior to inclusion
12. Any condition that in the view of the study worker would suggest that the patient is unable to comply with study protocol and procedures.

Female participants under the age of 50 years will be asked explicitly about possible pregnancy. If no clear information is available, the paramedic shall include or exclude based on his/her best judgment at the time of inclusion.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

Not applicable

5.3.2. Caffeine, Alcohol, and Tobacco

Not applicable

5.3.3. Activity

Not applicable.

5.4. Screen Failures

Screen failures are defined as subjects who are assessed for selection criteria in the clinical trial but are never subsequently randomised. These will be included in a screening log with a minimum dataset (gender, age and reason not randomised) to ensure transparent reporting of screen failures to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities.

5.5. Criteria for Temporarily Delaying

Not applicable.

6. Study Intervention and Concomitant Therapy

Study intervention is defined as any marketed products intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention Administered

Study intervention is given with the clinical aim of reducing NRS to below 3.

ARM name	1	2	3
Intervention Name	Methoxyflurane (Penthrox®)	Fentanyl (Instanyl®)	Morphine hydrochloride
Type	Drug	Drug	Drug
Formulation	Inhalation vapour, liquid	Intranasal spray, solution	Solution for injection
Unit Dose Strength	3 ml methoxyflurane 99,9%	50 µg/dose or 100 µg/dose	10 mg/ml
Dosage Level	• 3 ml inhalation • Can be repeated once (3 ml) • Maximum total dose of 6 ml	• 100 µg IN, • Patients >70 years: 50 µg IN • Can be repeated • Maximum total dose 500 µg IN	• 0.1 mg/kg IV • Patients ≥ 70 years or fragile: 0.05 mg/kg IV • Can be repeated • Maximum total dose 0.5 mg/kg IV
Rescue analgesia	From 10 min and/or after maximum dose	From 10 min and/or after maximum dose	From 10 min and/or after maximum dose
Route of Administration	Inhalation	Intranasal spray	Intravenous injection
Use	Experimental	Experimental	Control intervention
IMP	yes	yes	yes
Sourcing	OUH Hospital Pharmacy	OUH Hospital Pharmacy	OUH Hospital Pharmacy
Packaging and Labelling	IMP in original packaging (commercial), available in study kit, no additional labelling	IMP in original packaging (commercial), available in study kit, no additional labelling	IMP in original packaging (commercial), available in study kit, no additional labelling

6.1.1. Medical Devices

Not applicable

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. The attending ambulance worker will use the study drug only within the framework of this clinical study and in accordance with this protocol.
3. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area (according to guidelines for narcotics) in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.
4. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records) in the Trial Master File (TMF).
5. Further guidance and information for the final disposition of unused study interventions are provided in the Investigator Site File.

All three drugs can be stored in room temperature, cross ref SPC. Methoxyflurane does not require any specific storage temperature requirement. Intranasal fentanyl has to be stored in upright position in the outer carton and not above 30 degree Celsius. Morphine has to be stored in the outer carton in order to protect from light and not above 25 degree Celsius.

All IMPs in this trial has a Marketing Authorization in the EU and is sourced from the EU market. They are used in the trial without modification and the packaging and labelling is carried out for local use only as per article 9.2. of the Directive 2005/28/EC (GCP Directive). The IMP will be stocked separately from the ambulance pharmaceuticals and be available for use in a specific study kit. The kit will be returned to study Nurse/paramedic or principal investigator after each included patient, in exchange for a ready-made kit for next inclusion. To ensure accountability, any IMP administered to a patient will be noted in the CRF, and accounted for in the study drug accountability form with the following information:

Patient's initials
Patient's enrolment code
Batch of drug dispensed
Date dispensed
Name of administering ambulance personnel

6.2.1. Instruction for the preparation of IMP

See 10.7Appendix 11: Instruction for the preparation of IMP

6.3. Measures to Minimize Bias: Randomization and Blinding

The SOP DM07 Randomization and unblinding from NORCRIN will be used.
The sealed randomization envelopes will be distributed to the attending ambulance in medicament bags/kits also containing the IMP. The bags will be packed by the study nurse or study workers before distribution to study centre.
The randomization is to take place after the screening for eligibility process and oral consent is obtained. The medicament storage bags with the randomization envelope will be opened immediately prior to the start of study intervention administration for each participant. The personnel will record the date and time the envelope was opened.

Allocation- sequence generation
Computer generated block randomization with variable block sizes stratified by centre will be provided by department of clinical trial unit (CTU), Oslo University Hospital.

Allocation- procedure to randomize a participant
Included patients will be treated with the study drug in the ambulance at the scene. The participant number will become the participant study number. The randomisation will take place at the scene after the eligibility process.
Once a participant has been randomized the participant will not be reassigned.

Blinding and emergency un-blinding
This is an open label study for study workers, DMC, sponsor and study personnel.
The statistician will be blinded for allocation until after the analysis on the primary and secondary endpoints.

6.4. Study Intervention Compliance

The Norwegian national identity number will be used in the source document (EPJ) and in the code list. Participants will be administered drugs in the ambulance in accordance with the protocol dosing schedule. The dose of study intervention will be confirmed at the time of dosing by the second paramedic on scene. Dose and time of each dose administered by the paramedic on scene will be recorded in the source document.

6.5. Dose Modification

The decision to proceed to the next dose level of IMP will be made by the attending ambulance personnel based on NRS, dosing schedule and tolerability of the patient with respect to respiration rate, blood pressure and level of consciousness. Dosing interval with IMP shall not be shorter than 5 minutes. Rescue analgesia will be analgesics other than the allocated IMP. Rescue medication shall only be given if IMP is considered insufficient for the patient. If Rescue medication is administered before the assessment of primary endpoint at 10 minutes, the patient is not considered per-protocol. See also 4.3

6.6. Continued Access to Study Intervention after the End of the Study

Not applicable.

6.7. Treatment of Overdose

Overdose intranasal fentanyl or morphine:

- Oxygen is supplied and assisted ventilation is given when needed (RR < 10).
- The patient is physically stimulated to keep awake.
- Intravenous or intramuscular naloxone is administered according to ambulance service procedures.

Overdose methoxyflurane

The expected acute overdose symptoms of methoxyflurane are self-limited due to the fact that the participant administer the IMP themselves (43) and if too drowsy, the inhalation of the drug will pause. Because of the short duration of action, the patient will wake up.

Participants will be observed for signs of overdose following IMP and rescue medication administration during pre-hospital phase and till hospital admission.
For medical emergencies during treatment in this trial the standard operating procedures for the participating ambulance will be followed. For the ambulances this includes telephone or radio contact with colleague via emergency medical dispatch centre (AMK), with the potential for additional resources to be dispatched to the scene and transport to nearest hospital.

High doses of methoxyflurane cause dose related nephrotoxicity. High output renal failure has occurred several hours or days after the administration of repeated high analgesic or anaesthetic doses of methoxyflurane. In the PreMeFen study the participants are allowed to use two units of methoxyflurane, which is considered to be safe in regards to renal failure(44).

Definition of overdose is related to age. See cross reference appendix 10.3.1.

For adverse event or overdose of study medications, the following rescue medications will be available: oxygen supplementation (anaphylaxis, opioid overdose), naloxone (adverse effects to opioids), hydrocortisone (anaphylaxis), adrenaline (low blood pressure, overdose, anaphylaxis), atropine (bradycardia) and intravenous infusion of Ringer Acetate (low blood pressure, overdose, anaphylaxis).
The paramedics are all trained in handling of opioid overdose and anaphylactic shock.
The handling of opioid overdose and anaphylactic shock are recorded in the ambulance medical records, as well as in the CRF.

6.8. Concomitant Therapy

All drugs administered by ambulance service during the study will be recorded in CRF with generic name, dose and route of administration.
All tasks and medical procedures normally performed by ambulance service are allowed during the study. Procedure attempts and procedure performed by ambulance service will also be noted in CRF.

This study protocol takes precedence over any local ambulance guideline such as the advice to administer morphine to patients with suspected acute coronary syndrome. Patients with this condition will be randomized and receive any of the three IMPs in lieu of non-IMP morphine.

Patients with suspected cholelithiasis or nephrolithiasis related pain are allowed to receive NSAIDS 10 minutes after IMP administration (after t-10) according to local procedure. Cross ref 6.8.1.

6.8.1. Rescue Medicine

Rescue analgesia is all analgesics other than the allocated IMP. Rescue medication shall only be given if IMP is considered insufficient for the patient. If rescue medication is administered before the assessment of primary endpoint at 10 minutes, the patient will not be part of the per-protocol analysis.
Data about rescue analgesics will be recorded in the CRF, herein generic name, time, dose and route of administration. Rescue analgesia will be chosen according to availability in the ambulance and dosed according to local procedures.
Examples of rescue medicine:

- IV/IM morphine (can be rescue for non-morphine IMP) ATC N02AA01
- IV/IN/IM ketamine ATC N01A X03
- IV/IN/IM esketamine ATC N01A X14
- IV/PO/SUPP paracetamol ATC N02B E01
- IM/PO diclofenac ATC M01A B05
- IN fentanyl (can be rescue for non-fentanyl IMP) ATC N02A B03
- Inhalation Methoxyflurane (can be rescue for non-Methoxyflurane IMP) ATC N02B G09

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for safety. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

7.1.1. Liver Chemistry Stopping Criteria

Not applicable

7.1.2. QTc Stopping Criteria

Not applicable

7.1.3. Temporary Discontinuation

Not applicable

7.1.4. Not applicable Rechallenge

Not applicable

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at her/his own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, or compliance reasons. This is expected to be uncommon.

The participant will be permanently discontinued both from the study intervention and from the study at that time.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

7.3. Lost to Follow up

Before a participant is deemed lost to follow up, the investigator or study nurse will make every effort to regain contact with the participant (where possible, telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's medical record.

Not reaching the patient at the follow-up phone call at day 14 does not result in lost to follow up. The study nurse or investigator will get the final diagnosis and status of patient from the hospital electronic medical record where the patient was last treated.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the Schedule of Activities (SoA). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns will be discussed with the study team immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Telephone number to study team is immediately available on scene. A designated on-call physician will be reachable at 24/7.

Training of study personnel
The become study personnel, ambulance workers must complete study specific training session according to the training protocol. The training will be documented in a training log and included in the Investigator Site File (ISF) during the study and included in the TMF at the end of the study. The final version of the training manuals will be completed after the approval of this study protocol.

The training will consist of:

- Lecture outlining background of study, primary and secondary outcomes and design
- Familiarising participants with IMP and training in administration of IMP.
- The use of a mannequin to play out a study scenario
- Practice of recording variables and points in time, fill in study forms
- Practice in documenting drugs accountability form at ambulance station
- Lecture focusing on AE, SAE, SUSARs and procedures in case of emergency- study emergency telephone and criteria for code break.
- Training in evaluating which participants are eligible to give oral consent
- Talk focusing on patient information, consent and about withdrawal from participation

Documentation of study personnel
Individual ambulance personnel that complete training and pass the test at the end of the training session will be certified as study personnel. This means that they can be delegated the tasks to: IMP preparation, IMP administration, IMP dispensation, collection & accountability, evaluate inclusion & exclusion criteria, record medical history, record & evaluate AE, record concomitant medication, record vital signs, treatment allocation/randomization and perform physical examination.

A record of certified study personnel including completed training and proof of delegation will be stored in the ISF and filed in the TMF at the end of study. There will not be a copy of the curriculum vitae of each study worker in the ISF/TMF.

One certified study worker is sufficient for the conduct of the trial in the attending ambulance.

Data collection
Data from the CRF will be plotted in Viedoc.

Intervention procedures
After the patient is screened (including a brief clinical examination, NRS value obtained and vital signs monitoring established) and oral consent is obtained, the patient is allocated to one of three treatment groups (arms). The patient will receive IMP according to the allocated treatment arm from the study kit (see Figure 2 Intervention overview). For the non-invasive groups, the IMP should be administration immediately after preparation, while in the IV morphine group, a peripheral venous access must be placed and verified, and the correct amount of injection solution prepared in a syringe before IV administration. The time of administration shall be noted on the CRF, and the stopwatch is started. Other non-trial clinical and operational tasks shall be carried out according to the situation and local routines. Physiological parameters shall be monitored every 10 minutes. NRS shall be assessed at 10, 20 and 30 minutes.

Additional IMP can be administered as follows, and still be within the treatment protocol for each treatment arm:
For methoxyflurane: when the inhalation liquid is consumed from the chamber, a new dose with 3 ml can be provided independent on timing.
For Intranasal fentanyl and IV morpine: a new dose can be considered after a minimum of 5 minutes from previous dose.
See 6.1 Study Intervention Administered for dosage level and maximum total doses.

If analgesic effect is insufficient, rescue medication can be administered to the patient. Any analgesic outside the allocated treatment arm/group is considered as rescue medication. If rescue medication is administered before the assessment of primary endpoint at 10 minutes (t-10), the patient is not considered per-protocol. If rescue medication is administered after t-10, the patient is still considered as per-protocol.

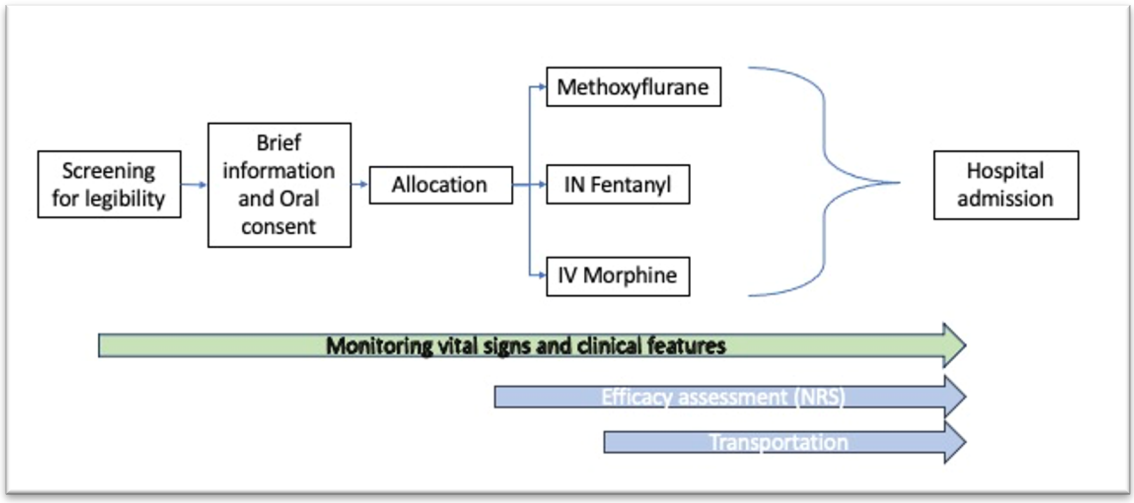


Figure 2 Intervention overview

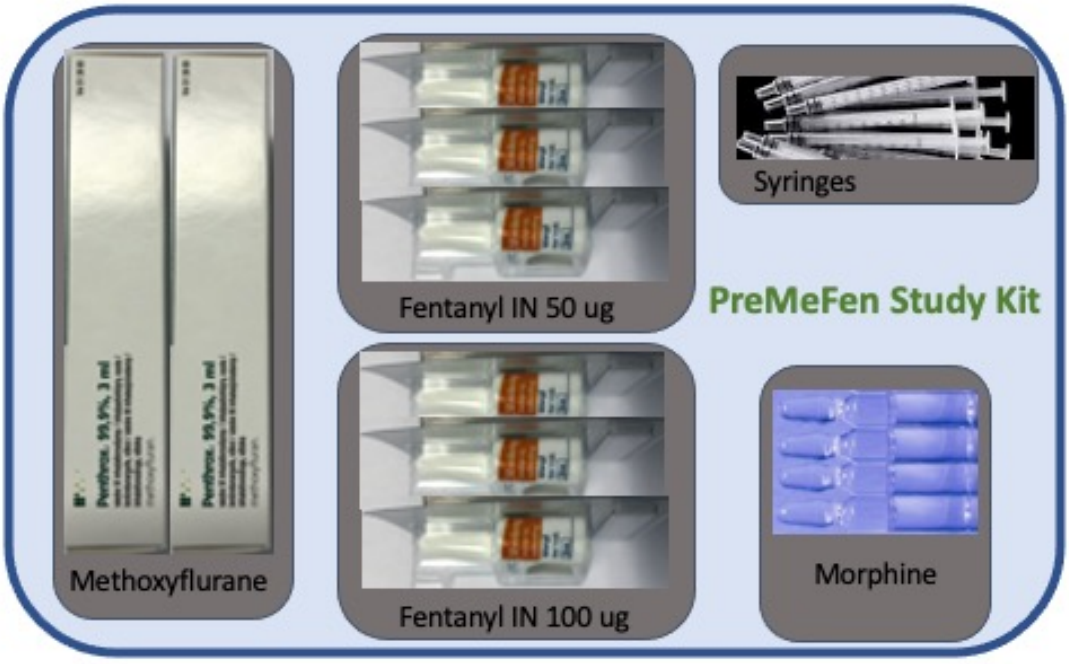


Figure 3 PreMeFen Study Kit

8.1. Efficacy Assessments

8.1.1. Numeric Rating Scale (NRS)

The main efficacy assessment is by measuring the reduction in pain score using the Numeric Rating Scale (NRS). This is the efficacy assessment for the primary objective. NRS is a Likert scale with integer values from 0 to 10. NRS consists of a numerical scale with verbal descriptors at the end and numbers marked along the line. Patients are asked to indicate on the line where the

pain is in relation to the extremes. The scale is 10 cm long and measured from the left-hand end to the mark. NRS data are discrete, consisting of the possible responses: 0,1,2,3,4,5,6,7,8,9,10. 0 is no pain and 10 is worst pain possible. Pain is considered moderate to severe from NRS ≥4. **T**herapeutic interventions aim to reduce pain to a NRS value of <4 **(35, 45)**. The use of pain scales is age-independent, such that both adolescents and adults can rate their pain using NRS.

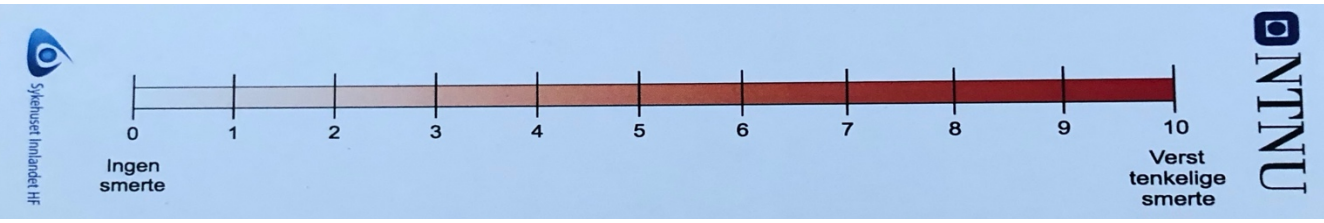


Figure 4 Numeric Rating Scale (NRS) for pain evaluation

8.1.2. Need for rescue analgesics

For secondary outcomes, a proxy measurement for efficacy would be absence of a need for rescue medication. The administration of rescue medication will be noted in the CRF with time of administration, type of drug, dose and route of administration.

8.1.3. Patient and healthcare worker satisfaction

For secondary outcomes, Patient-reported outcome (PRO) measures satisfaction with the treatment, assessed by the patient using a 5-point Likert scale at end of mission/30 min.
The patient will be asked to rate the overall satisfaction with the IMP by answering the question" *Altogether, how do you rate your satisfaction with the pain therapy that was given to you?"*

Assessment of clinician-reported outcome (ClinRO) uses a 5-point Likert Scale to measure the ambulance worker's overall satisfaction with the use of the IMP at this particular patient. The ambulance worker will answer the question "*Altogether, how do you rate your satisfaction with the pain treatment you have given?"*

Each will be rated on a 5-point Likert qualitative scale:

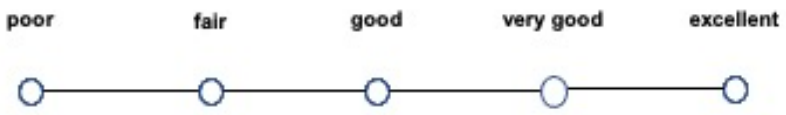


Figure 5 The Likert Scales

Assessments of patient's satisfaction and ambulance worker satisfaction will take place at end of mission at the handover in ED. In case that Likert scale assessments are not possible at end of mission, study nurse/paramedic can obtain this information in the following days.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

Follow-up.
Study nurse/paramedic will call or visit the patient at day 14±3. If patient is unavailable, a search in the hospital electronical patient record will be performed. The follow-up is to collate data.

8.2.1. Physical Examinations

A brief physical examination will include assessments of the skin by observation and assessment of vital signs.

8.2.2. Vital Signs

Vital signs include GCS, blood pressure, heart rate, oxygen saturation and respiratory rate. Vital signs will be measured before study intervention and every 10 minutes until end of intervention/handover at the hospital. GCS < 14, respiratory rate < 10/min, Oxygen saturation < 90%, MAP < 60 mmHg are regarded as relevant reduction in vital signs.

Continuous 3-channel ECG, blood pressure and oxygen saturation will be assed using a multimonitor (LIFEPAK® 15 monitor/defibrillator from Physio-Control or equally).). The monitor is standard equipment in all attending ambulances. All multimonitors are maintained in a maintenance program with regular control and calibration performed by the medical technical departments of Innlandet Medical Trust and Oslo University Hospital Ambulance Service.

8.2.3. Electrocardiograms

12-lead ECG is part of the diagnostic examination in patients with suspected acute coronary disease according to standard ambulance service procedure. Patients with chest pain will have a 12 lead ECG done within the first 10 minutes after ambulance scene arrival.
ECG will be assessed by the ambulance worker on site and later by physician in ED after admission. If the ambulance worker assesses the pre-hospital ECG as suspicious of cardiac infarction (STEMI), the ECG will be transmitted to cardiologic expertise at receiving hospital for interpretation and clinical decision-making.

8.2.4. Clinical Safety Laboratory Assessments

Not applicable

8.2.5. Pregnancy Testing

Not applicable

8.2.6. Suicidal Ideation and Behavior Risk Monitoring

Not applicable in the period of this trial

8.3. Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an adverse event (AE) or serious adverse event (SAE) as described in appendix 3.

The nature of the patient population studied, the pre-hospital environment, range of medical complaints, conditions, illnesses included, and multitude of medical interventions makes the AE reporting challenging. Almost all of our participants are expected to be admitted to hospital for treatment of the underlying condition.

The time period which ambulance personnel spend with the patient is limited, and AE reporting will not continue after the treatment time of pre-hospital services has ended. Several events that meet the AE criteria are expected in the natural history of acute pain, critical illness and in the treatment offered to patients included in this trial. We have established a system that balance the regulatory concerns with the need to conduct clinical trials in the pre-hospital environment.

Each adverse event will be described by the investigator in precise standard medical terminology. The duration of the event will be described in terms of event onset time and event ended time, if known. For each AE a description of any interventions and outcome will be described if known to pre-hospital personnel or investigator. AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) system by investigator.

Each adverse event will be assessed for:

- Seriousness using the GCP definitions described in this protocol
- Causality classified as "reasonable possibility of causality" or "not a reasonable possibility of causality" between event and IMP.
- Severity according to according to the division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events
- Expectedness based on available information in each drug summary of product characteristics

Please note the difference in severity and seriousness: 'severe' is used to describe the intensity of a specific event. The event itself, however, may be of relatively minor medical significance (such as severe headache). Seriousness is based on event outcome or action criteria serves such as hospitalization or significant disability.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

- For each participant the standard time period for collecting and recording AE and SAE will be from first IMP dose until end of intervention.
- An attempt will be made to follow the event until resolution if study team has access to records of the hospital treating the SAE
- Any information regarding SAE that comes to investigators attention for any included participant prior to End of Trial will be assessed according to this protocol.

- Every effort will be made to obtain a resolution for all events, even if the events continue after follow up.

8.3.2. Method of Detecting AEs and SAEs

Ambulance personnel will note the following:

- The nature of the event will be described by the paramedic.
- The duration of the event will be described in terms of onset time and event end time or if present at the time defined as End of Intervention
- The severity of the adverse event.

Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences. For participants unable to answer questions, or with language barriers study personnel will do their best to use clinical judgment to assess AEs

The CRF will include prespecified AEs that will be assed, unique to each medication, in addition to general questions and physical examination normal to the pre-hospital treatment situation.

8.3.3. Follow-up and local reporting of AEs and SAEs

Adverse Events
will be recorded continuously in the patient CRF.

Serious Adverse Events
Investigators who detect SAE must report this to PI withn 24 hours. When a SAE is recorded in Viedoc, an automated message will be sent to the Medical Monitor, who will examine the relation between the IMP and the SAE. In case this is considered a SUSAR, a report is sent to the Norwegian Medicines Agency. The PI must consider expectedness.

Suspected Unexpected serious adverse reactions

The PI is delegated the responsibility for SUSAR reporting from the sponsor, and will ensure that all relevant information about suspected serious adverse reaction that are fatal or lift-threatening is recorded and reported as soon as possible to the Competent Authority in any case no later than 7 days after knowledge by the PI of such a case, and that relevant follow-up information is subsequently communicated within an additional 8 days.
All other suspected serious adverse reactions will be reported to the Competent Authority concerned as soon as possible but within a maximum of 15 days from first knowledge of sponsor. SUSAR will be reported to The Norwegian Medicine Agency using the online forms available at Norwegian Medicines Agency and The Council for International Organizations of Medical Sciences (CIOMS) designated form

After the initial SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and AEs of special interest (as defined in Section 8.3.8, will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Independent Ethics Committees (IEC), and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary (see 8.3.3 above).

8.3.5. Pregnancy

Not applicable in this trial with short intervention

8.3.6. Cardiovascular and Death Events

IMP in this trial carries no particular risk of cardiovascular events described as as very common or common in their individual SPC.

8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

As participants in this trial have a wide range of reasons to contact the ambulance service it is impossible to pre- specify all disease-related events (DREs) that may arise.

In all AEs the investigator and Medical monitor must consider each event at its own merit and interpret the event in relation to the patients and his/ her medical condition at the time of inclusion to decide if an event is an AE or a DRE.

1: The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.

Or

2: The investigator considers if there is a reasonable possibility that the event is related to study intervention.

The event shall be classified as an AE.

8.3.8. Adverse Events of Special Interest

Sedation – resulting in a GCS <11 without other medical explanation
Respiratory depression – RR < 10 without other medical explanation

Both of these clinical events will be detected by the monitoring of vital signs, see Vital Signs

8.3.9. Medical Device Deficiencies

Not applicable

8.4. Pharmacology

Not applicable, See SPC for all IMP.

8.5. Genetics and Pharmacogenomics

Pharmacodynamic parameters are not evaluated in this study.

Genetics are not evaluated in this study.

8.6. Biomarkers

Biomarkers are not evaluated in this study.

8.7. Immunogenicity Assessments

Immunogenicity Assessments are not evaluated in this study.

8.8. Health Economics

Health Economics OR Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. Statistical Considerations

9.1. Statistical Hypotheses

The primary hypothesis compares the mean reduction in pain 10 minutes after administration for three analgesics, and are as follows:

$$H1\colon h0\colon \mu_{\text{met}}-\mu_{\text{fen}} \le \delta_I, \quad ha\colon \mu_{\text{met}}-\mu_{\text{fen}} > \delta_I$$
$$H2\colon h0\colon \mu_{\text{met}}-\mu_{\text{mor}} \le \delta_I, \quad ha\colon \mu_{\text{met}}-\mu_{\text{mor}} > \delta_I$$
$$H3\colon h0\colon \mu_{\text{fen}}-\mu_{\text{mor}} \le \delta_I, \quad ha\colon \mu_{\text{fen}}-\mu_{\text{mor}} > \delta_I$$

where μx is the mean reduction in NRS for treatment $x \in (18)$and δI is the non-inferiority margin.

The hypothesis $H1$, $H2$ and $H3$ will be tested using the fixed-sequence procedure, which do not inflate the significant level for the overall test. Thus the FWER (family-wise error rate) will be the same as the local nominal significance level α. The test will be performed in the following order:

$$H1 \rightarrow H2 \rightarrow H3$$

The primary hypothesis are:
#1a the null hypothesis ($H0_{1A}$): The methoxyflurane regimen is inferior to the intranasal fentanyl regimen for treating moderate to severe pain, measured by reduction in NRS 10 minutes after administration.

#1a the null hypothesis ($H0_{1B}$): The methoxyflurane regimen is inferior to the intravenous morphine regimen for treating moderate to severe pain, measured by reduction in NRS 10 minutes after administration.

#1a the null hypothesis ($H0_{1C}$): The intranasal fentanyl regimen is inferior to the intravenous morphine regimen for treating moderate to severe pain, measured by reduction in NRS 10 minutes after administration.

1b the hypothesis ($H1_{1A}$): The methoxyflurane regimen is non-inferior to the intranasal fentanyl regimen for treating moderate to severe pain, measured by reduction in NRS 10 minutes after administration

1b the hypothesis ($H1_{1B}$): The methoxyflurane regimen is non-inferior to the intravenous morphine regimen for treating moderate to severe pain, measured by reduction in NRS 10 minutes after administration

1b the hypothesis ($H1_{1C}$): The intranasal fentanyl regimen is non-inferior to the intravenous morphine regimen for treating moderate to severe pain, measured by reduction in NRS 10 minutes after administration

Secondary objective is to compare the need of rescue medication associated with 50 or 100 **µ** intranasal fentanyl, inhalation of 3 ml methoxyflurane and intravenous morphine.

2a null hypothesis: there will be significant difference in the need of rescue medication associated with 50 or 100 **µ** intranasal fentanyl, inhalation of 3 ml methoxyflurane and intravenous 0.05-0.1 mg/kg morphine ($p > 0.05$).

2b hypothesis: there will be a non-significant difference in the need of rescue medication associated with 50 or 100 **µ** intranasal fentanyl, inhalation of 3 ml methoxyflurane and intravenous 0.05-0.1 mg/kg morphine ($p < 0.05$).

Tertiary Objective is to define and compare the level of sedation using GSC and rate of respiration associated with 50 or 100 **µ** intranasal fentanyl, inhalation of 3 ml methoxyflurane and intravenous morphine.

#3a hypothesis there will be no significant difference in mean GCS between the intranasal fentanyl group, the inhalation of methoxyflurane group and intravenous morphine group.

#3b hypothesis there will be no significant difference in the respiratory rate mean of the three groups. Patients in both groups will not experience hypopnaeic hypoventilation

Multiplicity control strategy: In order to control the problem of multiplicity we are using a hierarchical testing strategy: We rank our endpoints in descending order of importance and test the most important first, then test second most important etc, considering $p < 0.05$ as significant difference. The testing continues until a nonsignificant result ($p > 0.05$). Subsequent tests will be considered exploratory with weaker clinical impact.

9.2. Sample Size Determination

Approximately 300 participants will be randomly assigned to the study intervention to achieve an estimated total of 90 evaluable participants per intervention group per protocol. This will provide at least 90% power at 5% significant level for each of the tests in the fixed-sequence procedure.

The sample size estimate was calculated using a two-sided t-test. The expected pain reduction after 10 min was set to 3.77 for methoxyflurane-, 2.54 for fentanyl- and 2.70 for morphine-treatment regimen, and a common conservative standard variation of 2.20 was used. These numbers based on a literature review of previous studies, and the results by (Kress et al. 2009)(46), (Blancher et al. 2019)(33), (Borobia et al. 2020)(47) is used in the calculation. The

non-inferiority margin is set to δI=1.3 NRS based on studies (Gallagher, Liebman, and Bijur 2001) showing this is the minimum clinically significant difference in VAS is 13 mm(48).

The null hypothesis is that the difference in means in change of NRS given methoxyflurane is smaller than given intranasal fentanyl.

$$H0_{1a}: p_{Metho} - p_{IN} > \Delta\ 1.3$$

The alternative hypothesis is that the difference in means in change of NRS given methoxyflurane is non-inferior to given intranasal fentanyl

$$H1_{1a}: p_{Metho} - p_{INF} \leq \Delta\ 1.3$$

From this it follows that the upper bound of the 95% confidence interval of the difference between the groups shall not exceed 1.3 in order to reject H0 and confirm H1.

The treatment with methoxyflurane can be recommended if it is similar to the reference treatment for the prespecified primary outcome but not if it is worse than Δ1.3.

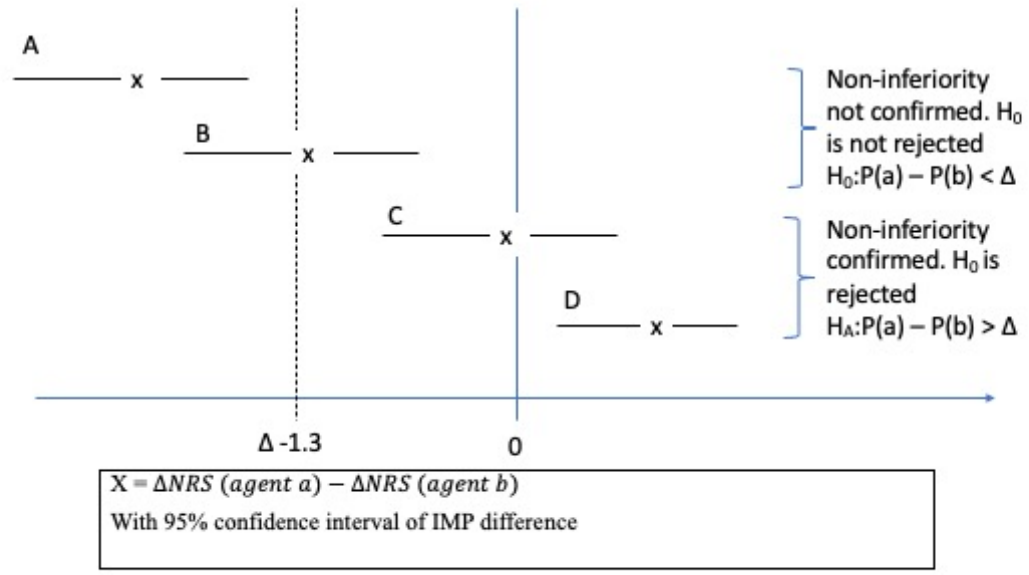


Figure 6 non-inferiority chart

The lines A-D represent mean and Confidence Interval of the differences in NRS-changes in the two treatment groups a and b. Examples A and B show that the agent a is inferior to agent b, while examples C and D confirm that agent a is non-inferior to agent b.

With an alfa of 0.05 and a beta of 0.1 (90% power) the sample size required to detect this difference was estimated to be n=88 in each arm by time 10 minutes for administration of IMP. That **gives a total number of participants of 264, and the plan is to include 3x90 = 270 patients per protocol.** In order to achieve this number, we plan to enrol approximately 300 subjects, anticipating not all subjects enrolled will adhere to the protocol completely.

The study will be conducted at the Innlandet Hospital, Pre-hospital Division, which has a population of 360 000, 44 ambulance stations and the area to operate is 52 000 square kilometres. The Innlandet ambulance service responds to about 59 000 and 55 000 emergencies in 2018 and 2019. The average percentage of patients receiving morphine is about 7%. Numbers of patients in Innlandet in need for pain management is estimated to be more than 3900 annually. Even at a low inclusion rate, the study is feasible in terms of patients needed.

Screening failure definition see 5.4

Non-evaluable participants definition:
Eligible participants who consent and are given IMP are evaluable in order to assess primary endpoint when NRS at t0 and t10min are measured even if vital parameters are missing.
Due to the pre-hospital circumstances with patients in pain and a situation of urgency some missing data are to be accepted. The principal investigator is to decide evaluable participants with missing data. In cases of missing data and evaluable participants information is to be evaluated by DMC and missing data are to be recorded and reported in order to maintain transparency. Examples of accepted missing data are RR, saturation, GCS, Likert scale values and blood pressure.
Requirement for non-evaluable participants:

- Missing NRS value at t0 – t10 min
- Use of rescue analgesia but missing information about administration time
- Information about occurrence of SAE or SUSAR but missing important information about of SAE or SUSAR at the discretion of DMC, monitor or principal investigator.

9.3. Case Report Forms (CRFs)

The CRF contain two parts
1: For the inclusion and study intervention. This will capture data on endpoints, length of intervention and details regarding IMP administration and dosing, need for rescue drugs, protocol adherence and safety data. This will be completed by the ambulance worker.

2: post-intervention data collection
Data on diagnoses and other relevant clinical data from hospital EPJ and/or phone call to the patient will be completed by the study nurse/paramedic.

9.3.1 Confidentiality

The investigator shall arrange for the secure retention of the patient identification and the code list following the guidelines set out by Oslo University Hospital and its Data Protection Officer. Patient files shall be kept for the maximum period of time permitted by each hospital. The study documentation (CRFs, Site File etc.) shall be retained and stored during the study and for 25 years after study closure. All information concerning the study will be stored in a safe place inaccessible to unauthorized personnel.

9.4. Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

Defined Analysis Data Sets	***Description***
Enrolled	All participants who sign the ICF. The enrolled set will include all patients who have provided the informed consent and have been included into the study data base.
Randomized	All participants who have been randomized
Full analysis set	The full analysis set will be defined as all patients randomly assigned to a treatment group and who have started the allocated intervention defined as having completed regular visit after baseline visit. The full analysis set will form the primary analysis set of the study and used for primary analyses.
Safety Analysis Set	The Safety Set will include all patients who completed regular visit after the baseline visit. All randomized participants who are exposed to study intervention. Participants will be analysed according to the intervention they actually received
Completer Analysis Set	The Completer Analysis Set will include all randomized patients having started the allocated intervention and not withdrawn during the study.
Per Protocol Analysis Set	The Per Protocol Analysis Set will include all randomized patients meeting the entry criteria who followed the study protocol with no major protocol deviations.
Analysis set for primary estimand	Randomized participants who receive intervention with no major missing data. Rescue analgesia after 10 min is allowed. For participants who discontinue study intervention, post intervention discontinuation will not be included.
Analysis set for secondary estimand	Randomized participants who are exposed to study intervention and rescue analgesia with no major missing data. For participants who discontinue study intervention and/or receive rescue therapy, all post discontinuation or post rescue observations will not be included in the secondary analysis set.

This is a non-inferiority trial, and the aim is to show no clinically significant treatment difference. In this situation the intention-to-treat principle is no longer regarded as conservative, thus the primary analysis will therefore be performed on the Per-protocol (PP) population. The PP population consists of randomised patients who have received at least one dose of medication and otherwise do not have any major protocol deviations affecting efficacy. Such deviations will be detailed in the statistical analysis plan.

9.5. Statistical Analyses

The statistical analysis plan will be finalized prior to un-blinding and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.5.1. General Considerations

The hypothesis stated in Section 9.1 will be tested and the primary endpoint will be evaluated by the 95% confidence limits (95% CI), and a conclusion of non-inferiority will be made if the 95% CI of the estimated treatment difference fully lie within the inferiority margin.
The statistical chain of testing and decisions will be:

1. Test *H*1. If the 95% confidence interval is not above the non-inferiority margin, we stop testing without any conclusion on efficacy. If the 95% confidence interval is above the non-inferiority margin, then we claim non-inferiority of methoxyflurane vs fentanyl and proceed with testing *H2*.
2. If this 95% confidence interval is not above the non-inferiority margin, we stop testing without any further conclusion on efficacy. If the 95% confidence interval is above the non-inferiority margin, then we claim non-inferiority of methoxyflurane vs morphine and proceed with testing *H*3.
3. If this 95% confidence interval is not above the non-inferiority margin, we stop testing without any further conclusion on efficacy. If the 95% confidence interval is above the non-inferiority margin, then we claim non-inferiority of fentanyl vs morphine.

The nominal significance level is set to 5%, and the non-inferiority margin is set to 1.3.

Eligible participant will be allocated in a 1:1:1 ratio between the treatments and receive only one type of treatment regimen bevor 10 minutes in order to be evaluable. The randomization will be stratified by centre, age group and initial NRS value.

We plan to compare the incidence of serious and non-serious adverse events between the groups using a chi-squared test, or a Fisher exact test if necessary (expected frequency less than 5).
We will summarize patient satisfaction and medical personnel view on practicality

The clinical study report will contain the following:

- Baseline demographic variables of included and excluded participants.
- Baseline ambulance data such as dispatch times, duration of call, other temporal data etc.
- Demographic Data Summary figures and table
- Efficacy Data Summary figures and tables.
- Safety Data Summary figures and tables.
- Displays of Adverse Events.
- Need of rescue medication, type and dosage of rescue medication.
- Listings of Serious Adverse Events.
- Performed procedures during pre-hospital time.

- Level of troponin after hospital admission and type of ECG-changes in patients with chest pain during pre-hospital time and after hospital admission.

Demographic and baseline information of the 3 study groups will be compared using t-tests (means), Mann-Whitney U (medians), and chi-square (proportions) tests. If there are any significant differences, linear regression will be performed to adjust for significantly different covariates.

9.5.2. Primary Endpoint(s)

The Statistical Analysis Plan will describe the handling of missing data in greater detail.

The rationale for selecting the primary endpoint is based on valid outcome measures gained from previous research(16, 33, 49, 50). Mean difference in NRS/VAS at 15 and 30 minutes from the first administration of pain treatment is the primary outcome in these studies. In the STOP! study the greatest estimated effect of methoxyflurane was seen at 15 minutes after administration. In the Magpie protocol for an RCT with methoxyflurane versus placebo in children with traumatic pain ΔVAS at 15 minutes is primary endpoint.

Non-inferiority is determined on the basis of a 1-sided equivalence *t* test on the per protocol population and confirmed, for sensitivity reasons, on the modified intention to treat population. Missing data will be replaced using multiple imputation process. We will perform a linear regression adjustment for baseline pain and centre.

9.5.3. Secondary Endpoints

- change in pain score as measured by the NRS at 5, 20, 30 and end of mission after study intervention
- need for rescue analgesia: time of administration, type of medication, dose, route of administration and methoxyflurane use of diluter hole
- time from scene arrival to administration of IMP (Δ tx -t0)
- Time from ambulance personnel arrival to at least 2 points reduction in NRS from baseline
- level of sedation associated with IMP as measured by the GCS.
- change in respiration rate with the IMP measured by change in respiration rate/minutes at different time.
- Change in SBP
- AE and SAE associated with IMP

Change in NRS and need for rescue analgesia are generating hypothesis which will be analyzed statistically according to the statistic plan appropriate significance testing.

9.5.4. Exploratory Endpoints

- Primary and secondary efficacy endpoints stratified by diagnosis or diagnosis groups at discharge or at follow-up at day 14
- Proportion of patient receiving rescue treatment in different subgroups, e.g. diagnosis groups, complex relocation or evacuation, painful medical procedures, age and gender groups
- Attempts of vascular cannulation access
- Change in NRS and time to a significant NRS reduction compared to level of competence
- Ambulance personnel competence and patient satisfaction assessed by 5-point Likert scale
- Level of troponin after ED admission and change in ECG at scene and after ED-admission in relation with IMP

9.5.5. Safety Analysis

All safety analyses will be made on the Safety Population. Safety analysis not defined as primary or secondary endpoint are described below.

- SUSAR will be continusly monitored and analysed according to cross reference 8.3.
- DRE will be recorded and described after follow-up visit at day 14 in cross reference 8.3

9.6. Interim Analysis

No will be no interim analysis.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

The study will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice and applicable regulatory requirements. Registration of patient data will be carried out in accordance with national personal data laws.
Consent is normally confirmed in writing and a cooling off period is provided to allow subjects to change their minds. Due to the situation with acute pain a cooling off period is not considered appropriate.
Comparation of an active agent against placebo when an exciting active substance is available is generally regarded as unethical in the Declaration of Helsinki Item 33(27): *The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:*
Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or
Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention
and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.
Extreme care must be taken to avoid abuse of this option.

Ethical considerations regarding informed consent process see Cross reference 10.1.2.

Ethical considerations regarding study design.
Randomised control trials remain the gold standard to ensure the safety and efficacy of medical interventions. No other design can reduce bias to the same degree. It is important to study the IMP in relevant setting in order to bridge the knowledge gap in pre-hospital setting without physician presence and as close to daily life in pre-hospital care as possible.
Blinding is considered too complicated and too costly in our pre-hospital setting with two ambulance workers. Research in healthy volunteers can give important information regarding the pharmacology of the substance, but clinical response must be studied in the field. We aim for 90% power and two- sided 95% confidence intervals, which are common in comparable studies.

Ethical considerations regarding use of investigational product outside approved indication: There is a need for more knowledge about non-invasive methods in pre-hospital care to ensure higher regularity regarding management of acute pain due to difficulties in getting vascular access.

There is a knowledge -gap regarding non-invasive methods of administering analgesics. A high proportion of patients are experiencing difficulties with peripheral vascular access. This can lead to lack of necessary treatment and pain. There is an unmet need for non-invasive and non-opioid analgesics to patients with pain related to other conditions than the approved indication.
The SPC of morphine, methoxyflurane and high concentrated intranasal fentanyl are showing a higher rate of AE in the morphine group compared to methoxyflurane and intranasal fentanyl. Fentanyl is a drug with a known safety profile in pre-hospital conditions such as chest pain, abdominal pain and trauma (15, 51)
The treatment of severe pain, such as the pain of myocardial pain is approved in the SPC of intravenous fentanyl. https://www.medicines.org.uk/emc/product/2852.
In the hands of ambulance personnel in Denmark intravenous fentanyl and intranasal fentanyl caused clinically significant pain reduction and was safe. Intranasal fentanyl has a bioavailability of about 70-89% and has a predictable serum concentration resulting in a predictable pain reduction (17). The intranasal fentanyl formula has a higher concentration and is especially suited to intranasal administration according to a randomized study in children from Borland in 2011. It is of interest to investigate the non-invasive properties of intranasal fentanyl to a broader patient group with different acute pain conditions. The retrospective study from Bandall in 2011 compared methoxyflurane, intranasal fentanyl and intravenous morphine to 3504 paediatric patients from 5-15 years with trauma, abdominal pain/problems, back pain, others (nonspecific) and other(23). Scene time was significantly longer for patients given morphine or analgesic combinations than for patients given fentanyl or methoxyflurane. Transport times for patients given methoxyflurane were significantly shorter than those for the other groups, but intranasal fentanyl and IV morphine appear equivalent in this population. Methoxyflurane provided effective analgesia in almost four out of every five children treated. Morphine and intranasal fentanyl appeared to produce better analgesic effect. The authors of the study stress the need for further prospective studies to bridge the knowledge gap(23).

In the review from Hartshorn et Al from 2018 Methoxyflurane appears to be well tolerated by children and there were no reported nephrotoxicity or liver damage with low-dose methoxyflurane(21). One retrospective study compared intranasal fentanyl with inhaled methoxyflurane for visceral pre-hospital pain in 1024 patients(52). Methoxyflurane produced the greatest initial pain scores reduction, and intranasal fentanyl provided greater pain reduction by hospital arrival. They concluded that methoxyflurane provided a more rapid onset of pain relief, but intranasal fentanyl provided a superior analgesia in female, cardiac and older patients.
According to Venkat et Al there is a growing tension between the moral and professional obligation of emergency physicians to treat pain and human suffering and their reluctance to contribute to the growing epidemic of opioid abuse and diversion(53).
In case of serious adverse event caused by the study drugs the participating paramedics have mitigating options by using oxygen, IV or intramuscular naloxone or simply taking the methoxyflurane inhaler away from the participants. See 6.7

Ethical considerations regarding inferiority margin.
A non-inferiority trial seeks to determine whether a new treatment is not worse than a reference treatment by more than an acceptable and pre-specified margin. Because proof of exact equivalence is impossible, a pre-stated margin of non- inferiority (Δ) for the treatment effect in a primary patient outcome is defined. Non- inferiority of the new treatment with respect to the reference treatment is of interest on the premise that the new treatment has some other advantage, such as greater availability, reduced cost or less invasiveness It is important to investigate a relevant and recognised difference of NRS. The inferiority margin of 1.3 is a known relevant reduction of NRS in clinical setting and is used in comparable critical care studies. The inferiority margin is always a clinical decision based on the evidence and experience available. Members of the planed DMC are a statistician and two physicians with broad experience from research and emergency medicine.

Ethical considerations regarding research on vulnerable groups:
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.* Small children and unstable patients are not part of the study. However, other vulnerable groups such as patients from low socioeconomic conditions and patients in acute crisis, will be included. Vulnerable patients may benefit from this study as reflected in the benefit section of the risk-benefit analysis (2.3.2), and the potential risk is considered very low.

Ethical considerations regarding rescue analgesia and timing of rescue analgesia: A wide range of rescue analgesia is available in the ambulance service participating in the study. All IMP can be re-dosed if needed within 10 minutes in the allocated arm in order to achieve a relevant reduction in NRS. In the methoxyflurane arm, closure of the diluter hole is possible to achieve a higher concentration of IMP.

In cases where no vascular access is possible in the morphine arm, non-invasive IN fentanyl or methoxyflurane are available. The rescue analgesia is familiar to the attending ambulance personnel. Patients in need of rescue analgesia will continue in the trial and need of rescue is a secondary objective in the study(29).

Ethic Committee Approval
The study protocol, including the patient information and informed consent form to be used, must be approved by the Regional Ethics Committee (REK) before enrolment of any patients into the study. The investigator is responsible for informing the Ethics Committee of any serious and unexpected adverse events and/or major amendments to the protocol as per national requirements.

Other Regulatory Approvals

The protocol will be submitted and approved by the Norwegian Medicines Agency prior to study start.

Informed Consent Procedure

The inclusion criterion in this study is acute pain and hence represents an acute and possible severe medical condition. The nature of the clinical emergency medical setting does not allow for written consent prior to inclusion. In addition, written consent might lead to a delay in pain management, and this concern could represent an inclusion hindrance (54). We therefore base the consent procedure on informed oral consent before inclusion. The oral consent will be witnessed and confirmed on the ICF by the ambulance study worker.

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable ICH Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure and other relevant documents (e.g., advertisements) must be submitted to REK by the investigator and reviewed and approved by the REK before the study is initiated.
- Any amendments to the protocol will require REK approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the REK annually or more frequently in accordance with the requirements, policies, and procedures established by the REK
    - Notifying the REK of SAEs or other significant safety findings as required by REK procedures
    - Providing oversight of the conduct of the study at each centre and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

- Part of the salaries for the researchers are directly or indirectly (via OUH) paid for by the Norwegian Air Ambulance Foundation.
- Sykehuset Innlandet Trust is financing the study assistant.
- The funding source will have no role in the study design, data collection, data analysis, data interpretation or writing of the report. All authors agreed to submit for publication.

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant with a standardized text and answer all questions regarding the study.
- The patient will receive written information about the project and implication for the patient, with detailed information on how to withdraw from the study, both electronically by web-solution and email, and by telephone to study personnel.
- The patient will give oral consent, witnessed and confirmed in the ICF by the ambulance study worker
- Administration of study intervention

A copy of the ICF will be provided to the participant or their legally authorized representative.

Figure 7 Consent process

10.1.4. Data Protection

Study Monitoring

The investigator will be visited on a regular basis by the Clinical Study Monitor, who will check the following:

- Informed consent process
- Reporting of adverse events and all other safety data
- Adherence to protocol
- Study drug accountability
- Maintenance of required regulatory documents
- Study Supply accountability
- Drug storage at station and in the ambulance
- Data completion on the CRFs including source data verification (SDV).

The monitor will review the relevant CRFs for accuracy and completeness and will ask the personnel to adjust any discrepancies as required.
Sponsor's representatives (e.g. monitors, auditors) and/or competent authorities will be allowed access to source data for source data verification in which case a review of those parts of the hospital records relevant to the study may be required.

Data management and monitoring

Data management will be performed by the data management unit at the Clinical Trials Unit, Oslo University Hospital. The Data management procedures will be performed in accordance with the department's SOPs and ICH guidelines. The data management process will be described in the study specific Data Handling Plan and the study specific Data Handling Report after database closure.

Data entered into the eCRF will be validated as defined in the Data Validation Plan. Validation includes, but is not limited to, validity checks (e.g. range checks), consistency checks and customized checks (logical checks between variables to ensure that study data are accurately reported) for eCRF data and external data (e.g. laboratory data). A majority of edit checks will be triggered during data entry and will therefore facilitate efficient 'point of entry' data cleaning.

Data management personnel will perform both manual eCRF review and review of additional electronic edit checks to ensure that the data are complete, consistent and reasonable. The electronic edit checks will run continually throughout the course of the study and the issues will be reviewed manually online to determine what action needs to be taken.

Manual queries may be added to the system by clinical data management or study monitor. Clinical data managers and study monitors are able to remotely and proactively monitor the patient eCRFs to improve data quality.

All updates to queried data will be made by authorized study centre personnel only and all modifications to the database will be recorded in an audit trail. Once all the queries have been resolved, eCRFs will be signed by electronic signature. Any changes to signed eCRFs will be approved and resigned by the Investigator.

Adverse events will be coded from the verbatim description (Investigator term) using the Medical Dictionary for Regulatory Activities (MedDRA).

Once the full set of eCRFs have been completed and locked, the Sponsor will authorize database lock and all electronic data will be sent to the designated statistician for analysis. Subsequent changes to the database will then be made only by written agreement.

The data will be stored in a dedicated and secured area at Oslo University Hospital. Data will be stored in a de-identified manner, where each study participant is recognizable by his/her unique trial subject number. The data will be stored until 15 years following the last patient's final study visit.

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be

explained to the participant who will be required to give consent for their data to be used as described in the informed consent

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

Data Monitoring Committee (DMC) will be put in place before stud start and will review safety at given intervals.

- Participant safety will be continuously monitored by the Sponsors internal safety review committee, which includes safety signal detection at any time during the study
- In addition, an early aggregated safety data review will be performed, the goal of which is to allow for a cautious, stepwise approach to intervention administration. An initial safety review for this study is planned for the first 50% of participants who are dosed and have provided safety data.
- All safety data collected will be summarized and reviewed by the DMC for agreement of next steps.
- Case unblinding may be performed for above reviews if necessary.

The monitor will review the relevant CRFs for accuracy and completeness and will ask the personnel to adjust any discrepancies as required. Patient record in the study and will be made available on request.
Sponsor's representatives and/or competent authorities will be allowed access to source data for source data verification in which case a review of those parts of the hospital records relevant to the study may be required.
The monitoring during the PreMeFen study will follow the Norcrin Monitoring SOP.

Tasks of the DMC are as followed and further described in Monitoring Plan:
To ensure the safety and wellbeing of trial patients and to assist and advise the Principal Investigator, so as to protect the validity and credibility of the trial.
To assess the progress of the trial and monitor the overall conduct of the clinical trial.
To assess the safety of the interventions during the trial.
To assess the safety and efficacy of the interventions during the trial, and monitor the overall conduct of the clinical trial.
To make recommendations to the sponsor regarding study modification, continuation or termination.

10.1.6. Dissemination of Clinical Study Data

OUH has complete ownershipownership of all data and publishing rights of all results.

Metadata:
The full protocol, Statistical Analysis Plan, information letter for consent and other trial documents will be published open access. The Clinical Study report and Statistical analysis report will also be made openly available but may be altered to hide information that may lead to identification of individual study participants. These documents will be shared at Norwegian Centre for Research Data (NSD). NSD is a corporation owned by the Ministry of Education and Research and is a national archive and centre for research data.

Individual participant data:
All of the individual participant data collected during the trial, after de-identification will be made available to anyone who wishes to access the data. Data will be made indefinitely available through Norwegian Centre for Research Data (NSD). De-identified data can only be distributed in accordance with the data processor agreement entered into between the Sponsor and NSD. Data sharing with editors or peer-reviewers of scientific journals, conferences or the like will not require specific consent or data access agreement with Oslo University Hospital, in the understanding that the data will not be shared onward or used beyond reviewing this trial.

After data sharing Oslo University Hospital, Pre-Hospital Division must be acknowledged in any publication resulting from the shared data. For closer collaboration authorship based on the Vancouver Convention must be considered.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in Investigators Brochure.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8. Source Documents

- Source data in this trial includes study specific case report form (CRF) including data from day 14 follow-up visit. This includes records from the ambulance monitor device, GCS recorded by responsible attending paramedic on scene, Likert scale values from patient and responsible paramedic plotted in CRF and data from the hospital electronic patient journal system at the receiving hospitals.

- Sponsor's representatives (e.g. monitors, auditors) and/or competent authorities will be allowed access to source data for source data verification in which case a review of those parts of the hospital records relevant to the study may be required.

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site file.

- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

- Definition of what constitutes source data can be found in the source data list.

- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9. Study Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

Study Termination

The sponsor or designee reserves the right to close the study centre or terminate the study at any time for any reason at the sole discretion of the sponsor. Study centres will be closed upon study completion. A study centre is considered closed when all required documents and study supplies have been collected and a study-centre closure visit has been performed.

The investigator may initiate study-centre closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study centre by the sponsor or investigator may include but are not limited to:

For study termination:

- Occurrence of AEs unknown to date in respect of their nature, severity and duration
- Medical or ethical reasons affecting the continued performance of the trial

For centre termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment of participants by the investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

Not applicable

10.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition
• Any abnormal laboratory test results or other safety assessments (e.g., ECG~~,~~ vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

An SAE is defined as any serious adverse event that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfilsfulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is a suspected transmission of any infectious agent via an authorised medicinal product

g. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse.

Anaphylactic shock, serotonin syndrome, renal toxicity, liver failure and malign hyperthermia are defined as serious adverse events.
These events will be recorded from EPJ and follow-up visit.

10.3.3. Definition of SUSAR

A SUSAR (Suspected unexpected Serious Adverse Reaction) is defined as any SAE (se 10.3.2) that is unexpected and have a reasonable possibility of a causal relationship with the study drug.

- The primary investigator decides whether an SAE is unexpected or not in accordance with table 2 in section 2.3, and whether it has a reasonable possibility of a causal relationship with the study drug or not.
- If an SAE is unexpected (not listed in table 2, section 2.3) and has a reasonable possibility of a causal relationship with the study drug, it classifies as a SUSAR.
- ALL SUSARs must be promptly reported to The Norwegian Medicines Agency (, see section 10.3.6.

10.3.4. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Severity

Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

Corrected Version 2.1 July 2017

Grade 1 indicates a mild event
• Grade 2 indicates a moderate event
• Grade 3 indicates a severe event
• Grade 4 indicates a potentially life-threatening event
• Grade 5 indicates death

An event is defined as ‘serious’ when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.

- A “reasonable possibility” of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the SPC, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the study file that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the medical monitor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the medical monitor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- For the purpose of this trial this well be a dichotomous assessment: “reasonable possibility of causality” or “not a reasonable possibility of causality”

Follow-up of and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the medical monitor to elucidate the nature and/or causality of the SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies from a suspected SAE, not DRE, during participation in the study or during a recognized follow-up period, the investigator will provide the medical monitor with a copy of any postmortem findings
- New or updated information will be recorded in the originally submitted documents.

10.3.5. Reporting of AE, SAE and SUSAR

Please consult 8.3.4

10.4. Appendix 7: AEs, ADEs, SAEs, SADEs, USADEs and Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies

Not applicable.

10.5. Appendix 9: Abbreviations

Abbreviation or special term	Explanation
AE	Adverse Event
CRF	Case Report Form (electronic/paper)
CSA	Clinical Study Agreement
DAE	Discontinuation due to Adverse Event
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
eCRF	Electronic Case Report Form
ED	Emergency Department
GCP	Good Clinical Practice
GCS	Glasgow Coma Scale
IB	Investigator's Brochure
IRB	Institutional Review Board
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product (includes active comparator and placebo)
Norcrin	Norwegian clinical Research Infrastructure Network
NRS	Numeric Rating Scale
OUH	Oslo University Hospital
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SoA	Schedule of Activities

STEMI	ST Elevation Myocardial Infarction
SUSAR	Suspected Unexpected serious adverse reaction
TMF	Trial Master File

10.6. Appendix 10: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment [amendment number]: ([date])
This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.
Overall Rationale for the Amendment
[Rationale]

Section # and Name	Description of Change	Brief Rationale

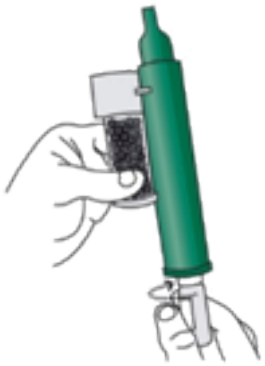
10.7. Appendix 11: Instruction for the preparation of IMP

10.7.1. Inhalational Methoxyflurane

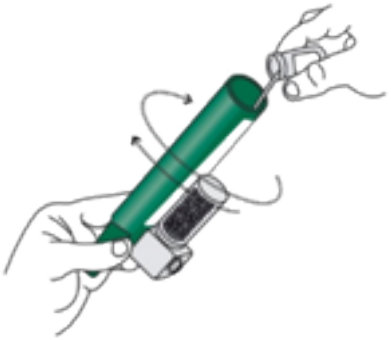
Instructions on the preparation of the methoxyflurane inhaler and correct administration are provided in the IB and the figures:

1 Ensure the Activated Carbon (AC) Chamber is inserted into the dilutor hole on the top of the PENTHROX Inhaler.

2 Remove the cap of the bottle by hand. Alternatively, use the base of the PENTHROX Inhaler to loosen the cap with a ½ turn. Separate the Inhaler from the bottle and remove the cap by hand.



3 Tilt the PENTHROX Inhaler to a 45° angle and pour the total contents of one PENTHROX bottle into the base of the Inhaler whilst rotating.

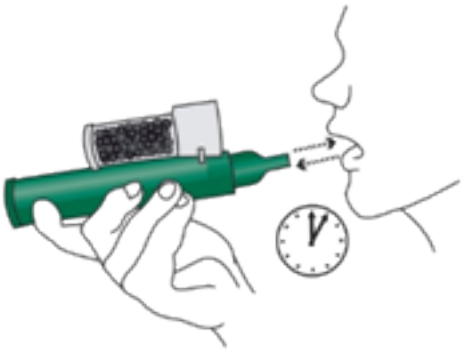


4 Place wrist loop over patient's wrist. Patient inhales and exhales PENTHROX through the mouthpiece to obtain analgesia. First few breaths should be gentle and then breathe normally through Inhaler.

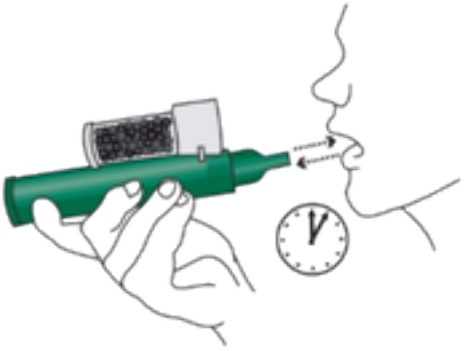
5 Patient exhales into the PENTHROX Inhaler. The exhaled vapour passes through the AC Chamber to adsorb any exhaled methoxyflurane.

6 If stronger analgesia is required, patient can cover dilutor hole on the AC chamber with finger during use.

7 If further pain relief is required, after the first bottle has been used use a second bottle if available. Alternatively use a second bottle from a new combination pack. Use in the same way as the first bottle in step 2 and 3. No need to remove the AC Chamber. Put used bottle into the plastic bag provided.



8 Patient should be instructed to inhale intermittently to achieve adequate analgesia. Continuous inhalation will reduce duration of use. Minimum dose to achieve analgesia should be administered.



9	Replace cap onto PENTHROX bottle. Place used PENTHROX Inhaler and used bottle in sealed plastic bag and dispose of responsibly. The paramedic trained in administering PENTHROX will provide and explain the Package Leaflet to the patient. The participants are allowed to use the diluter hole and a second inhaler if needed.	

10.7.2. Intranasal Fentanyl:

Use of single dose intranasal fentanyl: We will use 50 and 100μ *singel dose high concentrated intranasal fentanyl*. Each single-dose container is sealed in a child-resistant blister. Each single-dose container contains only one dose of fentanyl. One nostril is to be blocked by placing a finger against the side of the nose and insert the spray tip into the other nostril (approximately 1cm) see figure 1. It does not matter which nostril is used. The plunger is to be firmly pressed upwards to release the dose, see figure 2. The single-dose container is then empty. More information about the use of IN fentanyl is to be found in the SPC.

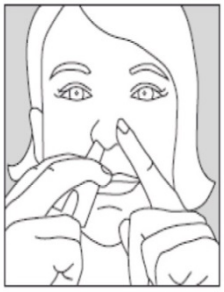


Figure 1

Figure 2

10.7.3. Intravenous morphine:

The skin on the intended site of vascular access will be disinfected with Clorohexidine®. The paramedic will insert a peripheral intravascular access. The correct placement of the vascular access will be confirmed together with the second attending paramedic by using a dose of 5-10ml intravenous NaCl®. After administration of morphine in the intravenous catheter the ambulance worker will infuse 5-10 ml NaCl in the catheter in order to let the morphine reach central circulation.

11. References

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