Clinical trial results:
A randomised, double-blind, parallel group study comparing patient controlled analgesia with Penthrox® (methoxyflurane) versus placebo during colonoscopy

Summary

EudraCT number	2017-003767-35
Trial protocol	BG FI SE
Global end of trial date	02 July 2018

Results information

Result version number	v1 (current)
This version publication date	28 July 2019
First version publication date	28 July 2019

Trial information

Trial identification

Sponsor protocol code	MR311-3501

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Mundipharma Research Limited
Sponsor organisation address	Unit 194 Cambridge Science Park, Milton Road, Cambridge, United Kingdom, CB4 0AB
Public contact	Clinical Operations, Mundipharma Research Limited, +44 1223424900, clinicaltrials@mundipharma-rd.eu
Scientific contact	Clinical Operations, Mundipharma Research Limited, +44 1223424900, clinicaltrials@mundipharma-rd.eu

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 July 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 July 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to demonstrate superiority in the efficacy of Penthrox (methoxyflurane) versus placebo based on mean pain profile during colonoscopy; a difference of 1.5 on the numerical rating scale (NRS) between the 2 groups was regarded as clinically meaningful.

Protection of trial subjects:

This study was performed in full compliance with applicable Good Clinical Practice as required by Declaration of Helsinki, International Council for Harmonisation and local and national regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 May 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 8
Country: Number of subjects enrolled	Bulgaria: 64
Country: Number of subjects enrolled	Finland: 14
Worldwide total number of subjects	86
EEA total number of subjects	86

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	63
From 65 to 84 years	23

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted in 5 centres across 3 countries between 21 May 2018 and 02 Jul 2018. Subjects who had been referred to colonoscopy for clinical indications or cancer screening were recruited.

Pre-assignment

Screening details:

A total of 86 subjects were randomised to 1 of 2 treatment groups in a 1:1 ratio. Randomisation was stratified according to indication for colonoscopy (clinical indication/cancer screening).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Penthrox

Arm description:

Subjects received maximum of 6 millilitre (mL) Penthrox inhalation for the duration of the colonoscopy procedure. Subjects were instructed to inhale the Penthrox for approximately 2 minutes as a premedication in a stepwise fashion from shallow to deep breaths. During the colonoscopy the subject was instructed to inhale the lowest possible dose to provide adequate analgesia. In addition, they were instructed to inhale further doses of Penthrox if the colonoscopist anticipated a potential for discomfort during the procedure. Rescue medication [intravenous (IV) opioids] could also be administered if required.

Arm type	Experimental
Investigational medicinal product name	Penthrox
Investigational medicinal product code	
Other name	Methoxyflurane
Pharmaceutical forms	Inhalation vapour, liquid
Routes of administration	Inhalation use

Dosage and administration details:

A 3 mL Penthrox inhaler device was provided immediately prior to the start of the colonoscopy procedure on Day 1. A second loaded inhaler could be provided on the subject’s request when the first device was deemed to be empty.

Arm title	Placebo

Arm description:

Subjects received a maximum of 10 mL of placebo (matching with Penthrox) inhalation for the duration of the colonoscopy procedure. Subjects were instructed to inhale the placebo for approximately 2 minutes as a premedication in a stepwise fashion from shallow to deep breaths. During the colonoscopy the subject was instructed to inhale the lowest possible dose to provide adequate analgesia. In addition, they were instructed to inhale further doses of placebo if the colonoscopist anticipated a potential for discomfort during the procedure. Rescue medication (IV opioids) could also be administered if required.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	Saline
Pharmaceutical forms	Inhalation vapour, liquid
Routes of administration	Inhalation use

Dosage and administration details:

A 5 mL saline placebo in a Penthrox inhaler device was provided immediately prior to the start of the colonoscopy procedure on Day 1. A second loaded inhaler could be provided on the subject's request when the first device was deemed to be empty.

Number of subjects in period 1	Penthrox	Placebo
Started	42	44
Received treatment	42	44
Intent-to-treat (ITT) population	41 [1]	44
Completed	42	44

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The ITT population included all subjects in the enrolled set who were randomised to IMP.

Baseline characteristics

Reporting groups

Reporting group title	Penthrox

Reporting group description:

Subjects received maximum of 6 millilitre (mL) Penthrox inhalation for the duration of the colonoscopy procedure. Subjects were instructed to inhale the Penthrox for approximately 2 minutes as a premedication in a stepwise fashion from shallow to deep breaths. During the colonoscopy the subject was instructed to inhale the lowest possible dose to provide adequate analgesia. In addition, they were instructed to inhale further doses of Penthrox if the colonoscopist anticipated a potential for discomfort during the procedure. Rescue medication [intravenous (IV) opioids] could also be administered if required.

Reporting group title	Placebo

Reporting group description:

Subjects received a maximum of 10 mL of placebo (matching with Penthrox) inhalation for the duration of the colonoscopy procedure. Subjects were instructed to inhale the placebo for approximately 2 minutes as a premedication in a stepwise fashion from shallow to deep breaths. During the colonoscopy the subject was instructed to inhale the lowest possible dose to provide adequate analgesia. In addition, they were instructed to inhale further doses of placebo if the colonoscopist anticipated a potential for discomfort during the procedure. Rescue medication (IV opioids) could also be administered if required.

Reporting group values	Penthrox	Placebo	Total
Number of subjects	42	44	86
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	34	29	63
From 65-84 years	8	15	23
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	23	26	49
Male	19	18	37

End points

End points reporting groups

Reporting group title	Penthrox

Reporting group description:

Subjects received maximum of 6 millilitre (mL) Penthrox inhalation for the duration of the colonoscopy procedure. Subjects were instructed to inhale the Penthrox for approximately 2 minutes as a premedication in a stepwise fashion from shallow to deep breaths. During the colonoscopy the subject was instructed to inhale the lowest possible dose to provide adequate analgesia. In addition, they were instructed to inhale further doses of Penthrox if the colonoscopist anticipated a potential for discomfort during the procedure. Rescue medication [intravenous (IV) opioids] could also be administered if required.

Reporting group title	Placebo

Reporting group description:

Subjects received a maximum of 10 mL of placebo (matching with Penthrox) inhalation for the duration of the colonoscopy procedure. Subjects were instructed to inhale the placebo for approximately 2 minutes as a premedication in a stepwise fashion from shallow to deep breaths. During the colonoscopy the subject was instructed to inhale the lowest possible dose to provide adequate analgesia. In addition, they were instructed to inhale further doses of placebo if the colonoscopist anticipated a potential for discomfort during the procedure. Rescue medication (IV opioids) could also be administered if required.

Primary: Mean Worst Pain Measured on NRS During Colonoscopy

End point title	Mean Worst Pain Measured on NRS During Colonoscopy

End point description:

Pain was assessed on the NRS from start of the colonoscopy to the time the endoscope reaches the caecum (way in), every 5 min after reaching the caecum (way out) and immediately after colonoscopy. The NRS is a 11 point scale, where subjects rated their worst pain from 0 (no pain) to 10 (pain as bad as you can imagine). The mean of the worst pain was calculated for the ITT population [ITT which included all subjects in the enrolled set who were randomised to investigational medicinal product (IMP)] and had data available for analysis.

End point type	Primary

End point timeframe:

Every 2 minutes from start of colonoscopy procedure until the start of way-out, every 5 minutes after the start of way-out, and immediately after colonoscopy on Day 1.

End point values	Penthrox	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	44		
Units: Units on a scale				
arithmetic mean (standard deviation)	2.49 (± 1.635)	3.61 (± 1.134)		

Statistical analyses

Statistical analysis title	Treatment difference: Penthrox Vs Placebo

Statistical analysis description:

The least square mean, 95% confidence interval (CI) and p-value from an analysis of covariance (ANCOVA) model with randomised treatment group and baseline NRS as fixed effects, centre and stratification factor as random effects.

Comparison groups	Penthrox v Placebo
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.49
upper limit	-0.4

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first inhalation of IMP until end of the study, approximately 15 to 18 days.

Adverse event reporting additional description:

The safety population included all subjects in the ITT population who received at least one inhalation of IMP (whether before or during the colonoscopy procedure).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Penthrox

Reporting group description:

Subjects received maximum of 6 mL Penthrox inhalation for the duration of the colonoscopy procedure. Subjects were instructed to inhale the Penthrox for approximately 2 minutes as a premedication in a stepwise fashion from shallow to deep breaths. During the colonoscopy the subject was instructed to inhale the lowest possible dose to provide adequate analgesia. In addition, they were instructed to inhale further doses of Penthrox if the colonoscopist anticipated a potential for discomfort during the procedure. Rescue medication (IV opioids) could also be administered if required.

Reporting group title	Placebo

Reporting group description:

Subjects received a maximum of 10 mL of placebo (matching with Penthrox) inhalation for the duration of the colonoscopy procedure. Subjects were instructed to inhale the placebo for approximately 2 minutes as a premedication in a stepwise fashion from shallow to deep breaths. During the colonoscopy the subject was instructed to inhale the lowest possible dose to provide adequate analgesia. In addition, they were instructed to inhale further doses of placebo if the colonoscopist anticipated a potential for discomfort during the procedure. Rescue medication (IV opioids) could also be administered if required.

Serious adverse events	Penthrox	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Penthrox	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 42 (26.19%)	11 / 44 (25.00%)	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Tension headache			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	3 / 42 (7.14%)	2 / 44 (4.55%)	
occurrences (all)	3	2	
Diverticulum intestinal			
subjects affected / exposed	3 / 42 (7.14%)	1 / 44 (2.27%)	
occurrences (all)	3	1	
Haemorrhoids			
subjects affected / exposed	5 / 42 (11.90%)	5 / 44 (11.36%)	
occurrences (all)	5	5	
Diverticulum			
subjects affected / exposed	2 / 42 (4.76%)	2 / 44 (4.55%)	
occurrences (all)	2	2	
Large intestine polyp			
subjects affected / exposed	0 / 42 (0.00%)	2 / 44 (4.55%)	
occurrences (all)	0	2	
Infections and infestations			
Diverticulitis			
subjects affected / exposed	2 / 42 (4.76%)	0 / 44 (0.00%)	
occurrences (all)	2	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

One randomised subject was not included in the ITT population due to significant potential bias on statistical reporting due to knowledge of the study.

Notes: