Clinical trial results:
Reducing painful colonoscopies in women participating in a colorectal cancer screening program: A randomized controlled trial

Summary

EudraCT number	2016-005090-13
Trial protocol	NO
Global end of trial date	15 May 2020

Results information

Result version number	v1 (current)
This version publication date	12 March 2022
First version publication date	12 March 2022

Trial information

Trial identification

Sponsor protocol code	"Painstudy"1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01538550
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cancer Registry of Norway
Sponsor organisation address	P.O. box 5313 Majorstuen, Oslo, Norway, 0304
Public contact	Tarmkreftscreening, Cancer Registry of Norway, anna.schult@kreftregisteret.no
Scientific contact	Tarmkreftscreening, Cancer Registry of Norway, anna.schult@kreftregisteret.no

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 February 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 May 2020
Global end of trial reached?	Yes
Global end of trial date	15 May 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of the present trial is firstly to evaluate whether Fentanyl administrated prior to colonoscopy is associated with a lower risk of moderate or severe pain as compared to Fentanyl given on demand, to women undergoing colonoscopy; secondly to evaluate whether Rapifen on demand is associated with a lower risk of moderate or severe pain compared to Fentanyl given on demand, to women undergoing colonoscopy.

Protection of trial subjects:

Adverse events occuring during colonoscopy or within 30 days after colonoscopy were registered and documented and reported to the Norwegian Medicines Agency and the regional ethical committee if appropriate. Events were graded according to the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE).
An endoscopy nurse were continously monitoring the patient and kept verbal contact with the patient. Oxygen saturation and heart rate were continously monitored and blood pressure was measured every 10th minute.

Background therapy:

NA

Evidence for comparator:

Strategies to prevent painful colonoscopies include amongst others improved medication strategy. A recent review of current sedation recommendations concluded that there is a lack of harmonisation regarding the recommended level of sedation and type of drugs. Sedation is associated with adverse events and may also influence the effect of screening because it hampers dynamic position change and thus may reduce the adenoma detection rate. Furthermore, sedation has been identified as a barrier to CRC screening, probably because healthy screenees do not accept potential risks and inconveniences of medication. If sedation-free colonoscopies are the standard, on-demand medication is commonly offered if pain occurs. Unsedated colonoscopy minimizes complications and costs and enables patients to return to normal daily activities immediately after the procedure.
Studies comparing sedation on-demand medication to medication before colonoscopy are inconsistent. Targeted preemptive medication in individuals at high risk for pain like women might be more appropriate than medication prior to colonoscopy to everyone.
Both fentanyl and alfentanil are well tolerated and commonly used during colonoscopies but Alfentanil has a superior pharmacodynamical profile for on-demand administration as it is more potent and has an extremely rapid onset of action.
The present trial aimed to investigate whether fentanyl administered before colonoscopy in women is more effective in reducing the proportion of painful colonoscopies than fentanyl administered on-demand. Further, in an exploratory setting, we also investigated the effectiveness of a third strategy of analgesia, alfentanil on-demand. Fentanyl on-demand was the standard medication at the two participating units.

Actual start date of recruitment	12 June 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Norway: 539
Worldwide total number of subjects	539
EEA total number of subjects	539

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)	217
From 65 to 84 years	322
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

From 06/2017 to 05/2020, all women aged 55–79years who were referred to colonoscopy in a Norwegian CRC screening trial after a positive screeningtest were eligible. To reach the required sample size, women of the same age scheduled for a clinical non-screening outpatient colonoscopy at the two centres were recruited from 05/2018.

Pre-assignment

Screening details:

1819 women were invited to participate. 568 consented and were randomised. After randomisation, 29 individuals were excluded (exclusion criteria were detected, consent was withdrawn, colonoscopy could not be carried out due to insufficient bowel cleaning). 539 participants were included in ITT analysis and 477 in per-protocol analysis.

Period 1

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

Arms

Arm title	all over
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Fentanyl
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

50 + 50 mcg initially, step-up with 50 mcg. Lower dose for those < 50 kg

Investigational medicinal product name	Alfentanil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

0.5 mg initially, step up with o.25 or 0.5 mg

Number of subjects in period 1	all over
Started	539
Completed	539

Baseline characteristics

Reporting groups	
Reporting group title	all over

Reporting group description: -

Reporting group values	all over	Total	
Number of subjects	539	539	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
55-79	539	539	
Age continuous Units: years			
arithmetic mean	66.8		
standard deviation	± 6.0	-	
Gender categorical Units: Subjects			
Female	539	539	
Male	0	0	
Adequate bowel cleansing Units: Subjects			
Bowel cleansing	539	539	
Expectation painful colonoscopy Units: Subjects			
Expect pain	539	539	
Previous painful colonoscopy Units: Subjects			
Previous pain	539	539	
Abdominal surgery Units: Subjects			
Surgery	539	539	
Previous diverticulitis Units: Subjects			
Diverticulitis	539	539	
IBS with pain Units: Subjects			
IBS	539	539	

Heart rate Units: per minute arithmetic mean standard deviation	± 	- 	
VAS before examination			
Pain score before			
Units: mm arithmetic mean standard deviation	± 	- 	
BMI			
Bodymass index			
Units: kg/m2 arithmetic mean standard deviation	± 	- 	
Oxygen saturation (pre-procedure) Units: percent arithmetic mean standard deviation	± 	- 	

Subject analysis sets	
Subject analysis set title	Fentanyl on-demand
Subject analysis set type	Intention-to-treat
Subject analysis set description: Those randomised to Fentanyl on-demand	
Subject analysis set title	Fentanyl prior
Subject analysis set type	Intention-to-treat
Subject analysis set description: Those randomised to Fentanyl prior to colonoscopy	
Subject analysis set title	Alfentanil on-demand
Subject analysis set type	Intention-to-treat
Subject analysis set description: those randomised to Alfentanul on-demand	

Reporting group values	Fentanyl on-demand	Fentanyl prior	Alfentanil on-demand
Number of subjects	183	177	179
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over 55-79	 183	 177	 179

Age continuous Units: years			
arithmetic mean	66.8	66.7	67.1
standard deviation	± 6.1	± 5.9	± 5.8
Gender categorical Units: Subjects			
Female	183	177	179
Male			
Adequate bowel cleansing Units: Subjects			
Bowel cleansing	165	161	162
Expectation painful colonoscopy Units: Subjects			
Expect pain	89	88	96
Previous painful colonoscopy Units: Subjects			
Previous pain	34	44	49
Abdominal surgery Units: Subjects			
Surgery	96	91	86
Previous diverticulitis Units: Subjects			
Diverticulitis	9	12	7
IBS with pain Units: Subjects			
IBS	12	9	14
Heart rate Units: per minute			
arithmetic mean	75.8	74.9	75.0
standard deviation	± 12.5	± 12.4	± 12.5
VAS before examination			
Pain score before			
Units: mm			
arithmetic mean	0.5	0.3	0.3
standard deviation	± 1.1	± 0.9	± 0.8
BMI			
Bodymass index			
Units: kg/m2			
arithmetic mean	26.0	26.5	26.4
standard deviation	± 4.9	± 5.2	± 5.2
Oxygen saturation (pre-procedure) Units: percent			
arithmetic mean	97.1	97.0	96.8
standard deviation	± 1.8	± 1.7	± 2.0

End points

End points reporting groups

Reporting group title	all over
Reporting group description: -	
Subject analysis set title	Fentanyl on-demand
Subject analysis set type	Intention-to-treat
Subject analysis set description: Those randomised to Fentanyl on-demand	
Subject analysis set title	Fentanyl prior
Subject analysis set type	Intention-to-treat
Subject analysis set description: Those randomised to Fentanyl prior to colonoscopy	
Subject analysis set title	Alfentanil on-demand
Subject analysis set type	Intention-to-treat
Subject analysis set description: those randomised to Alfentanul on-demand	

Primary: Pain

End point title	Pain
End point description: The primary endpoint was the proportion of women who experienced moderate or severe pain during colonoscopy, defined as painful colonoscopy, recorded within the Gastronet questionnaire the first post-colonoscopy day.	
End point type	Primary
End point timeframe: Pain during colonoscopy	

End point values	Fentanyl on-demand	Fentanyl prior	Alfentanil on-demand	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	161	151	162	
Units: number				
Painful colonoscopy	71	38	64	

Attachments (see zip file)	Figure2_colour.tif

Statistical analyses

Statistical analysis title	Pain comparison Fentanyl arms
Comparison groups	Fentanyl on-demand v Fentanyl prior

Number of subjects included in analysis	312
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Chi-squared

Statistical analysis title	Pain comparison on-demand
Comparison groups	Fentanyl on-demand v Alfentanil on-demand
Number of subjects included in analysis	323
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4
Method	Chi-squared

Secondary: Willingness to repeat	
End point title	Willingness to repeat
End point description: Secondary endpoints were willingness to repeat the colonoscopy with identical procedural process	
End point type	Secondary
End point timeframe: Asked the day after colonoscopy	

End point values	Fentanyl on-demand	Fentanyl prior	Alfentanil on-demand	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	151	157	163	
Units: Number				
Willingness to repeat	142	151	145	

Statistical analyses

Statistical analysis title	Willingness to repeat Fentanyl arms
Comparison groups	Fentanyl on-demand v Fentanyl prior
Number of subjects included in analysis	308
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4
Method	Chi-squared

Statistical analysis title	Willingness to repeat on demand arms
Comparison groups	Fentanyl on-demand v Alfentanil on-demand
Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1
Method	Chi-squared

Secondary: Serious adverse events

End point title	Serious adverse events

End point description:

Adverse events with impairment of vital parameters (i.e., systolic blood pressure <100mmHg, heart rate <50 beats/minute, oxygen saturation <90% without oxygen supplement) were defined as serious adverse events.

End point type	Secondary

End point timeframe:

During colonoscopy and within 30 days after

End point values	Fentanyl on-demand	Fentanyl prior	Alfentanil on-demand	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	183	177	179	
Units: Number				
Serious adverse events	5	6	5	

Statistical analyses

Statistical analysis title	SAE comparison Fentanyl arms
Comparison groups	Fentanyl on-demand v Fentanyl prior
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7
Method	Chi-squared

Statistical analysis title	SAE comparison on-demand groups
Comparison groups	Fentanyl on-demand v Alfentanil on-demand

Number of subjects included in analysis	362
Analysis specification	Pre-specified
Analysis type	other
P-value	= 1
Method	Chi-squared

Secondary: Cecum intubation rate

End point title	Cecum intubation rate

End point description:

Cecum intubation was defined as reaching the cecum with a CF colonoscope and without administration of benzodiazepine (midazolam) during the examination.

End point type	Secondary

End point timeframe:

during colonoscopy

End point values	Fentanyl on-demand	Fentanyl prior	Alfentanil on-demand	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	179	175	176	
Units: Number				
Cecum intiubation rate	159	160	166	

Statistical analyses

Statistical analysis title	CIR comparison Fentanyl arms
Comparison groups	Fentanyl on-demand v Fentanyl prior
Number of subjects included in analysis	354
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4
Method	Chi-squared

Statistical analysis title	CIR comparison on-demand arms
Comparison groups	Fentanyl on-demand v Alfentanil on-demand
Number of subjects included in analysis	355
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.06
Method	Chi-squared

Secondary: Need for recovery	
End point title	Need for recovery
End point description:	
The proportion of participants who were not able to leave the endoscopy unit immediately after a colonoscopy.	
End point type	Secondary
End point timeframe:	
At the day of colonoscopy	

End point values	Fentanyl on-demand	Fentanyl prior	Alfentanil on-demand	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	155	158	164	
Units: Number				
Need for recovery	52	60	46	

Attachments (see zip file)	Supplementary.docx

Statistical analyses

Statistical analysis title	Comparison on-demand groups-need for recovery
Comparison groups	Alfentanil on-demand v Fentanyl on-demand
Number of subjects included in analysis	319
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3
Method	Chi-squared

Statistical analysis title	Comparison Fentanyl groups-need for recovery
Comparison groups	Fentanyl on-demand v Fentanyl prior
Number of subjects included in analysis	313
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4
Method	Chi-squared

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious adverse event occured during colonoscopy or within 30 days after examination

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	Adverse Evens- Fentanyl prior

Reporting group description:

all adverse events, both defined as non-serious and serious

Reporting group title	Adverse events-Fentanyl on demand

Reporting group description: -

Reporting group title	Adverse events - Alfentanil on demand

Reporting group description: -

Serious adverse events	Adverse Evens- Fentanyl prior	Adverse events- Fentanyl on demand	Adverse events - Alfentanil on demand
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 183 (2.73%)	6 / 177 (3.39%)	5 / 179 (2.79%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Product issues			
SAEs related to analgesia	Additional description: Systolic blood pressure < 100 mmHg and/or heart rate < 50 bpm and/or oxygen saturation < 90 % without supplemental oxygen		
subjects affected / exposed	5 / 183 (2.73%)	6 / 177 (3.39%)	5 / 179 (2.79%)
occurrences causally related to treatment / all	5 / 5	6 / 6	5 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Adverse Evens- Fentanyl prior	Adverse events- Fentanyl on demand	Adverse events - Alfentanil on demand
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 183 (4.37%)	15 / 177 (8.47%)	11 / 179 (6.15%)
Product issues			
AEs related to analgesia	Additional description: Events requiring intravenous antiemetics, intravenous fluids, intravenous spasmolytics, elevating lower extremities.		

subjects affected / exposed occurrences (all)	8 / 183 (4.37%) 8	15 / 177 (8.47%) 15	11 / 179 (6.15%) 11

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 May 2017	Sample size increased to 480, admission from the reginal ethical committee and Norwegian Medicines Agency

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/34534048