Clinical trial results:
Use of long acting opioids for pre- and postoperative analgesia in primary total knee arthroplasty. A double-blinded randomized control trial. Tapentadol vs Oxycodon vs Placebo

Summary

EudraCT number	2015-000295-94
Trial protocol	NO
Global end of trial date	28 February 2019

Results information

Result version number	v1 (current)
This version publication date	29 November 2021
First version publication date	29 November 2021
Summary attachment (see zip file)	Summary 121121 (Summary 121121.pdf)

Trial information

Trial identification

Sponsor protocol code	TPO-150

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02604446
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	St. Olavs Hospital, Trondheim, Norway
Sponsor organisation address	Olav Kyrrs gate, Trondheim, Norway, 7006
Public contact	Head of Clinic, Orthopedic surgery, St. Olavs University Hospital, +47 72823244, knut.hagen@stolav.no
Scientific contact	Head of Clinic, Orthopedic surgery, St. Olavs University Hospital, +47 72823244, knut.hagen@stolav.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	28 February 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 February 2019
Global end of trial reached?	Yes
Global end of trial date	28 February 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective of the trial is to measure variations in pain relief between three different pain treatments

Protection of trial subjects:

Before surgery, all patients received acetaminophen tablets 2/ 1.5 g above/below 70 kg, dexamethasone tablets 20/16 mg above/below 70 kg, naproxen 500 mg 1 esomeprazole 20 mg. Acetaminophen, naproxen and esomeprazole were repeated on the day of surgery. After the day of surgery, patients received study medication twice daily, naproxen 500 mg1esomeprazole 20 mg twice daily, and acetaminophen 1000 mg 4 times daily for 6 days. For rescue analgesia, patients in all 3 study groups had the opportunity to take oral oxycodone immediate-release (IR) 5 mg on demand.

Background therapy:

Acetaminophen tablets 2/ 1.5 g above/below 70 kg, dexamethasone tablets 20/16 mg above/below 70 kg, naproxen 500 mg 1 esomeprazole 20 mg. Acetaminophen, naproxen 1 esomeprazole were repeated on the day of surgery. After the day of surgery, patients received study medication twice daily, naproxen 500 mg1esomeprazole 20 mg twice daily, and acetaminophen 1000 mg 4 times daily for 6 days. For rescue analgesia, patients in all 3 study groups had the opportunity to take oral oxycodone immediate-release (IR) 5 mg on demand.

Evidence for comparator:

Opioids are effective drugs for pain relief, with increased efficacy with increased doses. Tapentadol is an analgesic drug that provides analgesia through both the opioid and alpha-2-adrenergic receptors

Actual start date of recruitment	01 September 2015
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: 149
Worldwide total number of subjects	149
EEA total number of subjects	149

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)	149
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Enrollment was done by an anesthesiologist at the preoperative outpatient clinic in the period between September 2015 and February 2019.

Pre-assignment

Screening details:

Patients scheduled for surgerywith TKA between 18 and 80 years of age were included in the study.

Period 1

Period 1 title	Drug intervention (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind[1]
Roles blinded	Subject, Monitor, Carer, Assessor

Blinding implementation details:

Randomization was performed by the Unit for Applied Clinical Research (AKF NTNU). Computer-generated block randomization with block sizes of 30, 30, 30, 21, 21, and 18 was used. The randomization of study drugs was only known by the hospital
pharmacy (for emergency unblinding), the monitor unit (AKF NTNU) who generated the list, and the manufacturer of the study drugs. The 3 different study drugs were packed in identical resorbable capsules and swallowed whole. Ward staff did all handling.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo group

Arm description:

Placebo drug x 2 Day of surgery and day 1-6

Arm type	Placebo
Investigational medicinal product name	Tapentadol
Investigational medicinal product code	
Other name	Tapentadol
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tapentadol 50 mg x 2

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet x 2 in seven days

Arm title	Tapentadol

Arm description:

tapentadol 50 mg x 2 for seven days

Arm type	Experimental

Investigational medicinal product name	Tapentadol
Investigational medicinal product code	
Other name	Tapentadol
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tapentadol 50 mg x 2

Arm title	Oxycodone

Arm description:

Oxycodone 19 mg x 2 for seven days

Arm type	Active comparator
Investigational medicinal product name	oxycodone
Investigational medicinal product code	
Other name	oxycodone
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

oxycodone 20 mg x 2 for seven days

Notes:

[1] - The roles blinded appear to be inconsistent with a double blind trial.

Justification: The randomization of study drugs was only known by the hospital pharmacy (for emergency unblinding), the monitor unit (AKF NTNU) who generated the list, and the manufacturer of the study
drugs. The 3 different study drugs were packed in identical resorbable capsules and swallowed whole. Ward staff did all handling of study drugs and other analgesic drugs in the study. All participants, healthcare personnel, and investigators were blinded for the study drug allocation.

Number of subjects in period 1	Placebo group	Tapentadol	Oxycodone
Started	50	49	50
Completed	50	49	50

Baseline characteristics

Reporting groups	
Reporting group title	Placebo group
Reporting group description: Placebo drug x 2 Day of surgery and day 1-6	
Reporting group title	Tapentadol
Reporting group description: tapentadol 50 mg x 2 for seven days	
Reporting group title	Oxycodone
Reporting group description: Oxycodone 19 mg x 2 for seven days	

Reporting group values	Placebo group	Tapentadol	Oxycodone
Number of subjects	50	49	50
Age categorical			
Age			
Units: Subjects			
Adults (18-64 years)	50	49	50
Gender categorical Units: Subjects			
Female	7	1	1
Male	43	48	49

Reporting group values	Total		
Number of subjects	149		
Age categorical			
Age			
Units: Subjects			
Adults (18-64 years)	149		
Gender categorical Units: Subjects			
Female	9		
Male	140		

End points

End points reporting groups

Reporting group title	Placebo group
Reporting group description: Placebo drug x 2 Day of surgery and day 1-6	
Reporting group title	Tapentadol
Reporting group description: tapentadol 50 mg x 2 for seven days	
Reporting group title	Oxycodone
Reporting group description: Oxycodone 19 mg x 2 for seven days	

Primary: Pain at day seven

End point title	Pain at day seven
End point description: The patients were asked "How much pain do you have now when you move, where 0 is no pain and 10 is the worst pain imaginable." The primary outcome is reported as area under the pain curve (AUC) and the corresponding mean value of pain for each patient and the groups for the first 7 postoperative days.	
End point type	Primary
End point timeframe: Seven days	

End point values	Placebo group	Tapentadol	Oxycodone	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	43[1]	45[2]	46[3]	
Units: Area under the curve				
Pain	528	427	508	

Notes:

[1] - 7 without follow-up data

[2] - 4 without follow-up data

[3] - 4 without follow-up data

Statistical analyses

Statistical analysis title	Kruskal-Wallis
Statistical analysis description: For pain on mobilization and pain at rest, AUC was calculated and divided by elapsed time from first to last postoperative measurement fromthe first to the seventh day to yield a measure of mean pain in this period. Mean pain was then compared between the experimental groups using the nonparametric Kruskal–Wallis test.	
Comparison groups	Placebo group v Tapentadol v Oxycodone

Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05 [4]
Method	Kruskal-wallis
Parameter estimate	Median difference (final values)
Point estimate	0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	0.14
Variability estimate	Standard deviation
Dispersion value	204

Notes:

[4] - No statistical difference found between the group for prarimary (or secobdary) outcome (P=12)

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: 14 days	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	1

Reporting groups	
Reporting group title	Placebo group
Reporting group description: Placebo drug x 2 Day of surgery and day 1-6	
Reporting group title	Tapentadol
Reporting group description: tapentadol 50 mg x 2 for seven days	
Reporting group title	Oxycodone
Reporting group description: Oxycodone 19 mg x 2 for seven days	

Serious adverse events	Placebo group	Tapentadol	Oxycodone
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 43 (0.00%)	0 / 45 (0.00%)	0 / 45 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	Placebo group	Tapentadol	Oxycodone
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 43 (0.00%)	0 / 45 (0.00%)	0 / 45 (0.00%)

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: No adverse event occured more frequent than 5%. Constipatiom occured more frequent iin the oxycondone group than the other groups (p=0.02)

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.

The sample size of 150 patients was not large enough to rule out a small difference of in pain NRS scores

Notes: