Clinical trial results:
Analgetic effect of perioperative klorzoxazon at total hip or knee arthroplasty

Summary

EudraCT number	2015-001214-10
Trial protocol	DK
Global end of trial date	31 December 2017

Results information

Result version number	v1 (current)
This version publication date	18 July 2020
First version publication date	18 July 2020
Summary attachment (see zip file)	Protokol: Analgetisk effekt af perioperativ Chlorzoxazone ved Total hip- and knee surgery (Protokol Klorzoxazon ver 5 0 (MU) 20 05 2015.pdf) Investigating the Effect of Perioperative Chlorzoxazone (Investigating_the_Effect_of_Perioperative. Artikel til Klorzoxazon.pdf)

Trial information

Trial identification

Sponsor protocol code	AAUH-01-2015

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Aalborg University Hospital, Farsø
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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	29 December 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Investigate the effect of perioperative treatment with klorzoxazon compared to placebo. Out of need of suplementary analgentics and expierence of pain after incertion of hip or knee arthroplasty

Protection of trial subjects:

With any discomfort patient was treated with all necessary means and measures

Background therapy:

Morphine, ibumetin, celecoxib, dulculax, pantoprazole, cefuroxime, xarelto, cyclonova, pamol

Evidence for comparator: -

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	Denmark: 393
Worldwide total number of subjects	393
EEA total number of subjects	393

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)	129
From 65 to 84 years	258
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

Inclusion criteria:
Set to primary, optional, one-sided THA or TKA.
18 years and over
Pt. has normal cognitive and linguistic functioning
Pt. has given his oral informed consent

Pre-assignment

Screening details:

Exclusion criteria:
Taking one or more of the following medications in the period from 4 weeks before OP to OP: Gapentins, Glucocorticoid, Opioids with daily consumption, Anxiolytics, Anti-epileptics.
Alcohol abuse
Current malignant disorder
BMI greater than 40
Disease-affecting central or peripheral
Allergy to Chlorzoxazone.
Liver disease

Pre-assignment period milestones

Number of subjects started	393
Number of subjects completed	393

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Gr. 1 THA active Chlorzoxazone

Arm description:

First 7 days from surgery day, patient receive:
Gr. 1 THA:
8 AM: 250 mg Klorzoxazone, 4 PM: 250 mg Klorzoxazone, 22 PM: 250 mg Klorzoxazone

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

Dosage and administration details:

1 tbl x 3/day in 7 days

Arm title	Gr. 2 THA Look a like placebo

Arm description:

First 7 days from surgery day patients received:
Gr. 2 THA:
8 AM: Placebo, 4 PM: Placebo, 22 PM: Placebo

Arm type	Placebo

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

Dosage and administration details:

1 tbl. x 3/day in 7 days

Arm title	Gr. 3 TKA Active Chlorzoxazone

Arm description:

First 7 days from surgery day patients received
Gr. 3 TKA:
8 AM: 250 mg Klorzoxazone, 4 PM: 250 mg Klorzoxazone, 22 PM: 250 mg Klorzoxazone

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

Dosage and administration details:

1 tbl x 3/day in 7 days

Arm title	Gr. 4: TKA placebo

Arm description:

In 7 days from from surgery day patients received
Gr. 4 TKA:
8 AM: Placebo, 4 PM: Placebo, 10 PM: Placebo

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

Dosage and administration details:

1 tablet 3 times a day in 7 days

Number of subjects in period 1	Gr. 1 THA active Chlorzoxazone	Gr. 2 THA Look a like placebo	Gr. 3 TKA Active Chlorzoxazone
Started	97	98	100
Completed	95	96	98
Not completed	2	2	2
Physician decision	-	2	2
Consent withdrawn by subject	-	-	-
Adverse event, non-fatal	2	-	-
Protocol deviation	-	-	-

Number of subjects in period 1	Gr. 4: TKA placebo
Started	98

Completed	91
Not completed	7
Physician decision	4
Consent withdrawn by subject	2
Adverse event, non-fatal	-
Protocol deviation	1

Baseline characteristics

Reporting groups

Reporting group title	overall trail

Reporting group description: -

Reporting group values	overall trail	Total	
Number of subjects	393	393	
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)	129	129	
From 65-84 years	258	258	
85 years and over	6	6	
Age continuous Units: years			
arithmetic mean	67.97		
standard deviation	± 25	-	
Gender categorical			
males and females, adults (18-100 years)			
Units: Subjects			
Female	184	184	
Male	209	209	

Subject analysis sets

Subject analysis set title	age
Subject analysis set type	Full analysis

Subject analysis set description:

Only adults are included in this study. There are no comparisons among age

Reporting group values	age		
Number of subjects	393		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		

Adults (18-64 years)	129		
From 65-84 years	258		
85 years and over	6		
Age continuous			
Units: years			
arithmetic mean	67.97		
standard deviation	± 25		
Gender categorical			
males and females, adults (18-100 years)			
Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	Gr. 1 THA active Chlorzoxazone

Reporting group description:

First 7 days from surgery day, patient receive:
Gr. 1 THA:
8 AM: 250 mg Klorzoxazone, 4 PM: 250 mg Klorzoxazone, 22 PM: 250 mg Klorzoxazone

Reporting group title	Gr. 2 THA Look a like placebo

Reporting group description:

First 7 days from surgery day patients received:
Gr. 2 THA:
8 AM: Placebo, 4 PM: Placebo, 22 PM: Placebo

Reporting group title	Gr. 3 TKA Active Chlorzoxazone

Reporting group description:

First 7 days from surgery day patients received
Gr. 3 TKA:
8 AM: 250 mg Klorzoxazone, 4 PM: 250 mg Klorzoxazone, 22 PM: 250 mg Klorzoxazone

Reporting group title	Gr. 4: TKA placebo

Reporting group description:

In 7 days from from surgery day patients received
Gr. 4 TKA:
8 AM: Placebo, 4 PM: Placebo, 10 PM: Placebo

Subject analysis set title	age
Subject analysis set type	Full analysis

Subject analysis set description:

Only adults are included in this study. There are no comparisons among age

Primary: Pain

End point title	Pain[1]

End point description:

Pain experienced before surgery was registred with all patients when they were resting and when they were active. After surgery experienced pain was registred twise a day in 14 days, at rest and in activity

End point type	Primary

End point timeframe:

See chart 1 in the protokol

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: We refer to the protocol on page 21

End point values	Gr. 1 THA active Chlorzoxazone	Gr. 2 THA Look a like placebo	Gr. 3 TKA Active Chlorzoxazone	Gr. 4: TKA placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	97	98	100	98
Units: 1-100	97	98	100	98

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

A SAE is recorded if it occurs within 7 days of the last project drug administration

Adverse event reporting additional description:

In conclusion, patients have experienced the same side effects as we might expect after a hip or knee alloplasty surgery, whether they were given chlorzoxazone or placebo - There is no significant difference between the two groups. We do not have any additional data which detect side effects or add other details to the drug chlorzoxazone

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10

Reporting groups

Reporting group title	Arm: Gr. 4: TKA placebo
Reporting group description: -	
Reporting group title	Arm: Gr. 3 TKA Active Chlorzoxazone
Reporting group description: -	
Reporting group title	Arm: Gr. 1 THA active Chlorzoxazone
Reporting group description: -	

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: We refer to the article: Investigating the effect of Perioperative Chlorzoxazone on Acute Postoperative Pain After Total Hip and Knee Replacement Surgery

Serious adverse events	Arm: Gr. 4: TKA placebo	Arm: Gr. 3 TKA Active Chlorzoxazone	Arm: Gr. 1 THA active Chlorzoxazone
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 98 (3.06%)	2 / 100 (2.00%)	2 / 97 (2.06%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Yellow skin	Additional description: the patient had misread the medication instructions and taken a double dose of acetaminophen for a day and a half. However, S-paracetamol was normal. The symptoms are estimated to come from a gallstone. Patient was hospitalized for 2 days		
subjects affected / exposed	3 / 98 (3.06%)	2 / 100 (2.00%)	2 / 97 (2.06%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Hypotennsion and general discomfort	Additional description: Blood percentage drops after surgery. Starting point 9.1 mmol / l decreased to 4.8 mmol / l. Treated with blood transfusion		
subjects affected / exposed	3 / 98 (3.06%)	2 / 100 (2.00%)	2 / 97 (2.06%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

General physical condition abnormal	Additional description: Blood percentage drops after surgery. Starting point 8,5 mmol / l decreased to 5,0 mmol / l. Treated with blood transfusion		
subjects affected / exposed	3 / 98 (3.06%)	2 / 100 (2.00%)	2 / 97 (2.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Seizure	Additional description: After premedication, epileptic seizures are triggered. The patient is not familiar with epilepsy		
subjects affected / exposed	3 / 98 (3.06%)	2 / 100 (2.00%)	2 / 97 (2.06%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Blood in stools	Additional description: Bleeding from the rectum after toilet visits. Familiar with angiodysplasia after radiotherapy back in March 2015		
subjects affected / exposed	3 / 98 (3.06%)	2 / 100 (2.00%)	2 / 97 (2.06%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
blood in vomiting	Additional description: NSAID is discontinued and the symptoms ceased.		
subjects affected / exposed	3 / 98 (3.06%)	2 / 100 (2.00%)	2 / 97 (2.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nausea, vomiting and Hypotension	Additional description: Turned out patient had increased S-creatine. NSAID was discontinued		
subjects affected / exposed	3 / 98 (3.06%)	2 / 100 (2.00%)	2 / 97 (2.06%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 1.78 %

Non-serious adverse events	Arm: Gr. 4: TKA placebo	Arm: Gr. 3 TKA Active Chlorzoxazone	Arm: Gr. 1 THA active Chlorzoxazone
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 98 (0.00%)	0 / 100 (0.00%)	0 / 97 (0.00%)

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported