Clinical trial results:
Highdose steroid for total knee arthroplasty - A randomized doubleblindet controlled trial.

Summary

EudraCT number	2018-002634-20
Trial protocol	DK
Global end of trial date	01 February 2022

Results information

Result version number	v1 (current)
This version publication date	26 September 2022
First version publication date	26 September 2022

Trial information

Trial identification

Sponsor protocol code	NBF_HK_01_2018

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03758170
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Hvidovre Hospital
Sponsor organisation address	Kettegaards alle 30, Hvidovre, Denmark, 2650
Public contact	Research group, anaesthesia Dept., Anaesthesia Department, Hvidovre Hospital, Capital Region of Denmark, +45 38623862, Nicolai.Bang.Foss@regionH.dk
Scientific contact	Research group, anaesthesia Dept., Anaesthesia Department, Hvidovre Hospital, Capital Region of Denmark, +45 38623862, Nicolai.Bang.Foss@regionH.dk

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	01 March 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 January 2022
Global end of trial reached?	Yes
Global end of trial date	01 February 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the amount of patients with VAS >30 in a 5-meter walk test, 24 hours postoperatively efter total kneearthroplasty.

Protection of trial subjects:

All patients had standardized care, surgery, and treatments as part of a Fast-track surgery regimen in Total Knee Arthroplasty surgery, and both study-treatment-groups had active treatment (standard-dose vs. higher dose).

Background therapy:

Multimodal opioid-sparring analgesia including Cox-2 inhibitors, acetaminophen(paracetamol) and rescue opioids (morphine or oxycodone).
All patients had pre- and postoperative tranexamic acid.
Thromboprophylaxis was used in-hospital only (xarelto or eliquis).
All patients had neuraxial anesthesia with bupivacaine.

Evidence for comparator:

The use of steroids as a perioperative mean of reducing postoperative stress and hence reducing postoperative pain is well-known, and several articles exist on the topic.

Lunn TH, Andersen LO, Kristensen BB, Husted H, Gaarn-Larsen L, Bandholm T, Ladelund S, Kehlet H:
Effect of high-dose preoperative methylprednisolone on recovery after total hip arthroplasty: A randomized, double-blind, placebo-controlled trial.
Br J Anaesth 2013; 110:66–73

De Oliveira GS, Almeida MD, Benzon HT, McCarthy RJ.
Perioperative single dose systemic dexamethasone for postoperative pain: A meta-analysis of randomized controlled trials.
Anesthesiology 2011; 115: 575–88

C.C. Jørgensen, F.T. Pitter, H. Kehlet
Safety aspects of preoperative high-dose glucocorticoid in primary total knee replacement
Br J Anaesth, 119 (2017), pp. 267-275

A. Toner, V. Ganeshanathan, M. Chan, K. Ho, T. Corcoran
Safety of perioperative glucocorticoids in elective noncardiac surgery, a systematic review and metaanalysis
Anesthesiology, 126 (2017), pp. 234-248

Actual start date of recruitment	03 December 2018
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: 157
Worldwide total number of subjects	157
EEA total number of subjects	157

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)	40
From 65 to 84 years	113
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

Patients were recruited before surgery at their information meeting. All participants had had oral and written project information in accordance with guidelines and had at least 24 hours of consideration. All participants gave informed consent. Patients were screened at Hvidovre Hospital and Vejle sygehus from January 2019 to September 2021

Pre-assignment

Screening details:

From January 29, 2019, to september 31, 2021, a total of 1277 patients planned for hip arthroplasty were
assessed for inclusion in accordance with inclusion and exclusion criteria. 75% of screened patients were eligible and 160 patients were included and 157 randomized.

Period 1

Period 1 title	Overall period (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

Blinding implementation details:

Randomization sequence were made by unblinded physicians not otherwise connected to the study or the participants with double-control.
Study-specific trained unblinded nurses at each site, not having any contact with the participants were responsible for preparing the study drug and blinding this for all other personnel.
Study-drug was mixed into a blinded 100 ml. container, and intervention and control were alike in both volume and appearance.

Arms

Are arms mutually exclusive?	Yes
Arm title	Intervention

Arm description:

Intervention arm, High dose Dexamethasone 1mg/kg of patient's actual bodyweight.

Arm type	Experimental
Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Dexamethasone 10mg/ml, added to a 100 ml. NaCl container in accordance with the patient's actual weight, thus the intervention dose was 1mg/kg.
Infusion initiated after application of neuraxial anesthesia and administered within 10-15 minutes.

Arm title	Intermediate comparator

Arm description:

Intermediate dose dexamethasone 0.3mg/kg of actual bodyweight

Arm type	Active comparator

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Concentrate for solution for infusion

Dosage and administration details:

Dexamethasone 10mg/ml, added to a 100 ml. NaCl container in accordance to the patient's actual weight, thus the intervention dose was 0.3mg/kg.
Infusion initiated after application of neuraxial anesthesia and administered within 10-15 minutes.

Number of subjects in period 1	Intervention	Intermediate comparator
Started	80	77
Completed	80	77

Baseline characteristics

Reporting groups	
Reporting group title	Intervention
Reporting group description:	
Intervention arm, High dose Dexamethasone 1mg/kg of patient's actual bodyweight.	
Reporting group title	Intermediate comparator
Reporting group description:	
Intermediate dose dexamethasone 0.3mg/kg of actual bodyweight	

Reporting group values	Intervention	Intermediate comparator	Total
Number of subjects	80	77	157
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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Age			
Units: years			
median	72	68	
full range (min-max)	46 to 87	43 to 89	-
Gender categorical			
Gender, female			
Units: Subjects			
Female	51	36	87
Male	29	41	70
ASA			
ASA-score			
Units: Subjects			
ASA 1	5	11	16
ASA 2	63	46	109
ASA 3	12	20	32
Body mass index			
BMI			
Units: Kg/M3			
median	30	28	
inter-quartile range (Q1-Q3)	27 to 34	25 to 32	-

End points

End points reporting groups

Reporting group title	Intervention
Reporting group description: Intervention arm, High dose Dexamethasone 1mg/kg of patient's actual bodyweight.	
Reporting group title	Intermediate comparator
Reporting group description: Intermediate dose dexamethasone 0.3mg/kg of actual bodyweight	

Primary: Primary Outcome: Percentage of patients experiencing VAS>30mm on a 0-100 mm. VAS scale 24 hours after surgery upon ambulation

End point title	Primary Outcome: Percentage of patients experiencing VAS>30mm on a 0-100 mm. VAS scale 24 hours after surgery upon ambulation
End point description: Percentage of patients experiencing VAS>30mm on a 0-100 mm VAS scale 24 hours after surgery upon ambulation in a 5 meter walk test.	
End point type	Primary
End point timeframe: 24 hours after knee replacement surgery (a timeframe of 1 hour before and after precise timepoint of end of surgery).	

End point values	Intervention	Intermediate comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	77		
Units: Number/percentage				
Mild pain (<30 mm on VAS 0-100 mm)	35	36		
Moderate to severe pain (>30 mm on VAS 0-100 mm)	45	41		

Statistical analyses

Statistical analysis title	Chi squared primary outcome
Comparison groups	Intervention v Intermediate comparator
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.65
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	1.07

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.4

Secondary: PAIN (VAS-score) 24hours after surgery upon ambulation

End point title	PAIN (VAS-score) 24hours after surgery upon ambulation

End point description:

VAS-score upon ambulation in a 0-100mm. VAS scale upon a 5 meter walk test 24 hours after surgery.

End point type	Secondary

End point timeframe:

24 hours after surgery (prespecified timeframe of 1 hour before and after actual end of surgery timepoint).

End point values	Intervention	Intermediate comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	77		
Units: VAS score in mm				
median (inter-quartile range (Q1-Q3))	34 (19 to 50)	35 (17 to 57)		

Statistical analyses

Statistical analysis title	Mann whitney
Comparison groups	Intervention v Intermediate comparator
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.88
Method	Wilcoxon (Mann-Whitney)

Secondary: VAS>30mm 24hours after surgery upon rest

End point title	VAS>30mm 24hours after surgery upon rest

End point description:

Percentage of patients experiencing VAS>30mm upon rest in a 0-100mm. VAS scale 24 hours after surgery.

End point type	Secondary

End point timeframe:

24 hours after surgery (prespecified timeframe of 1 hour before and after actual end of surgery timepoint).

End point values	Intervention	Intermediate comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	77		
Units: number				
>30 mm on 0-100 mm VAS	26	20		
<30 mm on 0-100mm VAS	54	57		

Statistical analyses

No statistical analyses for this end point

Secondary: CRP after surgery

End point title	CRP after surgery

End point description:

C-reactive protein (CRP) as a measure of inflammatory response (mg/L)

End point type	Secondary

End point timeframe:

24 and 48 hour after surgery

End point values	Intervention	Intermediate comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	77		
Units: mg/L				
median (inter-quartile range (Q1-Q3))	13 (6 to 25)	16 (9 to 38)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Serious adverse events were reported on day 0, 1, 2, 7, 30 or 90, or when alerted via our electronic patient record-system, and all SAE were reported within 24h of alert to the Sponsor.

Adverse event reporting additional description:

Only Serious adverse events were recorded and reported in accordance with the approval of the Danish medicines agency and local ethics committee, as Dexamethasone is a broadly used and well-approved drug.
If adverse events (not serious adverse events) were reported or suspected of occurring in more than 5% of patients, the sponsor was informed.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.0

Reporting groups

Reporting group title	Intervention 1mg/kg

Reporting group description:

Intervention arm, High dose Dexamethasone 1mg/kg of patient's actual bodyweight.

Reporting group title	Intermediate 0.3 mg/kg

Reporting group description:

Intermediate dose dexamethasone 0.3mg/kg of actual bodyweight

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 non-serious adverse events were recorded, as accepted in the protocol by the local ethics committee and DKMA

Serious adverse events	Intervention 1mg/kg	Intermediate 0.3 mg/kg	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 80 (8.75%)	3 / 77 (3.90%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Deep vein thrombosis postoperative	Additional description: Deep vein thrombosis postoperative, assessed to be due to lack of mobilization after discharge.		
subjects affected / exposed	1 / 80 (1.25%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation	Additional description: Atrial fibrillation in a patient not formerly known to have atrial fibrillation		
subjects affected / exposed	2 / 80 (2.50%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia	Additional description: 2. degree AV- block demanding insertion of a pacemaker.		

subjects affected / exposed	1 / 80 (1.25%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Soft tissue infection	Additional description: Postoperative soft tissue infection in the area of surgery, treated by antibiotics, no revision needed.		
subjects affected / exposed	2 / 80 (2.50%)	2 / 77 (2.60%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection	Additional description: Postoperative wound infection including the arthroplasty and demanding revision surgery		
subjects affected / exposed	1 / 80 (1.25%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Intervention 1mg/kg	Intermediate 0.3 mg/kg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 80 (0.00%)	0 / 77 (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? Yes

Date	Interruption	Restart date
17 March 2020	Elective surgery was shut down due to the global Covid crisis.	02 June 2020

Notes:

Limitations and caveats

None reported