Clinical trial results:
NSAIDs INFLUENCE ON HEAL OF COLLES FRACTURE

Summary

EudraCT number	2010-018543-34
Trial protocol	DK
Global end of trial date	27 September 2017

Results information

Result version number	v1 (current)
This version publication date	12 January 2018
First version publication date	06 February 2019

Trial information

Trial identification

Sponsor protocol code	12153599

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01567072
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Aalborg University Hospital
Sponsor organisation address	Hobrovej 18 - 22, Aalborg, Denmark, 9000
Public contact	Sponsor - investigator Marius Aliuskevicius, Aalborg University Hospital, +45 26910156, aliuskevicius@yahoo.dk
Scientific contact	Sponsor - investigator Marius Aliuskevicius, Aalborg University Hospital, +45 26910156, aliuskevicius@yahoo.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	15 December 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 June 2017
Global end of trial reached?	Yes
Global end of trial date	27 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary point: assessment of radiological secondary dislocation: any migration larger than in the other group will be an expression of instability and thus slower or absent healing. It is possible to determine the migration of approx. 0.5 mm and 1 ° accuracy. Incidence of secondary dislocations and those, which need an operation, will be manufactured in absolute and percentage figures.

Protection of trial subjects:

Escape medicine for pain treatment: Tramadol 50 mg

Background therapy:

Paracetamaol 1 g 4 times a day

Evidence for comparator: -

Actual start date of recruitment	01 June 2012
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: 95
Worldwide total number of subjects	95
EEA total number of subjects	95

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)	46
From 65 to 84 years	48
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Patients with acute unstable Colles fracture were informed about the study and asked to participate. Major exclusion criteria were age less than 40 or older than 85 years; systematic treatment with NSAIDs; previous fracture at the actual wrist; lack of mental and physical capacity to follow study instructions; medical contraindications to NSAIDs.

Pre-assignment

Screening details:

From 01.06.2012 till 20.06.2015 we have screened 281 patients and included 95. 121 (43%) patients were not asked due to the bustle conditions at the emergency department, 45 (16%) patients were not interested, and 19 patients (6.8%) were excluded due to exclusions criteria. One pack of tablets was lost at the emergency department.

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, Data analyst

Blinding implementation details:

The Hospital Pharmaceutical Department performed block randomization: five blocks with nine patients in each, eight blocks with six patients in each and one block with three patients in. Tablets according to randomisation was supplied in packets. The patient, operator, data manager and statistician were all blinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo/Placebo

Arm description:

Placebo treatment during the first 7 days

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

Dosage and administration details:

1 tab. 3 times per day in 7 days

Arm title	Ibuprofen/Placebo

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Ibuprofen 600 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 tab. 3 times per day during the first 3 days days

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 tab. 3 times per day from the day 4 until day 7

Arm title	Ibuprofen/Ibuprofen

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Ibuprofen 600 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 tab. 3 times per day in 7 days

Number of subjects in period 1	Placebo/Placebo	Ibuprofen/Placebo	Ibuprofen/Ibuprofen
Started	32	32	31
Completed	28	28	27
Not completed	4	4	4
Adverse event, serious fatal	-	-	1
Consent withdrawn by subject	4	4	3

Baseline characteristics

Reporting groups	
Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	95	95	
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			
Mean age 64,75 years (min. 42, max 85)			
Units: years			
arithmetic mean	64.75		
full range (min-max)	42 to 85	-	
Gender categorical			
15 of all operated patients in our study them were male, 84 – female			
Units: Subjects			
Male	15	15	
Female	80	80	

End points

End points reporting groups

Reporting group title	Placebo/Placebo
Reporting group description: Placebo treatment during the first 7 days	
Reporting group title	Ibuprofen/Placebo
Reporting group description: -	
Reporting group title	Ibuprofen/Ibuprofen
Reporting group description: -	

Primary: Mean pain score during 1-3 days

End point title	Mean pain score during 1-3 days
End point description:	
End point type	Primary
End point timeframe: Day 1-3 from the enrollment	

End point values	Placebo/Placebo	Ibuprofen/Placebo	Ibuprofen/Ibuprofen	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	28	28	
Units: Medium VAS pain score				
arithmetic mean (standard deviation)	4.18 (± 1.9)	4.25 (± 1.71)	4.3 (± 1.92)	

Statistical analyses

Statistical analysis title	Students t-test
Comparison groups	Placebo/Placebo v Ibuprofen/Placebo v Ibuprofen/Ibuprofen
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4
Method	t-test, 2-sided

Primary: Mean pain score 1-3 days

End point title	Mean pain score 1-3 days
End point description:	
End point type	Primary

End point timeframe:
First 1-3 days from enrollment

End point values	Placebo/Placebo	Ibuprofen/Placebo	Ibuprofen/Ibuprofen	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	28	28	
Units: VAS pain scala units				
arithmetic mean (standard deviation)	4.18 (± 1.9)	4.25 (± 1.71)	4.3 (± 1.92)	

Statistical analyses

Statistical analysis title	Students t-test
Comparison groups	Placebo/Placebo v Ibuprofen/Placebo v Ibuprofen/Ibuprofen
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4
Method	t-test, 1-sided

Primary: Mean pain score during 4-7 days

End point title	Mean pain score during 4-7 days
End point description:	
End point type	Primary
End point timeframe:	
The 4-th - 7-th day from the enrollment	

End point values	Placebo/Placebo	Ibuprofen/Placebo	Ibuprofen/Ibuprofen	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	28	28	
Units: VAS pain score units				
arithmetic mean (standard deviation)	2.98 (± 1.88)	3.88 (± 2.04)	2.98 (± 1.47)	

Statistical analyses

Statistical analysis title	Kruskal wallis test
Comparison groups	Ibuprofen/Placebo v Ibuprofen/Ibuprofen v Placebo/Placebo

Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.13
Method	Kruskal-wallis

Primary: Mean pain score 8 - 14 days

End point title	Mean pain score 8 - 14 days

End point description:

End point type	Primary

End point timeframe:

The 8-th - 14-th day from the enrollment

End point values	Placebo/Placebo	Ibuprofen/Placebo	Ibuprofen/Ibuprofen	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	28	28	
Units: VAS pain score units				
arithmetic mean (standard deviation)	2.18 (± 1.35)	2.54 (± 1.75)	2.17 (± 1)	

Statistical analyses

Statistical analysis title	Kruskal wallis test
Comparison groups	Placebo/Placebo v Ibuprofen/Placebo v Ibuprofen/Ibuprofen
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.98
Method	Kruskal-wallis

Primary: Range of movement

End point title	Range of movement

End point description:

End point type	Primary

End point timeframe:

6 weeks, 3 months, 1 year

End point values	Placebo/Placebo	Ibuprofen/Placebo	Ibuprofen/Ibuprofen	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	28	27	
Units: Percent of healthy contralateral ROM				
arithmetic mean (standard deviation)				
Pronation suppination 6 weeks	58.41 (± 19.12)	63.62 (± 19.74)	66.11 (± 16.72)	
Flexion extension 6 weeks	22.42 (± 11.29)	29.31 (± 17.87)	27.91 (± 13.04)	
Radial ulnar deviation 6 weeks	31.95 (± 12.35)	38.16 (± 15.91)	33.82 (± 14.23)	
Pronation suppination 3 months	86.94 (± 12.01)	85.72 (± 12.44)	91.51 (± 7.59)	
Flexion extension 3 months	66.02 (± 11.5)	69.63 (± 21.04)	71.77 (± 15.65)	
Pronation suppination 1 year	94.2 (± 9.18)	93.55 (± 9.18)	95.91 (± 4.28)	
Flexion extension 1 year	87.15 (± 10.12)	92.05 (± 15.45)	89.47 (± 16.73)	
Radial ulnar deviation 1 year	93.86 (± 20.19)	89.6 (± 14.57)	92.49 (± 18.08)	
Radial ulnar deviation 3 months	71.23 (± 19.04)	68.22 (± 20.16)	77.4 (± 16.07)	

Statistical analyses

Statistical analysis title	Kruskal wallis test
Comparison groups	Ibuprofen/Placebo v Ibuprofen/Ibuprofen v Placebo/Placebo
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	≥ 0.148
Method	Kruskal-wallis

Primary: Mean DASH score

End point title	Mean DASH score

End point description:

End point type	Primary

End point timeframe:

3 months, 1 year

End point values	Placebo/Placebo	Ibuprofen/Placebo	Ibuprofen/Ibuprofen	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	28	27	27	
Units: DASH score units				
arithmetic mean (standard deviation)	19.95 (± 14.18)	17.87 (± 14.47)	15.07 (± 10.77)	

Statistical analyses

Statistical analysis title	Kruskal wallis test
Comparison groups	Placebo/Placebo v Ibuprofen/Placebo v Ibuprofen/Ibuprofen
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.47
Method	Kruskal-wallis
Parameter estimate	Cox proportional hazard

Primary: Radiological migration

End point title	Radiological migration
End point description:	
Changes in radius inclination, lenght and tilt: values, measured at 6 weeks control are substracted from values, measured just after operation	
End point type	Primary
End point timeframe:	
Just after operation and at 6 weeks control	

End point values	Placebo/Placebo	Ibuprofen/Placebo	Ibuprofen/Ibuprofen	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30	30	28	
Units: grades and millimetres				
arithmetic mean (standard deviation)				
Inclination	1.29 (± 2.38)	0.7 (± 3.59)	2.4 (± 2.88)	
Lenght	-1.82 (± 2.36)	-1.44 (± 2.41)	-1.6 (± 2.28)	
Tilt	-1 (± 4.1)	-0.13 (± 4.58)	-0.71 (± 4.17)	

Statistical analyses

Statistical analysis title	Kruskal wallis test
Comparison groups	Placebo/Placebo v Ibuprofen/Placebo v Ibuprofen/Ibuprofen

Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	≥ 0.061
Method	Kruskal-wallis

Secondary: Use of Tramadol at day two

End point title	Use of Tramadol at day two
End point description:	

End point type	Secondary
End point timeframe: at day two	

End point values	Placebo/Placebo	Ibuprofen/Placebo	Ibuprofen/Ibuprofen	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	28	28	
Units: Average of used Tramadol tablets				
arithmetic mean (standard deviation)	1 (± 1.13)	0.6 (± 0.87)	0.58 (± 1.09)	

Statistical analyses

Statistical analysis title	Kruskal wallis test
Comparison groups	Ibuprofen/Ibuprofen v Placebo/Placebo v Ibuprofen/Placebo
Number of subjects included in analysis	85
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.2
Method	Kruskal-wallis

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 01.06.2012 - 20. 06. 2016	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0
Reporting groups	
Reporting group title	Ibuprofen/Ibuprofen, operated patients
Reporting group description: Treatment with Ibuprofen in 7 days	
Reporting group title	Ibuprofen/Placebo, operated patients
Reporting group description: Ibuprofen treatment during the first three days, Placebo treatment during the next four days	
Reporting group title	Placebo/Placebo, operated patients
Reporting group description: Placebo treatment during the first 7 days	

Serious adverse events	Ibuprofen/Ibuprofen, operated patients	Ibuprofen/Placebo, operated patients	Placebo/Placebo, operated patients
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 29 (3.45%)	1 / 30 (3.33%)	0 / 30 (0.00%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
Bradycardia and assystolia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
death by drowning			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

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

Non-serious adverse events	Ibuprofen/Ibuprofen, operated patients	Ibuprofen/Placebo, operated patients	Placebo/Placebo, operated patients
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 29 (55.17%)	13 / 30 (43.33%)	10 / 30 (33.33%)
Surgical and medical procedures			
Loosening of external fixation			
subjects affected / exposed	0 / 29 (0.00%)	2 / 30 (6.67%)	0 / 30 (0.00%)
occurrences (all)	0	2	0
Nervous system disorders			
numbness in operated arm			
subjects affected / exposed	5 / 29 (17.24%)	2 / 30 (6.67%)	6 / 30 (20.00%)
occurrences (all)	5	2	6
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	8 / 29 (27.59%)	7 / 30 (23.33%)	4 / 30 (13.33%)
occurrences (all)	8	7	4
Skin and subcutaneous tissue disorders			
Pinholles infection			
subjects affected / exposed	2 / 29 (6.90%)	1 / 30 (3.33%)	0 / 30 (0.00%)
occurrences (all)	2	1	0
Musculoskeletal and connective tissue disorders			
Serious secondary dislocation of the fracture			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	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.

Difficulty of treatments' standardisation is limitation in our study. Patients broke their extremities at different times of the day one and were operated latest on the third day from the injury.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/3063314

http://www.ncbi.nlm.nih.gov/pubmed/8323840