Clinical trial results:
Efficacy of zoledronic acid 5 mg for chronic low back pain due to Modic changes

Summary

EudraCT number	2008-005351-14
Trial protocol	FI
Global end of trial date	19 March 2012

Results information

Result version number	v1 (current)
This version publication date	04 October 2019
First version publication date	04 October 2019
Summary attachment (see zip file)	Efficacy of zoledronic acid for chronic low back pain associated with Modic changes in magnetic resonance imaging (Koivisto 2014.pdf) The Effect of zoledronic acid on type and volume of Modic changes among patients with low back pain (Koivisto 2017.pdf)

Trial information

Trial identification

Sponsor protocol code	CZOL446HFI03

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01330238
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Oulu, Department of Physical and Rehabilitation Medicine
Sponsor organisation address	PL 5000, Oulu, Finland, 90014
Public contact	Department of Physical and Rehabilitation Medicine, Department of Physical and Rehabilitation Medicine, 041 4462859, jaro.karppinen@ttl.fi
Scientific contact	Department of Physical and Rehabilitation Medicine, Department of Physical and Rehabilitation Medicine, 041 4462859, jaro.karppinen@ttl.fi

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	19 March 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 March 2012
Global end of trial reached?	Yes
Global end of trial date	19 March 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Bisphosphonates could be effective in Modic changes causing low back pain through two mechanisms: 1.) they could consolidate the vertebral bodies thereby improving the tolerance to mechanical load and 2.) they could disminish inflammation as observed recently in case of ibandronate in an experimental inflammation model

Protection of trial subjects:

Before administration of the infusion, all patients re- ceived oral ibuprofen 600 mg or paracetamol 1 g as prophylaxis for potential acute phase reactions such as flu-like symptoms, headache or fever. Patients were advised to use the same medication should post-dose symptoms appear. They all also received 100 000 units of Vitamin D (Vigantol®) orally to prevent hypocalcae- mia. Information on use of the concomitant medication and hospital admissions were recorded. Blood samples were taken for the assessment of safety, inflammatory mediators and markers of bone turnover at baseline, one month and one year.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 November 2008
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Ethical reason, Safety, Regulatory reason, Scientific research
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Finland: 40
Worldwide total number of subjects	40
EEA total number of subjects	40

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	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients referred from primary health care units to Oulu University Hospital, where they were screened, between 11/2008 and 3/2011.Blood samples for the assessment of safety, inflammatory mediators and markers of bone turnover at bl, 1 m and 1 y.Clinical examination, MRI of lumbar spine, a signed informed, visual analog scale, Oswestry, RAND-36.

Pre-assignment

Screening details:

Inclusion criteria were low back symptoms for at least three months, an LBP intensity of at least six (6) on a 10-cm Visual Analog Scale (VAS) or an Oswestry Disability Index (ODI) of at least 30% [21], and an M1, mixed M1/2 or M2 in MRI performed within six months at most prior to enrolment.

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	Investigator, Monitor, Subject, Data analyst, Carer

Blinding implementation details:

A master randomization list was generated by a computer in blocks of eight, containing four placebo and four ZA allocations in random order. Patients were assigned a unique randomization number according to the order of inclusion. Patients, the principal investiga- tor performing the screening and follow-up assessments, the nurse, the radiologist evaluating the MRI scans, and the statistician were blinded to the treatment allocation. The ZA and placebo were supplied in in identical bottles.

Arms

Are arms mutually exclusive?	Yes
Arm title	Zoledronic acid

Arm description:

Patients were randomized to receive a single intravenous infusion of 5 mg ZA in 100 ml saline (n=20) or 100 ml saline as placebo (n = 20) over a 15-minute period.

Arm type	Active comparator
Investigational medicinal product name	Aclasta/zoledronic acid 5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

patients were randomized to receive a single intravenous infusion of 5 mg ZA in 100 ml saline (n=20) or 100 ml saline as placebo (n = 20) over a 15-minute period.

Arm title	Placebo

Arm description:

Patients were randomized to receive a single intravenous infusion of 5 mg ZA in 100 ml saline (n=20) or 100 ml saline as placebo (n = 20) over a 15-minute period.

Arm type	Placebo
Investigational medicinal product name	100 ml saline as placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients were randomized to receive a single intravenous infusion of 5 mg ZA in 100 ml saline (n=20) or

100 ml saline as placebo (n = 20) over a 15-minute period.

Number of subjects in period 1	Zoledronic acid	Placebo
Started	20	20
Completed	20	20

Baseline characteristics

Reporting groups	
Reporting group title	Zoledronic acid
Reporting group description:	
Patients were randomized to receive a single intravenous infusion of 5 mg ZA in 100 ml saline (n=20) or 100 ml saline as placebo (n = 20) over a 15-minute period.	
Reporting group title	Placebo
Reporting group description:	
Patients were randomized to receive a single intravenous infusion of 5 mg ZA in 100 ml saline (n=20) or 100 ml saline as placebo (n = 20) over a 15-minute period.	

Reporting group values	Zoledronic acid	Placebo	Total
Number of subjects	20	20	40
Age categorical			
The patients' mean age was 50 years			
Units: Subjects			
Adults (18-64 years)	20	20	40
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical			
There were 26 men, 15 in zoledronic acid group and 11 in placebo group			
Units: Subjects			
Female	5	9	14
Male	15	11	26

End points

End points reporting groups

Reporting group title	Zoledronic acid
Reporting group description:	
Patients were randomized to receive a single intravenous infusion of 5 mg ZA in 100 ml saline (n=20) or 100 ml saline as placebo (n = 20) over a 15-minute period.	
Reporting group title	Placebo
Reporting group description:	
Patients were randomized to receive a single intravenous infusion of 5 mg ZA in 100 ml saline (n=20) or 100 ml saline as placebo (n = 20) over a 15-minute period.	
Subject analysis set title	Treatment effect by comparing the change in the outcomes
Subject analysis set type	Full analysis
Subject analysis set description:	
independent samples t-test	

Primary: Change in intensity of low back pain

End point title	Change in intensity of low back pain
End point description:	
Primary endpoint was change in intensity of low back pain (10 cm VAS) form baseline to one year	
End point type	Primary
End point timeframe:	
The mean difference (MD) between the treatment groups in the primary outcome, intensity of LBP	

End point values	Zoledronic acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: cm				
number (confidence interval 95%)	2.8 (-1.0 to 2.8)	2.2 (-1.0 to 2.4)		

Statistical analyses

Statistical analysis title	Treatment effect by comparing change in outcome
Statistical analysis description:	
independent samples t-test	
Comparison groups	Zoledronic acid v Placebo
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.05
Method	t-test, 2-sided

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were asked at 1 month and 1 year follow-up.The occurrence of any adverse effects was observed during the infusion and inquired about at each of the follow-up visits.

Adverse event reporting additional description:

Despite prophylaxis, acute post-infusion phase reactions (fever, headache, myalgia, arthralgia, pain, nau- sea and flu-like symptoms) were observed in 19/20 patients in the ZA vs. 7/20 patients in the placebo group

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Zoledronic acid group

Reporting group description:

Patients received a single intravenous infusion of 5 mg ZA in 100 ml saline.

Despite prophylaxis, acute post-infusion phase reactions (fever, headache, myalgia, arthralgia, pain, nau- sea and flu-like symptoms) were observed in 19/20 patients in the ZA vs. 7/20 patients in the placebo group. One event met the criteria for serious adverse effect (SAE) in the ZA group; sinusitis requiring temporary hospitalization after the infusion.

Reporting group title	Placebo group

Reporting group description:

Patients received a single intravenous infusion of 100 ml saline as placebo

Serious adverse events	Zoledronic acid group	Placebo group	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Infections and infestations			
Sinusitis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Zoledronic acid group	Placebo group	
Total subjects affected by non-serious adverse events subjects affected / exposed	19 / 20 (95.00%)	7 / 20 (35.00%)	
Musculoskeletal and connective tissue disorders			
Myalgia	Additional description: Myalgia, flu like symptoms		
subjects affected / exposed	19 / 20 (95.00%)	7 / 20 (35.00%)	
occurrences (all)	19	7	

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

Online references

http://www.ncbi.nlm.nih.gov/pubmed/24588905