Clinical trial results:
Treatment with Zoledronate Subsequent to Denosumab in Osteoporosis: a Randomized Trial

Summary

EudraCT number	2015-005529-37
Trial protocol	DK
Global end of trial date	01 November 2020

Results information

Result version number	v1 (current)
This version publication date	10 December 2020
First version publication date	10 December 2020

Trial information

Trial identification

Sponsor protocol code	07.12.2015

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03087851
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Dept. of Endocrinology and Internal Medicine, Aarhus University Hospital
Sponsor organisation address	Pall Juul-Jensens Boulevard 99, Aarhus , Denmark, 8200
Public contact	Bente Lomholt Langdahl, Dept. of Endocrinology and Internal Medicine, Aarhus University Hospital, benlan@rm.dk
Scientific contact	Bente Lomholt Langdahl, Dept. of Endocrinology and Internal Medicine, Aarhus University Hospital, benlan@rm.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 November 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 November 2020
Global end of trial reached?	Yes
Global end of trial date	01 November 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate if infusion of zoledronic acid can prevent increases in bone turnover and bone loss in patients previously treated with denosumab and if there is difference between infusing zoledronic acid at six or nine months after the last injection with denosumab or when bone turnover is increased.

Protection of trial subjects:

At baseline, which was 6 months 10 days after the last denosumab (DMAB) injection, we acquired information about medical history, age at menopause, medication, calcium intake, smoking, and alcohol consumption. Treatment consisted of an intravenous infusion of 5 mg zoledronate (ZOL). We secured a daily intake of 1000 mg calcium and 38 µg vitamin D by supplementation.
mx refers to month x after baseline and Mx refers to months x after the ZOL infusion.
We treated the 6-month group with ZOL at baseline, which was 6 months after the last DMAB injection and the 9-month group at month three, which was 9 months after the last DMAB injection (treatment window 14 days). As a precaution, however, if p-CTX increased above 1.26 µg/L at month 1 (m1) or month 2 (m2) in the 9-month group, we administered ZOL at that time point. Also, if a patient experienced a VFx or HFx, infusion of ZOL was administered at that time point. In the OBS group we administered ZOL if p-CTX increased above 1.26 µg/L (monitored monthly), if BMD decreased more than 5% at the TH or LS at m3, or if a patient experienced a VFx or HFx. We administered ZOL no later than m6. The time point when participants randomized to the OBS group were treated with ZOL was denoted month x (Mx), thus Mx + 1 was 1 month after the initial ZOL treatment.
We re-treated with ZOL if p-CTX increased above 1.26 µg/L, BMD decreased more than 5% or if a patient experienced a VFx or HFx.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 February 2016
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: 61
Worldwide total number of subjects	61
EEA total number of subjects	61

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	27
From 65 to 84 years	34
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The Department of Endocrinology, Aarhus University Hospital, Denmark. Advertisements in newspapers and online. Data extractions from The Danish Health Data Authority.

Pre-assignment

Screening details:

DXA. Blood samples. Inclusion and exclusion criteria.

Period 1

Period 1 title	Overall period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

2-year randomized, open label, interventional study

Arms

Are arms mutually exclusive?	Yes
Arm title	6-month group

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Zoledronate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

5 mg/100 mL

Arm title	9-month group

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Zoledronate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

5 mg/100 mL

Arm title	Observation group

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Zoledronate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

5 mg/100 mL

Number of subjects in period 1	6-month group	9-month group	Observation group
Started	20	20	21
Completed	20	19	19
Not completed	0	1	2
Adverse event, non-fatal	-	1	2

Baseline characteristics

Reporting groups	
Reporting group title	6-month group
Reporting group description: -	
Reporting group title	9-month group
Reporting group description: -	
Reporting group title	Observation group
Reporting group description: -	

Reporting group values	6-month group	9-month group	Observation group
Number of subjects	20	20	21
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
arithmetic mean	68	65	69
standard deviation	± 8	± 7	± 9
Gender categorical Units: Subjects			
Female	18	17	19
Male	2	3	2

Reporting group values	Total		
Number of subjects	61		
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 Units: years arithmetic mean standard deviation	- 		
Gender categorical Units: Subjects			
Female Male	54 7		

Subject analysis sets

Subject analysis set title	Baseline characteristics
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Baseline characteristics: analysis of variance (ANOVA), chi-square test.
Changes in BMD, TBS, and BTM within groups: mixed model analysis of variance with repeated measures. Between-group differences: ANOVA.
The proportion of patients who failed to maintain BMD: chi-square test.
Associations: linear regression.

Subject analysis set title	BMD, TBS, BTM
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Baseline characteristics: analysis of variance (ANOVA), chi-square test.
Changes in BMD, TBS, and BTM within groups: mixed model analysis of variance with repeated measures. Between-group differences: ANOVA.
The proportion of patients who failed to maintain BMD: chi-square test.
Associations: linear regression.

Subject analysis set title	Associations
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Baseline characteristics: analysis of variance (ANOVA), chi-square test.
Changes in BMD, TBS, and BTM within groups: mixed model analysis of variance with repeated measures. Between-group differences: ANOVA.
The proportion of patients who failed to maintain BMD: chi-square test.
Associations: linear regression.

Reporting group values	Baseline characteristics	BMD, TBS, BTM	Associations
Number of subjects	61	61	61
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years arithmetic mean standard deviation	 68 ± 8	 65 ± 7	 69 ± 9

Gender categorical Units: Subjects			
Female	54	54	54
Male	7	7	7

End points

End points reporting groups

Reporting group title	6-month group
Reporting group description: -	
Reporting group title	9-month group
Reporting group description: -	
Reporting group title	Observation group
Reporting group description: -	
Subject analysis set title	Baseline characteristics
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Baseline characteristics: analysis of variance (ANOVA), chi-square test. Changes in BMD, TBS, and BTM within groups: mixed model analysis of variance with repeated measures. Between-group differences: ANOVA. The proportion of patients who failed to maintain BMD: chi-square test. Associations: linear regression.	
Subject analysis set title	BMD, TBS, BTM
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Baseline characteristics: analysis of variance (ANOVA), chi-square test. Changes in BMD, TBS, and BTM within groups: mixed model analysis of variance with repeated measures. Between-group differences: ANOVA. The proportion of patients who failed to maintain BMD: chi-square test. Associations: linear regression.	
Subject analysis set title	Associations
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Baseline characteristics: analysis of variance (ANOVA), chi-square test. Changes in BMD, TBS, and BTM within groups: mixed model analysis of variance with repeated measures. Between-group differences: ANOVA. The proportion of patients who failed to maintain BMD: chi-square test. Associations: linear regression.	

Primary: Primary endpoint

End point title	Primary endpoint
End point description:	
Our primary endpoints were change in LSBMD from baseline to six months after the initial ZOL and the proportion of patients who failed to maintain BMD, defined as ≥ 3% loss at the lumbar spine or ≥ 5% BMD loss at the femoral neck or total hip.	
End point type	Primary
End point timeframe:	
6 months and two years	

End point values	6-month group	9-month group	Observation group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	20	20	
Units: %				
arithmetic mean (standard error)	2 (± 1)	4 (± 1)	3 (± 1)	

Statistical analyses

Statistical analysis title	Primary endpoint

Statistical analysis description:

Baseline characteristics: analysis of variance (ANOVA), chi-square test.
Changes in BMD, TBS, and BTM within groups: mixed model analysis of variance with repeated measures. Between-group differences: ANOVA.
The proportion of patients who failed to maintain BMD: chi-square test.
Associations: linear regression.

Comparison groups	6-month group v 9-month group v Observation group
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0 [1]
Method	ANOVA

Notes:

[1] - Statistical hypothesis tested p <= 0.05

Adverse events

Adverse events information	
Timeframe for reporting adverse events: April 12 2017 - June 30 2020	
Assessment type	Systematic
Dictionary used	
Dictionary name	not specified
Dictionary version	x
Reporting groups	
Reporting group title	All participants

Reporting group description: -

Serious adverse events	All participants		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 61 (8.20%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Cancer			
subjects affected / exposed	5 / 61 (8.20%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	All participants		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	55 / 61 (90.16%)		
Musculoskeletal and connective tissue disorders			
Fracture			
subjects affected / exposed	6 / 61 (9.84%)		
occurrences (all)	6		
Arthralgia, osteoarthritis, back pain and unspecified			
subjects affected / exposed	25 / 61 (40.98%)		
occurrences (all)	25		
Product issues			

Flu-like symptoms after ZOL subjects affected / exposed occurrences (all)	37 / 61 (60.66%) 37		
Infections and infestations Infection (unspecified) subjects affected / exposed occurrences (all)	15 / 61 (24.59%) 15		

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/32459005