

**Clinical trial results:**

Uncemented total hip implant and subcutaneous injection of Denosumab for patients with osteoarthritis of the hip. A randomised double blind placebo controlled study on the effects on bone evaluated with DXA, PET/CT, and biochemical markers.

Summary

EudraCT number	2011-001481-18
Trial protocol	SE
Global end of trial date	30 March 2017

Results information

Result version number	v1 (current)
This version publication date	12 March 2020
First version publication date	12 March 2020
Summary attachment (see zip file)	Synopsis (Synopsis_Clinical Trial ReportI_EudraCT2011-001481-18_180427.pdf)

Trial information**Trial identification**

Sponsor protocol code	6925
-----------------------	------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01630941
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Uppsala University Hospital
Sponsor organisation address	Sjukhusvägen, Uppsala, Sweden, 751 85
Public contact	Hans Mallmin, Uppsala University, 46 186114478, hans.mallmin@akademiska.se
Scientific contact	Hans Mallmin, Uppsala University, 46 186114478, hans.mallmin@akademiska.se

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	03 May 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 March 2017
Global end of trial reached?	Yes
Global end of trial date	30 March 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to study the effect of Denosumab on Bone Mineral Density, Standardised Uptake Value and bone metabolism in patients with total hip arthroplasty. The primary hypothesis is to demonstrate that Denosumab is superior to placebo.

Protection of trial subjects:

The patients were informed that there will be 3 PET and 5 DXA assessments which are not clinical praxis. These assessments were not to result in higher radiation load than normally. However, it has been shown that the radiation level will not give any increased discomfort under normal circumstances. Adverse Events were continuously followed from Baseline until last follow-up visit after 24 months.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 November 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	24 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 64
Worldwide total number of subjects	64
EEA total number of subjects	64

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)	64

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited at the Dept of Orthopedics, Uppsala University Hospital during the time period Aug 2012 - Oct 2015.

Pre-assignment

Screening details:

461 patients were pre-screened, of these 64 patients were randomised and 63 patients completed treatment in the study.

Period 1

Period 1 title	Baseline period (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:

An authorized research nurse administered 1 ml prefilled syringe of Denosumab or placebo (0.9 % sterile Saline) according to the randomization list without the presence of the investigators or other personnel involved in the study. An additional nurse, not involved in the study team, recorded the procedure in the compliance log.

Arms

Are arms mutually exclusive?	Yes
Arm title	Denosumab

Arm description:

1 ml prefilled syringe of Denosumab, Prolia®, 60 mg/ml

Arm type	Experimental
Investigational medicinal product name	Denosumab, Prolia®, 60 mg/ml
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion in pre-filled syringe
Routes of administration	Intravenous use

Dosage and administration details:

1 ml, 60 mg/ml

Arm title	Placebo
------------------	---------

Arm description:

0,9% sterile Saline

Arm type	Placebo
Investigational medicinal product name	0,9% saline solution
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion in pre-filled syringe
Routes of administration	Intravenous use

Dosage and administration details:

1 ml, 0,9%

Number of subjects in period 1	Denosumab	Placebo
Started	32	32
Completed	32	32

Baseline characteristics

Reporting groups

Reporting group title	Denosumab
Reporting group description:	1 ml prefilled syringe of Denosumab, Prolia®, 60 mg/ml
Reporting group title	Placebo
Reporting group description:	0,9% sterile Saline

Reporting group values	Denosumab	Placebo	Total
Number of subjects	32	32	64
Age categorical			
Units: Subjects			
Age continuous			
Age 35-65 years			
Units: years			
arithmetic mean	58.4	58.8	
full range (min-max)	47 to 65	48 to 65	-
Gender categorical			
Female/Male			
Units: Subjects			
Female	20	19	39
Male	12	13	25

Subject analysis sets

Subject analysis set title	Started
Subject analysis set type	Intention-to-treat
Subject analysis set description:	All patients receiving at least one dose of study medication.

Reporting group values	Started		
Number of subjects	64		
Age categorical			
Units: Subjects			
Age continuous			
Age 35-65 years			
Units: years			
arithmetic mean	58.6		
full range (min-max)	47 to 65		
Gender categorical			
Female/Male			
Units: Subjects			
Female	39		
Male	25		

End points

End points reporting groups

Reporting group title	Denosumab
Reporting group description:	1 ml prefilled syringe of Denosumab, Prolia®, 60 mg/ml
Reporting group title	Placebo
Reporting group description:	0,9% sterile Saline
Subject analysis set title	Started
Subject analysis set type	Intention-to-treat
Subject analysis set description:	All patients receiving at least one dose of study medication.

Primary: BMD (Bone Mineral Density) in Gruen zone 7

End point title	BMD (Bone Mineral Density) in Gruen zone 7
End point description:	
End point type	Primary
End point timeframe:	After 12 months

End point values	Denosumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	31		
Units: g/cm ²				
arithmetic mean (inter-quartile range (Q1-Q3))				
BMD in Gruen zone 7	1.54 (1.46 to 1.63)	1.16 (1.10 to 1.23)		

Statistical analyses

Statistical analysis title	Descriptive statistics
Statistical analysis description:	Baseline characteristics and outcome variables were summarized by descriptive statistics.
Comparison groups	Denosumab v Placebo
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	≤ 0.05 ^[2]
Method	ANCOVA
Parameter estimate	geometric mean ratio
Point estimate	1.32

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.22
upper limit	1.44

Notes:

[1] - Analysis of covariance (ANCOVA) with treatment group and baseline value were used to test the null-hypoth of no difference between Denosumab and placebo with respect to each continuous outcome variable. To control the overall type I error, the primary variables were tested in a hierarchical fashion starting with 'BMD Gruen zone 7.

[2] - If p-value was less than 0.05, test for sum of all Gruen zones was done at 0.05 level.

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

From Baseline visit until last follow up visit after 24 months.

Adverse event reporting additional description:

An AE can be any unfavorable, unintended clinical sign, symptom, medical complaint or clinically relevant change in laboratory variables or clinical tests. The Investigator will assess the maximum intensity of the AE and judge the possible relationship between the AE and the investigational product as well as any concomitant medications.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	Not coded
-----------------	-----------

Dictionary version	0
--------------------	---

Reporting groups

Reporting group title	Denosumab
-----------------------	-----------

Reporting group description:

Active treatment

Reporting group title	Placebo
-----------------------	---------

Reporting group description:

Comparison

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: Only one patient exposed, but not possible to fill in 0 in the other treatment group.

Serious adverse events	Denosumab	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 32 (9.38%)	4 / 24 (16.67%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cyst	Additional description: Patient no 1227. Placebo patient (female). Arachnoid cyst 3 weeks after second dose of study med.Resolved after 8 months.		
subjects affected / exposed ^[2]	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Implant loosening	Additional description: Placebo pt no 1118. Implant loosening at one month after second dose, resolved after one day. Second implant loosening 2.5 months after second dose, resolved after 3.5 months. Denosumab pt no 1119. Implant loosening six months after second dose.		
subjects affected / exposed ^[3]	1 / 1 (100.00%)	1 / 1 (100.00%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			

Gynecological bleeding	Additional description: Placebo patient no 1111. 5 months after second dose of study medication. Resolved after 17 days.		
subjects affected / exposed ^[4]	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders	Additional description: Placebo patient 1111 (female). Six and a half months after second dose of study medication. Resolved after two days.		
Perimyocardit			
subjects affected / exposed ^[5]	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders	Additional description: Patient 1134 (female). Denosumab patient experiencing elevated pressure anterior chamber right eye three weeks after second dose of study med. Resolved after 3,5 months.		
Eye disorder			
subjects affected / exposed ^[6]	1 / 1 (100.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders	Additional description: Placebo patient no 1111. Six months after second dose of study medication. Resolved after 13 days.		
Myoma			
subjects affected / exposed ^[7]	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders	Additional description: Patient no 1124 (female). Placebo patient, osteoarthritis 7 months after the second dose of study med. Resolved after 4 months.		
Osteoarthritis			
subjects affected / exposed ^[8]	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis reactive	Additional description: Patient no 1205. Denomsumab patient. Worsening of her hip arthritis right side (ie unaffected hip) three months after first dose of study med.		
subjects affected / exposed ^[9]	1 / 1 (100.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Notes:

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Only one patient exposed, but not possible to fill in 0 in the other treatment group.

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: One patient experienced the same event twice causing prolonged hospitalisation.

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: Only one patient exposed, but not possible to fill in 0 in the other treatment group.

[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: Only one patient exposed, but not possible to fill in 0 in the other treatment group.

[6] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: Only one patient exposed, but not possible to fill in 0 in the other treatment group.

[7] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: Only one patient exposed, but not possible to fill in 0 in the other treatment group.

[8] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: Only one patient exposed, but not possible to fill in 0 in the other treatment group.

[9] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: Only one patient exposed, but not possible to fill in 0 in the other treatment group.

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

Non-serious adverse events	Denosumab	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 32 (0.00%)	0 / 24 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 February 2012	The study is available after 24 months. Schedule of event updated and clarified. PIC is completed at visit 1 instead of visit 0. Clarification of BMI. Exclusion crit 9: persons suffering from claustrophobia are not suitable for PET scanning. Section 11 Assessment of efficacy: Additional text "Investigators decision".

Notes:

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/31589776>