



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 | | | |
| | Perimyocardit | Additional description: Placebo patient 1111 (female). Six and a half months after second dose of study medication. Resolved after two days. | |
| | subjects affected / exposed ^[5] | 0 / 1 (0.00%) | 1 / 1 (100.00%) |
| | occurrences causally related to treatment / all | 0 / 0 | 0 / 1 |
| Eye disorders | | | |
| | Eye disorder | 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. | |
| | subjects affected / exposed ^[6] | 1 / 1 (100.00%) | 0 / 1 (0.00%) |
| | occurrences causally related to treatment / all | 0 / 1 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| | Myoma | Additional description: Placebo patient no 1111. Six months after second dose of study medication. Resolved after 13 days. | |
| | subjects affected / exposed ^[7] | 0 / 1 (0.00%) | 1 / 1 (100.00%) |
| | occurrences causally related to treatment / all | 0 / 0 | 0 / 1 |
| Musculoskeletal and connective tissue disorders | | | |
| | Osteoarthritis | Additional description: Patient no 1124 (female). Placebo patient, osteoarthritis 7 months after the second dose of study med. Resolved after 4 months. | |
| | subjects affected / exposed ^[8] | 0 / 1 (0.00%) | 1 / 1 (100.00%) |
| | occurrences causally related to treatment / all | 0 / 0 | 0 / 1 |
| Arthritis reactive | | | |
| | 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>