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CLINICAL STUDY REPORT

"Uncemented total hip implant and subcutaneous injections 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"
Development Phase 2

EudraCT number	2011-001481-18
Sponsor Project No:	6925
Registration in public database:	ClinicalTrials.gov NCT01630941
Investigational Product:	Denosumab, Prolia®
Indication:	Unilateral osteoarthritis of the hip
Sponsor:	Hans Mallmin, MD, PhD
Principal Investigator:	Hans Mallmin, MD, PhD
Study initiation date (first patient visit)	
Date for completion (last patient visit)	
Date of this report	27 APRIL 2018

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1 SIGNATURE PAGE

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2 SYNOPSIS

Name of Sponsor: Uppsala University Hospital/Hans Mallmin **Name of investigational product:** Prolia® **Name of active ingredient:** Denosumab		(For regulatory authority use only)
Title of study: Uncemented total hip implant and subcutaneous injections 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.		
Clinical Study Number: 6925		
EudraCT number: 2011-001481-18		
Indication: Unilateral osteoarthritis of the hip (OAH)		
Principal Investigator: Professor Hans Mallmin, MD PhD		
Study Centre(s): Dept of Orthopedics, Uppsala University Hospital		
Study period (FPI –LPO): Aug 2012 – Jan 2017		
Phase of development: II		
Duration: The patients were observed for approximately two years after surgery.		
Primary objective: Effects of Denosumab on bone mineral density (BMD) and bone apposition adjacent to uncemented hip implants		
Secondary objective: The secondary objectives are to: Evaluate the safety and tolerability of Denosumab in patients with total hip arthroplasty Evaluate quality of life after treatment with Denosumab in patients with total hip arthroplasty		
Number of subjects 64 patients (from originally planned 64 patients) were enrolled.		
Inclusion Criteria The patients had to fulfill the following criteria to be included: 1. Male or female patient 35-65 years of age with an unilateral OAH requiring a THA and a healthy contralateral hip 2. Body weight ≤110 kg or body mass index (BMI) ≤35 kg/m^2 3. Living in the Uppsala County 4. The eligible patients should have been given oral information, a written Patient Information and signed an Informed Consent		

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Exclusion criteria

The presence of any of the following criteria will exclude the patient from participating in the study:

1. On or previously have had bone-specific treatment, e.g. bisphophonates, raloxiphene, parathyroid hormone, strontium ranelate, during the last five years
2. Patients on systemical corticosteroid for more than 3 months should not be considered
3. Patients with diagnosed malignant disease during the last five years or known to have metastasis from malignant disease should be excluded
4. Patients with compromised general conditions and an American Society of Anesthesiologists, ASA-score >31 should not be regarded eligible
5. Patients with known drug or alcohol abuse or regarded as socially dysfunctional, as judged by the investigator, should not be considered for the study
6. Pregnant women or women planning for pregnancy or fertile women (premenopausal) without contraceptives should not be accepted for the study
7. Patients that have been exposed frequently and/or have had large irradiation doses, as judged by the investigator, must not be included in the study.
8. Enrolled in either another investigational drug study, in another investigational device study, or in another investigational study of an approved drug within 30 days prior to Visit 1 of the current study
9. Any condition or laboratory findings which in the opinion of the Investigator makes the patient unsuitable for inclusion (for example claustrophobia)

Investigational product, dosage and mode of administration:
Denosumab, 60 mg/ml in a prefilled 1 ml syringe

Control, dosage and mode of administration:
Placebo control. 1 mL sterile saline injection

Formulation:
Denosumab (Prolia®) 60 mg/ml or Placebo (Physiological saline)

Duration of treatment:
At study start and after 6 months.

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Criteria for evaluation

Primary endpoint

To evaluate the study drug's effect on BMD, g/cm2, adjacent to the femur implant, Gruen zone 7, and the sum for all Gruen zones 12 months after surgery.

Secondary endpoints

1. To evaluate the study drug's effects on:
    - BMD, g/cm2, adjacent to the femur implant, 3, 6, and 24 months after surgery.
    - fluoride isotope uptake, measured as (SUV), adjacent to the femoral stem, 3 and 6 months after surgery.
    - SUV measured with PET scanning adjacent to the acetabular cup 3 and 6 months after surgery
    - SUV at the lumbar spine and at the contra lateral hip after surgical treatment with an uncemented THA after 3 and 6 months
    - BMD adjacent to the acetabular cup during the follow up period, i.e. after 3, 6, 12 and 24 months
    - BMD at the lumbar spine and at the contralateral hip after surgical treatment with an uncemented THA 6, 12 and 24 months after surgery
    - biochemical markers for bone turnover and the relation to PET and BMD findings at the proximal femur and acetabulum during the follow up period, i.e. 3, 6, 12 and 24 months after surgery
    - biochemical markers for bone turnover and the relation to PET and BMD findings at anatomical sites not exposed to surgery, i.e. the lumbar spine and the contra lateral hip 3 and 6 months after surgery
2. To evaluate the natural course of :
    - an uncemented THA on BMD, i.e. the placebo group 3, 6, 12 and 24 months after surgery
    - an uncemented THA on SUV measured with PET, i.e. the placebo group 3 and 6 months after surgery
    - an uncemented THA on biochemical markers, i.e. the placebo group 3, 6, 12 and 24 months after surgery
3. To evaluate the patients Quality of Life, measured by Harris Hip score and EQ-5D questionnaire
4. To evaluate incidence and severity of adverse events (AEs) during the study period

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Statistical methods:
Baseline characteristics and continuous outcome variables were summarized using descriptive statistics. Analysis of covariance (ANCOVA) with treatment group and baseline value for the corresponding variable as independent variables were used to test the null-hypothesis of no difference between Denosumab and placebo with respect to each continuous outcome variable. In order to control the overall type I error, the primary variables were tested in a hierarchical fashion starting with 'BMD Gruen zone 7'. If the p-value for 'Gruen zone 7' was less than 0.05, the test for the 'sum for all Gruen zones' was performed at the 0.05 level.

Efficacy conclusion

Denosumab administered at Baseline and 6 months has been shown to be effective to prevent loss of periprosthetic bone mineral density (BMD) up to 12 months as compared to Placebo (geometric mean ratio Gruen zone 7: 1.32, Sum of Gruen zones 1-7: 1.11, $p<0.001$ for both outcomes) and to decrease bone metabolism (geometric mean ratio P1NP: 0.54, $p<0.001$) in patients suffering from osteoarthritis of the hip operated with an uncemented Total Hip Arthroplasty (THA). However, after withdrawal of study drug the positive treatment effect on periprosthetic BMD was attenuated and the treatment effect on bone metabolism seemed to be negative after 24 months.

To obtain a consistent positive effect on periprosthetic BMD it is hypothesized that Denosumab may have to be administered for an extended time period.

Safety conclusion

Overall, 43 adverse events were reported, however only 7, distributed as 2 events in the Denosumab group and 5 in the Placebo group, were classified as possibly related to the study medication. The events possibly related to Denosumab were stress depression and acute abdominal pain, both events were recovered. In the placebo group the events possibly related were posterior vitreous detachment, depression, rectal cancer and vertigo. All events but the rectal cancer were recovered.

There were ten (10) adverse events classified as SAEs, due to hospitalization, all of which were deemed as unrelated to the study treatment.

The results indicate that two subcutaneous injections of Denosumab during the first six months after an uncemented total hip arthroplasty are not associated with any considerable risks for the patient´s health.

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OVERALL CONCLUSION

Two subcutaneous injections of Denosumab have a short-term positive effect on periprosthetic bone mineral density for patients suffering from osteoarthritis of the hip operated with an uncemented total hip arthroplasty.

The safety results indicate that Denosumab can be used without any increased risk of safety issues.