Final Study Report

Study Title:

RANKL-blockade for the treatment of erosive osteoarthritis (OA) of interphalangeal finger joints

Randomized, double blind, placebo-controlled study to evaluate the efficacy of denosumab 60mg sc every 3 months in patients with erosive osteoarthritis of the interphalangeal finger joints

EudraCT number: 2015-003223-53

Eudamed number: NA

Study protocol code: AGO/2015/008

ClinicalTrial.gov identifier: NCT02771860

Sponsor: UZ Ghent

Funder: Amgen is the party that provides funding and study medication.

Date of report: 11 April 2022

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1. Background and Rationale

1.1 Disease background

Erosive osteoarthritis (OA) of the interphalangeal (IP) finger joints is considered an inflammatory subset of osteoarthritis of the hand. Its inflammatory clinical presentation and destructive nature are unmistakable. [1,2,3,4,5] The cumulation of destructive changes in the IP joints eventually results in considerable disability.[6,7,8] There are no significant differences in hand function, stiffness and level of pain between patients with hand OA and rheumatoid arthritis. Scores for both patient groups differ significantly from those of healthy controls.[9]
Patients with erosive OA show more functional impairment and significantly more pain compared to patients with controlled inflammatory arthritis affecting the hands. The acquired structural damage of the IP joints due to destructive/reparative phenomena is the largest contributor to functional limitations.[8]
Radiological prevalence of moderate to severe hand OA is estimated to occur in 7.3% (2.65 million) US adults aged 60+ years.[10] Similar data have been reported in European countries.[7,11,12,13,14]

A significant proportion of these patients suffer from the erosive type of hand OA. In a prospective study of 500 consecutive patients attending a rheumatology clinic with symptomatic limb joint OA, 4.8% cases were identified with erosive IP joint OA.[15]

In a survey on the entire health district in the Venetian area, 2.2% out of 640 subjects aged 40+ years had erosive OA of their IP joints.[16] Mainly women in the perimenopauzal age were affected.[17]

Even higher prevalences were seen in a British cohort study[18] on 2.986 people[18]. Numbers in this study were based on clinics and the authors proposed that a proportion of their polyarticular cases were "inflammatory types of OA in association with erosions". This assumption was based on an earlier study where clinical examination was validated against hand radiography (Egger et al., J Rheumatol 1995;22:1509–13).
Though the proportions of "erosive IP OA" reported here were probably overrated, the prevalence of what is considered to be "erosive IP OA" in this 53 years of age population was twice as high in women (10,6%), compared to men (5,9%).
More recently, these data were confirmed in 2 large population studies where the prevalence of radiographic erosive IP OA in subjects over 55 years of age ranged between 5.0 and 9.9%.[19,20]. The prevalence for men was lower at 3.3%.

These studies showed that erosive type of hand OA occurred predominantly in women.
Haugen IK et al. et al.[20] defined erosive IP OA at a joint level as Kellgren/Lawrence ≥2 plus erosions. The authors reported a prevalence of erosive IP OA in women of 9,9%, 3 times as high as in men (3,3%). In essence, the Kwok W-Y et al. figures[19] agree with the data above.

Moreover, the Haugen IK et al.[20] reported that symptomatic OA was twice as high in women (15,9%), compared to men (8,2%). Symptomatic OA here was defined as Kellgren/Lawrence stage ≥2 plus pain/aching/stiffness.

From these epidemiological studies we can conclude that the incidence of erosive OA of the IP finger joints ranges from five to ten percent particularly in women.

The aggressive destructive nature of the erosive OA is only recognized late in the disease and the radiological image of the "exhausted" final phase mimics a robust OA. Therefore, the disease was hitherto regarded as a form of primary OA - a degenerative joint disease that is caused by biomechanical overload of the joint structures. There is so far no therapy sought or found for the structural changes in the articular tissues occurring during the course of so-called degenerative joint diseases. Thus, no therapeutic measures are available that act on underlying disease mechanisms and therefore slow down or halt the progression of tissue degradation in joints affected by erosive hand OA. The current standard treatment of care in these patients is limited to symptomatic therapy to reduce pain.

There is still lack of agreement concerning the nature and specificity of erosive IP joint OA. Obviously, in erosive IP OA an important bone resorption is noted in the subchondral bone of IP finger joints, this bone resorption is readily visualized on conventional radiographs (Figure 1). The osteolytic 'erosive' lesions result in the collaps of the subchondral plate which supports the overlaying articular cartilage.[5,21] This is compatible with a pathologic osteoclast activity supported by the effects of RANKL (Receptor Activator of Nuclear Factor kappa-β Ligand).[22] RANKL is a key driver of maturation and activation of osteoclasts in bone in health and disease.[22] In pathologic conditions, RANKL can be strongly induced in a variety of cell types including stromal cells under the influence of locally produced proinflammatory cytokines such TNFα [23,24] and IL-1β.[25,26]
At the same time, a resorption of articular cartilage of the affected IP joints is also noted. As a result, the joint space gradually disappears on X-rays. Likely key factors in this process are TNF and IL-1 which both have important catabolic effects on human chondrocytes.[27] Indeed, during the course of the disease inflammatory processes in the synovial membrane of IP finger joints could be visualized.[28,29] Cytokines release thereof will have important catabolic effects on the neighbouring chondrocytes.

Thus, similar as observed in other destructive processes noted in inflammatory rheumatic diseases, the **TNF→ IL-1→ RANKL-pathway** appears to be a key therapeutic target in erosive hand OA.

Blockade of these cytokines has shown to delay ongoing tissue destruction in murine arthritis and in rheumatoid arthritis in human. [30,31,32,33,34]

Recently, TNFα-blockade was shown to retard the progression of joint damage in erosive IP finger joint OA.[35]

Considering the analogies between rheumatoid arthritis and erosive IP OA in the metabolic pathways that mediate tissue destruction, and the lack of any structure modifying treatment option in the latter, a pilot study exploring the effects of Denosumab on ongoing tissue destruction in IP finger joint OA is proposed.

1.2 Denosumab

Denosumab (Amgen), is a fully human monoclonal antibody designed to inhibit RANKL (RANK Ligand). RANKL binds to RANK, which exists as a cell surface receptor molecule on "pre"-osteoclasts: precursors of osteoclasts.

Binding of RANKL to RANK acts as the primary signal for bone removal in normal physiological bone remodeling and in a number of pathological conditions, e.g. malignant

tumors and bone metastasis.

Activation of RANK by RANKL promotes the maturation of pre-osteoclasts into osteoclasts. Denosumab inhibits osteoclasts' maturation, function and survival by binding to and inhibiting RANKL. This mimics the natural action of osteoprotegerin, an endogenous RANKL inhibitor that presents with decreasing concentrations in patients who are suffering from osteoporosis. This protects bone from degradation, and helps to counter the progression of the disease.

Denosumab was approved by the EMA for use in postmenopausal women with osteoporosis at increased risk for fracture at the dose of 60 mg sc every 6 months (Prolia®), and for the prevention of skeletal-related events in patients with bone metastasis from solid tumors at the dose of 120 mg every 4 weeks (XGEVA®).
More recently, denosumab was shown to retard the progression of structural lesions in rheumatoid arthritis, an unapproved indication for the drug.[33,34] Its dosing and safety profile depended on the different medical conditions in which the drug was used. Patients with osteoporosis and rheumatoid arthritis received 60 mg and up to 180 mg injected SC, every 6 months, respectively.

Experience from clinical studies indicates that side effects depend on the dosage.

According to Prolia® Summary of Product Characteristics (SmPC) [36], pain in extremities and musculoskeletal pain (including back pain and joint pain) were among the most common adverse reactions.
In patients treated for osteoporosis a rare unwanted effect included low calcium levels, especially when in case of an impaired kidney function. Patients must therefore be adequately supplemented with calcium and vitamin D levels before starting and during denosumab therapy. In the postmarketing setting, rare cases of severe symptomatic hypocalcaemia have been reported. Clinical monitoring of calcium level is recommended before each dose and, in patients predisposed to hypocalcaemia, within two weeks after the initial dose.
There have been rare cases of atypical femoral fracture reported in association with Prolia.
Infections of the urinary and respiratory tracts were reported as well as cellulitis, ear infection and diverticulitis. The SmPC includes a Warning Statement regarding skin infections (predominantly cellulitis) leading to hospitalization. It has been proposed that this increase in infections under denosumab treatment might be connected to the role of RANKL in the immune system.
Cataracts, constipation, skin rashes and eczema were also seen.
Osteonecrosis of the jaw (ONJ) was reported rarely in Prolia osteoporosis clinical development program. Primarily, at the high dosages used in patients with bone metastases, similarly to bisphosphonates, denosumab appeared to be implicated in increasing the risk of osteonecrosis of the jaw (ONJ) especially following extraction of teeth or oral surgical procedures.

In the post-marketing setting, rare events of drug-related hypersensitivity, including rash, urticaria, facial swelling, erythema, and anaphylactic reactions have been reported.

In the FREEDOM extension study[37,38], with up to 8 years of denosumab 60 mg Q6M exposure, the incidence rates of adverse events did not increase over time.

Denosumab safety data were reported in RA phase 2 studies[33,34]. The safety profile appears to be consistent with that in patients with postmenopausal osteoporosis. Denosumab did not have an effect on RA disease activity, as measured by the ACR response criteria, the DAS28 scores, and the occurrence of RA flares.

1.3 Rationale for study design

In RA, the initial changes are seen in the synovium where inflammatory lymphomyeloid cells massively produce TNF, and secondarily, IL-1 and RANKL. These two cytokines are responsible for the invasion of the adjacent cartilage and bone by the inflamed and proliferative synovial pannus.

In erosive IP joint OA, the osteolytic changes in subchondral bone occur before or concurrently with resorption of cartilage. The primary drivers of the cartilage damage thus are these osteolytic processes in the subchondral bone area and the collapse of the subchondral bone plate. RANKL is the cytokine primarily responsible for this osteolytic (osteoclast) activity.

The enhanced osteoclast activity and tissue remodeling initially seen in arthritic IP joint bone is clearly illustrated in figure 1.

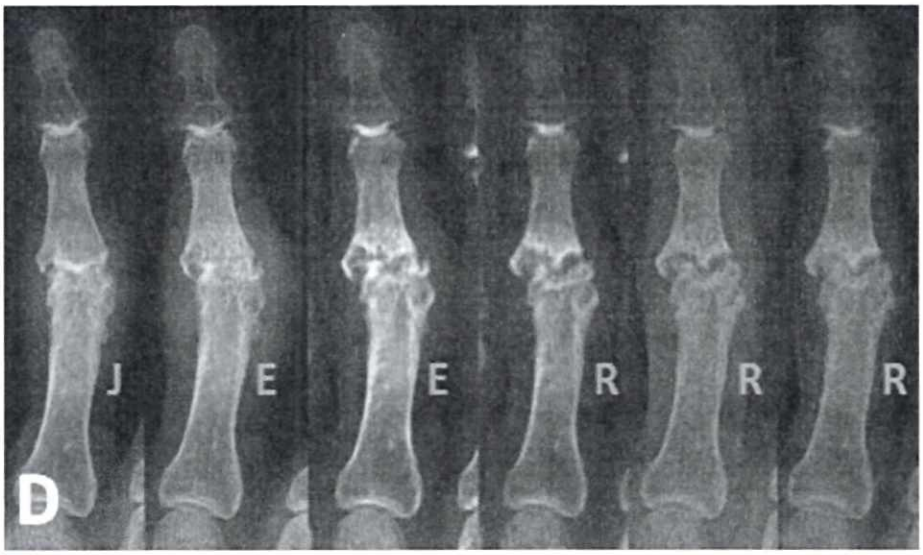


Figure 1: radiographic progression of a proximal IP joint from 'J' phase with loss of joint space to the 'E' phase with osteolytic activity in the subchondral bone area, and final remodeling of the destroyed tissues (R). Radiographs were taken with 6-months interval.

The effect of TNF alpha inhibitors on disease progression, previously seen in erosive IP joint OA[24], was an indirect effect on osteoclast activation. Obviously, this effect would be larger by directly inhibiting osteoclasts with Denosumab. Once the erosive process is blocked with Denosumab, subchondral bone remodeling will be inhibited and one should see preservation of joint structure.

A proof-of-concept study is proposed herein to test the ability of repeated administration of denosumab to control the structural damage– and thus to maintain hand function - in erosive hand OA. These tests will be conducted compared to placebo during a first placebo controlled double-blind phase but also in a second open-label phase in which all subjects will receive denosumab. The 2 main factors that support conducting this second open-label phase are the following:

- This would enable the Long-term outcome assessment with the cumulative exposure over time; more substantial effect would be expected.
- The open label with help supporting patients' engagement in a placebo trial where no disease modifying drugs exist.

The adequate dose of denosumab should completely inhibit the erosive process in order to fully test the hypothesis. In the phase 2 RA studies [33,34], the higher dose or shorter interval dosing regimen showed an earlier or a trend to more inhibition of bone destruction respectively. Considering further the well-established safety profile for denosumab at high doses, a higher frequency for denosumab 60 mg is proposed: denosumab 60 mg sc every 3 months.

During previous studies an increased impact on the structural progression of the IP joints was shown over time in a subgroups of this population. Beside the one year placebo controlled phase followed by an open label phase, the extension phase will allow us to explore the benefit for the patient of one extra year of treatment. To compare the clinical benefits between study groups the treatment frequency cannot be interrupted. Approximately 50 patients, whom received the last injection of denosumab not more than 3 months prior to the inclusion in the extension phase can be included.

1.4 Hypotheses

The main hypothesis is that the repeated administration of denosumab 60 mg every 3 months in erosive hand OA can inhibit structural progression of already affected joints and prevent occurrence of newly affected joints.
As it has been shown that denosumab, reduces structural damage in RA while having no effect on clinical symptoms [34], no clinical benefit is expected within the one-year period of this study. So, the effects of denosumab on the clinical manifestations of the disease will only be part of an exploratory study.

2. Study Objectives and Endpoints

The objective of this proof of concept study is to investigate the efficacy of denosumab 60 mg sc every 12 weeks for 48 weeks as a therapeutic intervention in erosive IP joint OA. In general, the expected outcome of this study would be the control of the structural damage.

Changes in the architecture of the joint will be assessed by the GUSS™. This score system allows an overall score to be calculated for an affected IP joint over time. The overall score is the sum of scores obtained for 3 compartments of the IP finger joint: the synovial space (articular cartilage), the subchondral bone plates and the subchondral bone area at each side of the synovial space. Overall scores, as well as scores for each individual compartment can be taken into consideration. Examples of the calculated scores for 2 different IP joints are given in appendix 1.

The **primary objective** is to assess the effect of denosumab on the reduction of radiographic erosive progression using GUSS™ (Ghent University Score System).
The **primary endpoints of this objective** is the change in the negative evolution in GUSS™ scores in the target IP joints from baseline to week 24.
Other endpoints are the changes in the negative evolution of GUSS™ scores in the target IP joints from week 24 to week 48 and from baseline to week 48.
The **secondary objective** is to evaluate a reduction in radiographic erosive progression as defined by diminishing the appearance of new erosive IP finger joints.
This will be assessed by 2 endpoints:
1. the number of patients that develop new erosive IP joints ('S/J' to 'E' phases) at 48 weeks.
2. the number of 'S/J' IP joints that develop 'E' phases at 48 weeks.

Radiological score systems are given in appendix 1.

The **exploratory** objective is to assess if denosumab provides clinical benefits (improvement of pain and functional limitations) compared to placebo. We will also evaluate the impact on ultrasonography and DEXA.
The endpoints of this objective are:

a. Changes in clinical and patient recorded outcome measures from baseline (day 1) to week 48 after administration of denosumab compared to placebo. The following outcome measures will be recorded: AUSCAN (AUStralian CANadian Osteoarthritis Hand Index), FIHOA (Functional Index of Hand Osteoarthritis), Pain on VAS scale, consumption of analgesics (paracetamol)/NSAIDs to be recorded by each patient on a diary, tenderness upon pressure, diameter of selected target joints, and grip strength of both hands.
b. Changes in sonographic inflammatory signals at week 12 and 48 compared to baseline. Inflammatory changes will be assessed by measuring the amount of effusion and Power Doppler signal (scoring on a semi-quantitative scale).
c. Effect of denosumab on bone mass densitometry score in this group of patients compared to placebo from baseline to week 48. Changes from baseline (day 1) in T-score at lumbar spine and hip measured by bone densitometry at week 48 after administration of denosumab compared to placebo.

Other exploratory endpoints are to describe the above radiographic progression parameters at the end of the open-label phase.

Safety-objective

The safety profile of denosumab 60 mg (Prolia®) every 6 months in postmenopausal women with osteoporosis at increased risk of fracture is well established (Prolia SmPC). This study will assess the safety of the administration of denosumab 60 mg every 3 months in the population of patients with erosive OA. Safety evaluations will be made by recording the incidence of AE/SAE (see also paragraph 8).

During the extension phase the objective is to explore the benefit of 1 year extra treatment.
The endpoints of this objective are:

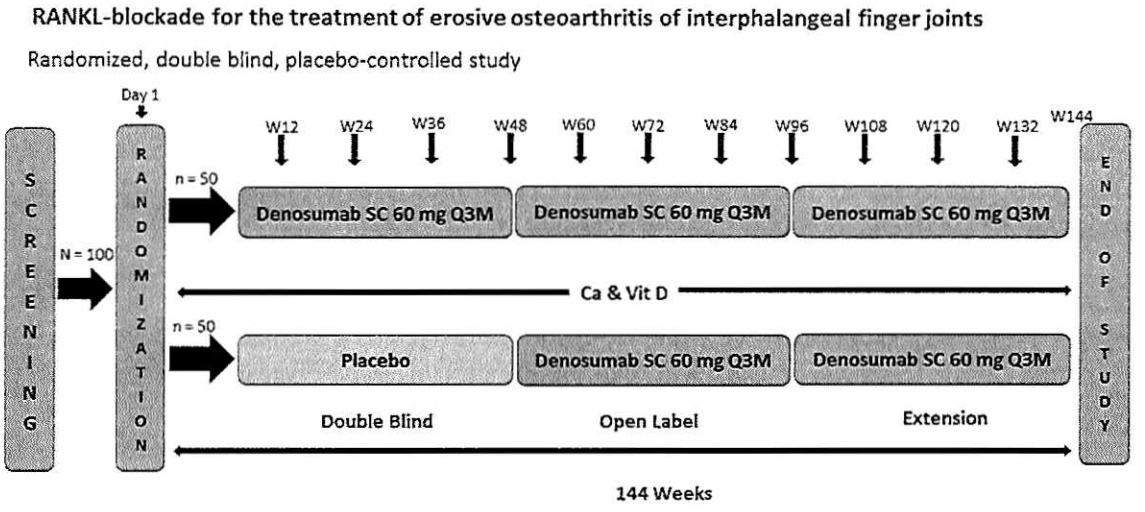
a. Changes in the negative evolution in GUSS™ scores in the target IP joints from week 96 to week 144 and BL to week 144.
b. The number of 'E' IP joints that develop 'R' phases at 144 weeks.
c. Effect of denosumab on bone mass densitometry score in this group of patients compared from week 96 to week 144 and BL to week 144.

3. Experimental Plan

3.1 Study design and schematic

This is a randomized, double blind, placebo-controlled, one-site proof of concept study to investigate the effect of denosumab 60 mg every 12 weeks on the radiological evolution of erosive OA of the digital joints.
Two groups of 50 patients each will be enrolled in the study with a total treatment duration of 24 months (96 weeks): 48 weeks double-blind placebo controlled phase (denosumab (60 mg sc every 12 weeks or placebo) followed by a 48-weeks open–label phase in which all subjects will receive denosumab 60 mg every 12 weeks in an "Open Label Design" type study.
This 2 year study will be followed by an optional extension phase of 48 weeks.

Study schematic



3.2 Number of sites

The study will be conducted in one site – the Ghent site in Belgium.

3.3 Number of subjects

A total of 100 subjects will be recruited in this study with an enrolment period of 18 months. Approximately 50 patients will qualify for the extension phase of the study.

3.4 Estimated study duration

The total treatment duration per subject is 24 months (96 weeks). The duration of the extension phase per subject is 12 months. The expected total trial duration defined as the time from first patient first visit to last patient last visit is 62 months.

4 Subject Eligibility

4.1 Inclusion criteria

A subject will be eligible for study participation if he/she meets the following criteria:

- Males and females ≥ 30 years of age.
- Subjects with hand OA having suffered from transient inflammatory attacks of the interphalangeal finger joints characteristic for what has been termed 'inflammatory' or 'erosive' hand OA.
- Subjects with hand OA showing inflammatory signs, either clinically or ultrasonographically, of the interphalangeal finger joints.
- Subjects with hand OA in which at least 1 interphalangeal finger joint has the typical appearance on the X-rays of a 'J' or 'E' phase joint as defined by the criteria mentioned above.
- Subjects with hand OA where at least 1 interphalangeal finger joint in the 'J' or 'E' phase presents a palpable swelling.

- Able and willing to give written informed consent and to comply with the requirements of the study protocol.

Inclusion criteria for the extension phase

- Subjects must have completed the 48 weeks of the randomised placebo-controlled study phase followed by the 48 weeks open label denosumab 60 mg SC every 3 months phase.
- Last injection of the investigational product denosumab was not more than 3 months prior to the inclusion in the extension phase.

4.2 Exclusion criteria

A subject will be excluded from the study if he/she meets any of the following criteria:

- Patients with known hypersensitivities to mammalian-derived drug preparations.
- Patients with clinically significant hypersensitivity to any of the components of Prolia.
- Current and/or Prior treatment with any investigational agent within 90 days, or five half-lives of the product, whichever is longer.
- Previous administration of denosumab from clinical trials or others (e.g. commercial use).
- Vitamin D deficiency [25(OH) vitamin D level < 20 ng/mL (< 49.9 nmol/L)]. Possibility of replenishment and re-screening.
- Subjects with current hypo- or hypercalcemia (normal serum calcium levels: 8.5-10.5 mg/dl or 2.12-2.62 mmol/L).
- Patients currently under bisphosphonate (BP) treatment or any use of oral BPs within 12 months of study enrollment or intravenous BPs or strontium ranelate within 5 years of study enrollment
- Prior use of any chondroprotective drug within 90 days e.g. chondroitin sulfate, glucosamine, avocado-soybean unsaponifiables, tetracyclins, corticosteroids (oral, intramuscular, intra-articular or intralesional).
- Prior use of any immunomodulating drug with possible effects on proinflammatory cytokine metabolism within 90 days a.o. corticosteroids (oral, intramuscular, intra-articular or intralesional), methotrexate, sulfasalazine, leflunomide, D-Penicillin, anti-malarials, cytotoxic drugs, TNF blocking agents.
- History of drug or alcohol abuse in the last year.
- Patients suffering from chronic inflammatory rheumatic disease (e.g. rheumatoid arthritis, spondylarthropathy, psoriatic arthritis, gout, chondrocalcinosis or other auto-immune diseases, e.g. systemic lupus erythematosus).
- History of cancer or lymphoproliferative disease within the past five years, other than a successfully and completely treated squamous cell or basal cell carcinoma of the skin or cervical dysplasia, with no recurrence within the last two years.
- History of any Solid Organ or Bone Marrow Transplant.
    - Comorbidities: significant renal function impairment (glomerular filtration < 30 ml/min/1.73m^2 or <50% of normal value), uncontrolled diabetes, unstable ischemic heart disease, congestive heart failure (NYHA III, IV), uncontrolled hypo or hyperparathyroidism, active inflammatory bowel disease, malabsorption, liver failure or chronic hepatic disease (serum AST/ALT levels 3 times above normal), recent stroke (within three months), chronic leg ulcer and any other condition (*e.g.*. indwelling urinary catheter) which, in the opinion of the investigator, would put the subject at risk by participation in the protocol.
- Subject has any kind of disorder that compromises the ability of the subject to give written informed consent and/or to comply with study procedures .

- Patient who is pregnant or planning pregnancy; if the female subject is of child-bearing age, she must use a valid mean of contraception during the study and for 9 months after last dose of study medication. For males with a partner of childbearing potential: subject refuses to use 1 effective methods of contraception for the duration of the study and for 10 months after the last dose of study medication.
- Female subjects who are breast-feeding.
- History of osteonecrosis of the jaw, and/or recent (within 3 months) tooth extraction or other unhealed dental surgery; or planned invasive dental work during the study.

5 Treatment and Study Procedures

5.1 ***Investigational product*** *(see also paragraph 1.2)*
The study drug used in this clinical trial is denosumab 60 mg subcutaneously every 3 months. It will be provided as sterile, solution for injection in 1 ml pre-filled syringes containing denosumab 60mg/ ml or placebo. Placebo for Denosumab will be presented in identical containers and stored/packaged the same as drug product denosumab. Denosumab prefilled syringe placebo product is supplied in a prefilled syringe as a sterile, single use, preservative free solution for subcutaneous injection. Each prefilled syringe contains 1 mL deliverable volume of buffer consisting of 10 mM sodium acetate, 5% (w/v) sorbitol, 0.01% (w/v) polysorbate 20, at a pH of 5.2. The IP is packed with 1 PFS per box. Both Denosumab and Placebo are manufactured by Amgen Inc, United States and released in the EU by Amgen Breda, Netherlands. Amgen will provide batch release certificates that will be made available with each shipment of the drug. Amgen will provide GMP certification and investigational medicinal product dossiers directly to the Belgian Agency in the regulatory submission by Amgen for this ISS. The injections will be given at the study site. Instructions for the drug handling, packaging and storage are provided in details below. Briefly, the drug will be given under the skin of the thigh, abdomen or upper arm. The clinical supplies should be stored in the refrigerator at 2-8°C. Do not freeze. Do not shake excessively. The clinical supplies must be protected from light by storing in the outer carton.

Patients who completed the 1-year interventional study will have the opportunity to enter a second 1-year open-label extension (OLE) study with Denosumab (60 mg every 12 weeks, SC). The 1-year radiographic progression of their IP finger joints will be monitored after 6 and 12 months of treatment in the OLE. After completion of the open label phase, patients will have the option to enter a second year extension with the same treatment. During this extension radiographic progression of their IP finger joints will also be monitored after 6 and 12 months of treatment.

Drug Handling:
"Denosumab is supplied as a sterile, colorless to slightly yellow, preservative-free solution for injection in a 1mL prefilled syringe (PFS). The formulation of IP is 60 mg/mL denosumab per mL, formulated with10 mM Sodium Acetate, 5% Sorbitol, 0.01% Polysorbate, to a pH of 5.2. Each PFS of IP is intended for single use only. The IP is packed with 1 PFS per box. Placebo for denosumab will be presented in identical containers and stored/packaged in the same way as drug product denosumab.

The IP is shipped by air courier maintained at 2°C to 8°C in a qualified shipper suitable for biological substance shipments. IP in a PFS will arrive in a secondary packaging container and should be immediately placed in a refrigerator maintained at 2°C to 8°C in a secured location until planned use. The set point for the refrigerator should be at 5°C.
IP must be properly labelled and dispensed in accordance with current ICH GCP and local/regional requirements prior to dispensing for administration.
Before preparation check that IP:

- is visually intact and suitable for use
- is not expired
- has not been subjected to any potential temperature excursion
- label of the box and vial is correct

Prior to administration, IP may be removed from the refrigerator and brought to room temperature (up to 25°C) in the original container. This generally takes 15 to 30 minutes. Do not warm IP in any other way. Once removed from the refrigerator, IP must not be exposed to temperatures above 25°C/77°F and must be used within 24 hours. If not used within this time duration, IP must be discarded. Do not freeze IP. Protect IP from light and heat. Avoid vigorous shaking. Preparation of the clinical supplies should be performed using aseptic techniques and under sterile conditions.

All SC injections must be administered by authorized site personnel. All subjects will receive 1 SC injection at each dosing visit (of either 60mg/ml Denosumab or Placebo) administered in the subject's upper arm, upper thigh or abdomen by a trained and qualified staff member. The injection should not be administered in the same arm from which blood is drawn."

5.2 *Concomitant therapy*

All patients will have a daily calcium (1000 mg) and vitamin D (880 IU) supplementation. Subjects who are current or previous users of denosumab will be excluded at screening (see exclusion criteria).
Concomitant medication: NSAIDs and analgesics are allowed throughout during the study, but the dosages are kept constant during the first 12 weeks. Patients will keep records of their daily use of symptom modifying drugs.

5.3 *Study procedures and schedule of assessments*

A screening visit will include a clinical assessment, a hand radiograph and the laboratory investigations required. These will comprise a calcium and vitamin D status, peripheral blood cell count (PBC), serum chemistry glucose levels, liver (ALT, AST, alkaline phosphatase) and kidney function (serum ureum, serum creatinine, GFR) tests, Bone turnover markers (BTM) and, if appropriate, a pregnancy test.
An electrocardiogram (ECG) and an ultrasound (US) exam of the IP joints are part of the screening program.

Patients will be evaluated for risk factors for ONJ before starting treatment. A dental examination with appropriate preventive dentistry is recommended prior to treatment with Prolia in patients with concomitant risk factors.

The maximum window allowed between the screening visit and the baseline visit is of 3 weeks.

Upon selection, patients will be included in the study during **the baseline visit**, which will include a clinical examination and an ultrasound (US) exam of the IP joints. Magnetic

resonance imaging (MRI[39]) of the hand is optional. Study products (denosumab/placebo) will then be administered on-site by the investigator/study nurse. Calcium and vit D supplementation will be installed. Dual energy X-ray absorptiometry (DXA).

Schedule of assessments are provided in detail as Appendix 2. Clinical assessment is the standard practice and will be detailed in the CRF and the SAP. Safety assessment is clarified in the safety paragraph.

At week 6: a clinical/safety evaluation is planned.
At week 12: clinical/safety assessment, PBC and serum chemistry, serum calcium levels and BTM, US. MRI of the hand is optional. Study products (denosumab/placebo) to be administered on-site by the investigator/study nurse.
At week 24: clinical/safety assessment, serum calcium levels, hand radiographs.
Study products (denosumab/placebo) to be administered on-site by the investigator/study nurse.
At week 36: clinical/safety assessment, serum calcium levels. Study products (denosumab/placebo) to be administered.
W36 is the timing for the last IP dose in the blinded period.
At week 48: clinical/safety assessment, US, hand radiographs, DXA. Serum calcium levels, PBC and serum chemistry (glucose levels, liver and kidney function tests, and BTM. Study products (denosumab/placebo) to be administered.

The visit at week 48 is the first visit of the Open Label Extension (OLE) program, which will encompass clinical/ safety exams, laboratory tests and hand radiographs as indicated in the table. The clinical monitoring of serum calcium during the OLE phase will follow the same schedule as in the placebo controlled phase.
All patients will receive a denosumab injection at W48 after the above assessment. This would be the first denosumab dose administered in the open label phase.

At week 96: clinical/safety assessment, hand radiographs, DXA. Serum calcium levels, PBC and serum chemistry (glucose levels, liver and kidney function tests, and BTM.

The visit at week 96 is the first visit of the Extension phase which will encompass clinical/ safety exams, laboratory tests and hand radiographs as indicated in the table. The clinical monitoring of serum calcium during the Extension phase will follow the same schedule as in the placebo controlled and OLE phase.

Safety: Patients will be able to report any unwanted effect during the regular visits and through telephone contact at any time in between these visits. Clinical examination is part of this safety assessment. Templates for AE/SAE recording created by the Investigators will be used.

As unwanted effects – other than these reported in previous Prolia osteoporosis programs - are not expected, the collection of other laboratory safety data beyond week 12 during the randomized treatment phase is not arranged.

A negative pregnancy test will be an entry requirement in female premenopausal patients. Premenopausal patients at risk to become pregnant will be excluded if no valid anti-conceptive method is used. In practice, premenopausal women will be an absolute minority in this study

population. During the study and during the OLE phase, pregnancy tests will be done before each injection of denosumab in these subjects.

6 Statistical and Analytical Plans

6.1 Efficacy analysis

Complete and specific details of the final statistical analysis will be described and fully documented in the Statistical Analysis Plan (SAP). The SAP will be finalized prior to the database lock. The analysis will be performed using the statistical software package IBM SPSS .

Demographic and baseline characteristics will be summarized. The number of observations, mean, standard deviation, median, minimum and maximum will be summarized for continuous variables. Discrete variables will be summarized by counts and percentages.

The primary efficacy variables will be the changes from baseline to week 24 in radiographic outcome measures, more specifically changes in GUSS. The primary efficacy comparisons will be between the denosumab treatment group and the placebo treatment group using GEE modelling with treatment as factors and baseline radiographic scores as a covariate. Additional endpoints will be assessed because several assumptions are made in this pilot study that are derived from a previous clinical study with a TNF-α blocking agent. The kinetics of TNF inhibitors might be different from the kinetics of denosumab on the bone level because of the different mode of action. Therefore it is not possible to predict if a similar rapid response on GUSS™ scores will be observed. Since the whole study is a proof-of-concept and to guarantee that a later response will not be missed, the study period needs to be extended to 48 weeks and the GUSS changes between week 24 and week 48, as well as GUSS changes between baseline and week 48 will be assessed.
Other analyses of radiographic measures will be the number of patients that develop new erosive joints and the number of patients in which erosive joints start the process of remodeling between baseline and 48 weeks. From previous studies it is known that the anatomical phase scoring system is not as sensitive on short term as GUSS.

Exploratory efficacy endpoints including change in Total AUSCAN score and individual subdomain (pain, physical function and stiffness) scores from baseline, change in FIHOA scores from baseline, change in pain scales (NRS pain) from baseline, change in consumption of analgesics (paracetamol)/NSAIDs, changes in number of painful and tender joints from baseline will be analyzed similarly at week 48. Other exploratory endpoints, including the change in number of joints with effusion and/or Power Doppler signal by ultrasound, ultrasound sum scores and the changes in bone densitometry measures from baseline will be analyzed. Additional details will be provided in the SAP.

Primary and exploratory analyses will be repeated on subgroups defined by presence of soft tissue swelling at baseline. Details of analyses of efficacy endpoints at different time points as well as subgroups of interest will be given in the SAP.

The primary and exploratory efficacy variables will be analyzed on the intent-to-treat (ITT) population, defined as all subjects who were randomized. To evaluate the impact of major protocol violations on the results of the study, additional analyses of the primary efficacy analysis may be conducted on the per protocol population, which consists of all ITT subjects

who completed the study and are not major protocol violators. The safety population consists of all subjects who received at least one dose of double-blind study medication.

In general, mean change analyses to compare the denosumab and placebo treatment group will be performed using GEE modelling with treatment group as factor. Correction will be made for possible dependency between joints in the same patient by using an exchangeable matrix. Categorical data will be summarized using frequencies and percentages. Continuous data will be summarized with the number of non-missing observations by mean, standard deviation, median, maximum, and minimum values. In addition to the analyses based on observed data, analysis with imputed missing data will be conducted for selected efficacy variables. The details of such sensitivity analyses will be provided in the SAP. All statistical tests will be conducted at $\alpha = 0.05$ level (two-sided), unless otherwise stated. The last evaluation prior to the first study drug will be used as baseline for all analyses.

6.2 Safety analysis

Safety analyses will be carried out using the safety population, which includes all subjects who received at least one dose of study drug. Treatment-emergent AEs and SAEs will be summarized and reported. The number and percentage of subjects experiencing adverse events will be provided by system organ class and Medical Dictionary for Drug Regulatory Activities (MedDRA) preferred term. In addition, summary of AEs by severity and relationship to study drug will be presented. Serious, severe AEs, or AEs that lead to premature study discontinuation will be listed and described in detail. Mean change in vital signs and laboratory variables at each visit will be summarized for all treated subjects, and compared between treatment groups using one way Analysis of Variance (ANOVA).

6.3 Determination of Sample size

From a placebo controlled trial with adalimumab, we learned that, the risk that an individual IP joint evolves from J/S phase to the E phase is 2-3% per year. This risk increases to 15% for joints with a clinical effusion and to 25% for a painful joint with effusion. Adalimumab therapy reduced this risk for these inflammatory joints from 25% to 3% .

From these data 50 patients in each arm are needed to demonstrate a similar effect of denosumab with a power of 80%.
This power analysis took into account the following assumptions:
1) denosumab has a similar effect as adalimumab
2) a mean of minimal 1 inflamed joint (effusion and painful) per patient at baseline and in case of inclusion of patients with non-inflammatory joints, a within patient independent risk to evolve from J/S to E phase.
3) 5% drop-out
4) The proposed study involves two treatment arms. The level of significance (α) is 0.05.
5) a similar background risk for evolution from J/S to E phase.

Considering the semi-quantitative outcome measure, GUSS™, a second power analysis was performed. Several assumptions were made, based on data from a previous study (Verbruggen G et al. ARD 2012;71(6):891-8). Power calculation was performed based on the estimated difference in the semi-quantitative outcome measure, GUSS ™ over time. This outcome measure is selected to detect the radiographic progression in the selected joints after treatment. The following assumptions were made:

- the natural progression (mean change) that can be expected over a period of 6 months is + 24 units (data from the placebo treated group), the mean difference in GUSS™

change between the placebo and adalimumab treated group after 6 months was 25 units. This was considered as clinically significant since

- the smallest detectable difference of GUSS™ was calculated as 40 units (Verbruggen G et al. ARD 2010;69(5):862-7) and improved to 10 units after intensive training.
- the standard deviation of the mean change in GUSS™ is 29,
- based on the above data, a total change of at least (24+ 25) 49 units in GUSS™ in the treatment group is considered to be a clinical relevant effect from a treatment.

The proposed study involves two treatment arms. The level of significance (α) is 0.05. From previous studies performed at our department, an drop out rate of 5% can be expected.
A sample size of 25 patients in each treatment arm will have 80% power to detect a difference in mean change GUSS™ of 25 units between the placebo and treated group, assuming that the standard deviation is 29 using a t-test with a two-sided 0.05 level of significance.
Taking into account a drop out rate of 5%, a total of 27 patients (25/ 1 – 0.05) should be included in each arm.
Taken into consideration both outcome measures, a minimum of 50 patients is required in both treatment arms in order to provide sufficient power for the study.

The complete Statistical analysis plan v. 1.0 dd. 29/03/2020 will be provided in a separate document.

7 Independent Ethics Committee and Competent Authority

This trial was reviewed and approved by the ethical committee of the UZ Ghent as well as the local authority 'FAGG'.

OVERVIEW APPROVED DOCUMENTS		
Initial submission: - *Protocol version 1.0 dd. 12/08/2015* - *ICF version 1.0 dd. 14/08/2015*	***Approval date Central EC:*** *03/12/2015*	***Approval date FAMPH:*** *15/10/2015*
Amendment 1: - *Protocol version* 2.0 dd. 16/02/2016 - *ICF, version 2.0 dd. 16/02/2016*	***Approval date Central EC:*** *19/08/2016*	***Approval date FAMPH:*** *NA*
Amendment 2: - *Protocol version 3.0 dd. 03/06/2016* - *ICF, version 3.0 dd. 02/06/2016*	***Approval date Central EC:*** *19/08/2016*	***Approval date FAMPH:*** *NA*
Amendment 3: - *Protocol version 3.1 dd. 29/08/2018* -	***Approval date Central EC:*** *12/09/2018*	***Approval date FAMPH:*** *NA*
Amendment 4: - *Protocol version 4.0 dd. 17/10/2018*	***Approval date Central EC:*** *14/11/2018*	***Approval date FAMPH:*** *14/11/2018*
Amendment 5: - *ICF version 5.0 dd 18/01/2019*	***Approval date Central EC:*** *13/03/2019*	***Approval date FAMPH:*** *NA*

8 Results

8.1 Subject enrollment and demographics

According to the protocol 100 subjects were planned for this study and 100 subjects were randomized. The date of first randomization was 30/03/2016 and the 'last patient last visit' (LPLV) was performed on 28/04/2021.

Study Arm	Number of subjects completed	Number of subjects prematurely discontinued
Denosumab / placebo	92	8
Prolia® 1st year	87	5
Prolia® 2nd year (extension)	36	6

Discontinuations during the placebo controlled phase:
The following subjects discontinued the placebo controlled phase due to safety issues, 033; 063; 065; 083; 081; 047. See below "9. Safety"
Subject 099 was excluded from the study due to non-compliance.
Subject 097 changed her mind and decided to discontinue the trial.

Discontinuations during the first year of open label treatment:
Subject 015 discontinued the trial due to mild adverse events.
Subjects 028; 075;085 and 029 decided to discontinue the trial because it was too demanding.

Discontinuations during the second year of open label treatment:
Subject 072 decided to discontinue the extension phase, too demanding.
Subjects 058 and 098 discontinued due to the Covid-19 pandemic.
Subjects 064; 088 and 080 discontinued the extension phase due to safety issues.

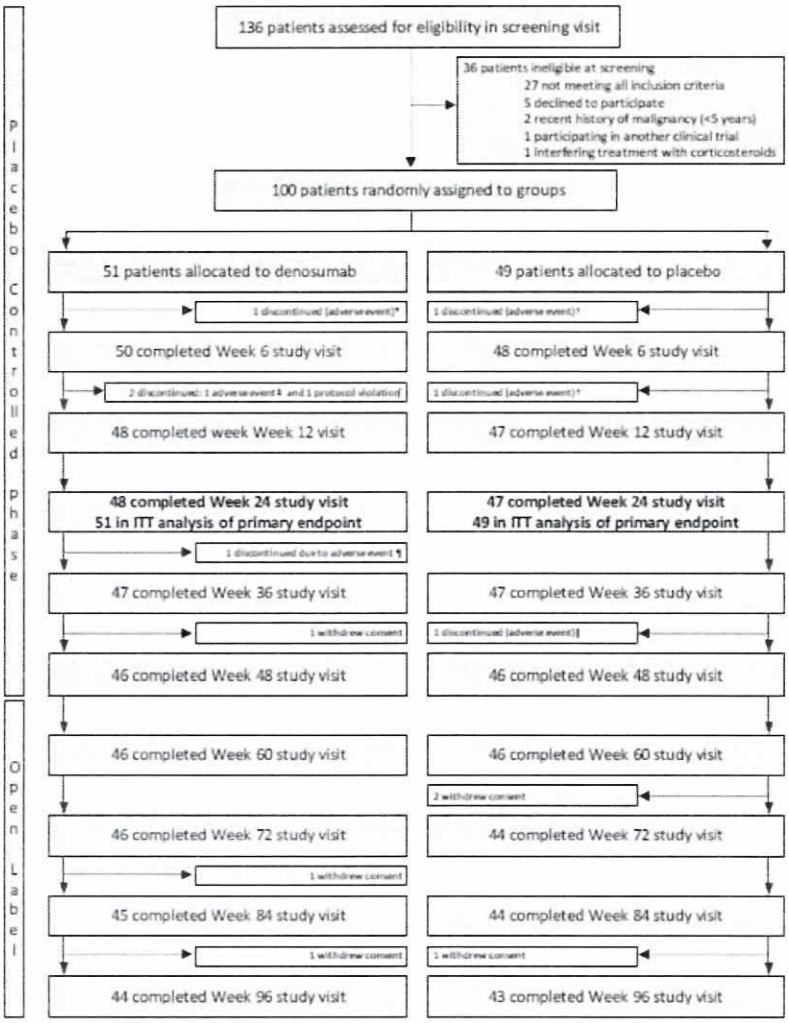
More details will be shown in future publications/manuscripts.

8.2 Study specific results

Subjects and target joints

In this study, patients were screened for enrolment between March 2016 and July 2018. 136 patients were screened, 100 were randomized and received at least one administration of the study medication (Figure 1). The most common reason for exclusion was not meeting one or more of the inclusion criteria (most often absence of radiographic eligible joint(s) with soft tissue swelling). Of treated subjects, 49 were assigned to placebo (49%) and 51 to denosumab (51%) and were included in the ITT analysis of the primary endpoint. 46 patients in the denosumab and 46 in the placebo group completed the 48-week study. Five patients in the denosumab (9.8%) (1 because of SAE, 3 due to withdrawal of consent and 1 because of protocol deviation (use of corticosteroids)) and 3 (6.1%) in the placebo group (all because of SAE) discontinued from the study. Demographic and baseline characteristics were well balanced between the groups (Table 1). The mean number of radiographically affected joints per patient was 3.6 and 4.0 in denosumab and placebo group respectively ($p > 0.05$). 168 target joints were selected for ITT analysis of the primary outcome. All joints (n = 1590) were analyzed for secondary imaging endpoint. Ten joints were missing due to amputation (n = 9) or prosthesis (n = 1). All patients were included for secondary clinical endpoints in the per protocol analysis.

Figure 1:



ITT: intention-to-treat
* Acute coronary syndrome (a serious adverse event);
† Breast carcinoma (a serious adverse event);
‡ Subjective calcium/vitD intolerance;
∫ Use of oral corticosteroids;
¶ Urticarial reaction;
‖ Pancreas carcinoma (a serious adverse event)

Table 1: Demographic and clinical characteristics of the patients at baseline*

Characteristics	Denosumab (n = 51)	Placebo (n = 49)
Age - yr	62.0 (7.7)	60.6 (7.9)
Female sex - no. (%)	41 (80)	37 (76)
Disease duration - yr	6.3 (6.6)	6.0 (6.4)
Body-mass index†	25.3 (3.5)	25.3 (4.0)
NRS pain‡	4.7 (2.5)	4.8 (2.7)
AUSCAN∫	67.0 (4.9)	68.9 (5.5)
FIHOA¶	10.4 (0.9)	10.3 (1.0)
Mean GUSS™ (of 16 joints)‖	249 (66)	248 (67)

Anatomical phase according to Verbruggen and Veys – No. (%)**		
N joints	196 (24.3)	150 (19.2)
S joints	326 (40.4)	353 (45.1)
J joints	67 (8.3)	82 (10.5)
E joints	98 (13.3)	104 (13.3)
R joints	107 (13.3)	91 (11.6)
F joints	3 (0.4)	3 (0.4)
Number of affected joints (of 16 joints) ††	3.6 (2.2)	4.0 (2.2)

* Data are mean (SD) or n (%). Unadjusted P values were determined with the use of chi-square tests for categorical variables and T-test for continuous variables. No significant differences were found for any of the variables among the treatment groups at baseline.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ The numeric rating scale (NRS) pain is a scale from 0 to 10, with higher scores indicating greater severity.

∫ Scores of the Australian-Canadian Hand Osteoarthritis Index (AUSCAN) range from 0 to 150, with higher scores indicating more disability.

¶ Scores of the Functional Index for Hand Osteoarthritis (FIHOA) range from 0 to 30, with higher scores indicating more disability.

‖ The Ghent University scoring system (GUSS™) ranges from 0 to 300. This scoring system is composed of 3 subdomains: subchondral plate, subchondral bone and joint space. Specific features referring to the underlying pathology of the disease are being scored on a numerical scale from 0 to 100, with increments of 10. Higher scores indicate remodelling or repair. Thus, the maximum score refers to either a normal or a completely restored (i.e., non-erosive) joint. Lower scores indicate presence of more or greater erosions, loss of joint space or subchondral plate (13). The total score per joint is made by an equally weighted sum score of all 3 subdomains (min. 0; max. 300). Mean GUSS™ value of 16 joints per patient is shown.

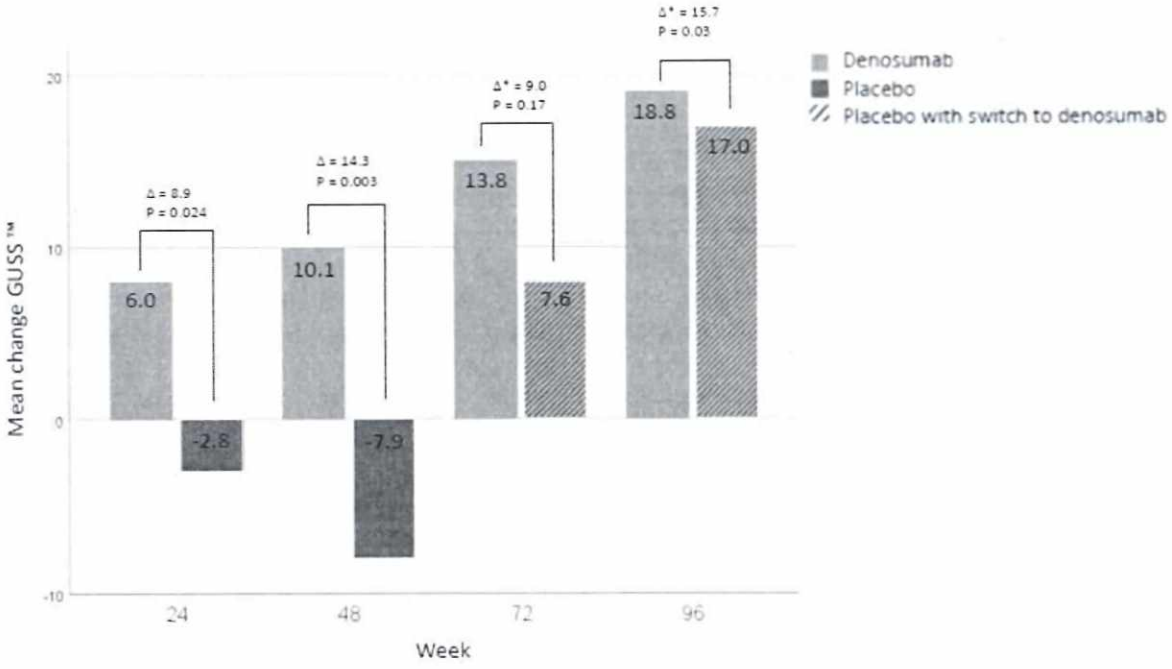
**The Verbruggen and Veys anatomical score system differentiates normal joints (N) from pre-erosive phases (S phase, i.e., stationary phase with minimal degenerative features such as subchondral sclerosis, joint space narrowing and presence of small osteophytes, and J phase with partial or complete loss of joint space), erosive phase (E) and phases of remodelling (R, i.e. signs of repair such as reappearance of subchondral plate and joint space width, disappearance of erosions at the subchondral bone and development of osteophytes at joint margins, and F, fused joint as extreme sign of remodelling) (19). The presence of anatomical phases were assessed by the Verbruggen and Veys scoring system on baseline, week 24, 48, 72 and 96 radiographs.

†† Any radiographically defined S, J, E, R joint, according to the Verbruggen and Veys score.

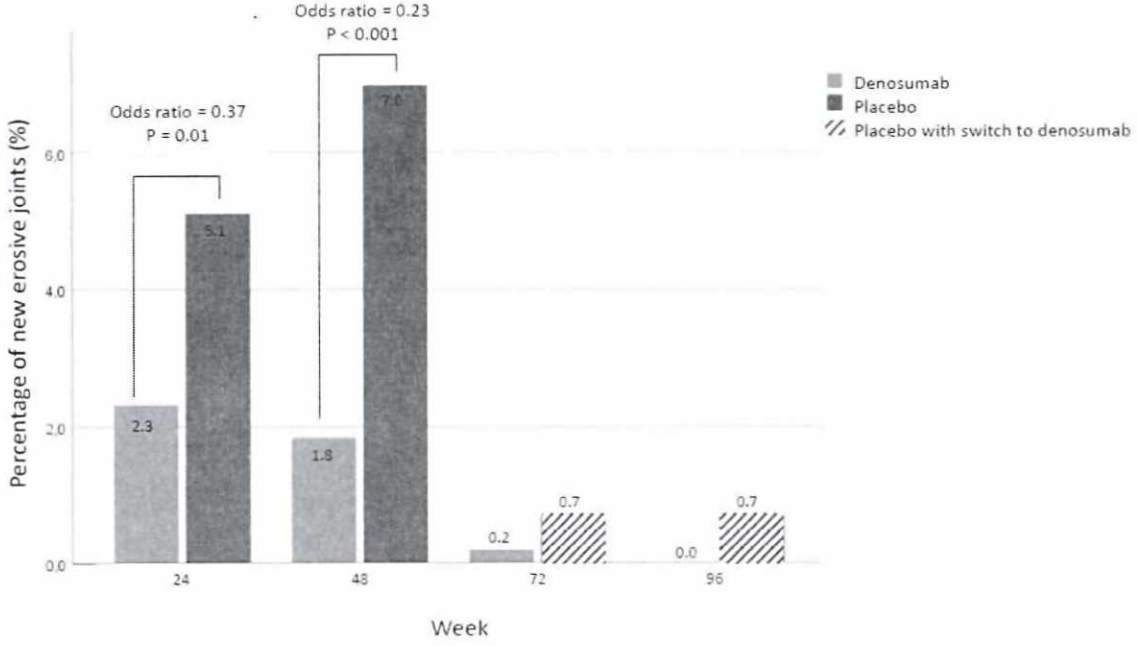
Primary radiographic efficacy endpoint

Change in total GUSS™ was found to be statistically higher in the denosumab group compared to the placebo group at week 24, indicating more remodeling and less erosive progression (estimated mean difference total GUSS™ = 8.9 (95% CI: 1.0 to 16.9; p = 0.024)(Figure 2A). This effect was confirmed at week 48 (estimated mean difference total GUSS™ = 14.3 (95% CI: 4.6 to 24.0; p = 0.003)). Inter- and intrareader reliability data were excellent for all radiographic scores (Appendix 3).

Figure 2: Mean GUSS™ at week 24, 48, 72 and 96 and new erosive joints
A. Mean change GUSS™



B. Incidence of new erosive joints



Secondary imaging efficacy endpoint

At patient level, the development of new erosive joints was statistically higher in the placebo group compared to the denosumab group at week 48 (7.0% new E joints in placebo vs. 1.8% in denosumab)(Figure 2B). From baseline to week 48, the estimated odds ratio for erosive progression was 76.7% lower in the denosumab group compared to placebo (OR = 0.23 (95% CI: 0.11 to 0.50); $p < 0.001$).

Exploratory imaging endpoints

Both US effusion and US synovitis score at week 12 decreased significantly in the denosumab and placebo group at week 12 and week 48 compared to baseline. The US erosion score did reduce significantly in the denosumab group at week 48 compared to baseline while this was not the case in the placebo group. However, the adjusted mean between group difference from baseline to week 48 was not found statistically significant (Table 2).

Table 2: Changes in ultrasonographic features between the two treatment groups

	Group	Baseline	Week 12	Week 48	P-value $B_{aseline}$ vs. W12	P-value Baseline vs. W48	Mean changes*	P-value†
Effusion (0-3)	Denosumab	13.61 (6.55)	10.04 (5.50)	11.52 (6.11)	**0.001**	**0.024**	0.781	0.583
	Placebo	15.02 (8.32)	12.28 (6.53)	11.48 (5.51)	**0.004**	**0.002**		
Synovial proliferation (0 -3)	Denosumab	11.18 (5.96)	10.76 (6.62)	10.67 (6.22)	0.815	0.772	-0.587	0.640
	Placebo	11.55 (5.41)	10.81 (5.48)	12.57 (7.79)	0.398	0.434		
Synovitis (0-3)	Denosumab	24.78 (8.69)	20.80 (9.06)	22.20 (10.20)	**0.004**	**0.042**	0.194	0.915
	Placebo	26.57 (11.28)	23.09 (8.24)	24.04 (10.76)	**0.004**	**0.025**		
PD (0-3)	Denosumab	2.67 (2.73)	2.16 (2.72)	3.02 (2.96)	0.229	0.513	-0.711	0.323
	Placebo	3.18 (6.17)	2.02 (3.17)	2.65 (3.04)	0.056	0.534		
Erosions (0-1)	Denosumab	5.84 (3.15)	5.36 (3.06)	4.65 (2.97)	0.171	**0.002**	**0.925**[ʃ]	0.158[ʃ]
	Placebo	6.65 (3.12)	6.21 (3.29)	6.37 (3.24)	0.444	0.187		

Data are expressed as mean (standard deviation). Denosumab (N=51) and placebo (N=49) were included in the analysis. Significant p-values in bold ($\alpha = 0.05$)

* Adjusted mean changes between groups over 12 weeks, adjusted for baseline values

†Comparing changes between the two groups over 12 weeks using independent samples t-test.

[ʃ] change between baseline and week 48 for erosions

In this non-osteoporotic population, the mean bone mineral density T scores at lumbar spine and femoral neck increased consistently from baseline through to week 96 in the denosumab treated group. Also in the placebo group improvement was seen at the lumbar spine at week 48 but not at the femoral neck. At 48 weeks the percentage change from baseline was greater with denosumab than with placebo at the lumbar spine by 2.8 percentage points ($p < 0.001$)(Table 3).

Table 3: Bone Mineral Density at baseline and follow-up and percentage change from baseline.

	Group	T score			% change Week 48 from Baseline	% change Week 96 from Baseline	P-value Baseline vs. W48	P-value between groups*
		Baseline	Week 48	Week 96				
T score Femoral Neck	Denosumab	-0.89 (0.96) [-3.30; 2.00]	-0.83 (0.93) [-3.10; 2.00]	-0.73 (0.94) [-3.00; 2.00]	0.29 (5.88)	2.07 (6.18)	0.113	0.504
	Placebo	-0.70 (1.10) [-2.80; 1.80]	-0.74 (1.08) [-2.80; 1.90]	-0.58 (0.96) [-2.60; 1.70]	0.35 (3.89)	1.87 (3.88)	0.574	-
T score Lumbar Spine	Denosumab	-0.58 (1.22) [-3.30; 1.90]	-0.28 (1.20) [-3.10; 2.40]	-0.18 (1.21) [-3.30; 2.50]	4.41 (3.06)	6.65 (3.29)	**0.000**	**<0.001**
	Placebo	-0.61 (1.40) [-4.00; 2.30]	-0.52 (1.36) [-3.60; 2.30]	-0.63 (1.34) [-2.10; 3.00]	1.66 (3.01)	5.47 (4.02)	**0.001**	-
T score 1/3rd Distal Radius	Denosumab	-0.87 (0.97) [-3.30; 1.00]	-0.78 (1.00) [-3.20; 1.30]	-0.65 (0.98) [-3.10; 1.20	0.64 (3.28)	1.67 (2.73)	0.259	**0.050**
	Placebo	-0.80 (1.09) [-3.0; 2.10]	-0.96 (1.03) [-3.10; 1.10]	-0.88 (0.96) [-2.80; 1.20]	-0.55 (2.66)	-0.24 (2.89)	0.090	-

Data shown are mean (standard deviation)[range] unless otherwise stated; Denosumab (N=48) and placebo (N=47) were included in the analysis at week 48.
*Comparing changes between the two groups over 48 weeks using independent samples t-test. Significant p-values in bold ($\alpha = 0.05$)

Sensitivity analyses without imputations and with correction for baseline GUSS™ measures, and Per protocol analysis of the primary endpoint showed similar results as in the ITT (data not shown).
The interaction between the presence of baseline inflammation (yes/no) and treatment effect on change in GUSS™ scores was tested and showed no significant interaction between inflammation and treatment at week 24 (p=0.48) nor at week 48 (p=0.18).
A descriptive efficacy analysis performed on an extended group of target joints (n = 198) (i.e., all joints showing any progression to J, E or E/R phase throughout the study that were not defined J or E phase at baseline) showed a mean change in GUSS™ of 11.8 (95% CI = 3.6 to 20.0) higher in denosumab compared to placebo (p = 0.004) at week 24 and a change of 19.7 (95% CI = 9.4 to 29.9) in favor of denosumab treatment (p <0.001) at week 48.

Exploratory clinical endpoints
The change in pain (NRS) at week 24 versus baseline did not differ significantly between placebo and denosumab (-0.2 (95% CI: -1.0 to 0.6); p = 0.68)(Figure 3C). AUSCAN total and FIHOA were respectively -2.8 (95% CI: -11.8 to 6.2) and -1.2 (95% CI: -3.1 to 0.7) lower in the denosumab group compared to the placebo group at W24 without statistical significance being reached. NRS patient global opinion of efficacy is estimated to be 0.5 (95% CI: -0.7 to 1.8) higher in the denosumab group compared to the placebo group at W24 (p = 0.41). At week

48, the numerical difference in function (both AUSCAN and FIHOA) improved numerically but not statistically in the denosumab group compared to placebo (Appendix 4).

Extension phase

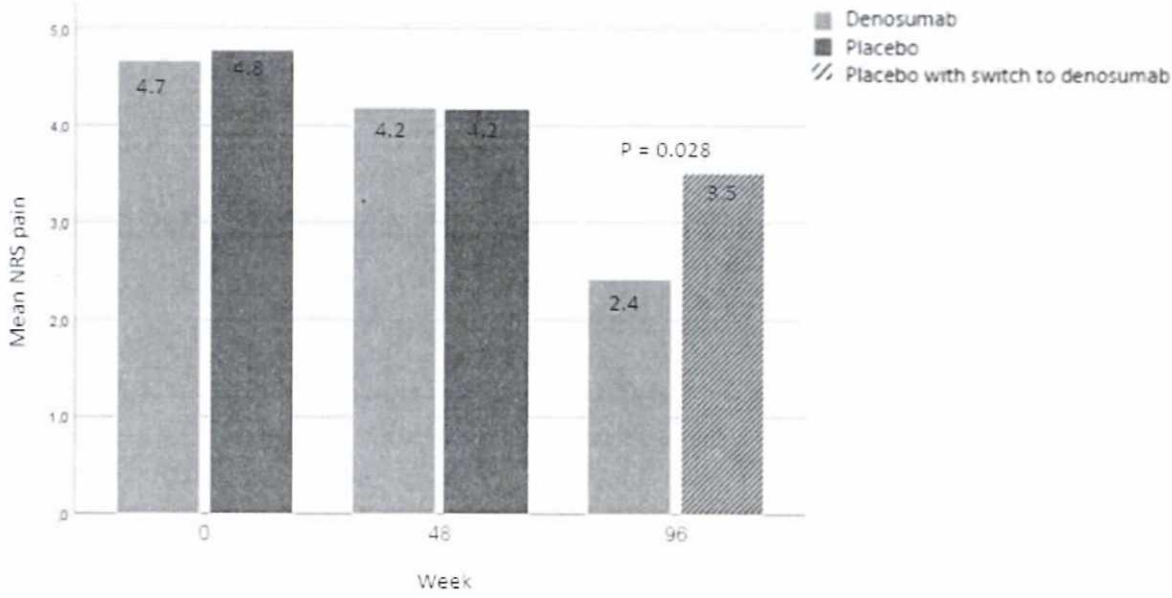
Ninety two patients entered the 1-year extension phase at week 48, of which 46 originally received denosumab and 46 placebo during the first year. Five patients prematurely discontinued the open-label extension phase.

Comparable to year 1, target joints evolved toward remodeling in the second year. Total GUSS™ kept increasing in both groups during the second year compared to baseline with a larger increase in the former placebo group at week 96 compared to the initial denosumab group (estimated mean difference total GUSS™ at week 72 = 2.3 (95% CI: -2.9 to 6.9; p = 0.32) and estimated mean difference total GUSS™ at week 96 = 3.5 (95% CI: -1.1 to 8.1; p = 0.13). Compared to week 48, the change in GUSS™ score significantly increased at week 96 in the former placebo group (estimated mean difference total GUSS™ placebo = 25.7 (95% CI: 16.2 to 35.1;) vs. estimated mean difference total GUSS™ denosumab = 9.9 (95% CI: -1.3 to 21.1); p = 0.035). When including 18 newly developed target joints in the placebo group during the first year for the analysis at week 48, similar results were confirmed (estimated mean difference total GUSS™ placebo = 27.0 (95% CI: 17.9 to 36.0;) vs. estimated mean difference total GUSS™ denosumab = 10.1 (95% CI: -0.4 to 20.6); p = 0.017). Only three new erosive joints developed during the extension phase: 2 joints in J phase in two former placebo treated patients, and one in E phase (coming from J in year 1) in a denosumab treated patient. Concerning the clinical exploratory endpoints, patients who initially received denosumab during the first year, showed a significant decrease in pain levels at week 96, compared to baseline and compared to the patients from the initial placebo group (NRS pain denosumab W96 = 2.42 vs. NRS pain denosumab baseline = 4.68, p <0.001, and NRS pain denosumab W96 = 2.42 vs. NRS pain initial placebo W96 = 3.52, p = 0.028, respectively)(Figure 3). Similar observations were done for FIHOA (mean difference within denosumab group W96 vs. baseline, p = 0.042; mean difference between groups W96, p = 0.025) but not AUSCAN, suggesting that clinical benefits were induced only after two years of treatment with denosumab (Appenix 4).

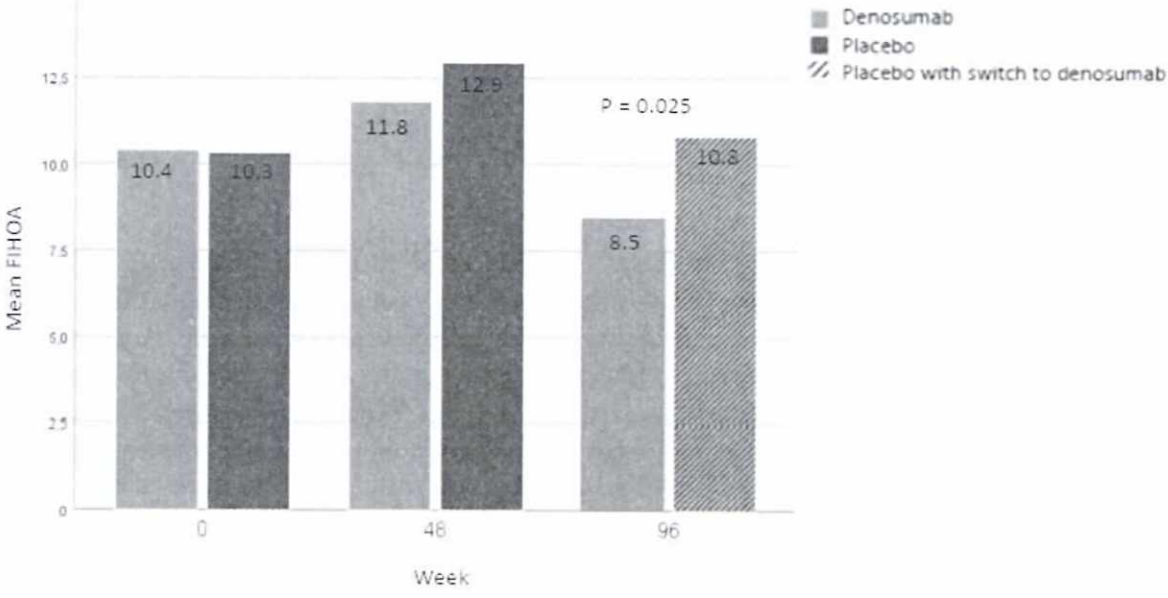
Figure 3: Changes in clinical data through the placebo-controlled and open-label extension phase.

Panel A shows the mean numeric rating scale (NRS) pain, ranging from 0 to 10, with higher scores indicating more pain. Panel B shows the mean Functional Index for Hand Osteoarthritis (FIHOA), ranging from 0 to 30, where higher scores indicate more disability. All the data are shown for the full analysis set, which included all the patients who underwent randomization and received at least one dose of denosumab or placebo. For the analyses in the extension phase, similar GEE logistic regression models were used with treatment groups based on the initial randomization code. P-value represent the comparison with placebo adjusted for baseline values by Generalized Estimation Equations.

A. NRS pain



B. FIHOA



9 Safety

Through to week 48, the incidence of adverse events was higher in the placebo group versus the denosumab group)(Table 4). Fourteen serious adverse events were reported during the study: seven in the denosumab group and seven in the placebo group (Table 4). All serious adverse events were reported according to the applicable regulatory requirements. No safety measures were incorporated in the trial as a result of the occurred serious adverse events. Six patients discontinued the study because of an adverse event (one acute coronary event, three malignancies, one urticarial reaction, and one due to subjective intolerance to calcium/vitamin D intake). The most common adverse events were infections and musculoskeletal complaints in both groups (in denosumab: n = 41 and n = 24; in placebo: n = 38 and n = 34, resp.). Cancer occurred in three patients (all allocated to placebo). Hypocalcemia during any time in the study occurred in five patients in the denosumab and in three in the placebo group (Table 5): all were asymptomatic. Three events (obstipation and diverticulitis) were found related to the study medication (all receiving denosumab). During the extension phase, eleven new serious adverse events occurred, all not related to the study medication. Asymptomatic hypocalcemia occurred in 2 patients at week 72 (one recovered, one persisted up to Week 96).

Table 4: Summary of safety events through week 48*

	Denosumab (N = 51)	Placebo (n = 49)
Event		
Any adverse event – no.	98	125
Serious adverse event - no.	7	7
Adverse event leading to discontinuation – no.	3†	3‡
Adverse event of special interest – no.		
Cancer	0	3‡
Infection	41	39
Major cardiovascular event∫	1	0
Gastrointestinal event	6	7
Surgical and medical procedures	3	9
Musculoskeletal complaints	26	34
Nervous system disorders (incl. dizziness, vertigo, headache)	4	17
Pulmonary and respiratory complaints (non-infectious)	2	1
Rash and skin problems	3	1
Allergy (systemic and urticaria)	3	1
Teeth problems	3	3
Hypocalcemia¶		
At week 12	2	0
At week 24	1	1
At week 36	2	1
At week 48‖	3	1
Reduced kidney function >25% from baseline		
At week 12	2	3
At week 48	2	1

* Analyses were performed with data from the intention-to-treat population.

† In the denosumab group, one patient experienced an acute coronary syndrome, one had an urticarial skin reaction and one experienced a subjective intolerance to the calcium and vitamin D administration and discontinued the study therefore.

‡ In the placebo group, two patients had breast cancer and one patient had a pancreatic adenocarcinoma with metastases and discontinued the study.

∫ One patient in the denosumab group experienced an acute coronary syndrome 4 weeks after start of the study.

¶ Hypocalcemia was defined as below 2.12 millimole per liter

‖ Hypocalcemia at week 48 was a new finding in one patient and already present in one patient at W12 in the denosumab group and a new finding in one patient in the placebo group.

Table 5: Longitudinal laboratory values

Variable	Group	Screening	Week 12	Week 24	Week 36	Week 48
Calcium (mmol/liter)	**Denosumab**	2.36 (0.09) [1.97 – 2.55]	2.38 (0.09) [2.13 – 2.57]	2.40 (0.12) [1.83 – 2.67]	2.38 (0.09) [2.14 – 2.61]	2.38 (0.11) [2.10 – 2.61]
	Placebo	2.38 (0.10) [2.21 – 2.71]	2.41 (0.10) [2.21 – 2.66]	2.38 (0.14) [1.84 – 2.67]	2.41 (0.11) [2.17 – 2.76]	2.39 (0.10) [2.16 – 2.66]
Phosphor (mmol/liter)	**Denosumab**	1.19 (0.18) [0.75 – 1.58]	1.14 (0.16) [0.76 – 1.52]	-	-	1.15 (0.18) [0.71 – 1.57]
	Placebo	1.18 (0.14) [0.92 – 1.48]	1.19 (0.13) [0.88 – 1.49]	-	-	1.17 (0.13) [0.94 – 1.45]
Creatinine (mg/dl)	**Denosumab**	0.80 (0.18) [0.51 – 1.34]	0.82 (0.14) [0.62 – 1.24]	-	-	0.81 (0.15) [0.59 – 1.21]
	Placebo	0.80 (0.18) [0.52 – 1.48]	0.85 (0.15) [0.58 – 1.23]	-	-	0.85 (0.17) [0.62 – 1.27]
C-reactive protein (mg/liter)	**Denosumab**	0.33 (0.61) [0.07 – 4.12]	0.29 (0.44) [0.08 -2.06]	-	-	0.26 (0.42) [0.09 - 2.30]
	Placebo	0.18 (0.20) [0.05 – 1.36]	0.20 (0.22) [0.07 – 1.39]	-	-	0.38 (0.74) [0.07 – 4.07]

Values are mean (SD)[range]

10 Protocol deviations

All protocol deviations are listed in the protocol deviation log (appendix 5).

11 Discussion and overall conclusions

In this 48-week, placebo-controlled, double-blind clinical study, denosumab at doses of 60mg every 3 months reduced the radiographic erosive progression in erosive hand OA versus placebo with no significant safety signals identified. We found a significant effect already being present at week 24, remaining consistent and even improving through 48 weeks. Furthermore, less new erosive joints developed through week 48 in the denosumab group. While clinical outcome measures did not significantly change between groups in the initial 48 weeks of treatment, we noted significant improvement in pain and disability levels in the extension phase through week 96, suggesting that prolonged treatment with denosumab not only inhibits structural progression but also culminates in clinical improvement over time. The safety profile of denosumab was found to be comparable with previous studies and use in clinical care (41) even though the dose regimen was doubled compared to standard regimens used in osteoporosis treatment. This is the first study that demonstrates consistent benefits on radiographic progression in erosive hand OA already after 24 weeks, and subsequent clinical benefits after long-term treatment.
Several previous studies in erosive hand OA with biological agents such as tumour necrosis factor α blocking agents (i.e., adalimumab (35, 42) and etanercept (43)), and anti-interleukin-1α and β inhibitor, lutikizumab (44), failed to show clinical efficacy in short- and long-term studies. Only one study showed some beneficial effect on structure modification, albeit in a post-hoc analysis including only the inflammatory joints (35). One recent, 6-week study with corticosteroids showed significant impact on pain in hand OA (45). Due to its short duration, any beneficial effects on structure modification nor disability could not be demonstrated. The present study confirms the ability of denosumab to primarily affect radiographic progression in hand OA, thereby improving clinical status on the long-term. This points to its potential as structure modifying drug in erosive hand OA. Recently, a novel elective cathepsin K inhibitor demonstrated structural improvement in patients with knee OA (46). However, no benefit on pain levels was seen in this relatively short trial. These findings might create a shift toward treatment of erosive hand OA from targeting solely pain relief towards prevention of structural or erosive damage with a cumulative impact on pain and function over time. The ultimate goal of treatment of erosive hand OA, like any other type of OA, is to avoid further joint space narrowing, cartilage degradation and bone formation, all features of OA. By arresting radiographic damage, the burden of the disease might substantially decrease for many patients.

It was hypothesized by inhibiting RANKL through its impact on maturation and activation of osteoclasts, the catabolic osteoclastic activity in erosive hand OA could be inhibited or even arrested, thereby slowing down progression of structural damage. Similar results were seen in rheumatoid arthritis (47, 3, 48-49), a prototypical inflammatory arthritis characterized by erosive disease. Here, erosions were prevented to develop when treated with denosumab , yet it had no impact on inflammatory signs and symptoms. The dosing regimen in RA was every 3 months, rather than the once every 6 months regimen used in postmenopausal osteoporosis. The increased dosing frequency was inspired by evidence that under chronic arthritic conditions cellular sources of RANKL are strongly increased extending it even to other cell types such as the synovial lining layer. Because of the similarities in the impact of structural progression in erosive hand OA and RA, it was decided to adopt a similar dosing regimen. However, unlike

RA, there is ample evidence that erosive hand OA is not a primarily inflammatory disease (50 - 53). Cartilage and subchondral bone degradation are driving the disease and inflammation may rather be a secondary phenomenon. Therefore, other pathways may need to be targeted in order to suppress the underlying inflammation in these patients. This explains why the number of swollen joints nor the sonographic outcomes for inflammation (i.e., effusion, PD signals) did not respond to treatment in our study. On the other hand, the sonographic erosions did also decrease, which is in line with the radiographic data. Thus, despite the pathogenic differences between either diseases, the observations with denosumab treatment in erosive hand OA mirror very well the results in RA.

In this current study, two validated scoring methods for structural radiographic or erosive progression were used, i.e., GUSS™ and Verbruggen and Veys anatomical phase. Both systems confirmed the reduced progression, at week 24 for the former and week 48 for the latter. The quantitative scoring system, GUSS™, was developed to demonstrate changes on short-term, the benefit of which is demonstrated here . Confirming similar evolution by another scoring system (i.e. Verbruggen and Veys) may serve as an internal validation. Reliability was found excellent amongst the two experienced readers. Multiple clinical outcome measures were included in this study, which eventually were improved by sustained treatment with denosumab. Unfortunately, a surrogate outcome measure for disease activity in erosive hand OA is still lacking (54). Development of such a tool could facilitate the clinical trial research in hand OA. Disease activity and structural progression are undeniably coupled, but may be disconnected in timing. This could explain very well our observation that denosumab treatment inhibits structural progression as early as 6 months after therapy initiation, whereas its impact on clinical outcome only emerges in the two years follow up. The data advocate a sustained need for RANKL inhibition in order to preserve hand function and onset of new erosive disease. In this context, the observation that in the first 48 weeks of the placebo controlled trial, the estimated odds ratio for erosive progression was 76.7% lower in the denosumab group compared to placebo, supports this concept of osteoclast dependent structural damage in erosive hand OA.

We found no safety signals for treatment with increased interval dosing of denosumab in our non-osteoporotic population. A higher number of non-serious and serious adverse events were reported in the placebo group. The adverse events leading to premature discontinuation of eight patients before week 48 were not related to the study medication. Hypocalcemia was reported rarely and easily manageable before the next administration of the study drug. As expected, all BMD values increased in the denosumab group, and only at the spine in the placebo group which might be attributed to the calcium and vitamin D administration.

Inclusion of a specific subset of patients (i.e., with signs of clinical and sonographic inflammation) is both a strength and a limitation: it limits the generalizability of the results to hand OA patients with no inflammatory signs, but on the other hand, it enables the likelihood to observe an effect of the targeted treatment. Since hand OA is a heterogeneous disease, probably clear patients stratification is required in clinical trials in order to identify the ones who will benefit from treatment. Another limitation of this study is that it was not powered or designed to include a pre-specified statistical comparison of efficacy between the denosumab treatment arms through week 96. Finally, due to the ongoing treatment until the end of the study, safety conclusions about a potential rebound effect after denosumab discontinuation on bone status in this non-osteoporotic populations cannot be drawn. In summary, this placebo-controlled trial provides the first proof of concept that structural damage in the erosive type of hand OA can be modulated by a targeted therapy. Clear benefits from treatment with

denosumab 60mg every 3 months were observed in erosive hand OA patients by reducing radiographic progression and development of new erosive joints. Subsequently, this leads to improvement in pain and disability after long-term treatment through 96 weeks. This study might add new promising treatment possibilities for patients suffering from a disease, erosive hand OA, with high unmet needs.

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13 Appendices

Appendix 1. Scoring systems

A. Categorical scoring system was proposed for the progressive radiographic changes in IP finger joint OA. These changes were characterized by complete loss of the joint space preceding or coinciding with the appearance of subchondral cysts eroding the entire subchondral plate. These erosive episodes subsided spontaneously and were followed by processes of repair.[28]

The anatomical phases in the evolution of IP finger joint OA are the following.

Normal ('N') joints: no signs of OA.
Stationary ('S') phase: classical appearance of OA. Small ossification centers and osteophytes are present at the joint margins. They can both increase in size and discrete narrowing of the joint space can occur.
Loss of joint space ('J' phase): after remaining for a variable time in the stationary phase, some joints (almost exclusively PIPs or DIPs) become destroyed. The joint space completely disappears within a relatively short period of time.
Erosive ('E') phase: concurrently with or shortly after the disappearance of the articular cartilage (J phase), the subchondral plate becomes eroded. The appearance is that of a pseudo-enlargement of an irregular joint space. Roentgenograms obtained at yearly intervals showed that changes in phases from 'S' over 'J' to 'E' could occur within one year. This destructive 'J' and 'E' phases are always followed by repair or remodeling.
Remodeling ('R') phase: new irregular sclerotic subchondral plates are formed, and in between these a new joint space becomes visible. Huge osteophytes are formed during this phase. No further evolution is seen in remodeled joints.

B. A quantitative radiographic scoring system, the Ghent University Scoring System, GUSS® [29], is a reliable method to score radiographic change over time in erosive IP OA and detects more progression over a shorter period of time than the classical scoring system. Erosive progression and signs of repair or remodeling are then scored by indicating the proportions of normal subchondral bone, subchondral plate and joint space over time.

The subchondral bone area. The proportions of the subchondral bone area with normal/abnormal-looking bone architecture were assessed in a quadrangle square of which the side equalled the width of the joint space. The joint space was positioned in the centre of this square (figure 2A). In this square, regions where osteolytic activity and remodelling caused a disarrangement of the trabecular pattern, as well as areas where a complete loss of the trabecular structure had occurred, are defined.
Identifiable osteolytic subchondral bone areas are marked on the radiographs and proportions of remaining intact subchondral bone will be calculated, considering the delineated IP joint area being the 100% value.

The subchondral bone plate. In an IP joint that had completely lost its joint space, an existing subchondral plate was defined as a regular radio-opaque linear structure within the position of the original joint space. When the joint space was still identifiable, the subchondral bone plate was identified as a regular linear radio-opaque bone margin flanking the joint space. Identifiable linear subchondral plate structures were marked on the radiographic images and proportions of

remaining subchondral bone plate were computed, considering a twofold joint space width being the 100% value (figure 2B).

The joint space was recognized as a radiotranslucent area bordered with two subchondral plates. Identifiable joint spaces were marked on the radiographic images. Proportions of remaining joint space were estimated as the proportion of the joint width, considering the total joint space width being the 100% value (figure 2B).

Computation of the changes in IP joints in "J", "E" and "E/R" phases. Pictures from the IP joints at three time points in the correct sequence will be read and used by the readers to evaluate the extent of the pathological changes in subchondral bone architecture, and to estimate the presence/absence of both subchondral bone plate and synovial joint space. Proportional changes in these three variables will be recorded. The sum of the three separate scorings constituted the total IP joint score. Equal weight will be attributed to each of the subdomains.

Appendix 2. Overall assessments

	admin dmab/plac	clinical assessm	safety	laboratory						CR hand	US hand	DXA	ECG
				PBC	serum chem	BTM	25OH Vit D	Ca++	preg test*				
SCREENING		X		X	X	X	X	X	X	X	X		X
BASELINE	X	X	X								X	X	
WEEK 6			X										
WEEK 12	X	X	X	X	X	X		X	X		X		
WEEK 24	X	X	X					X	X	X			
WEEK 36	X	X	X					X	X				
WEEK 48	X	X	X	X	X	X		X	X	X	X	X	
WEEK 60	X	X	X					X	X				
WEEK 72	X	X	X			X		X	X	X			
WEEK 84	X	X	X					X	X				
WEEK 96	X	X	X	X	X	X		X	X	X		X	
WEEK 108	X	X	X					X	X				
WEEK 120	X	X	X			X		X	X	X			
WEEK 132	X	X	X					X	X				
WEEK 144		X	X	X	X	X		X	X	X		X	
								* if appropriate					

dmab: denosumab; plac: placebo; PBC: peripheral blood cell count; chem: chemistry; BTM: bone turnover markers preg: pregnancy - sticks to be provided by the rheumatology dept.; CR: conventional radiography; US: ultrasound; MRI: magnetic resonace imaging; ECG: electrocardiogramDXA: dual energy X-ray absorptiomery

Basic Serum chemistry will include urea, creatinine, ASAT, ALAT, Albumin. Depending on the individual patient, additional parameters may be added.

W36 is the timing for the last IP dose in the blinded period. All patients will receive a denosumab injection at W48 after the assessment. This would be the first denosumab dose administered in the open label phase.

Appendix 3: Reliability analyses of radiographic readings

Inter- and intrareader reliability analyses of radiographic scores by GUSS™ and anatomical scoring system by Verbruggen and Veys. Baseline and follow up radiographs of the first 20 patients (n = 320 joints)

Readers	VV*	GUSS™						
	Baseline data					Change scores		
		SC plate W0	Joint Width W0	SC Bone W0	Total score W0	Δ Total score W0-W24	Δ Total score W0-W48	Δ Total score W24 -W48
Intrareader reliability								
Reader 1 (GV)	0.917	0.938	0.958	0.979	0.980	0.822	0.893	0.802
Reader 2 (RW)	0.950	0.915	0.923	0.968	0.952	0.866	0.911	0.815
Interreader reliability								
Reader 1 vs. Reader 2	0.925	0.998	1.0	0.943	0.988	0.991	0.994	0.993

Inter- and intrareader reliability analyses of the radiographic scores by two radiographic scoring system, i.e. GUSS™ and the anatomical scoring system by Verbruggen and Veys. Scores of subdomains are shown for baseline data, and change of the total scores for longitudinal data. Data shown are intra-class coefficients of correlation (ICC) by two-way mixed, absolute agreement, average measures, or stated if otherwise for GUSS™ from the first 20 patients (accounting for 320 joints).
* Weighted kappa statistics from baseline data shown.
VV: anatomical phase scoring system by Verbruggen and Veys; SC: subchondral; GUSS™: Ghent University scoring system; Δ: change; W: week

Appendix 4: Clinical data from the placebo-controlled and open-label extension phase

End point	Group	Week 24	P-value within groups vs. baseline	P-value between groups vs. baseline	Week 48	P-value within groups vs. baseline	P-value between groups vs. baseline	Week 96	P-value within groups vs. baseline	P-value between groups vs. baseline	P-value between groups vs. week 48
Change in NRS pain (%)	Denosumab	-0.8 (-17.3)	**0.018**	0.690	-0.5 (-10.5)	**0.002**	0.299	-2.3 (-48.3)	**<0.001**	**0.028**	0.748
	Placebo	-0.7 (-14.0)	**0.011**	-	-0.6 (-12.5)	**0.035**	-	-1.3 (-26.7)	**<0.001**	-	-
Change in FIHOA (%)	Denosumab	1.3 (12.7)	**0.049**	0.202	1.4 (13.5)	**0.045**	0.092	-1.9 (-18.6)	**0.042**	**0.025**	0.586
	Placebo	2.3 (22.7)	**0.001**	-	2.6 (25.3)	**<0.001**	-	-0.5 (4.9)	0.627	-	-
Change in AUSCAN (%)	Denosumab	-3.8 (-5.6)	0.318	0.714	-2.1 (-3.1)	0.597	0.567	-4.9 (-7.4)	0.273	0.785	0.062
	Placebo	-1.5 (-2.2)	0.766	-	1.0 (1.5)	0.621	-	-7.4 (-10.7)	0.393	-	-
Change in tender joint count (%)	Denosumab	-0.3 (-5.3)	0.855	0.971	-0.9 (-17.0)	0.154	0.563	-2.1 (-38.0)	**0.001**	0.579	0.188
	Placebo	-0.6 (-11.2)	0.971	-	-0.8 (-14.0)	0.375	-	-2.8 (-52.7)	**0.021**	-	-
Change in swollen joint count (%)	Denosumab	-0.3 (-7.9)	0.432	0.255	-0.1 (-1.9)	0.886	0.135	-1.2 (28.3)	**0.003**	0.263	0.366
	Placebo	-1.0 (-20.3)	**0.016**	-	-1.0 (-21.8)	**0.011**	-	-1.8 (-37.0)	**<0.001**	-	-
Change in grip strength (%)	Denosumab	0.4 (2.3)	0.519	0.754	0.7 (4.4)	0.212	0.485	0.2 (1.3)	0.818	0.063	**0.016**
	Placebo	-0.2 (-1.0)	0.787	-	-1.0 (-5.4)	0.451	-	0.6 (3.1)	0.569	-	-

Longitudinal changes compared to baseline are given and percentage changes compared to baseline. Comparisons between groups was done by Generalized Estimation Equations at patient level. Between group changes were compared versus baseline and versus week 48 for data at week 96. Statistically significant P-values are shown in bold.
NRS: numeric rating scale, FIHOA: functional index for hand osteoarthritis; AUSCAN: Australian-Canadian Hand Osteoarthritis Index

Appendix 5: Protocol deviation log

Subject number	Date of notification	Date of Protocol deviation	Classification * Minor / Major	Description of deviation	Action taken	Date solved
001	9/03/2016	9/03/2016	major	The ICF was discussed with the patient before starting the study procedures and orally consent was given but it was forgotten to sign the document.	ICF form was placed into the patient binder to make sure the document was signed before starting the screening visit	Patient wasn't eligible, impossible to obtain signature.
012	12/05/2016	11/05/2016	major	An issue occured while performing bone densitometry at baseline visit	Patient was asked to return as soon as possible to retake the exam.	18/05/2016
015	3/05/2017	1/06/2016	minor	At baseline bone densitometry only two scans were made, spine and fore-arm. The scan from the hip was missing	The DXA instructions were re-formulated	3/05/2017
016	3/05/2017	1/06/2016	minor	At baseline bone densitometry only two scans were made, spine and fore-arm. The scan from the hip was missing	The DXA instructions were re-formulated	3/05/2017
018	3/05/2017	1/06/2016	minor	At baseline bone densitometry only two scans were made, spine and fore-arm. The scan from the hip was missing	The DXA instructions were re-formulated	3/05/2017
034	22/07/2016	20/07/2016	minor	Pregnacy test was not performed at screening	Test done at baseline before drug administration.	10/08/2016
022	22/08/2016	3/08/2016	minor	Patient wasn't able to come for visit week 6 on the planned date due to vacation abroad.	Visit was postponed with two week after patient's return.	17/08/2016
008	20/07/2016	3/08/2016	major	Patient did not appear on the appointment, he was on vacation and didn't notify the study nurse.	Visit week 12 was postponed, patient came immedially after his return. Study drug was adminitered at week 14	3/08/2016
012	22/08/2016	17/08/2016	major	Due to holidays, patient was not able to come at the planned date for visit W12	Visit and injection study drug were postponed with 2 weeks and patient was asked to take the study schedule into account planning her holidays.	17/08/2016
043	20/04/2017	31/08/2016	major	Patient signed version 2 of the ICF, however version 3 was already approved by the EC (dd 19/8/2016- date received from EC 23/08/2016).	Old versions were archived/destroyed	21/04/2017
002	16/09/2016	14/09/2016	major	ICF v. 3.0 should have been signed at visit week 24. The changes were discussed orally but the ICF was signed at visit Week 36	New versions of the ICF was placed in all patient binders so it was clear the patient still had to be notified	7/12/2021
022	16/09/2016	14/09/2016	major	ICF v. 3.0 should have been signed at visit week 12. The changes were discussed orally but the ICF wasn't	The ICF was signed during the next study visit.	7/12/2016
016	30/11/2016	23/11/2016	major	ICF v. 3.0 should have been signed at visit week 24. The changes were orally discussed but the ICF was not	The ICF was signed during the next study visit.	8/02/2017

Subject number	Date of notification	Date of Protocol deviation	Classification * Minor / Major	Description of deviation	Action taken	Date solved
063	28/12/2016	28/12/2016 - 25/01/2017	major	During screening visit the patient was treated with a minor dose of oral corticoids for a respiratory infection. Due to this, some of the screening exams (PRO, echo and clin. ass.) were no performed during this visit. For the same reason the baseline visit was postponed with one week to wash-out the corticoid treatment. Despite suppletion the 25-OH vit D values were < 20µg/ml due to a history of gastric bypass.	An endocrinologist was consulted about the risk of the study in a patient with deficiencies due to a bypass. The investigator decided that the patient could be included on condition that the patient would be monitored very close. 4 weeks after the first visit a baseline visit was performed and the patient was randomized. Patient was excluded on Week 6 because of an SAE.	25/01/2017
028	5/01/2017	4/01/2017	minor	At visit week 24 the patient left the hospital before the RX of the hand was performed.	Patient was willing to return the next week and RX was performed at week 25.	11/01/2017
062	25/01/2017	25/01/2017	major	Subject had hypocalcemia at screening (1.97 mmol/L - nrml. range 2.12-2.62) due to iatrogene hypoparathyroïdie after thyroïdectomie.	Investigator contacted endocrinologist for consult. It was decided that the patient could be included provided that Ca would be monitored very close.	25/01/2017
068	22/02/2017	22/02/2017	major	Because of illness the period between screening and baseline was 4 weeks instead the 3 weeks mentioned in the protocol	Patient was asked to come as soon as possible/recovered	22/07/2017
066	22/02/2017	1/03/2017	major	Because of illness the period between screening and baseline was 4 weeks instead the 3 weeks mentioned in the protocol	Patient was asked to come as soon as possible/recovered	22/02/2017
004	8/03/2017	9/03/2017	major	Due to an SAE the patient was not able to come on the planned date for visit week 48	When she was able to walk again, the patient came for visit week 48. Visit and injection were postponed with 2 weeks.	22/03/2017
075	15/03/2017	15/03/2017	minor	During screening visit , patient left the hospital without ECG	ECG was performed at the start of the baseline visit before the drug administration.	29/03/2017
069	15/03/2017	15/03/2017	major	At baseline, patient's 25-OH Vit D was <20µg/ml	Investigator prescribed an extra suppletion therapy (D-Cure)	15/03/2017
002	24/05/2017	24/05/2017	major	The administration of the studie medication for week 60 was postponed because of AE.	Injected at week 64 when patient was recuvered	27/06/2017
091	1/10/2017	31/05/2017 - 03/04/2020	minor	Patient doesn't take the vit D/calcium supplement daily	Calcium levels are monitored very close during every visit	1/10/2017
073	26/04/2017	7/06/2017	major	The administration of the studie medication for week 12 was postponed because of patient's planned holiday.	Visit and injection study drug were postponed with 2 weeks and patient was asked to take the study schedule into account planning her holidays.	21/06/2017
045	12/07/2017	12/07/2017	major	Pregnacy test was not performed at W12	Physician decided the exam not applicable patient confirmed sexual abstinence	12/07/2017

Subject number	Date of notification	Date of Protocol deviation	Classification * Minor / Major	Description of deviation	Action taken	Date solved
055	26/07/2018	25/07/2018	major	Pregnacy test was not performed at week 84	Notified the lab but additional test could not be performed	26/07/2018
1064	16/08/2018	5/09/2018	major	Patient called to say she could not come to visit week 36	Visit was postponed to 22/08/2018, administered at week 38	22/08/2018
1081	5/10/2018	10/10/2018	major	Due to an AE the patient couldn't come for visit week 36	Visit was postponed to 15/01/2020 and study drug was administered at week 110	24/10/2018
1038	17/10/2018	17/10/2018	minor	Missing diary's at W36,	Patient stated not to have taken NSAID's nor analgetics	17/10/2018
100	7/11/2018	7/11/2018	minor	Grip assessment was not performed at W48	Informed the investigator that data was missing	7/11/2018
1077	21/11/2018	21/11/2018	major	At visit week 24, open label denosumab was administered by accident insteat of blinded study drug.	No action performed at that time. At the moment of unblinding we've checked in wich group the patient was randomised. tThis was the group of active treatment so the event didn't impact the study results.	20/08/2020
060	11/12/2018	11/12/2018	major	Due to late protocol approval the extention phase was started 16 weeks after the last injection.	As soon as the protocol was approve the extension phase was started. Study drug for week 96 was administered at week 100.	11/12/2018
059	12/12/2018	12/12/2018	major	Due to late protocol approval the extention phase was started 16 weeks after the last injection.	As soon as the protocol was approve the extension phase was started. Study drug for week 96 was administered at week 100.	12/12/2018
070	3/12/2018	2/01/2019	major	Patient is often abroad for work for longer periods, due to hisabsence visit week W96 was put forward.	Visit week 96 was put forward to , study drug injected at week 94.	19/12/2018
072	17/01/2019	16/01/2019	major	Although a pregnacy test for W96 was requested it wasn't performed by the lab.	Contacted the lab to check how this can be avoided. Extra mark on the order request.	17/01/2019
100	30/01/2019	30/01/2019	major	Patient forgot his appointment for visit W60	Contacted the patient and visit was postponed and study drug was administered at week 62	13/02/2019
061	6/03/2019	6/03/2019	major	Patient signed ICF v. 5.0 dd. 18/01/2019 before final approval of EC	none	6/03/2019
084	3/04/2019	3/04/2019	minor	Patient left the hospital before the DXA for week 96 was not perfomed.	Patient was not willing to return, to far.	4/04/2019
100	24/04/2019	24/04/2019	minor	On his way to the hospital, patient forgot his diary on the tram.	Patient stated not to have taken any NSAID's or analgetics	24/04/2019
076	27/02/2019	22/05/2019	major	The administration of the studie medication for week 96 was postponed because of patient's planned holiday.	Visit week 96 was postponed to , study drug injected at week 98.	5/06/2019
070	20/03/2019	19/06/2019	major	Patient is often abroad for work for longer periods, due to his absence visit week W120 was put forward.	Visit week 120 was put forward to , study drug injected at week 118.	3/06/2019
078	24/07/2019	1/07/2019	minor	Patient decided not to take the vit D / calcium supplement during his 3 weeks lasting vacation.	Explained the importance of drug compliance.	24/07/2019

Subject number	Date of notification	Date of Protocol deviation	Classification * Minor / Major	Description of deviation	Action taken	Date solved
092	19/07/2017	19/07/2017	minor	Patient doesn't want to take the provided Vit D/Calcium supplement	The supplement was replaced by by a magistral formula combined with Vit D supplement	19/07/2017
027	16/08/2017	16/08/2017	major	At visit week 48 patient reported an AE, the investigator decided not to administer the study drug for safety reasons	Study treatment was rechallenged the next visit, week 60.	16/08/2017
041	2/08/2017	25/10/2017	major	Patient was'n able to come on the planned date for visit week 60.	Vist was postponed to 08/11/2017, study drug injected at week 62	8/11/2017
044	31/10/2017	25/10/2017	minor	An issue occured while performing bone densitometry at visit week 48	The exam was performed the next visit, week 60	17/01/2018
055	17/11/2017	15/11/2017	major	Pregnacy test was not performed at week 48	Notified the lab but additional test could not be performed	17/11/2017
026	23/11/2017	22/11/2017	minor	At visit week 72 the patient left the hospital before the RX of the hand was performed.	The exam was performed the next visit	14/02/2018
006	13/12/2017	13/12/2017	major	The administration of the studie medication for week 84 was postponed because of patient's planned holiday.	Injected study drug at week 87 and asked the patient to take the study schedule into account planning his holidays.	13/12/2017
045	3/01/2018	3/01/2018	major	Pregnacy test was not performed at W12	Physician decided the exam not applicable patient confirmed sexual abstinence	3/01/2018
1030	2/02/2018	31/01/2018	major	Pregnancy test was not performed at SCR	Urine pregnancy test was done at baseline before the administration of the study drug.	7/02/2018
085	6/02/2018	7/02/2018	major	Patient called that she could not be present at visit week 36	Visit was postponed to 21/02/2018, drug was administrated at week 38	21/02/2018
1038	8/02/2018	8/02/2018	minor	Patient is no longer willing taking Ca-Vit D suppl. because of AE	Calcium levels are monitored very close during evry visit	8/02/2018
045	16/03/2018	16/03/2018	major	Pregnacy test was not performed at W12	Physician decided the exam not applicable patient confirmed sexual abstinence	16/03/2018
082	17/01/2018	11/04/2018	major	The administration of the studie medication for week 48 was postponed because of patient's planned holiday.	Visit week 48 was postponed to , study drug injected at week 46.	28/03/2018
023	9/05/2018	9/05/2018	minor	Patient didn't bring her NSAID diary to visit week 96. The document got lost at home.	None	9/05/2018
1064	7/03/2018	30/05/2018	major	Patient had planned a holiday on the date of visit W24	Visit was put forward to 16/05/2018, drug administered at week 22	16/05/2018
094	11/04/2018	4/07/2018	major	The administration of the studie medication for week 48 was postponed because of patient's planned holiday.	Visit week 48 was postponed to , study drug injected at week 50.	18/07/2018
070	25/04/2018	18/07/2018	major	Patient is often abroad for work for longer periods, due to his absence visit week W72 was postponed.	Visit week 72 was postponed to , study drug injected at week 78.	29/08/2018

Subject number	Date of notification	Date of Protocol deviation	Classification * Minor/ Major	Description of deviation	Action taken	Date solved
045	15/05/2019	7/08/2019	major	Due to vacation, patient was'n able to come on the planned date for visit week 120.	Vist was postponed to 21/08/2019, study drug injected at week 122.	21/08/2019
1058	14/08/2019	14/08/2019	minor	Patient was confiused and didn't know were his diary	none	14/08/2019
094	5/06/2019	28/08/2019	major	The administration of the studie medication for week 108 was postponed because of patient's planned holiday.	Visit week 108 was put forward to 14/08/2019 , study drug injected at week 106.	14/08/2019
5090	18/09/2019	18/09/2019	minor	Patient could not find her diary at home	No NSAID's nor analgetics were taken since previous	18/09/2019
1077	22/09/2019	23/10/2019	major	Patient had planned a surgery wich required revalidation at the time of visit week 72	Visit week 72 was put forward to 09/10/2019	9/10/2019
074	3/07/2019	25/10/2019	major	The administration of the studie medication for week 132 was postponed because of patient's planned holiday.	Visit and injection study drug were postponed with 2 weeks and patient was asked to take the study schedule into account planning her holidays.	9/10/2019
094	14/11/209	20/11/2019	major	The administration of the studie medication for week 120 was postponed because of patient's planned holiday.	Visit week 120 was postponed to 04/12/2019 , study drug injected at week 122.	4/12/2019
100	2/01/2020	2/01/2020	major	Patient called to postpone his visit week 108	Visit was postponed to 15/01/2020 and study drug was administered at week 110	15/01/2020
100	25/03/2020	25/03/2020	major	Due to the Covid-19 pandemic the patient wasn't willing to come to the hospital for visit week 120	Treatemnt was temporary discontinued and rechalenged at week 132	25/03/2020
1087	25/03/2020	25/03/2020	major	GP had the patient advised not to go to the hospital due to covid-19 pandemic	study drug week 96 was not injected, therapy was rechalenged at week 108	25/03/2020
080	22/04/2020	22/04/2020	major	During visit week 96 patient mentions an AE, administration of the study drug is postponed due to the AE	Patient returned 13/05/2020, after consult investigator considered it was safe to continue the therapy and injection week 96 was administered	13/05/2020
098	10/06/2020	10/06/2020	major	Due to Covid-19 pandemic patient wasn't willing to come to the hospital for the final visit week 96.	None	10/06/2020
1038	19/08/2020	19/08/2020	minor	Missing diary's at W132,	Patient stated not to have taken NSAID's nor	19/08/2020
1030	18/08/2020	19/08/2020	major	Patient called to postpone his visit week 132	Visit was postponed to 02/09/2020, study drug was administered at week 134	2/09/2020
3043	15/10/2020	14/10/2020	major	Patient forgot to go to the lab for blood tests	Since the Calcium levels for this patient were normal during the previous visits it was decided no action was needed.	15/10/2020
1038	25/11/2020	25/11/2020	minor	Missing diary's at W144	Patient stated not to have taken NSAID's nor	25/11/2020
1087	30/01/2021	30/01/2021	major	Patient couldn't come for visit week 36	visit was postponed to week 38, study drug was injected at week 38	13/02/2019