February 16, 2016

# Study Protocol

## 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

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## Protocol Signature Page

### Principal/Chief Investigator signature

I confirm that I have read and understood protocol version 2.0 - 16 FEBRUARY 2016 ~~xx dated xx January 2015~~. I agree to comply with the study protocol, the principals of GCP, research governance, clinical trial regulations and appropriate reporting requirements.

AVDB 25/4/17

Signature..... Date... 17 FEB 2016.....

Print name ..... PROF DR. FLEWAUT DIRK.....

## Protocol synopsis

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| **Study Type** | **I**nvestigator **S**ponsored **S**tudy |
| **Funder** | Amgen |
| **Study Design** | This is a randomized, double blind placebo controlled one-site proof-of-concept study in subjects with erosive osteoarthritis (OA) of interphangeal (IP) finger joints.<br>A total of 100 subjects will be enrolled into the study: 48 weeks placebo controlled double-blind phase with denosumab 60 mg every 12 weeks, followed by a 48-week open-label phase in which all subjects will receive denosumab. |
| **Investigational Therapy** | Denosumab 60 mg subcutaneous injection every 12 weeks. All subjects will receive Calcium/vit D supplementation. |
| **Efficacy Objectives** | The **primary objective** is to assess the effect of denosumab on the reduction of radiographic erosive progression using GUSS™ (Ghent University Score System).<br>The **secondary objective** is to assess the effect of denosumab on the reduction of radiographic erosive progression as defined by diminishing the appearance of new erosive IP finger joints.<br>The **exploratory objective** is mainly to assess the effect of denosumab on clinical variables, as well as ultrasonography and DEXA parameters. |
| **Main Endpoints** | **Primary Endpoint:** The change in the negative evolution of GUSS™ scores in the target IP joints from baseline to week 24.<br>**Other Endpoints:** 1) The change in the negative evolution of GUSS™ scores in the target IP joints from week 24 to week 48 and from baseline to week 48. 2) The number of patients that develop new erosive IP joints ('S/J' to 'E' phase joints) at 48 weeks; 3) The number of 'S/J' IP joints that develop 'E' phases at 48 weeks. |
| **Hypothesis** | **The main hypothesis** is that the repeated administration of denosumab 60 mg Q3 months can lead to reduce structural damage in erosive hand OA. |
| **Study Sites** | 1 site – the Ghent site |
| **Subjects** | 100 subjects |
| **Enrolment** | 18 months |
| **Main Eligibility Criteria** | Males and females ≥ 30 years of age, with hand erosive OA:<br>1) having suffered from transient inflammatory attacks of the IP finger joints<br>2) showing at the time of enrolment inflammatory signs and at least one IP finger joint with the typical X-rays appearance of a 'J' or 'E' phase joint |

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| **Study treatment Duration** | 96 weeks |

## Table of Contents

# 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.

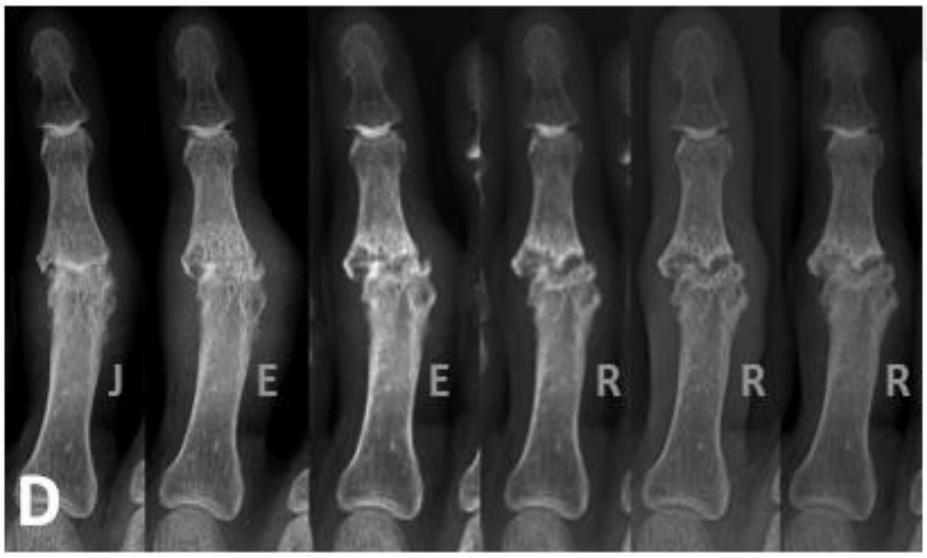



Figure 1: radiographic progression of a proximal IP joint from ‘J’ phase with loss of joint space to the ‘E’ phase with osteolytic activity in the subchondral bone area, and final remodeling of the destroyed tissues (R). Radiographs were taken with 6-months interval.

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.

### 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:
1. 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.
2. Changes in sonographic inflammatory signals at week 12 and 48 compared to screening and baseline. Inflammatory changes will be assessed by measuring the amount of effusion and Power Doppler signal (scoring on a semi-quantitative scale).
3. 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).

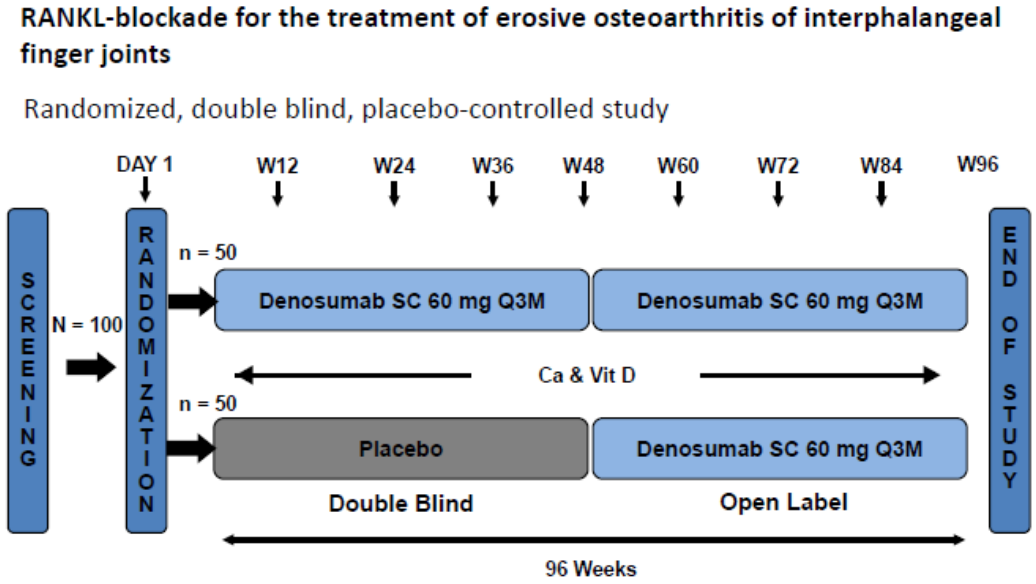
# 3. Experimental Plan

## 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.

**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.

### 3.4 Estimated study duration

The total treatment duration per subject is 24 months (96 weeks). The expected total trial duration defined as the time from first patient first visit to last patient last visit is 42 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.

## 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.
- Prior use of any immunomodulating drug with possible effects on proinflammatory cytokine metabolism within 90 days a.o. corticosteroids, 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 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.

**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.

Administration of IP must be performed as the last procedure after all the other study procedures have been completed for the visit. 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 Reporting requirements for investigational product complaints:**
The following could be considered potential product complaints that need to be reported to Amgen. The Investigator will use a Product Complaint Form as provided by Amgen to report any complaint. Should any such concerns or irregularities occur, the IP will not be used until Amgen confirms that it is permissible to use. Examples of Product Complaints:
• Packaging: for example, broken container or cracked container
• Devices: issues with delivery of IP by device
• Usage: for example, subject or healthcare provider cannot appropriately use the product
• Labeling: for example, missing labels, illegible labels, incorrect labels, and/or suspect labels
• Change in IP appearance: for example color change or presence of foreign material
• Unexpected quantity in bottle: for example number of tablets or amount of fluid
• Evidence of tampering or stolen material

**5.3 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.

**5.4 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. Serum calcium levels, PBC and serum chemistry (glucose levels, liver and kidney function tests, and BTM. Study products (denosumab/placebo) to be administered. DXA is optional.

**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.

**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 Statisticap 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 a 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 (VAS 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, the change in HOAMRIS 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 and correction for baseline radiographic damage. 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 ($\alpha$) 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.

# 7. Adverse Events/Adverse Event reporting

The investigator will monitor each subject for clinical and laboratory (serum $Ca^{++}$ levels) evidence of adverse events on a routine basis throughout the study. The investigator will assess and record any adverse event in detail on the adverse event DRF including the date and time of onset, description, seriousness severity, time course, duration and outcome, relationship of the adverse event to study drug, an alternate etiology for events not considered "probably related" to study drug, final diagnosis/syndrome (if known) and any action(s) taken. Adverse events, whether in response to a query, observed by study-site personnel, or reported spontaneously by the subject, will be recorded.

All adverse events will be followed to a satisfactory conclusion.

## 7.1 Definitions

### 7.1.1. Adverse Event

An **adverse event** is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in permanent

or temporary discontinuation of treatment with denosumab, necessitate therapeutic medical intervention and/or if the investigator considers them to be adverse events.

An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event. However, if a pre-existing condition deteriorates unexpectedly during the trial (*e.g.,* surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event.

**7.1.2. Serious Adverse Event**

If an adverse event meets any of the following criteria, it is to be considered as serious:

| | |
|---|---|
| **Death of Subject** | An event that results in the death of a subject. |
| **Life-Threatening** | An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form. |
| **Hospitalization** | An event that results in an admission to the hospital for any length of time. This does not include an emergency room visit or admission to an outpatient facility. |
| **Prolongation of Hospitalization** | An event that occurs while the study subject is hospitalized and prolongs the subject's hospital stay. |
| **Congenital Anomaly** | An anomaly detected at or after birth, or any anomaly that results in fetal loss. |
| **Persistent or Significant Disability/Incapacity** | An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (*e.g.*, sprained ankle). |
| **Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome** | An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (*i.e.,* death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. |
| **Spontaneous Abortion** | Miscarriage experienced by study subject. |
| **Elective Abortion** | Elective abortion performed on study subject. |

### 7.1.3. Adverse Event Severity

The investigator will use the following definitions to define/rate the severity of each adverse event:

| | |
|---|---|
| **Mild** | The adverse event is transient and easily tolerated by the subject. |
| **Moderate** | The adverse event causes the subject discomfort and interrupts the subject's usual activities. |
| **Severe** | The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening. |

### 7.1.4. Relationship to Study Drug

The investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug:

| | |
|---|---|
| **Probably Related** | An adverse event has a strong temporal relationship to study drug or recurs on re-challenge and another etiology is unlikely or significantly less likely. |
| **Possibly Related** | An adverse event has a strong temporal relationship to the study drug and an alternative etiology is equally or less likely compared to the potential relationship to study drug. |
| **Probably Not Related** | An adverse event has little or no temporal relationship to the study drug and/or a more likely alternative etiology exists. |
| **Not Related** | An adverse event is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug (*e.g.*, has no temporal relationship to study drug or has a much more likely alternative etiology). |

### 7.2. Adverse Event Reporting

Reporting will be consistent with current safety reporting standards. .Adverse events will be reported between the first dose administration of trial medication and the last trial related activity.

All AEs and SAE's will be recorded in the patient's file and in the CRF. All SAE's will be reported as described below.

SAE's occurring within a period of 30 days following the last intake of trial medication will also be handled as such if spontaneously reported to the investigator.

All serious adverse events (SAE) and pregnancies occurring during clinical trials must be reported by the local Principal Investigator within 2 working days after becoming aware of the SAE to:

- The local EC
- Bimetra Clinics of the University Hospital Ghent

This reporting is done by using the appropriate SAE form. For the contact details, see below.

It is the responsibility of the local Principal Investigator to report the local SAE's to the local EC.

In case the investigator decides the SAE is a SUSAR (Suspected Unexpected Serious Adverse Reaction), Bimetra Clinics will report the SUSAR to the Central EC and the CA within the timelines as defined in national legislation.

In case of a life-threatening SUSAR the entire reporting process must be completed within 7 calendar days. In case of a non life-threatening SUSAR the reporting proces must completed within 15 calendar days.

The first report of a serious adverse event may be made by telephone, e-mail or facsimile (FAX).

Contact details of Bimetra Clinics:

e-mail: bimetra.clinics@uzgent.be
tel.: 09/332 05 00
fax: 09/332 05 20

In the event of a serious, unexpected and related adverse event, the investigator will report this to the Amgen Affiliate by faxing the appropriate adverse event form within 24 hours of being made aware of the serious adverse event and simultaneously to Bimetra Clinics who will report the event to the local regulatory agency within the timelines as defined in the national legislation..

**Please fax SAE form to Martine Vansingel, Pharmacovigilance Manager : Fax number 0800 80877**

The investigator must provide the minimal information: i.e. trial number, subject's initials and date of birth, medication code number, period of intake, nature of the adverse event and investigator's attribution.
This report of a serious adverse event by telephone must always be confirmed by a written, more detailed report. For this purpose the appropriate SAE form will be used.
Pregnancies occurring during clinical trials are considered immediately reportable events. They must be reported as soon as possible using the same SAE form. The outcome of the pregnancy must also be reported.

**If the subjects are not under 24-hour supervision of the investigator or his/her staff (out-patients, volunteers), they (or their designee, if appropriate) must be provided with a "trial card" indicating the name of the investigational product, the trial number, the investigator's name and a 24-hour emergency contact number.**

# 8. Regulatory Obligations

### 8.1 Informed Consent

Signed informed consent will be obtained from the subject before any study procedures are undertaken, or before any medications are withheld from the subject in order to participate in this study. Subject may withdraw consent at any time without prejudice. All efforts will be made to continue the patient follow-up until the end of the study. At withdrawal, patients will be treated and assessed according to standard recommendations and as per latest guidance for contraception criteria in female subjects of child-bearing age or partners of childbearing potential (see exclusion criteria section 4.2).

### 8.2 Independent Ethics Committee/Institutional Review Board

The study will be declared at www.ClinicalTrials.gov and will comply with the principles of the Declaration of Helsinki. A copy of the study protocol will be submitted for approval to the ethical committee of Ghent University Hospital and to the Federal Agency for Medicines and Health Products *(FAGG; federal agentschap voor geneesmidddelen en gezondheidsproducten)*

# 9. Documentation relating to the clinical trial – Trial Master File

All documents related to the trial, e.g. study protocol, source documents, case report forms, … will be handled, stored and archived according to the EU Commission's Directive 2005/28/EC 63 Chapter 4.[40]

# 10. Publication Policy

The results of this study will be reported and published at conferences and in peer-reviewed clinical journals. Authorship publications will follow the Uniform Requirement for

Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors, 2009), which states:
Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published and (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, 3 and 4.
For further details , see http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html.

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## 12.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 | |

* 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.