Study Protocol

The use of buffered soluble alendronate 70 mg (Steovess/Binosto) after denosumab discontinuation to prevent increase in bone turnover.

Sponsor/Chief Investigator

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EudraCT number: 2019-003570-11

Protocolnumber: BC-6072

Protocol Signature Page

Principal/Chief Investigator signature

I confirm that I have read and understood protocol version 1.0 dd. 09 August 2019. I agree to comply with the study protocol, the principals of GCP, research governance, clinical trial regulations and appropriate reporting requirements.

Signature..... Date.....

Print name .....

Protocol synopsis

Study Type	**I**nvestigator **S**ponsored **S**tudy
Funder	Amgen and EffRx Pharmaceuticals
Study Design	This is a randomized study to investigate the effect of weekly 70mg effervescent alendronate [Steovess 70mg/weekly] on bone turnover after denosumab [Prolia 60 mg Q3M] discontinuation in patients with erosive osteoarthritis of the interphalangeal finger joints. At the earliest three months but no later than four months after the last denosumab injection, 40 subjects will be randomized to effervescent alendronate administered for either 24 (n=20) or 48 weeks (n=20).
Investigational Therapy	Subjects will be randomized to receive open label effervescent alendronate (Steovess/Binosto) for 24 or 48 weeks. All subjects will receive Calcium/vit D supplementation.
Efficacy Objectives	The primary objective of this studyis to investigate if weekly intake of 70mg effervescent alendronate can prevent increases in bone turnover above the premenopausal reference range at week 48 and if there is difference between using alendronate for 24 or 48 weeks, started three months after the last injection of denosumab. Other objectives of the study are: - to assess the changes in bone turnover after 12 and 24 weeks, - to explore the impact on dual-energy X-ray absorptiometry (DEXA) parameters after 24 and 48 weeks of treatment - to assess radiographic changes and investigate if new erosive joints develop at week 24 and 48
Main Endpoints	**The primary endpoint** of this objective is to assess the number of patients that maintain C-terminal telopeptide of type I collagen (CTx-I) levels within the premenopausal reference range at 48 weeks. **Secondary endpoints** are the assessment of the number of patients that maintain CTx-I levels within the premenopausal reference range at week 12 and 24 as well as the changes in CTx-I and N-terminal propeptide of type I procollagen (P1NP) levels from baseline until 12, 24 and 48 weeks after randomization to effervescent alendronate. **Co-exploratory objectives** are changes in T-score at lumbar spine and hip from baseline to week 24 and week 48, and the radiographic changes at the finger joints in terms of new erosive joints and GUSS change between W24 and W48 and baseline.
Hypothesis	**The main hypothesis** is that effervescent alendronate will be able to maintain bone turnover markers within the pre-menopausal reference range, thereby reducing the likelihood of bone turnover associated changes.
Study Sites	1 site – the UZ Ghent site
Subjects	40 subjects for the alendronate follow-up study
Enrolment	72 weeks
Main Eligibility Criteria	Subject must have completed our three year study 'RANKL-blockade for the treatment of erosive osteoarthritis (OA) of interphalangeal finger joints' (EudraCT number: 2015-003223-53; Protocolnumber: AGO/2015/008)
Study treatment Duration	48 weeks

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1. Background and Rationale

1.1 Disease background

Prolia (denosumab, anti-RANK ligand therapy) discontinuation is associated with a rebound in bone turnover and loss of bone mineral density (BMD).[1] These changes resulted in increases of fracture incidence in patients with postmenopausal osteoporosis back to background levels, however no excess in fracture incidence was observed.[2] Amongst the patients that presented with vertebral fractures after treatment discontinuation, there was a slightly higher incidence of multiple vertebral fractures in patients discontinuing Prolia versus those that discontinued placebo.[3]

In our study 'RANKL-blockade for the treatment of erosive hand osteoarthritis (OA) of interphalangeal finger joints' (EudraCT number: 2015-003223-53; Protocolnumber: AGO/2015/008) patients are randomized to placebo or denosumab (60 mg/Q3M) for 1 year followed by a two-year open label extension in which all subjects receive denosumab (60 mg/Q3M). Also in this non-osteoporotic population, increases in bone turnover are expected as soon as patients end study participation.

It is currently recommended that other anti-resorptive therapy may be warranted after Prolia discontinuation. One study describes the use of oral alendronate after denosumab therapy to maintain bone mineral density.[4] However, gastro-intestinal upset and tolerability, as well as difficulty swallowing pills may limit oral alendronate use. In the current study proposal we want to examine the use of effervescent alendronate (Steovess/Binosto) in subjects that completed our hand erosive osteoarthritis study and therefore discontinued denosumab 60 mg/Q3M.We hypothesize that Steovess/Binosto will be able to maintain bone turnover markers within the pre-menopausal reference range thereby reducing the likelihood of bone turnover associated changes.

In erosive hand OA, destructive erosive changes, followed by remodelling is key characteristic for the disease. As in inflammatory rheumatic diseases, the RANKL pathway appears to be involved in the pathogenesis and hence, a therapeutic role of its blockade has been studied in the study described above. It is unknown if a potential rebound effect in bone turnover might also be associated with a rebound in erosive destructive progression at the subchondral bone.

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.[5,6] 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)[7], 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[8,9], 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[5,6]. 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 Effervescent alendronate (Steovess/Binosto)

Bisphosphonates are widely used to prevent or to treat osteoporosis via inducing osteoclast apoptosis and inhibiting bone resorption.[10] In particular, alendronate has been reported to be an effective and well-tolerated drug for prevention and treatment of osteoporosis, offering sustained treatment benefits up to 2 years, with respect to increased BMD[11,12] and up to 4 years in terms of fracture prevention[13,14,15]. Alendronate, a second generation bisphosphonate, inhibits osteoclast activity, reduces bone resorption, and maintains the balance of bone resorption and formation.[16,17] Alendronate may also stimulate osteoblast differentiation, and prevent or mitigate bone cell and osteoblast apoptosis.[18,19]

A recent systemic review and meta-analysis including 1002 patients [20] on the use of alendronate in glucocorticoid-induced osteoporosis concluded that alendronate treatment significantly increased BMD of the lumbar spine and femoral neck during 6 to 24 months. These beneficial effects were apparent at 12 months after treatment for the lumbar spine but not the femoral neck BMD. Alendronate treatment did not significantly seem to change fracture risk. However, as relatively insufficient data regarding the fracture incidence has been reported, more research need to be carried out to determine the efficacy of alendronate in the prevention of fracture.

The most common adverse reactions[21] (incidence greater than or equal to 3%) are abdominal pain, acid regurgitation, constipation, diarrhea, dyspepsia, musculoskeletal pain, and nausea.

Bisphosphonates administered orally, may cause local irritation of the upper gastrointestinal mucosa. Because of these possible irritant effects and a potential for worsening of the underlying disease, caution should be used when alendronate is given to patients with active upper gastrointestinal problems (such as known Barrett's esophagus, dysphagia, other esophageal diseases, gastritis, duodenitis, or ulcers). Esophageal adverse experiences, such as esophagitis, esophageal ulcers and esophageal erosions, occasionally with bleeding and rarely followed by esophageal stricture or perforation, have been reported in patients receiving treatment with oral bisphosphonates including alendronate sodium. In some cases these have been severe and required hospitalization.

Hypocalcemia must be corrected before initiating therapy with alendronate. Other disorders affecting mineral metabolism (such as vitamin D deficiency) should also be effectively treated. In patients with these conditions, serum calcium and symptoms of hypocalcemia should be monitored during therapy with alendronate. Presumably due to the effects of alendronate on increasing bone mineral, small, asymptomatic decreases in serum calcium and phosphate may occur. Patients should receive adequate calcium and vitamin D intake.

Osteonecrosis of the jaw (ONJ), which can occur spontaneously, is generally associated with tooth extraction and/or local infection with delayed healing, and has been reported in patients taking bisphosphonates, including alendronate sodium. Known risk factors for osteonecrosis of the jaw include invasive dental procedures (e.g., tooth extraction, dental implants, boney surgery), diagnosis of cancer, concomitant therapies (e.g., chemotherapy, corticosteroids, angiogenesis inhibitors), poor oral hygiene, and co-morbid disorders (e.g., periodontal and/or

other pre-existing dental disease, anemia, coagulopathy, infection, ill-fitting dentures). The risk of ONJ may increase with duration of exposure to bisphosphonates. For patients requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk for ONJ. Clinical judgment of the treating physician and/or oral surgeon should guide the management plan of each patient based on individual benefit/risk assessment.

Atypical, low-energy, or low trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates. Atypical femur fractures most commonly occur with minimal or no trauma to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g., prednisone) at the time of fracture. Any patient with a history of bisphosphonate exposure who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out an incomplete femur fracture. Patients presenting with an atypical fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of bisphosphonate therapy should be considered, pending a risk/benefit assessment, on an individual basis.

1.4 Rationale for study design

Denosumab discontinuation is associated with a rebound in bone turnover and loss of BMD[1]. These changes resulted in an increase of fracture incidence in patients with postmenopausal osteoporosis back to background levels. However, no excess in fracture incidence was observed[2]. Amongst the patients who presented with vertebral fractures after treatment discontinuation, there was a slightly higher incidence of multiple vertebral fractures in patients discontinuing Prolia versus those who discontinued the placebo treatment[3].

A 2 year, randomized, crossover study demonstrated that alendronate intake after discontinuing denosumab treatment, lead to remaining stable BMD-values in postmenopausal women[4].

Also in the study with non-osteoporotic study population, ongoing in our department, increases in bone turnover are expected as soon as patients end study participation.

It is currently recommended that other anti-resorptive therapy may be warranted after Prolia discontinuation. One study describes the use of oral alendronate after denosumab therapy to maintain bone mineral density[4]. However, gastro-intestinal upset and tolerability, as well as difficulty swallowing pills may limit oral alendronate use, therefore possibly compromising patients adherence. To attenuate this concern, buffered soluble (effervescent) alendronate 70 mg will be used which was developed with the aim to improve the GI tolerability through full dissolution of alendronate in buffered palatable solution before ingestion[22].

This study wants to provide a follow up and examine the use of effervescent alendronate after denosumab treatment. Subjects that completed our erosive hand OA study and therefore

discontinued denosumab 60 mg/Q3M, will receive alendronate. Moreover, the study wants to asses if there is difference between using alendronate for six or twelve months, starting at the earliest three months but no later than four months after the last injection of denosumab.

1.5 Hypotheses

It is hypothesized that effervescent alendronate will be able to maintain bone turnover markers within the pre-menopausal reference range thereby reducing the likelihood of bone turnover associated changes, after discontinuation of Prolia treatment in a non-osteoporotic population.

2. Study Objectives and Endpoints

The objectives of the effervescent alendronate treatment after denosumab discontinuation are to investigate if weekly intake of effervescent alendronate can prevent increases in bone turnover above the premenopausal reference range* at week 48 and if there is difference between using alendronate for 24 or 48 weeks, started at the earliest three months but no later than four months after the last injection of denosumab.

* Reference range: CTX-I (IVD kit) Non menopausal women < 700ng/l. Menopausal women < 730ng/l. Adult male >20 to 120 years: < 695ng/L ; P1NP (IVD kit): Male > 45 years: 12.8-71.9 µg/L Non menopausal women: 13.7-71.1 µg/L Menopausal women: < 82.6 µg/L

Other objectives of the study are:

- to assess the changes in bone turnover after 12 and 24 weeks,
- to explore the impact on dual-energy X-ray absorptiometry (DEXA) parameters after 24 and 48 weeks of treatment
- to assess radiographic changes and investigate if new erosive joints develop at week 24 and 48

The primary endpoint of this objective is the number of patients that maintain C-terminal telopeptide of type I collagen (CTx-I) within the premenopausal reference range at 48 weeks.

Secondary endpoints are the number of patients that maintain CTx-I within the premenopausal reference range at week 12 and 24 as well as the changes in CTx-I and N-terminal propeptide of type I procollagen (P1NP) from baseline until 12, 24 and 48 weeks after randomization to effervescent alendronate.

Co-exploratory objectives are changes in T-score at lumbar spine and hip from baseline to week 24 and week 48, and related to the underlying erosive hand OA disease, the radiographic changes at the finger joints in terms of new (radiographic) erosive joints (n) and GUSS change (Δ) between W24 and W48 and baseline.

Safety-objective

This study will assess the safety of the weekly administration of effervescent alendronate 70mg in the population of patients with erosive OA. Safety evaluations will be made by recording the incidence of AE/SAE

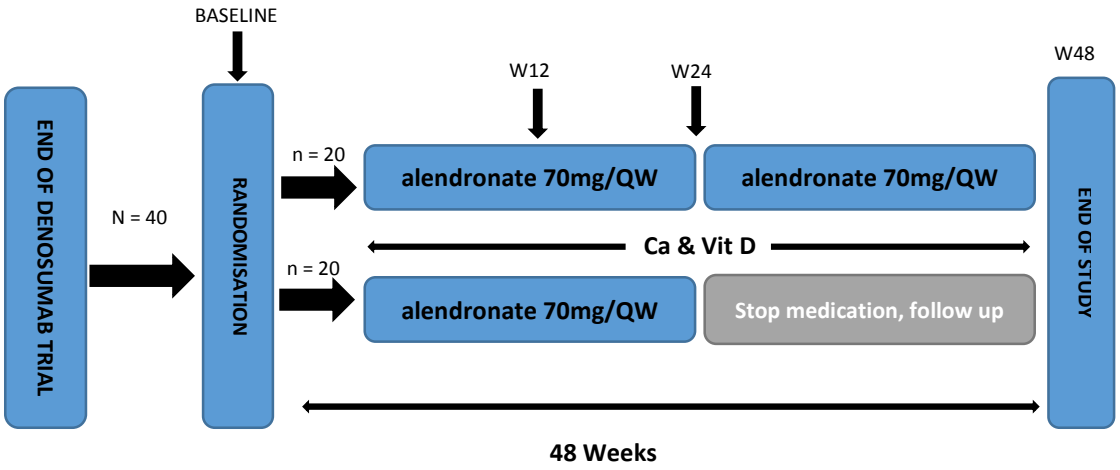
3. Experimental Plan

3.1 Study design and schematic

This is a randomized study to investigate the effect of effervescent alendronate on BTM after denosumab discontinuation.

At the earliest three months but no later than four months after the last denosumab injection, 40 subjects will be randomized to effervescent alendronate administered for either 24 (n=20) or 48 weeks (n=20). The randomization code will be generated by a randomization manager. Randomization will be done in blocks of four.

Study schematic



3.2 Number of sites

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

3.3 Number of subjects

Forty subjects, having finished the denosumab study, will be recruited within an enrolment period of 72 weeks.

3.4 Estimated study duration

The total treatment duration per subject is 48 weeks. The expected total trial duration defined as the time from first patient first visit to last patient last visit is 125 weeks.

3.5 Subject eligibility

3.5.1 Inclusion criteria

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

- Subjects must have completed the 48 weeks of the randomised placebo-controlled study phase followed by the 96 weeks open label denosumab 60 mg SC every 3 months phase. (EudraCT number: 2015-003223-53)
- Last denosumab injection less than four months ago
- Able and willing to give written informed consent and to comply with the requirements of the study protocol

3.5.2 Exclusion criteria

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

- Patients with clinically significant hypersensitivity to any of the components of effervescent alendronate.
- Patient who is pregnant or planning pregnancy
- 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
- 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
- Hypocalcaemia.
- Oesophageal disease, gastritis, duodenitis, ulcers, or with a recent history (within the previous year) of major gastro-intestinal disease such as peptic ulcer, or active gastro-intestinal bleeding, or surgery of the upper gastro-intestinal tract other than pyloroplasty.
- Abnormalities of the oesophagus and other factors which delay oesophageal emptying such as stricture or achalasia.
- Inability to stand or sit upright for at least 30 minutes.

3.6 Criteria for withdrawal

Subjects may prematurely discontinue from the study at any time. Premature discontinuation from the study is to be understood when the subject did not undergo end of study examination.

Subjects can be withdrawn under the following circumstances:

- at their own request
- if the investigator feels it would not be in the best interest of the subject to continue
- if the subject violates conditions laid out in the informed consent form or disregards instructions by the clinical investigation personal
- in case the subject experiences an adverse event due to the investigational product

In all cases, the reason why subjects are withdrawn must be recorded in detail in the CRF and in the subject's medical records.

4. Medication (see also paragraph 1.3)

4.1. Composition and dosing

After denosumab discontinuation subjects will be randomized to receive open label effervescent alendronate (Steovess) for 24 or 48 weeks. Effervescent alendronate a bisphosphonate as effervescent tablets that should be taken once a week. Each effervescent tablet contains 70 mg alendronic acid as 91.37 mg of alendronate sodium trihydrate. Excipients are sodium dihydrogen citrate, citric acid anhydrous, sodium hydrogen carbonate, sodium carbonate anhydrous, strawberry flavour [Maltodextrin (Maize), arabic gum, propylene glycol (E 1520), nature-identical flavouringsubstances], acesulfame potassium and sucralose. Each tablet contains 602.54 mg of sodium. Effervescent alendronate is supplied as a white to off-white round effervescent tablets of 25 mm diameter, flat faced with bevelled edges.

4.2. Producer

Steovess/Binosto is manufactured by Temmler Pharma GmbH - Temmlerstraße 2 - 35039 Marburg - Germany

4.3. Distributor

Steovess is released in the EU by Laboratoires Expanscience, Paris, France.

4.4. Packaging

The effervescent tablets are provided in strips of composite foil with effervescent 2 tablets packed in individual units per strip and packed with 4 or 12 tablets per box.

4.5. Administration way

Effervescent alendronate 70 mg should only be taken upon arising for the day dissolved in half a glass of plain water (not less than 120 ml or 4.2 fl.oz.). Dissolving the tablet in water yields a buffered solution of pH 4.8 – 5.4. The buffered solution should be drunk, once the fizzing has subsided and the effervescent tablet has completely dissolved to give a clear, colourless, buffered solution, followed by at least 30 ml (one sixth of a glass) of plain water. Additional plain water may be taken. Patients should not swallow the undissolved effervescent tablet, should not chew the effervescent tablet or allow the effervescent tablet to dissolve in their mouths because of the risk for oropharyngeal irritation. Patients should not lie down for at least 30 minutes after taking effervescent alendronate 70 mg.

Steovess will be distributed during study visits. Subjects should take one 70 mg effervescent tablet once weekly at home. Patients should be instructed that if they miss a dose of alendronate 70 mg, they should take one effervescent tablet on the morning after they remember. They should not take two effervescent tablets on the same day but should return to taking one effervescent tablet once a week, as originally scheduled on their chosen day.

Alendronate 70 mg must be taken at least 30 minutes before the first food, beverage, or medicinal product of the day with plain water only. Other beverages (including mineral water), food and some medicinal products are likely to reduce the absorption of alendronate.

Patients are requested not to take any study medication on the morning of a planned visit (week 12, week 24 or week 48): this accounts for the study medication (Steovess) and the calcium/ vitamine D supplements.

4.6. Labelling

The open-label STEOVESS will be delivered by Laboratoires Expanscience to the Ghent University Hospital Department of Rheumatology (via the Ghent University Hospital Pharmacy). All packages will be labeled study-specific following EU GMP guidelines and the hospital law by the Ghent University Hospital Pharmacy before dispensing to the subjects.

Example of the label can be found in annex I

4.7. Storage conditions

This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from moisture.

4.8. Known side effects of the medication

Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.
The safety of BINOSTO (alendronate sodium) effervescent tablet 70 mg is based on clinical trial data of alendronate sodium 10 mg daily and alendronate sodium 70 mg weekly.
Treatment of Osteoporosis in Postmenopausal Women
Daily Dosing The safety of alendronate sodium 10 mg daily in the treatment of postmenopausal osteoporosis was assessed in four clinical trials that enrolled 7453 women aged 44-84 years. Study 1 and Study 2 were identically designed, three-year, placebo-controlled, double-blind, multicenter studies (United States and Multinational n=994); Study 3 was the three year vertebral fracture cohort of the Fracture Intervention Trial [FIT] (n=2027) and Study 4 was the four-year clinical fracture cohort of FIT (n=4432). Overall, 3620 patients were exposed to placebo and 3432 patients exposed to alendronate. Patients with pre-existing gastrointestinal disease and concomitant use of non-steroidal anti-inflammatory drugs were included in these clinical trials. In Study 1 and Study 2 all women received 500 mg elemental calcium as carbonate. In Study 3 and Study 4 all women with dietary calcium intake less than 1000 mg per day received 500 mg calcium and 250 IU Vitamin D per day.
Among patients treated with alendronate 10 mg or placebo in Study 1 and Study 2, and all patients in Study 3 and Study 4, the incidence of all-cause mortality was 1.8% in the placebo group and 1.8% in the alendronate group. The incidence of serious adverse events was 30.7% in the placebo group and 30.9% in the alendronate group. The percentage of patients who discontinued the study due to any clinical adverse event was 9.5% in the placebo group and

8.9% in the alendronate group. Adverse reactions from these studies considered by the investigators as possibly, probably, or definitely drug related in greater than or equal to 1% of patients treated with either alendronate or placebo are presented in Table 1
Rarely, rash and erythema have occurred.

Gastrointestinal Adverse Reactions: One patient treated with alendronate sodium (10 mg/day),

Table 1 **Osteoporosis Treatment Studies in Postmenopausal Women Adverse Reactions Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in Greater Than or Equal to 1% of Patients**

	United States/Multinational Studies		Fracture Intervention Trial	
	Alendronate Sodium* % (N=196)	Placebo % (N=397)	Alendronate Sodium** % (N=3236)	Placebo % (N=3223)
Gastrointestinal				
Abdominal pain	6.6	4.8	1.5	1.5
Nausea	3.6	4.0	1.1	1.5
Dyspepsia	3.6	3.5	1.1	1.2
Constipation	3.1	1.8	0.0	0.2
Diarrhea	3.1	1.8	0.6	0.3
Flatulence	2.6	0.5	0.2	0.3
Acid regurgitation	2.0	4.3	1.1	0.9
Esophageal ulcer	1.5	0.0	0.1	0.1
Vomiting	1.0	1.5	0.2	0.3
Dysphagia	1.0	0.0	0.1	0.1
Abdominal distention	1.0	0.8	0.0	0.0
Gastritis	0.5	1.3	0.6	0.7
Musculoskeletal				
Musculoskeletal (bone, muscle or joint) pain	4.1	2.5	0.4	0.3
Muscle cramp	0.0	1.0	0.2	0.1
Nervous system/psychiatric				
Headache	2.6	1.5	0.2	0.2
Dizziness	0.0	1.0	0.0	0.1
Special senses				
Taste perversion	0.5	1.0	0.1	0.0

* 10 mg/day for three years
** 5 mg/day for 2 years and 10 mg/day for either 1 or 2 additional years

who had a history of peptic ulcer disease and gastrectomy and who was taking concomitant aspirin developed an anastomotic ulcer with mild hemorrhage, which was considered drug related. Aspirin and alendronate sodium were discontinued and the patient recovered. In the Study 1 and Study 2 populations, 49-54% had a history of gastrointestinal disorders at baseline and 54-89% used nonsteroidal anti-inflammatory drugs or aspirin at some time during the studies .

Laboratory Test Findings: In double-blind, multicenter, controlled studies, asymptomatic, mild, and transient decreases in serum calcium and phosphate were observed in approximately 18% and 10%, respectively, of patients taking alendronate versus approximately 12% and 3% of those taking placebo. However, the incidences of decreases in serum calcium to less than 8.0 mg/dL (2.0 mM) and serum phosphate to less than or equal to 2.0 mg/dL (0.65 mM) were similar in both treatment groups.
Weekly Dosing The safety of alendronate sodium 70 mg once weekly for the treatment of postmenopausal osteoporosis was assessed in a one-year, double-blind, multicenter study comparing alendronate 70 mg once weekly and alendronate 10 mg daily. The overall safety and

tolerability profiles of once weekly alendronate 70 mg and alendronate 10 mg daily were similar. The adverse reactions considered by the investigators as possibly, probably, or definitely drug related in greater than or equal to 1% of patients in either treatment group are presented in Table 2.

Table 2 **Osteoporosis Treatment Studies in Postmenopausal Women Adverse Reactions Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in Greater Than or Equal to 1% of Patients**

	Once Weekly Alendronate Sodium 70 mg % (N=519)	Once Daily Alendronate Sodium 10 mg % (N=370)
Gastrointestinal		
Abdominal pain	3.7	3.0
Dyspepsia	2.7	2.2
Acid regurgitation	1.9	2.4
Nausea	1.9	2.4
Abdominal distention	1.0	1.4
Constipation	0.8	1.6
Flatulence	0.4	1.6
Gastritis	0.2	1.1
Gastric ulcer	0.0	1.1
Musculoskeletal		
Musculoskeletal (bone, muscle, joint) pain	2.9	3.2
Muscle cramp	0.2	1.1

Osteoporosis in Men

In two placebo-controlled, double-blind, multicenter studies in men (a two-year study of alendronate sodium 10 mg/day and a one-year study of once weekly alendronate sodium 70 mg) the rates of discontinuation of therapy due to any clinical adverse event were 2.7% for alendronate 10 mg/day vs. 10.5% for placebo, and 6.4% for once weekly alendronate 70 mg vs. 8.6% for placebo. The adverse reactions considered by the investigators as possibly, probably, or definitely drug related in greater than or equal to 2% of patients treated with either alendronate or placebo are presented in the following table.

Table 3 **Osteoporosis Studies in Men Adverse Reactions Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in Greater Than or Equal to 2% of Patients**

	Two-Year Study		One-Year Study	
	Once Daily Alendronate Sodium 10 mg % (N=146)	Placebo % (N=95)	Once Weekly Alendronate Sodium 70 mg % (N=109)	Placebo % (N=58)
Gastrointestinal				
Acid regurgitation	4.1	3.2	0.0	0.0
Flatulence	4.1	1.1	0.0	0.0
Gastroesophageal reflux disease	0.7	3.2	2.8	0.0
Dyspepsia	3.4	0.0	2.8	1.7
Diarrhea	1.4	1.1	2.8	0.0
Abdominal pain	2.1	1.1	0.9	3.4
Nausea	2.1	0.0	0.0	0.0

Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of alendronate sodium. Because these reactions are reported voluntarily from a population of uncertain size, it

is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a Whole: hypersensitivity reactions including urticaria and angioedema. Transient symptoms of myalgia, malaise, asthenia and fever have been reported with alendronate, typically in association with initiation of treatment. Symptomatic hypocalcemia has occurred, generally in association with predisposing conditions. Peripheral edema.

Gastro intestinal: esophagitis, esophageal erosions, esophageal ulcers, esophageal stricture or perforation, and oropharyngeal ulceration. Gastric or duodenal ulcers, some severe and with complications have also been reported

Dental: Localized osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection with delayed healing, has been reported.

Musculoskeletal: bone, joint, and/or muscle pain, occasionally severe and incapacitating ;joint swelling; low-energy femoral shaft and subtrochanteric fractures

Nervous system: dizziness and vertigo.

Pulmonary: acute asthma exacerbations

Skin: rash (occasionally with photosensitivity), pruritus, alopecia, severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis.

Special Senses: uveitis, scleritis or episcleritis. Cholesteatoma of the external auditory canal (focal osteonecrosis).

4.9. Drug accountability

The arrival of the study medication at the hospital pharmacy and the delivery to the study site (Department of Rheumatology) will be documented. Drug accountability will be documented with the description of the batch number, expiration date and date distributed to the subject. Patients are requested to keep a medication log which contains the day and time of the administration.

5. Procedures

5.1 Study procedures

A screening visit will include explanation and signing of the informed consent form and overview of in- and exclusion criteria in order to participate. If appropriate, a pregnancy test will be performed.

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 completion of NRS pain, a hand radiograph, Dual energy X-ray absorptiometry (DXA) and the laboratory investigations required. These will comprise a calcium and vitamin D status, kidney function tests (serum ureum, serum creatinine, GFR), bone turnover markers (BTM), and, if appropriate, a pregnancy test. A maximum of 45 ml of blood will be collected each visit.

Patients will be randomized to alendronate for 24 weeks or 48 weeks: study products (Steovess, alendronate 70mg every week) will then be provided to the patient. Calcium/Vit D supplementation will be installed.

Schedule of assessments are provided in detail as Appendix 1. Safety assessment is clarified in the safety paragraph.

At week 12: safety assessment NRS pain, BTM

At week 24: safety assessment, NRS pain, serum calcium levels and BTM, hand radiographs and DXA

At week 48: safety assessment, NRS pain, hand radiographs, DXA and the laboratory investigations required.These will comprise a calcium and vitamin D status, kidney function tests (serum ureum, serum creatinine, GFR), and BTM.

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. Templates for AE/SAE recording created by the sponsor will be used.

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. All through the time of the study pregnancy tests will be done during the visits.

5.2 Study table

	Distribution IMP	**Safety**	**Laboratory[1]**					**CR hand**	**DXA**	**NRS pain**
			Kidney function	BTM	Vit D	Ca++	Preg. test*			
SCREENING / BASELINE	X	X	X	X	X	X	X	X	X	X
WEEK 12 (+/- 7 days)	X	X		X			X			X
WEEK 24 (+/- 7 days)	X	X	X	X		X	X	X	X	X
WEEK 48 (+/- 7 days)		X	X	X	X	X	X	X	X	X
						* if appropriate				

Kidney function tests including serum creatinine, ureum and glomerular filtration rate (GFR). Depending on the individual patient, additional parameters may be added.
[1] Samples must be obtained following an overnight fast during the morning.

5.3 Sample processing

Blood samples collected during the visits will be used for clinical analysis.

At baseline visit, W12, W24 and W48 three extra serum tubes will be collected. After centrifugation (4000 RT/10min) the serum will be allocated in vials of 1ml and stored at -80°C. At the end of the study those samples will be send to an external lab for analysis of the BTM.

6. Randomisation

The randomization code will be generated by a randomization manager. Randomization will be done in blocks of four.

7. Reporting requirements for investigational product complaints

The following could be considered potential product complaints that need to be reported to EffRx Pharmaceuticals. The Investigator will email the product complaint reports to sdriessen@effrx.com and safety@effrx.com. Should any such concerns or irregularities occur, the IMP will not be used until confirms that it is permissible to use was received.

Examples of Product Complaints:
• Packaging: for example, broken container or cracked container
• 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 IMP 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

8. Concomitant therapy

In patients treated for osteoporosis symptomatic hypocalcemia has occurred, generally in association with predisposing conditions. Therefore, patients must be adequately supplemented with calcium and vitamin D levels during Steovess therapy. A calcium (1000 mg) and vitamin D (880 IU) supplement will be provided during the study visits as of the baseline visit. Daily intake following the approved dosage and regimen is requested. This supplement is considered to be an auxiliary medicinal products. Relabeling is not requested.

9. End of study

End of study is 30 days after the last visit at week 48 of last patient.

10.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 CRF 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.

10.1. Definition

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 effervescent alendronate, 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.

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.

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.

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).

10.2. 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. A list of AEs considered possibly or probably related to Steovess/Binosto should be forwarded to EffRx at the end of the study at the latest.

Medical events that occur between signing of the Informed Consent and the first intake of trial medication will be documented on the medical and surgical history section and concomitant diseases page of the CRF.

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 spanning from the first intake of IMP until the end of the study must be reported by the local Principal Investigator within 24h after becoming aware of the SAE to:

- The local EC
- Health, innovation and research institute (HIRUZ)
- The designated contact person of the Marketing Authorisation Holder (MAH) or producer of the medicinal (investigational) product

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), HIRUZ 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 nonlife-threatening SUSAR the reporting process 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 HIRUZ:

e-mail: hiruz.ctu@uzgent.be

tel.: 09/332 05 00

fax: 09/332 05 20

Contact details of producer: Pharmacovigilance department

e-mail: safety@effrx.com

tel. : +41 44 503 78 60

The investigator must provide the minimal information: i.e. trial number, subject's initials and year of birth, medication code number, period of intake, nature of the adverse event and investigator's attribution.
A 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.

As the subjects are not under 24-hour supervision of the investigator or his/her staff, they 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.

Annual Safety and Progress Reporting

Hiruz CTU will ask the Chief Investigator for an annual report containing information on the status of the trial and an overview of all SSARs (Suspected Serious Adverse Reaction) and a summary regarding the safety of the trial subjects. Hiruz CTU will send this report to the Central EC and the CA within the timelines as defined in national legislation.

11.Statistical and Analytical Plans

11.1 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.
Primary analysis will be a per protocol approach, including all patients who completed the final visit (week 48). Missing data related to exploratory endpoints will be handled by last observation carried forward (LOCF) procedure.
The primary efficacy variables will be the number of patients that maintain CTx-I within the premenopausal reference range at week 48. Secondary efficacy variables will be the changes from baseline to week 12, 24 and 48 for CTx-I and P1NP levels. Co-exploratory variables will be DXA changes from baseline to week 24 and 48. Hand OA-related exploratory efficacy variables will be changes in NRS pain from baseline to week 12, 24 and 48, and changes in number of new erosive joints on X-rays and changes in GUSS values from baseline to W24 and 48.
All analyses be summarized by treatment group where treatment group equals ‘exposed to Alendronate for 48 weeks Vs Alendronate for 24 weeks’.

11.2 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).

11.3 Determination of Sample size

No formal sample size calculation has been performed: No recruitment or inclusion of patients that did not participated the previous phases (Randomized controlled trial and open label extension phase) is possible and the sample size of this study is therefore limited to a maximum, i.e. the number of patients ending the extension phase and being willing to participate.

12. Quality assurance and periodic monitoring

The investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents will be classified into two different categories: investigator's file, and subject clinical source documents.

The investigator's file will contain the documents as per Good Clinical Practice and local regulations.

Regular monitoring will be performed by Hiruz CTU according to ICH-GCP. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements. At least 3 monitoring visits are scheduled. An initiation visit, one routine visit and a final visit after the last patient had finished the study. The monitor will be working according to SOPs and will provide a monitoring report after each visit for the sponsor and the investigator. Depending on the quality of the data, additional monitoring visits will be necessary according to the sponsor's discretion.

More detailed information regarding the monitoring is described in the monitoring plan.

13. Indemnity insurance

An insurance with no fault responsibility has been foreseen by the sponsor in accordance with the Belgian law concerning experiments on humans, 7 May 2004..

14. 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.

15. Final Report

Within one year after the final completion of the study, a full final report will be written by the Chief Investigator and submitted to the central ethical committee and competent authority (via Hiruz CTU).

Part II : General part of the protocol

16. Independent Ethics Committee (IEC) / Institutional Review Bord (IRB)

This trial can only be undertaken after full approval of the protocol and addenda has been obtained from the IEC/IRB. This document must be dated and clearly identify the protocol, amendments (if any), the informed consent form and any applicable recruiting materials and subject compensation programs approved.
During the trial, the following documents will be sent to the IEC/IRB for their review:

- reports of adverse events that are serious, unexpected and associated with the investigational drug
- all protocol amendments and revised informed consent form (if any).

Amendments should not be implemented without prior review and documented approval / favorable opinion form the IEC/IRB except when necessary to eliminate an immediate hazard to trial subjects or when the change involves only logistical or administrative aspects of the trial.
Reports on, and reviews of the trial and its progress will be submitted to the IEC/IRB by the investigator at intervals stipulated in their guidelines.
At the end of the trial, the investigator will notify the IEC/IRB about the trial completion.

17. Competent Authority (CA)

This study must obtain approval from the competent authority (FAGG) prior to the start of the study. All protocol amendments will be notified to the competent authorities during the course of the trial.

Reports on safety, and reviews of the trial and its progress will be submitted to the CA by the sponsor (via Hiruz CTU) at intervals stipulated in their guidelines.

At the end of the trial, the sponsor will notify the CA (via Hiruz CTU) about the trial completion as per regulatory requirements.

18. Early termination

Early termination or suspension of the study or an investigational site may be necessary in case of major non-compliance, critical safety issues or premature trial discontinuation. This can occur at any time by the sponsor, principal investigator of the local site, EC or regulatory authority. In the event that the clinical investigation would be discontinued prematurely, all clinical investigation products will be retained, the terminating party shall justify its decision in writing and the sponsor will communicate (via Hiruz CTU) early termination, including the reason for early termination, to the EC and regulatory authority.

19. Protocol compliance

Prospective, planned deviations or waivers to the protocol are not allowed. Under emergency circumstances, deviations from the protocol to protect the rights, safety or well-being of human

subjects may proceed without prior approval of the sponsor and the EC. Such deviations shall be documented and reported to Hiruz CTU by email (hiruz.ctu@uzgent.be) and the EC as soon as possible. Accidental protocol deviations must be adequately documented and reported in the CRF on the protocol deviation log. In case accidental protocol deviations are considered as critical issues that significantly affect patient safety, data integrity and/or study conduct these should be reported to Hiruz CTU immediately by email (hiruz.ctu@uzgent.be). Hiruz CTU will subsequently communicate and discuss this with the EC.

The following items will be documented on the protocol deviation log: date of deviation, description of deviation, actions taken and classification of deviation. Deviations will be classified as minor or major. A minor protocol deviation is a deviation that does not affect the safety, rights or well-being of subjects or the quality of their data. A major protocol deviation is a deviation that affects safety, rights or well-being of subjects or quality of their data.

Any deviation that potentially interferes with and/or affects the efficiency and/or quality conduct of the study will be discussed by the monitor with the PI and will be documented on the monitoring report including a proposed plan of action for resolution if applicable.

20. ICH/GCP guidelines

This trial will be conducted in accordance with the protocol, current ICH-GCP guidelines and applicable law(s).
Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

21. Subject information and informed consent

Prior to entry in the trial, the investigator must explain to potential subjects the trial and the implication of participation. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. Participating subjects will be told that their records may be accessed by competent authorities and by authorized persons without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) and/or regulations. By signing the Informed Consent Form (ICF), the subjects are authorizing such access.
After this explanation and before entry to the trial, written, dated and signed informed consent should be obtained from the subject. The ICF should be provided in a language sufficiently understood by the subject. Subjects must be given the opportunity to ask questions.
The subject will be given sufficient time to read the ICF and to ask additional questions. After this explanation and before entry to the trial, consent should be appropriately recorded by means of the subject's dated signature or the signature of an independent witness who certifies the subject's consent in writing. After having obtained the consent, a copy of the ICF must be given to the subject.
In case the subject is unable to read, an impartial witness must attest the informed consent.

22. Case Report Forms

The source documents are to be completed at the time of the subject's visit. The CRFs are to be completed within reasonable time after the subject's visit.

The investigator must verify that all data entries in the CRFs are accurate and correct. If certain information is Not Done, Not Available or Not Applicable, the investigator must enter "N.D." or "N.AV." or "N.AP", respectively in the appropriate space.

23. Direct access to source data / documents

The investigator will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.

24. Data handling and record keeping

The investigator and sponsor specific essential documents will be retained for at least 20 years. At that moment, it will be judged whether it is necessary to retain them for a longer period, according to applicable regulatory or other requirement(s).

25. References

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Annex I

IMP label

EudraCT N°: 2019-003570-11
TRIAL subject ID nr°: _____ Initialen: _____ Datum visite: ____
ENKEL VOOR STUDIEGEBRUIK
Gebruiksaanwijzing: eenmaal per week een in leidingwater opgeloste bruistablet – 12 bruistabletten Elke bruistablet bevat 70mg alendronaat – Voor oraal gebruik – Buiten het zicht en bereik van kinderen houden – Bewaar in de originele verpakking ter bescherming tegen vocht.
UNIQUEMENT POUR UTILISATION DE L'ESSAI CLINIQUE
Mode d'emploi : un comprimé effervescent une fois par semaine, sous forme de solution buvable – 12 comprimés effervescents – Chaque comprimé contient d'alendronate 70mg – Voie orale – Tenir hors de la vue et de la portée des enfants - A conserver dans l'emballage extérieur d'origine, à l'abri de l'humidité.
NUR STUDIENGEBRAUCH KLINISCHER
Gebrauchsanweizung: Nehmen Sie einmal pro Woche eine in Leitungswasser gelöste Brausetablette ein. – 12 Brausetabletten - Jede Brausetablette enthält 70mg Alendronat - oraler Einnahme - Artznemittel für Kinder unzugänglich aufbewahren - In der Originalverpackung aufbewahren, um den Inhalt vor Feuchtigkeit zu schützen
Exp : dayMONTHyear
PROF. WITTOEK R. TEL: 09/332 25 22 – 09/332 21 11
SPONSOR: UZ GENT C. Heymanslaan 10 9000 GENT