Universitat de Girona

FINAL DEGREE PROJECT

Use of teriparatide to accelerate the healing of lower extremity stress fractures in high-level and high-performance athletes

- A phase IV/II multicenter randomized clinical trial -

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1. ABBREVIATIONS

AE	Adverse Event
AEMPS	Agencia Española de Medicamentos y Productos Sanitarios
AP	Anterior-Posterior
BC	Bone scintigraphy
BMD	Bone mineral density
BMI	Body Mass Index
BSI	Bone Stress Injury
CAR	Centre d'Alt Rendiment
CEIC	Comitè Ètic d'Investigació Clínica
CIMETRI	Centre Integral de Medicina Esportiva, Traumatologia i Rehabilitació
CSD	Consejo Superior de Deportes
eCRF	electronic Case Report Form
HUDJT	Hospital Universitari Doctor Josep Trueta
ICATME	Institut Català de Traumatologia i Medicina de l'Esport
LFT	Liver Function Tests
MRI	Magnetic resonance imaging
PTH	Parathyroid hormone
RTST	Return To Sport Time
SAE	Serious Adverse Event
SFX	Stress Fractures
SMC	Sports Medicine Centers
VAS	Visual Analog Scale

2. ABSTRACT

Background: Stress fractures (SFX) are a major problem for athletes, because they need to be a relatively long period of time away from activity. Most SFX are treated conservatively, and in some cases may result in delayed union or nonunion. To date, there is not any medication approved to accelerate the healing of SFX. Recently, teriparatide, an anabolic agent used in the treatment of osteoporosis, has shown as a promising treatment to accelerate the healing of fractures, by increasing bone formation.

Objectives: To evaluate the efficacy and safety of 20 µg and 40 µg of teriparatide compared with placebo, for treating lower extremity SFX in high-level and high-performance athletes. Efficacy endpoints will be the time to radiographic healing and the return to sport time, measured in weeks.

Design: A phase IV/II, multicenter, randomized, double-blind, placebo-controlled clinical trial.

Setting: Hospital Universitari Doctor Josep Trueta and five Sports Medicine Centers of Catalunya.

Participants: High-level and high-performance athletes diagnosed with lower extremity stress fractures.

Intervention: Teriparatide 20 µg (n=46), teriparatide 40 µg (n=46) and placebo (n=46), all as a daily subcutaneous injection for 8 weeks.

Keywords: Teriparatide; Stress fracture; Fracture healing; Return to sport

3. INTRODUCTION

3.1. Stress fractures

Stress fractures (SFX) are a type of fractures that result from the repeated application of loads on the bone, leading to an imbalance between bone resorption and formation (1). These overuse injuries are frequently observed in competitive as well as recreational athletes (2), and represent an important cause of suboptimal training and underperformance in competitive athletes (3).

Its precise incidence is difficult to determine (4). Competitive athletes are the most affected due to their harsh training activities. However, there has been an increase of SFX in recreational athletes due to their increased participation in sports events, such as a marathon (5).

Stress fractures can affect almost any bone of the body, but the majority (up to 95%) occur in the lower extremity weight bearing bones, especially the tibia, tarsals and metatarsals (1,5).

These fractures are site-specific, and occur in areas exposed to repeated loads. Thus, there are SFX sites that are commonly related to a specific sport, such as the tibia and the fibula in long-distance runners and jumpers, and the tarsals in gymnasts and basketball players (1,4,6).

Boden et al. described low-risk and high-risk stress fractures by their location (See *Table 1*), which differ in prognosis and treatment.
Low-risk stress fractures are healed without incidents when they are early diagnosed and treated with activity restriction. These fractures usually do not need advanced imaging modalities, such as magnetic resonance imaging (MRI) or bone scintigraphy (BS) for its study, and are diagnosed by a thorough history, physical examination and radiographs. If the initial X-ray is negative but the level of suspicion is high, the management with adequate rest and evaluation with serial radiographs is correct.

In contrast, high-risk stress fractures are at risk of delayed union, nonunion or complete fracture, especially if the diagnosis is delayed. In these fractures, advanced imaging modalities are recommended in patients with normal X-ray and chronic pain (1,7).

Low-risk	High-risk	
- Femoral shaft. - Tibial shaft. - Fibula/lateral malleolus. - Calcaneus. - Diaphysis of 2nd to 4th metatarsals.	- Femoral neck - Patella - Anterior cortex of the tibia - Medial malleolus - Talus	- Tarsal navicular - Proximal diaphysis of the 5th metatarsal - 2nd metatarsal base. - Great toe sesamoids

Table 1. Classification of stress fractures. Adapted from (1,7).

Pathophysiology of stress fractures

There is a spectrum of bone injuries as a result of repetitive stress, and includes bone strains, stress reactions, and nondisplaced and displaced stress fractures. These bone injuries appear when the bone is unable to remodel properly under the application of repetitive stress.

The ground reaction forces are between three and eight times greater during the running and jogging than during walking. For this reason, distance runners and track athletes have a higher risk of developing stress fractures (2).

Normal bone has two components; cortical (compact) and cancellous (trabecular) bone. Cortical bone, which makes up about 80% of the skeleton, is located in the diaphysis of long bones as well as the “shell” of cuboid-like bones including vertebral bodies and carpal or tarsal bones. However, cancellous bone is found at the epiphysis and metaphysis of long bones and in cuboid-like bones (2).

The metabolic turnover rate is eight times slower in cortical bone compared to cancellous bone (2). For this reason, most stress fractures in athletes occur in the cortical bone.

Because of these intrinsic characteristics of the bone, cortical fractures have been described classically as abnormal stresses to normal bone, and cancellous fractures as normal stresses on abnormal bone (3).

In cancellous bone, stress fractures can be found in female athletes with "the female athlete triad". This triad refers to the association of low bone mineral density (BMD), nutritional issues and menstrual irregularities in young athlete women (3).

The exact pathophysiology of stress fractures is not clear, and there are several models based on theory to explain their causal mechanism. One of these theoretical models is presented in *Figure 1* (4).

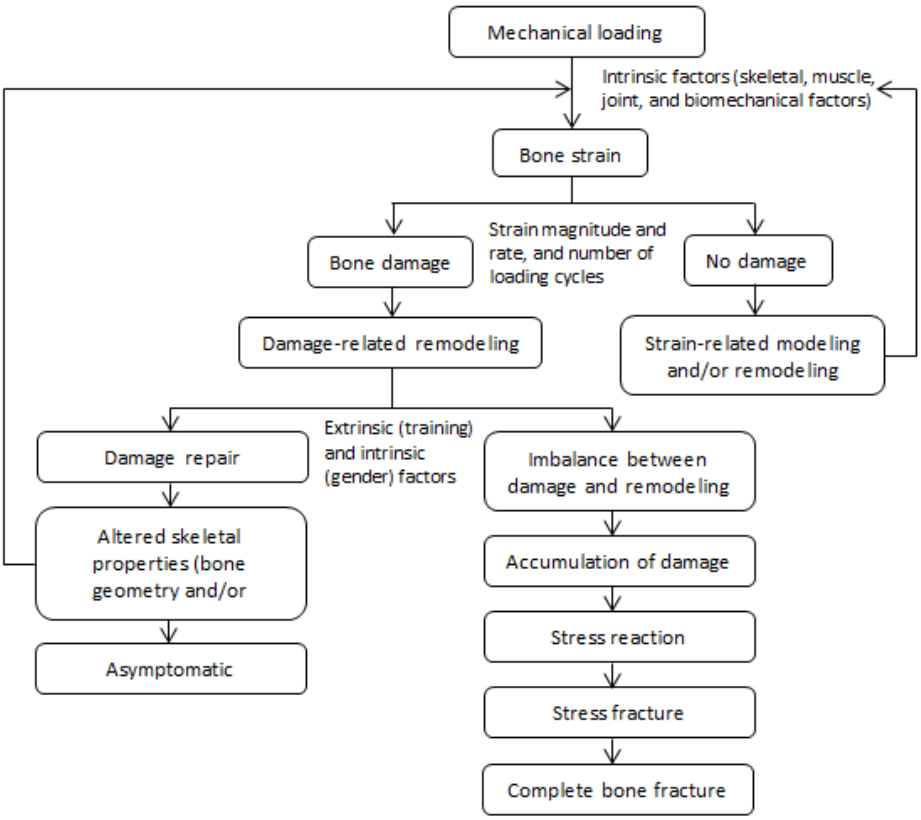


Figure 1. Proposed pathophysiology of stress fractures. Reproduced from *Warden* et al. (4)

The skeleton receives repetitive bouts of mechanical loading during the exercise, which produce a bone deformation (bone strain). The strain is the change in length per unit length of a bone. Although it is a unit-less value, it is often expressed as micro-strain (με) because it is considered very small for the bone.

The difference between normal bone strains (400-1500 με) and those required to fracture the bone (10.000 με) is large, but repetitive strains lower than that needed to fracture the bone in a single loading situation may cause damage (often termed microdamage) (4).

This damage is a natural and useful phenomenon, and serves as a stimulus to activate bone remodeling (4). This process occurs in basic multicellular units (BMU) by osteoblasts (bone forming cells) and osteoclasts (bone resorbing cells) (8) (*Figure 2*).

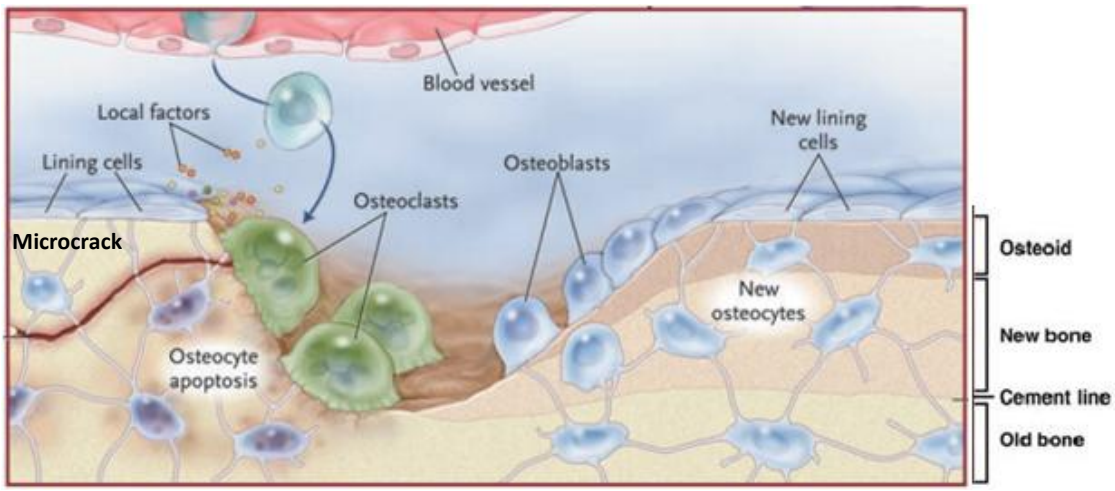


Figure 2. Bone remodeling in BMU. Reproduced from Canalis et al. (8)

A microcrack attracts osteoclasts to sites that become a bone-remodeling unit. Once resorption of bone is completed, approximately 3 to 5 weeks, the resorbed area attracts osteoblasts that produce a new matrix in the BMU, which is subsequently mineralized. The completion of the remodeling sequence takes between 3 and 5 months.

In some circumstances, however, an imbalance between damage generation and its removal can occur. The subsequent accumulated damage may be responsible to initiate the bone stress injury (BSI) pathology continuum, which includes stress reactions, stress fractures, and, ultimately, complete bone fractures (4).

Stress reaction is an area of prefracture bone remodeling, associated with periosteal and/or marrow edema, in which the bone is weakened but does not contain any fracture line (1,9).

The magnitude and rate at which strain is introduced and the absolute number of loading cycles are determinants of damage formation. The damage formation is threshold dependent; thus, damage increases with increasing strain. In relation to strain rate, strains that are introduced in shorter periods of time produce greater

damage. Therefore, sports that involve high loads that are introduced during short periods of time, such as the sprinters, have a higher risk of SFX. Purely cyclic overloading may also result in damage accumulation and stress fractures, due to an insufficient time to repair damage during remodeling. This would be the case of distance runners (4).

Risk factors

SFX may be recurrent due to the fact that there are many factors influencing the risk, with a variation among individuals regarding the relative contribution of each factor. In addition, many factors are interrelated and this complicates the independent analysis of each factor (2,4,6).

These factors are commonly divided into intrinsic and extrinsic factors.

Extrinsic factors are characteristics of the environment or external factors to the individual, and include type of activity or sport, factors involving training, equipment and the environment itself. The contribution of extrinsic factors in stress fracture development is important, because a mechanical load is required to generate and accumulate damage. However, it also depends on the body's response to loads, which can explain that not all individuals exposed to similar loading regimen will suffer a stress fracture. These are the intrinsic factors that include the characteristics of the individuals themselves and the body's response to the load and the damage that it may generate. Examples of intrinsic factors are skeletal, muscle, joint, and biomechanical factors, as well as, gender, age, race and physical fitness (2,4).

Clinical presentation

Prompt diagnosis of SFX is important to avoid complications and to secure early recovery. Patients typically come with an insidious onset of localizable pain, without remembering a specific inciting event or injury to the affected area. Initially this may lead to a misdiagnosis and delayed diagnosis of SFX.

First, this pain is presented during the activity and relieved with rest. Continued activity at the same level can lead to the progress of fracture, and pain may continue after physical exercise. Finally, the pain may even occur with rest or with routine ambulation (1,3,5).

A thorough history should be obtained, including predisposing factors to SFX, which are essential for the treatment and recurrence prevention. It is important to carry out a review of the training program, including adequate rest; also any recent change in training frequency, intensity, type or terrain should be assessed, as well as proper use and changes in training equipment (especially footwear). Patient's general health, medications, occupation, past injuries, eating habits and menstrual history (in women) should be obtained (1,3).

On physical examination, the most common finding of a stress fracture is a localized pain to palpation for superficial bones. For deep bones, such as femoral shaft, the pain can be identified through gentle range of motion or specific clinical tests. Sometimes, swelling and warmth may be present at the site of the stress fracture.
Limb biomechanics should be assessed to identify concomitant risk factors such as leg-length discrepancies, malalignment (especially excessive subtalar pronation), muscle imbalance or weakness (1,3,7).

The differential diagnosis for SFX includes stress reaction, periostitis, avulsion injuries, muscle strain, bursitis, nerve entrapment, exertional compartment syndrome, neoplasm and infection (1,7).

Diagnosis of stress fractures

SFX are often suspected by the training history and physical examination, but several imaging modalities are required to confirm the diagnosis and to provide prognostic information (1,6).

Radiographs are used as first-line of imaging study for SFX. In the early stages of these injuries, radiographs are usually "normal" and it can need up to 3-4 weeks after the onset of pain, for that the characteristic findings are manifested on radiographs (5,6).
In cortical bone, radiological abnormalities that may be observed on later films are periosteal reaction, cortical lucency or a fracture line. However, in cancellous bone the findings are even less well visible and consist of a band-like area of focal sclerosis without periosteal reaction (1).
In spite of its low sensitivity, this modality is mandatory as a first imaging study to rule out other diagnoses as infection, tumor or frank fracture.

If initial radiographs are negative but the level of suspicion is high, more advanced imaging modalities, such as magnetic resonance imaging (MRI) or bone scintigraphy (BS) , should be used to get an early diagnosis (5).

BS has traditionally been considered the gold standard to confirm the clinical suspicion of stress fracture in patients with negative radiographs. The sensitivity of BS is high for detecting SFX, but it has lower specificity; thus an increased focal uptake may be present in other conditions such as infection, bone infarction or neoplastic processes (6).

In a BS, a stress fracture appears as a discrete, localized area of increased uptake in the three phases. However, soft tissue injuries are presented by an increase in the first two phases only. During the healing of SFX, the angiographic phase (Phase I) becomes normal, followed by the soft tissue imaging (Phase II). However, the intensity of uptake on delayed images (Phase III) may take about 3 to 18 months to decrease, often later than the resolution of symptoms. For this reason, BS is a poor choice to monitor healing and return to activity (7).

In contrast, MRI has the advantage that is more specific than BS and avoids the exposure of patients to ionizing radiation (6).

In selected cases computer tomography (CT) may also be of value (6).

Management

An early diagnosis of stress fracture is essential. Once diagnosed, the management includes the treatment of the SFX and a strategy to prevent other episodes (10).

Considering that SFX appear when the applied load exceeds the capacity of the bone to resist the load without producing damage accumulation, the management requires strategies to reduce weight-bearing on the bone (1,9).

Treatment of SFX may differ on whether the fracture is considered at low-risk or high-risk of complications. However, the treatment strategy should be adapted to each individual according to their symptoms and needs (1,10).

Most low-risk stress fractures usually heal successfully without complications with conservative measures and restriction of activity (3). Initially, a period with activity modification and relative rest is usually required for approximately 2 to 6 weeks, during which the bone can heal and repair the stress fracture while the stress loading provides mechanical stimulation (1,3). Symptoms and pain-free threshold should be used as a guide to the amount of activity modification, considering that all activity should be carried out in a pain-free level. In more advanced cases, the athlete may suffer pain with walking and weight-bearing. In such circumstances, a short period of crutch walking or discharge of the affected extremity may be necessary, until the activity is pain-free (3).

This is followed by a period of low impact activities, such as swimming, biking and water running. High impact activities can be started once the patient can carry out low impact activities for prolonged time without suffering pain. A gradual return to activity is recommended (1,3).

However, high-risk SFX are at risk of progressing to delayed union, nonunion or displaced complete fracture. Thus, these fractures should be treated with more aggressive measures, like acute fractures.

An algorithm for treatment of high-risk SFX is presented in Figure 3.

Most of these fractures are treated with an aggressive non-operative protocol, which consists in non-weight-bearing cast immobilization, especially in cases diagnosed soon after the onset of symptoms. Surgery may be used in displaced fractures and those with chronic radiographic findings, or for elite athletes who require an early return to activity (7).

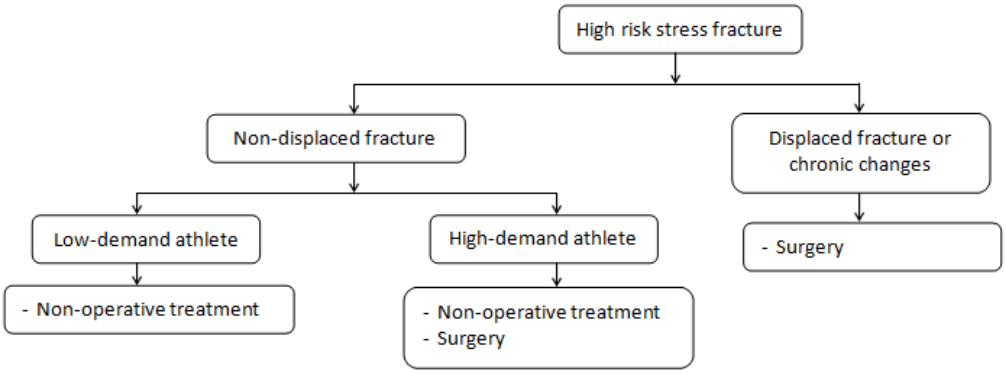


Figure 3. Algorithm for treatment of high risk stress fractures. Adapted from (7).

Ice compresses and analgesics can be used to provide symptomatic relief (3).
However, non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided or be used as short as possible, especially in cases of high risk stress fractures. Although there are no studies in humans, animal studies have shown that NSAIDs inhibit osteogenic activity, and that can affect fracture healing (11).

Apart of the stress fracture treatment, a key point in the management is to identify and modify any predisposing factor for future fractures. Training errors, new activities and the type or condition of the footwear should be assessed. In addition, it is important to educate athletes, coaches and parents about the harmful effects of overtraining and the relevance of periodic rest. Also, female athletes have been informed of the effects of eating disorders and hormonal abnormalities (1,7).

The healing of SFX can be slow and require a relatively long period of time away from physical activity (12). In addition, conservative treatment can lead in some cases to non-healing and result in delayed union or nonunion, especially in high-risk SFX (7,12). In some circumstances, the treatment may be surgical in order to accelerate the return to activity, but the process of fracture healing cannot be readily accelerated (12). For these reasons, there is a general interest in having an effective pharmacological treatment to accelerate the SFX healing (12).

Teriparatide, a recombinant human parathyroid hormone (1-34), was approved in 2003 by the European Medicines Agency (EMA). It is indicated for the treatment of osteoporosis in postmenopausal women and in men who are at risk for fractures, and in patients with osteoporosis associated with sustained systemic glucocorticoid therapy (13).

Teriparatide is the only anabolic drug available for the treatment of osteoporosis, and its mechanism of action is distinct from that of other agents used currently, such as bisphosphonates (14).

Human parathyroid hormone (PTH), an 84 amino acids peptide, is involved in the regulation of calcium and phosphate metabolism in bone and kidney. Low serum calcium levels stimulate the production of PTH, which acts by increasing the release of calcium from the bone and increasing renal calcium reabsorption. PTH also increase

intestinal absorption of calcium by formation of 1,25-dihydroxyvitamin D (15). Therefore, chronic elevation of PTH, as in hyperparathyroidism, leads to an increase of bone resorption by the osteoclasts. In contrast, intermittent exposure to PTH, as daily injections of teriparatide, stimulates new bone formation by osteoblasts. This effect is called “paradoxical effect of PTH” (14).

Teriparatide is licensed at a dose of 20 µg daily, for a maximum of 24 months (13). Studies in rats showed a dose-dependent increase in the incidence of osteosarcoma in rats treated with teriparatide during 2 years. However, there are important differences between the use of teriparatide in rats and the clinical use in humans; 2 years is approximately 80% to 90% of the normal life span in rats, while in humans represent only 2-3% of the life span, suggesting that is unlikely to increase the risk of osteosarcoma in humans (16).

Teriparatide has not been studied in pediatric population and young adults with open epiphyses. Thus, teriparatide should not be used in these patients (13).

Regarding to the safety, the most commonly reported adverse events in patients treated with teriparatide are nausea, pain in limb, headache and dizziness (13).

Several preclinical studies have been conducted to evaluate the potential of teriparatide on fracture healing. They showed that once-daily administration of teriparatide enhanced callus formation and mechanical strength of fracture in young (17) and old rats (18).

Andreassen et al. were the first to study the healing of fractures in intact rats with tibial fractures after once-daily administration of PTH (1-34). Two doses of teriparatide were used; 60 and 200 µg/kg/day. The efficacy was evaluated after 20 and 40 days of healing. The results showed an increased callus quantity and mechanical strength of fractures in rats treated with teriparatide, with a dose dependent response. They suggested that this treatment could be useful in the management of fracture healing (17).

The only randomized, double-blind, placebo-controlled study to test the hypothesis that teriparatide accelerates fracture repair in humans, was done by Aspenberg et al. in 2010. 102 postmenopausal women with distal radial fracture were randomized in a ratio of 1:1:1 as teriparatide 20 μg, 40 μg or placebo. Treatment was administered daily for 8 weeks. The primary efficacy variable was defined as the time to radiographic healing, and was periodically assessed at 2-week intervals. The median time to radiographic healing was 9.1, 7.4 and 8.8 weeks for placebo and teriparatide 20 μg and 40 μg, respectively. The results showed that there was not a statistically significant improvement in healing time at the dose of 40 μg; however, the time to healing was shorter in the teriparatide 20 μg group than in the placebo group ($p = 0.006$) (19). The lack of effect of the high dose of teriparatide (40 μg) compared with placebo was incongruous with the results of preclinical studies in rats, in which higher doses were more potent for the healing of fractures (17). The authors of the study concluded that fracture healing can be accelerated by teriparatide, but further studies are needed (19).

4. JUSTIFICATION

Stress fractures (SFX) are common overuse injuries in athletes and suppose a major problem for them because they need to be a relatively long period of time away from activity.

Most SFX are treated conservatively, and in some cases may not be healed and resulting in delayed union or nonunion. Surgical intervention can also be used in certain circumstances, in order to allow an early return to activity.

To date, there are not medications approved to accelerate the healing of SFX, but would be interesting to have an effective pharmacologic treatment to accelerate recovery. It would be especially important for those athletes whose livelihood depends on early return to competition, such as high-level and high-performance athletes.

Considering the pathogenesis of SFX, teriparatide, an anabolic agent used in the treatment of osteoporosis, may play an important role in the healing of SFX, by increasing bone formation through stimulation of osteoblasts.
Animal studies have shown an increase in callus quantity and mechanical strength of fractures, in rats treated with teriparatide, with a dose-dependent response (17).
A randomized, double-blind, placebo-controlled study in humans, showed an improvement in healing time of fractures at the dose of 20 μg of teriparatide, but they did not obtain a significant effect at the dose of 40 μg. The duration of treatment was 8 weeks. They concluded that further studies are necessary (19).

For these reasons, we want to determine if the teriparatide may be an effective treatment for SFX, accelerating the time to healing, and reducing the time to return to activity.

5. HYPOTHESIS

Teriparatide is an effective and safe medication for treating lower extremity stress fractures in high-level and high-performance athletes.

6. OBJECTIVES

6.1. Main objective

Evaluate the efficacy of 20 µg and 40 µg of teriparatide compared with placebo for treating lower extremity stress fractures in high-level and high-performance athletes.

6.2. Secondary objective

Evaluate the safety of 20 µg and 40 µg of teriparatide for treating lower extremity stress fractures in high-level and high-performance athletes.

7. SUBJECTS AND METHODS

7.1. Study design

This is a phase IV/II, multicenter, randomized, double-blind, placebo-controlled clinical trial.

The study will be conducted in the Hospital Universitari de Girona Doctor Josep Trueta (HUDJT) and in five Sports Medicine Centers (SMC) of Catalunya with Orthopedic Surgery and Traumatology department; Serveis Mèdics del Centre d'Alt Rendiment (CAR) de Sant Cugat del Vallés, Serveis Mèdics del FC Barcelona, Serveis Mèdics del RCD Espanyol, Institut Català de Traumatologia i Medicina de l'Esport (ICATME) and Centre Integral de Medicina Esportiva, Traumatologia i Rehabilitació (CIMETIR). The HUDJT will be the reference center.

Subjects will be randomized in a 1:1:1 ratio to one of the study groups (once-daily doses of teriparatide 20 µg or 40 µg or placebo), stratified according to the fracture site (low-risk or high-risk SFX). Randomization will be performed with a randomized electronic procedure. A numeric code will be assigned to each patient in order to respect the confidentiality of personal data, and only the pharmacist will have access to it.

The estimated time of recruitment is 2 years.

The study consists of three periods; a screening period of a maximum of 1 week from the day of diagnosis, a double-blind treatment period of 8 weeks (teriparatide 20 µg or 40 µg versus placebo) and a follow-up period of 10 months without treatment.

7.2. Study population

The study population will be high-level and high-performance athletes diagnosed with a SFX of the lower extremity, with the following inclusion and exclusion criteria:

7.2.1. Inclusion criteria

- High-level or high-performance athletes, according to the Spanish Royal Decree 971/2007 (20).

High-level athletes	Those who belong to the high-level athletes list that is annually published by the CSD in the BOE.
High-performance athletes	Those athletes with issued or approved license by the Spanish sports federations that meet any of the following conditions. a) Who have been selected by the different Spanish sports federations, to represent Spain in official international competitions at absolute category, in at least one of the last two years. b) Who have been selected by the different Spanish sports federations, to represent Spain in official international competitions in younger age categories, at least one of the last two years. c) That are classified as high-performance or equivalent by the autonomous communities, in accordance with its regulations. d) That follow programs supervised by Spanish sports federations in high performance centers recognized by the CSD. e) That follow technification programs supervised by Spanish sports federations, included in the National Program of Sport Technification of the CSD. f) That follow technification programs supervised by Spanish sports federations. g) That follow programs supervised by the autonomous communities or regional sports federations, in technification centers recognized by the CSD.

Table 2. Criteria for to be considered high-level or high-performance athlete (20).

- Age between 18 and 40 years.
- Closed epiphyses.
- A confirmed diagnosis of SFX by a positive finding on radiographs, MRI and/or BS. A SFX is defined as an area of focal pain associated with evidence of a fracture line on radiographs or MRI, or a localized area of markedly increased uptake on all three phases of the BS (21).
- Lower extremity SFX treated non-operatively.
- Athletes have given written informed consent after being informed of the risks, medications and procedures that will be performed in the study.

7.2.2. Exclusion criteria

- Displaced SFX and/or treated with surgery.
- Abnormal analytical values at the screening visit, including:
  - Total serum calcium, corrected for albumin or total proteins, abnormally high (≥10,6 mg/dL).
  - High levels of alkaline phosphatase (>129 U/L).
  - Serum PTH (1-84) >65 pg/mL.
- History of metabolic bone disease, including osteomalacia, osteoporosis and primary hyperparathyroidism.
- An increased risk of osteosarcoma. These include: Paget's disease of bone, previous primary skeletal malignancy or skeletal exposure to therapeutic irradiation. Unexplained elevations of alkaline phosphates may indicate Paget's disease of bone.
- Malignant neoplasm during the previous 5 years.
- Nephrolithiasis or urolithiasis within 2 years.
- Active liver disease or clinical jaundice.
- Impaired renal function.
- Previous fractures or bone surgery in the same site that the current stress fracture.
- Known allergy to Teriparatide or to any of the excipients.
- Alcohol or other drug abuse.
- Pregnancy or breast-feeding.

7.2.3. Withdrawal criteria

Subjects may be withdrawn from the study for the following reasons:

- Patient is not willing to comply with the protocol.
- For medical reasons (adverse event) under investigator criteria.
- Participant retires consent to continue in the study.

Subjects withdrawn from the trial will not be replaced.

7.3. Sampling

7.3.1. Sample selection

A non-probabilistic consecutive sampling will be performed with athletes diagnosed with stress fractures of the lower extremity. This is a multicenter trial, in which the HUDJT and five SMC of Catalunya will be involved. The sample recruitment will carry out in the traumatology department of these centers. Candidate patients will be invited to participate in the study, and an information sheet of the study (Annex I) will be given. After informed consent (Annex II) is signed, patients will be enrolled in the clinical trial.

7.3.2. Sample size

To calculate the sample size, we will use an adaptation from the library "Sample size" of the R software (v. 3.1.2), created by Marc Saez.

Accepting an alpha risk of 0,05 and a beta risk of 0,2 (statistical power of 0,8), the sample size will be 138 patients. It has been anticipated a drop-out rate of 15%.

46 patients in each of the three treatment groups (teriparatide 20 µg, 40 µg and placebo), stratified according to the fracture site (low-risk or high-risk SFX), are necessary to recognize as statistically significant a difference in the radiographic healing time greater than or equal to 2 weeks, and/or a difference in the return to sport time greater than or equal to 3 weeks.

Accuracy *	**Number of patients (n):**
5%	256
10%	95
15%	**46**
20%	27

Table 3. Sample size.

* Differences, in percentages, that we would like to detect.

In order to achieve a sample size of 138 patients, we propose a multicenter clinical trial based on the register of lower extremity SFX seen on a year in the Sports Medicine Center of CAR de Sant Cugat (unpublished data). We expect to find about 15 SFX per year in each of the participating SMC. The estimated time of recruitment is 2 years.

7.4. Variables

7.4.1. Independent variable

- The independent variable in this study is the *drug administered*: teriparatide 20 µg or 40 µg, or placebo.
  As it is a nominal qualitative variable, it will be measured as a percentage.

7.4.2. Dependent variable

- *Time to radiographic healing* is the time period, in weeks, from the diagnosis of the SFX to radiographic healing. Radiographic healing is defined by cortical bridging in three of four cortices seen on X-ray images (22).
  As it is a continuous quantitative variable, it will be measured as a median.

- *Return to sport time (RTST)* is the time period from the date of the diagnosis to the date of return to full sport. Return to sport is defined as the time point, when the athlete is able to return to sport and can jogging without restrictions and without clinical symptoms (23).
  As it is a continuous quantitative variable, it will be measured as a median.

7.4.3. Covariates

- *Age*, which is a discrete quantitative variable. It will be expressed in years.
- *Sex*, which is a dichotomous nominal qualitative variable. It will be assessed by male or female.
- *Ethnicity*, which is a nominal qualitative variable. It will be registered as: white, Black, Hispanic, Asian or other.
- *Body mass index (BMI)*, which is a continuous quantitative variable. It will be expressed in kg/m^2.
- *Menstrual status without hormone replacement therapy*: is a nominal qualitative variable. It will be registered as: eumenorrhea, oligomenorrhea or primary or secondary amenorrhea (24).

Amenorrhea is the absence of a menstrual period in a woman of reproductive age. - *Primary amenorrhea*: if menstrual cycles have never started. - *Secondary amenorrhea*: absence of menstruation for 3-6 months.
Oligomenorrhea: menstrual cycles at intervals over 35 days or less than 10 periods in a year.

Table 4. Menstrual status (24).

- *Sporting activity*, which is a nominal qualitative variable. It will be registered as: runners, jumpers, basketball players, gymnastics, among other.
- *Stress fracture site*, which is a nominal qualitative variable. It will be registered as fibula, calcaneus, fifth metatarsal, among other; and it will be stratified according to risk in low-risk or high-risk SFX.

Low-risk SFX	**High-risk SFX**	
- Femoral and tibial shaft - Fibula/lateral malleolus. - Calcaneus - Diaphysis of 2^{nd} to 4^{th} metatarsals	- Femoral neck - Patella - Anterior cortex of the tibia - Medial malleolus - Talus	- Tarsal navicular - Proximal diaphysis of the 5^{th} metatarsal - Second metatarsal base - Great toe sesamoids

Table 5. Stress fractures site (1,7).

- *Time period from onset of symptoms until diagnosis*: is a continuous quantitative variable and will be measured in days.
- *Discharge time*, is a continuous quantitative variable and will be measured in days.

- *Partial weight-bearing***,** is a continuous quantitative variable and will be measured in days.
- *Duration of symptoms (pain),* which is a continuous quantitative variable. It will be measured in days. Pain will be assessed through the score of the VAS (Annex 3) at each visit.

7.5. Interventions

7.5.1. Study treatments

The injections of teriparatide (20 µg or 40 µg) or placebo will be provided in a pre-filled device (injection pen). The three types of devices will be identical in appearance in order to ensure blindness throughout the study. The injection pens will be properly labeled according to Good Clinical Practice Guidelines.

Each pen contains 28 doses of teriparatide (20 µg or 40 µg) or placebo, for daily subcutaneous administration in the thigh or abdomen. Injection pen should be stored in a refrigerator at a temperature of 2ºC - 8ºC, and should be removed from the refrigerator 10 minutes before being used.
The pen must be returned to the hospital after 28 days from the first injection, even if it is not completely empty.

The treatments used in the study will be provided by Eli Lilly and Company. The pharmacy of the hospital will be the responsible for managing the assigned study treatment to each patient.

All patients will be taught to properly administer the injection at baseline visit (V2), and will also receive a user manual that describes the instructions for use of the injection pen (Annex 4).

- Teriparatide 20 µg group

The medication used will be FORSTEO 20 µg/80 µL solution for injection in pre-filled pen. According to its data sheet, FORSTEO is a colourless and clear solution. It is supplied in a cartridge contained in a pre-filled disposable pen. Each pen of 2,4 mL contains 600 µg of teriparatide (corresponding to 250 µg per mL), for 28 doses (13).

- Teriparatide 40 µg group

Patients allocated in this treatment group will receive teriparatide of 40 µg/80 µL (not approved dose) daily. This treatment will be prepared by the same laboratory, and will be identical in appearance. Each pen of 2,4 mL contains 1200 µg of teriparatide (corresponding to 500 µg per mL), for 28 doses, to ensure blinding.

- Placebo group

A solution of 80 µL of placebo will be given daily to patients allocated in the placebo group. This treatment will be also provided by Eli Lilly and Company. It is composed of physiological serum and has the same color and consistency that the other treatments, but it does not contain the active ingredient. This solution will be put in an identical injection pen, with the same doses in order to guarantee the blinding. In addition, patients will be taught to use it in the same way.

TREATMENT		Formulation and dose	Frequency	Duration of treatment	Route of administration
Active injection	**Teriparatide 20 µg**	Teriparatide 20µg/80 µL solution for injection in pre-filled pen	Once daily	8 weeks	Subcutaneous
	Teriparatide 40 µg	Teriparatide 40µg/80 µL solution for injection in pre-filled pen	Once daily	8 weeks	Subcutaneous
Placebo injection	**Placebo**	80 µL of placebo solution for injection in pre-filled pen	Once daily	8 weeks	subcutaneous

Table 6. Study treatments.

7.5.2. Therapeutic compliance

Treatment compliance will be assessed by the study staff at each patient visit, by direct questioning of the patients, and by quantifying the study drug returned in the pre-filled pen (used and unused) at visits 5 and 7.

7.5.3. Analgesic treatment

Non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided. The physician will recommend to patient the permitted analgesia to treat pain.

7.5.4. Conservative treatment guide for athletes with stress fractures

All injured patients will undergo a conservative treatment plan (*See Table 7*) (10,23), which will be managed by the physician at each visit. The physician will be coordinated with the physiotherapist of the athlete, to ensure a proper recovery.

All progressions will be documented in a rehabilitation data collection sheet that will be available for review.

Considering that the progression of the treatment depends on several factors, such as the stress fracture site, the progression of each patient will be made on the basis of symptoms (pain) rather than on a predetermined schedule.
Thus, pain will be assessed through the score of the Visual Analog Scale (VAS) (Annex 3) at each visit. The physician will be responsible to direct all process.

All confirmed SFX will be initially treated with conservative measures and restriction of activity. During the first phase of treatment, a discharge regime with an orthotic will be required in most cases. An immobilization with a cast may be indicated in some circumstances, but should not be used regularly, to prevent a further weakening of the bone and deconditioning of the surrounding soft tissue. Then, a period of partial weight-bearing with crutches will be necessary.

Once weight bearing can be tolerated without pain, the ambulation should progress from partial weight-bearing with crutches to full weight-bearing. In addition, low impact activities, such as swimming, biking or pool running, will be entered in order to maintain the level of fitness.

High impact activities will be initiated when the patient can perform low impact activities without pain during long periods of time. Finally, athletes will be gradually reintegrated into their regular training program, starting with shorter sessions, which will be prolonged depending on the symptoms. The activity should increase no more than 15-20% per week (10).

Phase	Activity
I	• *Non weight-bearing*; with an orthotic or a cast • *Partial weight-bearing*; with crutches
II	• *Full weight-bearing* • *Low impact activities*; such as biking, swimming or pool running
III	• *High impact activities* • *Gradual return to sport*

Table 7. Conservative treatment guide. Reproduced from (10).

7.6. Endpoints and assessments

7.6.1. Efficacy assessment

Primary endpoint

- *Time to radiographic healing*, is the interval in days between the diagnosis of the stress fracture and the radiographic healing. Radiographic healing is defined by cortical bridging in three of four cortices seen on X-ray images (23).

  In order to evaluate the radiographic healing of the SFX, conventional radiographs (AP and lateral view) will be performed at each visit.

  Radiographs will be assessed by a traumatologist of each center, who will have previously received a standardized training, in order to achieve the most homogeneous results. These radiographs will be subsequently reviewed by a central radiologist, who unaware the treatment allocations and other patient data.

  Efficacy will be defined as reduction of at least 2 weeks of radiographic healing time compared to placebo group. As it is a continuous quantitative variable, it will be measured as a median.

Secondary endpoint

- *Return to sport time (RTST)* is the time period from the diagnosis until return to full sport. Return to sport is defined as the point in time, when the athlete is able to return to sport and can jogging without restrictions and without clinical symptoms.

  During the follow up, pain at rest and under strain will be used to monitor improvement and allow an individualized progression of the intensity of treatment. The weight and duration of the treatments will be directed by physicians, who will be responsible to assess the return to sport.

  Efficacy will be defined as reduction of at least 3 weeks of RTST compared to placebo group. As it is a continuous quantitative variable, it will be measured as a median.

7.6.2. Safety assessment

An adverse event (AE) is the appearance or worsening of any sign, symptom or undesirable clinical state that occurs after the start of the study medication, even if it is considered that is not related to the study medication.

A serious adverse event (SAE) is any AE that results in any of the following outcomes: death, life threatening (places the patient at immediate risk of death), requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or produces a congenital anomaly or birth defect.
If an AE is considered medically significant, but does not meet any of the SAE criteria, the event could be also classified as a SAE.

- Severity of adverse events

The severity of each AE will be assessed by the investigator as follows:

- *Mild*: Transient AE that may require only minimal treatment and does not generally interfere with usual activities of daily living.
- *Moderate*: AE that is alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but represents no significant or permanent risk of harm to the participant.
- *Severe*: Event that interrupts usual activities of daily living, and generally requires intensive therapeutic intervention.

- Causality of adverse events

  The causal relationship of an AE to studied drug must be assessed by the investigator, and all AE will be classified as related or unrelated to studied drugs.
  The degree of certainty with which an event is attributed to the study treatment or an alternative cause will be determined by how well the event can be understood in terms of: known pharmacology of the studied drug, clinically and/or pathophysiologically plausible context, similar reaction observed previously with similar product or plausibility supported by the temporal relationship.

- Reporting procedures for AE

Any AE associated with the treatment will be reported and documented in a personal data collection sheet (Annex 5: Safety data collection sheet), included in the eCRF.

Each AE should be described in detail, along with its duration (dates of onset and resolution, if resolved), severity, relationship with the studied drug and action taken.

The most commonly reported adverse events in patients treated with teriparatide are nausea, limb pain, headache and dizziness (13).

If the study is carried out, it would be convenient to codify the AE in a homologated form like MedRA (Medical Dictionary for Regulatory Activities).

7.7. Procedures and data collection

Screening assessments and study procedures required for each visit are outlined in this section and in the schedule of assessments (*Annex 6*).

All athletes diagnosed with a SFX of the lower extremity in the participating Sports Medicine Centers, will be assessed by traumatologists to be included in the study. All participants must be considered high-level or high-performance athletes.

In the selection visit (visit 1), candidate patients will be invited to participate in the study and an informed consent must be signed before the start of screening tests. A numeric code will be assigned to each patient in order to respect the confidentiality of personal data.

General demographic data (age, sex, ethnicity, sporting activity, SFX site, beginning of symptoms, menstrual status), and medical and surgical history will be collected by questionnaires, and a complete physical examination (height, weight and BMI) will be performed. In addition, all SFX will be categorized by location as low or high risk stress fractures. At screening, laboratory tests will be performed to determine the suitability of the patients. These tests will be analyzed by local laboratories and include corrected calcium, creatinine, liver function tests (LFT), total alkaline phosphatase and serum PTH.

On the same day, eligible patients will be randomly assigned to receive once-daily doses of teriparatide 20 µg, teriparatide 40 µg or placebo, and stratified according to the SFX site in low-risk or high-risk. The three treatments will be identical in appearance and administration.

All injured patients will undergo a program of conservative treatment, which will be directed by physician (See 8.5. Interventions). All confirmed SF will be initially managed with an orthotic or a cast while the patient follows a discharge regime, with the objective to prevent any pain. During all follow-up visits, progressions will be documented in a rehabilitation data collection sheet, simultaneously with the evolution of pain assessment using the VAS.

In the baseline visit (visit 2), after a maximum period of 7 days from the day of diagnosis, all patients will be taught how to use the injection device and will receive a user manual with instructions for use (Annex 4). On the same day, treatments will be dispensed in the pharmacy department of the hospital and the first dose of treatment will be administered in the consultation.

Patients will also be informed of the possible AE associated with the treatment that may appear.

The double-blind treatment will last about 8 weeks (until visit 7). At visit 3, the medical staff will contact with the patient to review the proper use of the injection device and record any AE.

During the treatment period, visits will be scheduled for assessment of efficacy variables and safety at 2-week intervals. In addition, the proper use of the injection device and the treatment compliance will be assessed, and any adverse event will be reported. All the information will be collected in the database, including the date of fracture healing.

At week 8, interventions will be ceased. The treatments will be withdrawn before if the fracture has already healed.

Post-intervention follow-up period will be carried out at week 10, 3rd, 4th and 6th months and a year. Control radiographs will be performed, and the days of discharge and partial weight bearing, and the date of full return to sport will be documented.

A study scheme is presented in *Figure 4.*

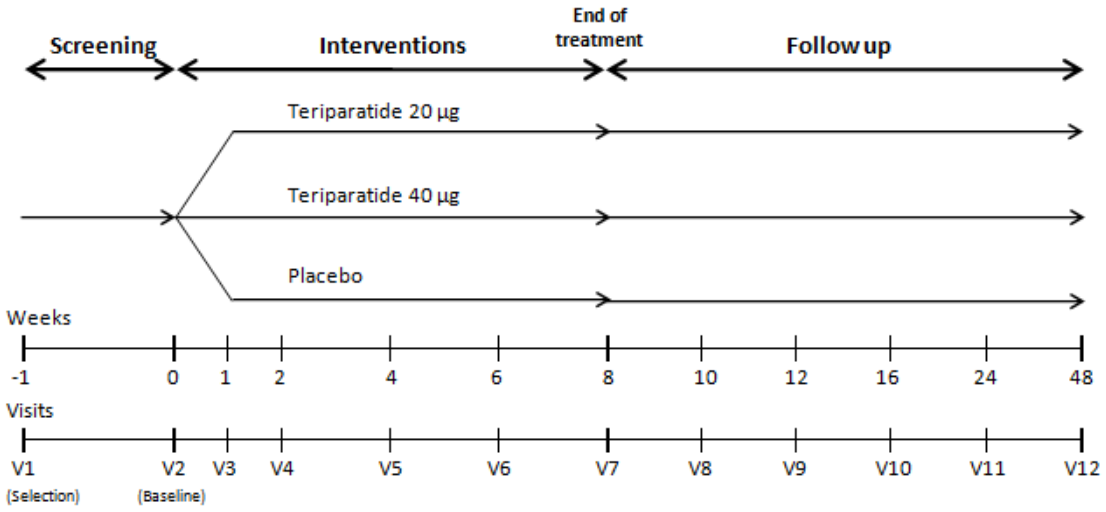


Figure 4. Study scheme

8. STATISTICAL ANALYSIS

Data will be introduced in the database and descriptive analysis will be performed using SPSS software.

In the univariate analysis, results will be expressed as percentages for qualitative variables; and as mean +/- standard deviation (SD) or median (interquartile range) for continuous quantitative variables, depending on whether or not they are normally distributed.

In the bivariate analysis, medians of each dependent variable in each group of treatment stratified by the fracture site will be compared using Mann-Whitney U test.

A multivariate analysis will be performed using Poisson regression, for the two dependent variables and for each of the interventions, because outcome variables are measured discreetly. The model will be adjusted for potential confounders (age, sex, ethnicity, menstrual status, sport discipline, stress fracture site, time period from onset of pain until diagnosis, discharge time, partial weight-bearing time and duration of symptoms).

Values of $p < 0.05$ will be considered statistically significant in all tests.
An intention-to-treat (ITT) analysis will be performed.

9. ETHICAL ASPECTS

This research protocol will be evaluated by the Comitè Ètic d'Investigació Clínica (CEIC) from Hospital Universitari Doctor Josep Trueta, and may be initiated only after receiving their approval. AEMPS must also authorize the clinical trial.

This clinical trial follows the Ethical Principles for Medical Research Involving Human Subjects stated by the World Health Association in the Declaration of Helsinki. It is also carried out according to Good Clinical Practice guidelines.

It will be performed in agreement with the legal framework related to clinical trials: "Ley 29/2006 de 26 Julio, de garantías y uso racional de los medicamentos y productos sanitarios" and "Real Decreto 223/2004 de 6 de febrero: ensayos clínicos con medicamentos".

Before the start of the study, the information sheet to be provided to the patients and the written informed consent must be subjected to the review and approval of the CEIC, together with the study protocol.
Patients will be informed about the procedures and an information sheet about the study in an understandable language by the patient (Annex I) will be given. Written informed consent (Annex II) must be obtained by investigator from each patient before taking part of the study. It will also be explained to the patients that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.

All personal study patient data collected and processed for the purposes of this study will be confidential, guaranteeing the anonymity of the patients involved in the study according to the "Ley Orgánica 15/1999, de 13 de diciembre, de Protección de Datos de Carácter Personal". Patients will not be identified by their names, but by their unique identification numeric code.

Information regarding compensation, insurance, and indemnity is addressed in the insurance policy.

An eCRF (electronic Case Report Form) will be used to record all patient data specified by this protocol. The eCRF must be completed by designed and trained study staff.

This trial will be registered in the EudraCT application.

In this clinical trial, ethics principles are respected.

Our justification for giving placebo is that there is not any accepted effective drug to accelerate the healing of fractures. Thus, the control group with placebo allows a proper comparison of the efficacy variables of athletes treated with teriparatide with the natural healing course of the stress fractures. Placebo will be administered by daily subcutaneous injections in order to mask the treatment allocations. Furthermore, adverse reactions which may occur are minimal and local, and the objective of the study justifies its use.

10.LIMITATIONS

- The sample refers only to high-level and high-performance athletes, which means that the results cannot be extrapolated to the general population with stress fractures.

- One of the efficacy endpoints is the time to radiographic healing. This variable will be measured by radiographs, and its interpretation can vary depending on the traumatologist involved. To minimize this subjectivity, all traumatologists will undergo to a standardized training to achieve the most homogeneous results. In addition, these radiographs will be subsequently reviewed by a central radiologist.

- Another efficacy endpoint is the time to return to sport. This variable may be influenced by the intensity and duration of conservative measures. For this reason, all athletes will undergo a conservative treatment plan individualized for each patient, and the pain will be used as a guide to all activity. In addition, the fact that they are elite athlete ensures that they will follow the doctor's recommendations, to achieve the quickest possible return to sport.

11.WORK PLAN AND CHRONOGRAM

Investigators: Mercè Oliveras (MO), Diana Noriego (DN)

Collaborators: Traumatologists (TR) from participating SMC, radiologist (RX), pharmacist (PH), physiotherapist (PHY), laboratory (LA) and statistician (ST).

This trial has been designed in six phases:

1. Coordination phase (1 month): All staff

   As it is a multicenter study, a meeting with all the research team will be held initially. It aims is to check that the protocol has been correctly understood and to be sure that it is going be followed as planned. The timeline of the study will be examined and the methods of data collection will be shared.

   In this period, it will also take place the standardized training of collaborators, to minimize the inter-observer variability in the patient's evaluation.

2. Field work (26 months): TR, MO, DN, PH, RX, LA, PHY

   A consecutive non-probability sampling will be performed in the participating SMC. The estimated time of recruitment will be 2 years.

   Once the patient is enrolled in the study, the intervention will last 8 weeks. Efficacy and safety assessment will be performed each two weeks, and the study variables will be collected.

3. Post intervention follow-up (34 months): TR, MO, DN, RX, PHY

   It will be carried out after 8 weeks of treatment. It will last 10 months.

4. Data collection (36 months): MO, DN, TR, RX, LA

   It will start in the recruitment phase until de follow up of the last patient. Data will be entered in the database simultaneously with the trial development. A control of data will be performed periodically in order to avoid errors and monitor its evolution.

5. Data analysis (3 months): MO, DN, ST

   All data collected in the database will be analyzed using the appropriate statistical test.

6. Interpretation, publication and dissemination of results (6 months): MO, DN

   The results will be interpreted and the conclusions will be drawn. The corresponding articles will be written and research findings will be published.

   The chronogram is provided in Annex 7.

12.BUDGET

All the planned costs are exposed in the following table:

REQUESTED BUDGET					
	Category	Cost	Quantity	Time	Total (€)
STAFF	Statistician	40€/hour	1	30 hours	1.200 €
STUDY MATERIAL[1]		Cost	Nº patients	Time	Total (€)
	Teriparatide 20	0 €	46	2 months	0 €
	Teriparatide 40	0 €	46	2 months	0 €
	Placebo	0 €	46	2 months	0 €
	Needles	0 €	138	2 months	0 €
ASSESSMENT		Cost	Nº patients	Nº	Total (€)
	Medical visit	51 €	138	4	28.152 €
	Laboratory analysis	62,47 €	138	1	8.620,86 €
	Pregnancy test	10 €	69	1	690 €
	X-ray (1-2 projections)	9 €	138	3	3.726 €
	Document print out (information sheet, informed consent, user manual)				100 €
					Total (€)
INSURANCE POLICY					6.000 €
PUBLICATIONS					1.500 €
MEETINGS	SECOT national congress				1.000€
				TOTAL:	**50.988,86€**

[1] All the study material will be provided by Eli Lilly and Company.

13.IMPACT OF THE PROJECT

Stress fractures are a major problem for those athletes that their livelihood depends on an early return to sport. Thus, if this clinical trial demonstrates that the teriparatide is an effective and safe treatment to accelerate the healing of stress fractures, many athletes might benefit of it.

In addition, in some circumstances, stress fractures are treated surgically in order to permit an early return to activity, but the healing process cannot be readily accelerated. Thus, the teriparatide can help to avoid the need for more aggressive interventions, such as surgery, in those cases that is planned to accelerate the return to activity.

Therefore, we believe that this treatment may have a useful contribution to current practice of the traumatology and sports medicine.

14.BIBLIOGRAPHY

1. Boden BP, Osbahr DC, Jimenez C. Low-risk stress fractures. Am J Sports Med [Internet]. 2001 Jan 1 [cited 2014 Dec 10];29(1):100–11. Available from: https://vpngateway.udg.edu/content/29/1/,DanaInfo=ajs.sagepub.com+100.full

2. Pepper M, Akuthota V, McCarty EC. The pathophysiology of stress fractures. Clin Sports Med [Internet]. 2006 Jan [cited 2014 Dec 15];25(1):1–16, vii. Available from: file:///C:/Users/Samsung/Downloads/0fcfd505c8b3cc6f4a000000 (10).pdf

3. McCormick F, Nwachukwu BU, Provencher MT. Stress fractures in runners. Clin Sports Med [Internet]. 2012 Apr 4 [cited 2014 Dec 15];31(2):291–306. Available from: http://www.sportsmed.theclinics.com/article/S0278591911001025/fulltext

4. Warden SJ, Burr DB, Brukner PD. Stress fractures: pathophysiology, epidemiology, and risk factors. Curr Osteoporos Rep [Internet]. 2006 Sep [cited 2014 Dec 21];4(3):103–9. Available from: file:///C:/Users/Samsung/Downloads/33_StressFractureReview(CurrOsteoRep) (4).pdf

5. Berger FH, de Jonge MC, Maas M. Stress fractures in the lower extremity. The importance of increasing awareness amongst radiologists. Eur J Radiol [Internet]. 2007 Apr [cited 2014 Dec 21];62(1):16–26. Available from: file:///C:/Users/Samsung/Downloads/Berger-2007-Eur J Radiol (1).pdf

6. Liong SY, Whitehouse RW. Lower extremity and pelvic stress fractures in athletes. Br J Radiol [Internet]. 2012 Aug [cited 2015 Jan 4];85(1016):1148–56. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3495575/?tool=pmcentrez

7. Boden BP, Osbahr DC. High-risk stress fractures: evaluation and treatment. J Am Acad Orthop Surg. 2000;8:344–53.

8. Canalis E, Giustina A, Bilezikian JP. Mechanisms of anabolic therapies for osteoporosis. N Engl J Med [Internet]. 2007 Aug 30 [cited 2015 Jan 14];357(9):905–16. Available from: http://enotes.us/osteoporosisRx2007.pdf

9. Warden SJ, Davis IS, Fredericson M. Management and Prevention of Bone Stress Injuries in Long Distance Runners. J Orthop Sports Phys Ther [Internet]. 2014 Aug 7 [cited 2014 Sep 30];44(10):1–50. Available from: http://www.jospt.org/doi/pdfplus/10.2519/jospt.2014.5334

10. Romani WA, Gieck JH, Perrin DH, Saliba EN, Kahler DM. Mechanisms and management of stress fractures in physically active persons. J Athl Train [Internet]. 2002 Jul [cited 2015 Jan 12];37(3):306–14. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC164361/?tool=pmcentrez

11. Mehallo CJ, Drezner JA, Bytomski JR. Practical management: nonsteroidal antiinflammatory drug (NSAID) use in athletic injuries. Clin J Sport Med [Internet]. 2006 Mar [cited 2015 Jan 12];16(2):170–4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16603889

12. Shima Y, Engebretsen L, Iwasa J, Kitaoka K, Tomita K. Use of bisphosphonates for the treatment of stress fractures in athletes. Knee Surg Sports Traumatol Arthrosc [Internet]. 2009 May [cited 2015 Jan 15];17(5):542–50. Available from: http://www.klokavskade.no/upload/Publication/Shima_2008_KSSTA_Use of bisphosphonates for the treatment of stress fracture in athletes.pdf

13. Ficha técnica Forsteo [Internet]. Agencia Europea del Medicamento; [cited 2014 Dec 27]. Available from: http://www.ema.europa.eu/docs/es_ES/document_library/EPAR_-_Product_Information/human/000425/WC500027994.pdf

14. Deal C, Gideon J. Recombinant human PTH 1-34 (Forteo): an anabolic drug for osteoporosis. Cleve Clin J Med [Internet]. 2003 Jul [cited 2015 Jan 15];70(7):585–6, 589–90, 592–4 passim. Available from: http://www.ccjm.org/fileadmin/content_pdf/ccjm/content_70_585.pdf

15. Cheng ML, Gupta V. Teriparatide - Indications beyond osteoporosis. Indian J Endocrinol Metab [Internet]. 2012 May [cited 2015 Jan 15];16(3):343–8. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3354838/?tool=pmcentrez

16. Vahle JL, Sato M, Long GG, Young JK, Francis PC, Engelhardt JA, et al. Skeletal changes in rats given daily subcutaneous injections of recombinant human parathyroid hormone (1-34) for 2 years and relevance to human safety. Toxicol Pathol [Internet]. [cited 2015 Jan 14];30(3):312–21. Available from: http://tpx.sagepub.com/content/30/3/312.full.pdf

17. Andreassen TT, Ejersted C, Oxlund H. Intermittent parathyroid hormone (1-34) treatment increases callus formation and mechanical strength of healing rat fractures. J Bone Miner Res [Internet]. 1999 Jun [cited 2015 Jan 15];14(6):960–8. Available from: http://onlinelibrary.wiley.com/doi/10.1359/jbmr.1999.14.6.960/pdf

18. Andreassen TT, Fledelius C, Ejersted C, Oxlund H. Increases in callus formation and mechanical strength of healing fractures in old rats treated with parathyroid hormone. Acta Orthop Scand [Internet]. 2001 Jun [cited 2015 Jan 15];72(3):304–7. Available from: http://informahealthcare.com/doi/pdf/10.1080/00016470152846673

19. Aspenberg P, Genant HK, Johansson T, Nino AJ, See K, Krohn K, et al. Teriparatide for acceleration of fracture repair in humans: a prospective, randomized, double-blind study of 102 postmenopausal women with distal radial fractures. J Bone Miner Res [Internet]. 2010 Feb [cited 2015 Jan

12];25(2):404–14. Available from: http://onlinelibrary.wiley.com/doi/10.1359/jbmr.090731/pdf

20. Sobre deportistas de alto nivel y alto rendimiento. Real Decreto 971/2007 de 13 de julio. Boletín Oficial del Estado, n°177, (25-07-2007). [Internet]. [cited 2014 Dec 20]. Available from: http://www.csd.gob.es/csd/estaticos/altonivel/legislacion/BOE_Real_Decreto_DAN_y_Alto_Rendimiento.pdf

21. Iwamoto J, Takeda T. Stress fractures in athletes: review of 196 cases. J Orthop Sci [Internet]. 2003 Jan [cited 2014 Dec 21];8(3):273–8. Available from: http://www.ais.up.ac.za/med/sport/stressfractures.pdf

22. Grigoryan M, Lynch JA, Fierlinger AL, Guermazi A, Fan B, MacLean DB, et al. Quantitative and qualitative assessment of closed fracture healing using computed tomography and conventional radiography. Acad Radiol [Internet]. 2003 Nov [cited 2015 Jan 13];10(11):1267–73. Available from: https://vpngateway.udg.edu/S1076633203004677/,DanaInfo=ac.els-cdn.com+1-s2.0-S1076633203004677-main.pdf?_tid=fde6f9f8-9ed5-11e4-ab8b-00000aacb362&acdnat=1421560445_d1bb1da0c942849022fc8b5803d51828

23. Dobrindt O, Hoffmeyer B, Ruf J, Seidensticker M, Steffen IG, Fischbach F, et al. Estimation of return-to-sports-time for athletes with stress fracture - an approach combining risk level of fracture site with severity based on imaging. BMC Musculoskelet Disord [Internet]. 2012 Jan [cited 2015 Jan 17];13:139. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3485631/?tool=pmcentrez

24. Hall J. Trastornos menstruales y dolor pélvico. In: Fauci A, Kasper D, Longo D, Braunwald E, Hauser S, Jameson J, et al., editors. Harrison Principios de medicina interna. 17th ed. México: Mc Graw Hill; 2008. p. 304.

15.ANNEXES

15.1. ANNEX 1: Information sheet

FULL D'INFORMACIÓ AL PACIENT

Títol de l'estudi: *Use of teriparatide to accelerate the healing of lower extremity stress fractures in high-level and high-performance athletes.*

Investigadors: Mercè Oliveras, Diana Noriego

Informació general:

Ens dirigim a vostè per informar-lo sobre un estudi d'investigació que s'està duent a terme en aquest centre i en el que se'l convida a participar, de manera completament voluntària.

La nostra intenció és que vostè rebi informació de manera correcta i suficient perquè pugui valorar si vol o no participar en aquest estudi. Per això, llegeixi aquest full informatiu amb atenció i nosaltres li aclarirem els dubtes que puguin sorgir.

Participació voluntària:

Ha de saber que la seva participació en aquest estudi és voluntària i que pot decidir no participar o canviar la seva decisió i retirar el consentiment en el moment que ho desitgi, sense que per això s'alteri la relació amb el seu metge ni es produeixi cap perjudici en el seu tractament.

Descripció de l'estudi:

L'objectiu d'aquest estudi és determinar l'eficàcia i la seguretat de la teriparatida pel tractament de les fractures d'estrès a les extremitats inferiors, comparat amb placebo, en esportistes d'elit, disminuint el temps necessari per la curació de la fractura i accelerant així el retorn a l'entrenament/competició.

El medicament objecte d'estudi és la teriparatida, que pertany al grup dels anomenats fàrmacs anabolitzants i que estimula directament la formació d'os. La teriparatida s'utilitza pel tractament de l'osteoporosi en adults en dosis de 20 µg, administrada diàriament ver via subcutània.

Aquest estudi es tracta d'un assaig clínic en què s'administrarà aleatòriament un dels següents tractaments; teriparatida de 20 µg, 40 µg o placebo (fàrmac injectable amb el mateix aspecte que la teriparatida, però que no conté substància farmacològicament activa) durant un període de 8 setmanes. Al tractar-se d'un procés aleatoritzat, tots els participants tindran les mateixes possibilitats de rebre un tractament o altre. I ni vostè ni el metge sabrà quin és el tractament que rebrà.

Els tractaments s'administraran mitjançant un dispositiu (ploma d'injecció) un cop al dia, per via subcutània a la cuixa o en l'abdomen. Cada ploma d'injecció té 28 dosis de medicament (per 28 dies), que vostè haurà de retornar al seu metge un cop passat aquest període.

El període de duració de l'estudi serà d' 1 any. Des d'un començament vostè haurà de seguir el tractament conservador proposat pel seu metge i podrà rebre o no tractament actiu, però sempre estarà sota supervisió mèdica.

A la primera visita, se li entregarà el tractament (ploma d'injecció amb les agulles) juntament amb "el manual de l'usuari de la ploma" i se li ensenyarà com utilitzar el dispositiu d'injecció. La primera injecció de tractament es realitzarà a la consulta.

Durant les 8 setmanes de tractament farmacològic, es programaran una sèrie de visites periòdiques, cada 2 setmanes, on es realitzaran radiografies per avaluar la curació de la fractura, i a la 4ª setmana es farà una analítica de control. Un cop finalitzat el tractament, es realitzaran visites de seguiment a les 10 setmanes, 3, 4 i 6 mesos i a l'any.

Durant l'assaig clínic està permès rebre analgèsia, evitant els antiinflamatoris no esteroïdals (AINES). El seu metge li recomanarà l'analgèsia permesa per tractar el dolor.

Beneficis i riscs derivats de la seva participació en l'estudi:

És possible que vostè no obtingui cap benefici directe per participar en aquest estudi. S'espera que la teriparatida acceleri el temps de consolidació de les fractures d'estrès, i sigui una nova alternativa de tractament en aquells casos que es requereixi un ràpid retorn a l'activitat/esport, com és el cas dels esportistes d'elit.

En aquest estudi no es realitzarà cap tipus de tècnica agressiva. Només es realitzarà una analítica sanguínia a la 4ª setmana de tractament,

Els efectes adversos més freqüents que poden aparèixer durant el tractament són: nàusees, dolor de les extremitats, cefalea i mareig. També pot presentar esdeveniments lleus i transitoris en el lloc de la injecció, incloent dolor, inflor, eritema, hematoma localitzat, prurit i lleuger sagnat en el lloc de la injecció.

En cas de patir algun dels efectes adversos, vostè ho haurà de comunicar al seu metge.

Responsabilitat i assegurança:

El promotor de l'estudi ha subscrit una pòlissa d'assegurança que cobreix els danys que vostè pogués patir com a conseqüència de la seva participació en aquest assaig, d'acord amb la legislació vigent.

Confidencialitat:

Totes les dades de caràcter personal i informació recollida o generada durant l'estudi quedarà protegida segons la Llei Orgànica 15/1999 de "Protecció de Dades de Caràcter Personal".

Les dades recollides durant l'estudi estaran identificades mitjançant un codi numèric i només el seu metge de l'estudi i els col·laboradors podran relacionar aquestes dades amb vostè i amb la seva història clínica. Per tant, la seva identitat no serà revelada.

Compensació econòmica:

La seva participació en l'estudi no li suposarà cap cost addicional. Vostè no haurà de pagar els medicaments de l'estudi.

Altra informació rellevant:

Qualsevol nova informació referent als fàrmacs o procediments utilitzats en l'estudi i que pot afectar a la seva disposició per participar en l'estudi, que es descobreixi durant la seva participació, li serà comunicada pel seu metge el més aviat possible.

Si vostè decideix retirar el consentiment per participar en aquest estudi, no s'afegiran noves dades a la base de dades.

També ha de saber que vostè pot ser exclòs de l'estudi si el promotor o els investigadors de l'estudi ho consideren oportú, ja sigui per motius de seguretat (efectes adversos produïts per la medicació de l'estudi), o perquè considerin que no està complint amb els procediments establers. En qualsevol dels casos, vostè rebrà una explicació adequada del motiu que ha ocasionat la seva retirada de l'estudi.

Persones de contacte:

Davant de qualsevol dubte o problema que succeeixi durant la realització de l'estudi, vostè podrà posar-se en contacte amb els responsables de l'estudi:

Mercè Oliveras i Dra. Diana Noriego
Telèfon: 972 94 02 00
Hospital Dr. Josep Trueta. Departament de Traumatologia
Av/ de França, s/n. 17007 - Girona.

Si us plau, no dubti en fer més preguntes al seu metge si alguna cosa no li ha quedat clara. Si decideix entrar a l'estudi, signi el consentiment informat.

15.2. ANNEX 2: Informed consent

FULL DE CONSENTIMENT INFORMAT DEL PACIENT

Títol de l'estudi: *Use of teriparatide to accelerate the healing of lower extremity stress fractures in high-level and high-performance athletes.*

Jo, (nom i cognoms).....

He llegit el full d'informació que se m'ha entregat.

He pogut fer preguntes sobre l'estudi.

He rebut suficient informació sobre l'estudi.

He parlat amb: (nom de l'investigador) .....

Comprenc que la participació és voluntària.

Comprenc que em puc retirar de l'estudi:

1. En el moment que ho desitgi.
2. Sense haver de donar cap tipus d'explicació.
3. Sense que suposi cap diferència en la meva assistència mèdica.

Així, dono la meva conformitat per participar en aquest estudi.

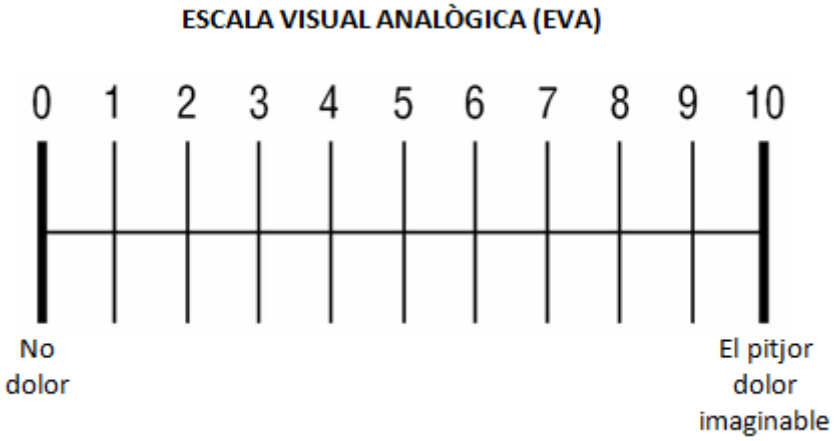
Signatura del pacient:	Signatura de l'investigador:
Nom:	Nom: .....
Data de la signatura:	Data de la signatura: .....

APARTAT PER LA REVOCACIÓ DEL CONSENTIMENT

Jo, ..., revoco el consentiment de participació en l'estudi a dalt indicat.

Signatura: Data: .....

15.3. ANNEX 3: Visual Analog Scale for Pain (VAS for Pain)

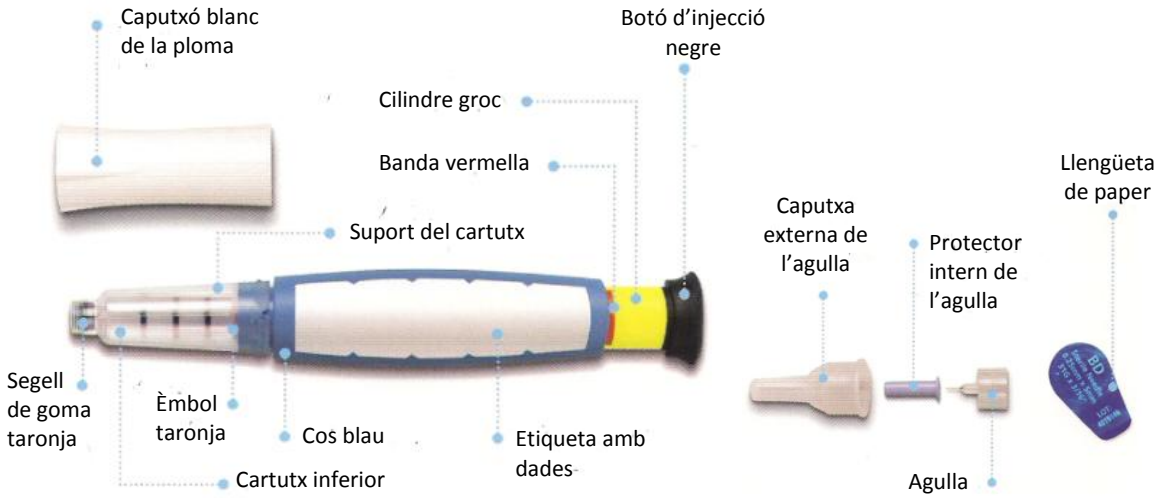


15.4. ANNEX 4: User manual

MANUAL DE L'USUARI DE LA PLOMA

Aquest medicament es tracta d'un fàrmac injectable que s'administra mitjançant un dispositiu (ploma) i que conté medicament per 28 dies.

Parts de la ploma:



Forma d'administració:

El medicament s'ha d'administrar **una vegada al dia** mitjançant una injecció sota la pell (via subcutània) a la cuixa o a l'abdomen.

Per tal de no oblidar injectar-se la seva medicació cada dia, es recomana fer-ho cada dia a la mateixa hora.

La durada del tractament serà de 8 setmanes. És molt important complir **tot** el període de tractament que li ha indicat el seu metge. Després de 28 dies de la seva primera administració, retorni la ploma d'injecció al seu metge.

**Información sobre el Programa y el uso de la Pluma (www.lillyosteoporosis.com)*

Punts importants:

La injecció del medicament s'ha de realitzar poc després de treure la ploma de la nevera (10 min). I s'ha de tornar a guardar a la nevera immediatament després del seu ús.

No s'ha de punxar mai més d'un cop al dia, tot i que no s'hagi administrat la dosis correcte.

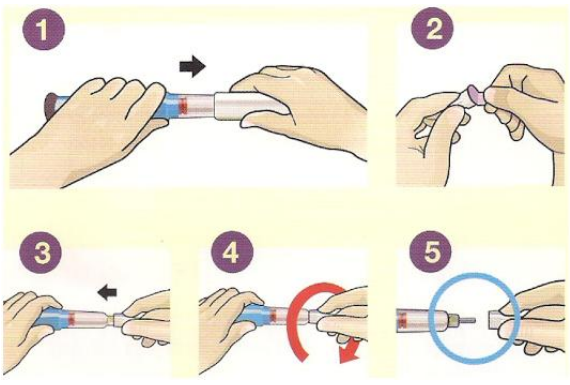
S'ha d'utilitzar una agulla nova per a cada injecció i s'ha de tirar després de cada ús. No es pot guardar la ploma amb l'agulla posada, ni compartir la ploma ni les agulles amb ningú més.

GUIA DE PREPARACIÓ DE LA PLOMA I ADMINISTRACIÓ DE LA DOSIS

Abans d'utilitzar la seva nova ploma, si us plau llegeixi tota la secció "guia de preparació de la ploma i administració de la dosis".

1er pas: Preparació de la ploma d'injecció i col·locació d'una agulla nova

1. Retiri el caputxó blanc de la ploma tirant d'ell.
2. Retiri la llengüeta de paper de la caputxa externa de l'agulla.
3. Col·loqui l'agulla tapada pressionant-la **directament** sobre el cartutx del medicament.
4. Enrosqui l'agulla fins que quedi perfectament fixada, sense forçar.
5. Retiri la caputxa externa de l'agulla i **guardi-la**.

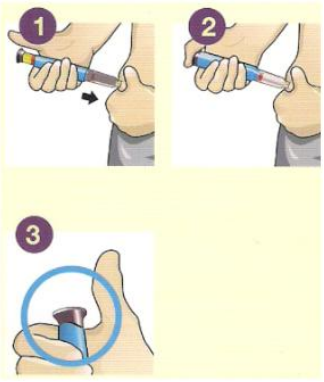


**Información sobre el Programa y el uso de la Pluma (www.lillyosteoporosis.com)*

2n pas: Ajust de la dosis

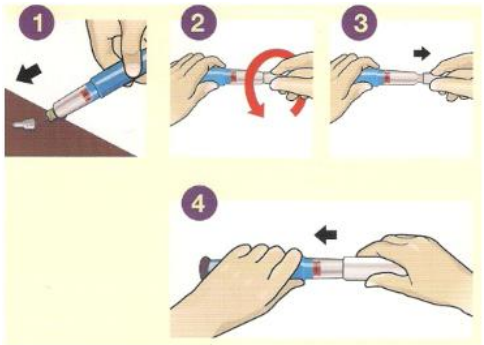
1. Tiri del botó d'injecció negre **fins que s'aturi**.
2. **Assegureu-vos** que es veu la banda vermella.
3. **Retiri** el protector intern de l'agulla i llenceu-lo.

3er pas: Injecció de la dosis



1. Pessigui suaument la pell de la cuixa o l'abdomen i introdueixi directament l'agulla sota la seva pell.
2. **Pressioni** el botó d'injecció negre fins que s'aturi. Manteniu-lo pressionat i **compti poc a poc fins a 5**. A continuació, retiri l'agulla de la pell.
3. Confirmi la dosis assegurant-se que el botó d'injecció negre ha estat introduït fins al final i de no tenir a la vista el cilindre groc.
   Si ja s'ha injectat el producte i encara es veu una part groga, **NO TORNI A INJECTAR-SE UNA SEGONA VEGADA EL MATEIX DIA.**

4t pas: Retirada de l'agulla i conservació de la ploma per la següent dosis



1. Col·loqui la caputxa externa de l'agulla.
2. Desenrosqui completament l'agulla tapada amb la caputxa, donant-li de 3 a 5 voltes completes.
3. Retiri l'agulla i llenci-la tal i com li ha indicat el seu professional sanitari.
4. Torni a col·locar el caputxó blanc.
   RECORDI GUARDAR LA PLOMA DE NOU A LA NEVERA. NO INTRODUEIXI MAI LA PLOMA AL CONGELADOR.

**Información sobre el Programa y el uso de la Pluma (www.lillyosteoporosis.com)*

15.5. ANNEX 5: Safety data collection sheet

FULL DE RECOLLIDA DE POSSIBLES ESDEVENIMENTS ADVERSOS

Codi del pacient: .....

Persona que recull les dades: .....

Esdeveniment advers: .....

Data d'inici: .....

Data de resolució (en cas afirmatiu): .....

Gravetat: Lleu / Moderat / Greu

Esdeveniment advers greu? Si / No

Criteri de gravetat (en cas afirmatiu):

Mort

En perill de vida

Hospitalització o prolongació de l'hospitalització existent

Invalidesa/discapacitat persistent o important

Anomalia congènita/defecte naixement

Esdeveniment mèdic important

L'EA està relacionat amb el fàrmac de l'estudi? Si / No

Accions preses (en cas afirmatiu): .....

15.6. ANNEX 6: Schedule of assessments

Phase	**Screening**	**Baseline**	**Interventions**					**Follow-up**				
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
Week	-1	0	1	2	4	6	8	10	12	16	24	48
Procedure												
General and safety assessments												
Diagnosis of SF (X-rays, MRI or BS)	X											
Information sheet	X											
Written informed consent	X											
Patient allocation (numeric code)	X											
Inclusion and exclusion criteria	X	(X)										
General demographic data	X											
Medical/surgical history	X											
Physical examination	X											
Randomization	X											
Delivery of study medication		X			X							
Administration of study medication		X	X	X	X	X	X					
Rehabilitation program	X	X	Record continuously until the RTS									
Pain assessment (VAS)	X	X	Record continuously until the RTS									
Discharge/non-weight bearing (days)	X	X	Record continuously until the RTS									
Proper use of the injection device			X	X	X	X	X					
Treatment compliance review			X	X	X	X	X					
Return of the injection device					X		X					
Record adverse events			X	X	X	X	X					
Laboratory assessments:												
Corrected calcium	X											
Creatinine	X											
LFT	X											
Alkaline phosphatase	X											
PTH	X											
Serum pregnancy test (females of childbearing potential)	X											
Efficacy assessment:												
X-rays (AP + lateral)				X	X	X	X	X	X	X	X	X

15.7. ANNEX 7: Chronogram

Investigators: Mercè Oliveras (MO), Diana Noriego (DN)

Collaborators: Traumatologists (TR) from participating SMC, radiologist (RX), pharmacist (PH), physiotherapist (PHY), laboratory (LA) and statistician (ST)

Year		**2015**					**2016**				**2017**					**2018**									
Months		1	2-3	4-6	7-9	10-12	1-3	4-6	7-9	10-12	1	2-3	4-6	7-9	10-12	1	2	3	4	5	6	7	8	9	10
ACTIVITY	**STAFF**																								
1. COORDINATION PHASE																									
Meeting	All staff																								
Standardized training																									
2. PATIENT INCLUSION, INTERVENTION AND DATA COLLECTION																									
Subjects recruitment	TR, MO, DN, RX, LA, PH, PHY																								
Interventions																									
3. FOLLOW UP																									
Follow up	TR, MO, DN, RX, PHY,																								
4. DATA COLLECTION																									
Data collection	TR, MO, DN, RX, LA																								
5. DATA ANALYSIS PHASE																									
Statistical analysis	MO, DN, ST																								
6. INTERPRETATION, PUBLICATION AND DISSEMINATION																									
Interpretation	MO, DN																								
Articles, conferences																									