A Phase 2, Multicenter, Randomized, Active-Controlled, Parallel-Group, Dose-Finding and Safety Study of Recombinant Human Bone Morphogenetic Protein-2 (rhBMP-2)/Calcium Phosphate Matrix (CPM) in Subjects With Decreased Bone Mineral Density.

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Bone, calcium, magnesium and phosphorus metabolism disorders
Study type	Interventional

Summary

ID

NL-OMON35312

Source
ToetsingOnline

Brief title
rhBMP-2 HIP STUDY

Condition

- Bone, calcium, magnesium and phosphorus metabolism disorders
- Fractures

Synonym

oseteoporosis or decalcification

Research involving
Human

Sponsors and support

Primary sponsor: Wyeth
Source(s) of monetary or material Support: Wyeth Pharmaceuticals

Intervention

Keyword: bone mineral density, hip, osteoporosis, recombinant human bone morphogenetic protein

Outcome measures

Primary outcome

Demonstrate increased BMD of the proximal femur (total hip BMD) after injection of rhBMP-2/CPM (either 1.0 mg/mL or 2.0 mg/mL) as an adjunct to systemic osteoporosis therapy. Endpoint: BMD measured by dual-energy x-ray absorptiometry (DXA) every 3 months from 6 to 12 months.

Secondary outcome

• Assess acute (6 weeks) and long-term (up to 36 months) safety of administering rhBMP-2/CPM in subjects with decreased BMD.

• Assess the feasibility of administering rhBMP-2/CPM as a minimally invasive technique in an outpatient (ambulatory care) setting.

• Identify a clinically meaningful difference in BMD between rhBMP-2/CPM treatment groups, allowing for a single dose (concentration) to be selected for the phase 3 program.

• Identify number of nonresponders-treated subjects who, after up to 12 months of follow-up, have changes in BMD from baseline that are less than or equal to changes observed in the contralateral (untreated) hip and for which an

attributable cause cannot otherwise be identified.

• Assess changes in BMD relative to femoral neck morphometry, exploring the relation between the femoral neck volume of individual study subjects or groups of subjects, the volume of rhBMP-2/CPM administered, and the overall response to treatment, measured by bone densitometry.

• Evaluate long-term (up to 36 months) changes in BMD after injection of rhBMP-2/CPM.

• Evaluate bone quality with emphasis on cortical thickness and trabecular volume in region(s) of interest (ROIs), utilizing quantitative computed tomography (volumetric rendering of proximal femur; vQCT).

• Evaluate changes in biochemical markers of bone turnover to identify markers that are predictive of changes in BMD from baseline.

o Markers of bone formation: bone-specific alkaline phosphatase (bone ALP), N-terminal propeptide of type I collagen (PINP), osteocalcin (OC).

o Markers of bone resorption: C-terminal cross-linked telopeptide of type I collagen (CTX-I) and tartrate-resistant acid phosphatase isoenzyme 5b (TRAcP5b).

Study description

Background summary

• Incidence of hip fracture continues to rise worldwide, representing an area of high medical need.
• Onset of effect of systemic therapy to enhance bone density (eg, bisphosphonates) is not immediate and may not adequately protect subjects with decreased bone density from fracture.
• Bisphosphonate therapy will typically require 2 to 3 years of active

treatment in order to achieve a 40% to 50% reduction in the first occurrence of a hip fracture.
• Preclinical studies in non human primates have established efficacy of recombinant human bone morphogenetic protein 2/calcium phosphate matrix (rhBMP-2/CPM) in osteoporotic bone, demonstrating increased cortical and trabecular bone volume and increased bone strength at the site of injection. rhBMP- 2/CPM offers a locally administered, minimally invasive surgical treatment for increasing bone mass at skeletal sites at risk for fracture; the effect of rhBMP-2/CPM is not inhibited by concomitant administration of bisphosphonate therapy, making the treatment compatible with the current standard of care (SOC).

Study objective

Onset of effect of systemic therapy to enhance bone density (eg, bisphosphonates) is not immediate and may not adequately protect subjects with decreased bone density from fracture.
Bisphosphonate therapy will typically require 2 to 3 years of active treatment in order to achieve a 40% to 50% reduction in the first occurrence of a hip fracture.
Preclinical studies in non human primates have established efficacy of recombinant human bone morphogenetic protein 2/calcium phosphate matrix (rhBMP-2/CPM) in osteoporotic bone, demonstrating increased cortical and trabecular bone volume and increased bone strength at the site of injection. rhBMP- 2/CPM offers a locally administered, minimally invasive surgical treatment for increasing bone mass at skeletal sites at risk for fracture; the effect of rhBMP-2/CPM is not inhibited by concomitant administration of bisphosphonate therapy, making the treatment compatible with the current standard of care (SOC).

Study design

Multicenter, randomized (by hip), active-controlled, stratified (by prior osteoporosis therapy), parallel group study of 2 concentrations of rhBMP-2/CPM as an adjunct to systemic osteoporosis (bisphosphonate) therapy, the active comparator.

Intervention

Single percutaneous intraosseous injection of rhBMP-2/CPM (either 1.0 mg/mL or 2.0 mg/mL delivered in a volume of 6 mL), administered unilaterally through a lateral approach under local anesthesia and conscious sedation and fluoroscopic control to the femoral neck and intertrochanteric region. Treatment with rhBMP 2/CPM is administered as an adjunct to systemic osteoporosis therapy.

Study burden and risks

Possible risks of rhBMP-2 (The most frequently reported side effects of rhBMP-2 are):
• Headache
• Increased amounts of amylase (an enzyme used in digestion) in the blood (high blood amylase) without obvious signs of inflammation of the pancreas
• Tachycardia (fast heart beat)
• Low magnesium in the blood

Other reported side effects are:
• Local swelling near the area of injection
• Fluid collection in some patients undergoing spine surgery with rhBMP-2/ACS, at times resulting in nerve compression and pain.
• Loss of bone (leading to bone weakness)
• Excess bone growth (too much bone growth) or abnormal bone growth in the surrounding tissues that could put pressure on nearby nerves or tendons.
• Antibodies to BMP-2 have been observed. Antibodies are substances in our bodies that recognize foreign agents (e.g., germs) and help fight infection. The long-term effects of antibodies to BMP-2 are unknown. Side effects suggesting an allergy or immune effects (inability to fight infections) have not been reported but cannot be excluded.
• Patients who take NSAID medications (certain pain killers) while being treated with rhBMP-2 may have wound healing problems, such as persistent wound drainage
• A 2mg/mL dose was tested in subjects with closed tibia fractures (broken shinbones). It was found that this dose slowed down healing of these closed broken bones. Therefore, this dose is no longer being tested for closed broken shinbones.

Potential risks that may occur with any injection:
• Contamination at the site of injection
• Unintentional (accidental) nerve damage
• Unintentional (accidental) damage to ligaments and/or tendons (for fractures occurring close to a joint)
• Unintentional (accidental) injection in a vein or artery (blood vessel) leading to breathing and/or blood circulation complications

rhBMP-2 has not been studied in the following patients therefore the safety is unknown:
• Patients with suppressed immune systems or autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus (lupus)
• Patients with kidney or liver problems
• Pediatric patients (children less than 18 years of age)
• Patients who have received this product previously
• Patients with diseases of the skeleton

Limited safety information is available for:
Elderly patients (>65 years of age)

Malignancy
Neither human nor animal studies have shown conclusively that rhBMP-2 can change normal cells into cancers cells in the body. There have been reports from laboratory experiments of existing cancer cells increasing in number when they have been exposed to rhBMP-2; however, other laboratory studies have shown that rhBMP-2 decreased the number of existing cancer cells. Because the risk of stimulating existing cancer growth is still unknown, subjects who have a previous history of cancer will not be included in studies (except for subjects who have had a history only of certain types of skin cancer).

Risks of Blood Collection
The risks involved in taking blood include pain, swelling, bruising, or infection around the vein where your blood is collected. You may feel dizzy or you may faint. The total amount of blood that will be collected for the study is 196 milliliters for the first group of patients that are enrolled in the study and 179 milliliters for the rest of the patients. In comparison, about 500 milliliters/16 ounces is collected at one time for a typical blood donation.

Risks of Radiation
You will be exposed to radiation as a result of participating in the study. The radiation comes from 4 different sources: X-rays, fluoroscopy, DXA and CT scans. X-rays are used to look at the inside parts of your body, like your bones or your lungs, to make sure nothing is wrong. Fluoroscopy is a special X-ray machine that the doctor uses in the surgery room to see where the injection should be put in your hip. DXA is the name of the bone density test which tells how strong your bones are. CT scans give a better picture of the bones than X-rays do and they can also be used to measure the size (thickness, density) of bones. For the CT scan, you will be lying on your back and a partly-open tunnel-shaped machine. You must not move, but relax and breathe normally. Some patients have felt claustrophobic during this test.

The total amount of radiation that you will be exposed to by participating in this study is approximately equal to 6.2 years of natural background radiation that you would normally receive from the sun or the soil in everyday life. We cannot guarantee that this amount of radiation exposure is not without risk.

Risks of Anesthesia
If you are chosen to receive an injection of rhBMP-2/CPM, you will be given a light medication (anesthesia) to numb the area around your hip and to make you feel more relaxed. The medication used for giving the injection may or may not make you feel
sleepy. You should not feel any pain when the injection is given.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. postmenopausal woman, age >=65 years.
2. BMD T-score (total hip or femoral neck) of -2.5 or less in at least 1 hip. Subjects with BMD T-scores of -2.0 or less may be enrolled if at least 1 of the following risk factors is also present.
a. Age >=75 years
b. Family (maternal) history of fragility fracture
c. Previous fragility fracture (self) after 45 years
3. Bilaterally intact proximal femora, without evidence of acute fracture, surgical hardware, or prosthetic implant.
4. Subjects may either be treatment naive or on a previously established regimen (>=1 year, but <5 years duration) of bisphosphonate therapy.
5. Subjects must be willing to comply with 1 of the 3 protocol-designated oral

bisphosphonates (risedronate, alendronate, or ibandronate sodium) with risedronate considered as first-line therapy.

Exclusion criteria

1. Metabolic bone disorder or disease affecting bone and mineral metabolism (eg, Pagets disease, vitamin D deficiency [<20 ng/mL], hyperparathyroidism, renal osteodystrophy, osteomalacia, hypocalcemia, hypercalcemia).
2. Previous use of agents that can be considered bone anabolic (eg, parathyroid hormone (PTH), growth hormone, anabolic steroids, or sodium fluoride at bone therapeutic doses).
3. Previous use of SERMs, HRT, or calcitonin within the past 12 months.
4. Previous use of strontium ranelate.
5. Continuous or intermittent disease that requires systemic glucocorticosteroid treatment within the past 6 months (eg, chronic obstructive pulmonary disease, asthma).
6. Active infection at any anatomical site.
7. History of severe pulmonary or respiratory disorder, such as acute respiratory distress syndrome (ARDS), pulmonary stenosis, or right-to-left venoarterial shunt.
8. Evidence of unstable clinically relevant disease (eg, cardiovascular, hepatic, renal, or thyroid disease).
9. Coagulopathy and/or history of venous thromboembolic events (deep vein thrombosis, pulmonary embolus, retinal vein thrombosis) within the past 12 months.
10. Body mass index (BMI) >35 kg/m2.
11. Documented history of malignancy, except basal or squamous cell carcinoma that has been treated and fully resolved.
12. Inflammatory arthritis including rheumatoid, psoriatic, or crystal-induced (gouty) arthritis, or those associated with systemic lupus erythematosus (SLE), spondyloarthropathy, Reiters syndrome, or Crohns disease.
13. Any condition requiring anticonvulsant therapy.
14. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin >=1.5 times the upper limit of normal (ULN) at screening.
15. ALP or serum creatinine >=2 times the (ULN) at screening.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial

Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-02-2010
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine

Ethics review

Approved WMO Date:	04-08-2009
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	30-11-2009
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	14-01-2010
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	22-01-2010
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO Date:	27-01-2010
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	12-04-2010
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	14-04-2010
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	11-05-2010
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2007-007456-34-NL
ClinicalTrials.gov	NCT00752557

Register	ID
CCMO	NL28128.068.09