

Mock lay summary

Research sponsor: Amneg

Drugs studied: zenosumab and denodronic acid

National Clinical Trial number: PML99988877

Study ID number: 88888888

Other ID: 2222-44444-22 (EudraCT number)

Thank you!

You, as a volunteer, play a key role in the discovery of new medicines. This study would not have been possible without your commitment of time and energy. Thank you for volunteering to participate in this study.

This clinical trial lasted 3 years. It began in November 2012 and ended in January 2015. We compared two drugs: zenosumab and denodronic acid. Zenosumab (also known as Proliz) and denodronic acid (also known as Rastiz) are prescription medications used to treat bone thinning in adult women.

Amneg, our sponsor company, thanks you for participating in this trial. Because you are an essential member of the team, we believe it is important for you to know the results. We hope this summary answers any questions you may have about this study. The staff members at your trial site will be happy to answer any additional questions you may have about this study.

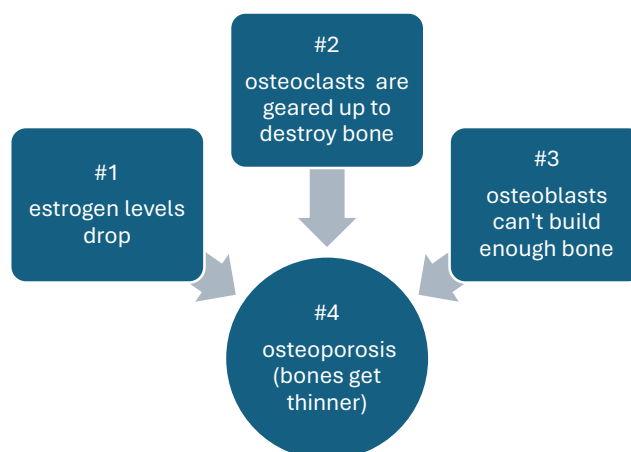
What has happened since I finished the study?

A total of 643 volunteers participated in this clinical trial. Volunteers took part in the study at different times over a 3-year period. Each volunteer spent a total of 12-months in the study. Volunteers included women over the age of 55 who were post-menopausal. Post-menopausal means they had stopped having monthly periods. All volunteers had osteoporosis and had been on medicine for osteoporosis for at least 6 years. Volunteers were from 37 centers located in Belgium, Denmark, Poland, Spain, Canada, the United States, and Australia. At the end of the study, researchers collected data to determine which medication—zenosumab or denodronic acid—worked better. This is a summary of what they found.

What is osteoporosis?

Estrogen is a hormone that plays an important role in maintaining bone thickness. Estrogen levels decrease when women go through menopause. This drop in estrogen has an impact on bone cells. We all have cells that build bone (osteoblasts) and cells that destroy bone (osteoclasts), and they are usually in perfect balance. As estrogen levels decrease, the bone destroying cells increase their activity. The bone building cells and the bone destroying cells are now out of balance. Bones become thin, brittle, and fragile. This is osteoporosis.

How menopause leads to osteoporosis



Why was this study done?

- Osteoporosis is very common. In the United States, 7 out of 10 women have osteoporosis by the age of 80. Bone fractures are an unwanted consequence of osteoporosis. These fractures usually occur in the hip and spine. They are painful.
- For those who get a fracture due to osteoporosis, it often becomes difficult or impossible to do daily activities without help. Most will require a surgical procedure to correct the fracture. After surgery, they are usually transferred to a rehabilitation center or nursing home. The recovery process takes months.
- The risk of death increases for anyone who has a fracture caused by osteoporosis. Even for those who undergo surgery to repair a fracture, 2 out of 10 will die within 1 year. For those who do not undergo surgery to repair a fracture, 7 out of 10 will die within 1 year.
- Most deaths caused by osteoporosis are a result of complications that occur from being bedridden after a fracture. The most common complications include pneumonia, bed sores, and blood clots in the legs or lungs. Each of these conditions can be fatal if not treated promptly.
- The good news is that bone fractures can be avoided if osteoporosis is treated early with medication.

How do zenosumab and denodronic acid improve bone thickness?

Zenosumab and denodronic acid decrease the activity of bone destroying cells, so that bone building cells have more time to work. Bones become thicker and stronger. Even though both zenosumab and denodronic acid decrease the activity of bone destroying cells, they do it in different ways.

Zenosumab *is given as a small injection under the skin every 6 months.*

- Zenosumab works by clinging to a molecule that scientists call RANKL. RANKL is the messenger molecule that tells bone destroying cells to start destroying bone. Zenosumab, like a football player, aggressively tackles RANKL to take it out of the game before it can find its teammate (the bone destroying cell) and tell it to start destroying bone.

Denodronic acid *is given through a venous catheter every 12 months.*

- Denodronic acid works by attaching to the calcium in bones where it hides. While the bone destroying cells are busy trying to grab the calcium out of bone, denodronic acid enters the bone destroying cells without being noticed. Denodronic acid, like a soldier who has snuck behind enemy lines, then attacks and destroys the bone destroying cell.

Standard treatment for osteoporosis is usually taken as a pill by mouth each month.

- Most drugs that treat osteoporosis attack bone destroying cells in the same manner as denodronic acid. In fact, denodronic acid (in the pill form) has been used as standard treatment for osteoporosis for years. In this study, we give denodronic acid directly into the blood stream to see if it works better using this route.



What questions did we want to answer in this study?

- 1) Zenosumab attacks bone destroying cells in a unique way. Is it better at treating osteoporosis than other drugs?
- 2) Does denodronic acid work better when given by mouth or when given directly into the blood stream?

What kind of study was this?

This study was a randomized, double-blind clinical trial that used a placebo.

- “Random” means that researchers were not allowed to choose who went into each treatment group. It is like shuffling a deck of cards and dealing them out into two different piles. In this case, the two piles were the zenosumab and denodronic acid treatment groups.
- “Double-blind” means that neither the researcher giving the injection nor the volunteer receiving the injection knew which drug the volunteer was getting.

[Mock plain language summary of a clinical trial]

- A “placebo” is like a sugar tablet. It has no medicine in it, but it looks like the drug being tested.

What happened during the study?

During the study we used two types of measurements to tell whether the drug was working.

- Bone turnover markers (BTMs) are released from bone cells as they are destroyed. BTMs can be measured in blood samples. BTM levels in the blood are high when a lot of bone is being destroyed. We measured BTM levels in the blood of some volunteers every 2-4 months.
- Our second measurement involved a special x-ray called a DEXA scan. A DEXA scan measures bone thickness. Each volunteer had a DEXA scan on day 1 and at the 12-month visit.

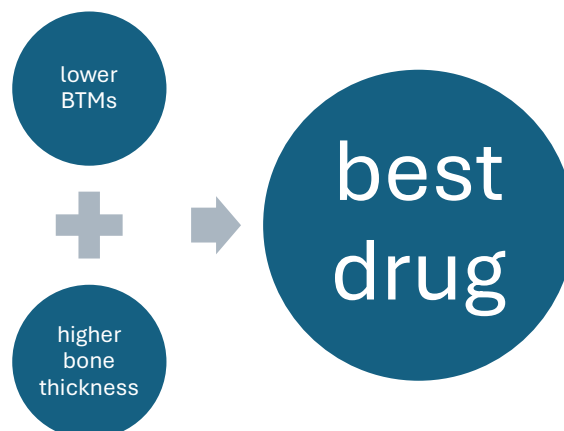


Bone turn over markers (BTMs) released into the blood are measured every 2-4 months



A DEXA scan measures bone thickness before and after treatment

The best drug to treat osteoporosis will have lower BTMs and higher bone thickness.

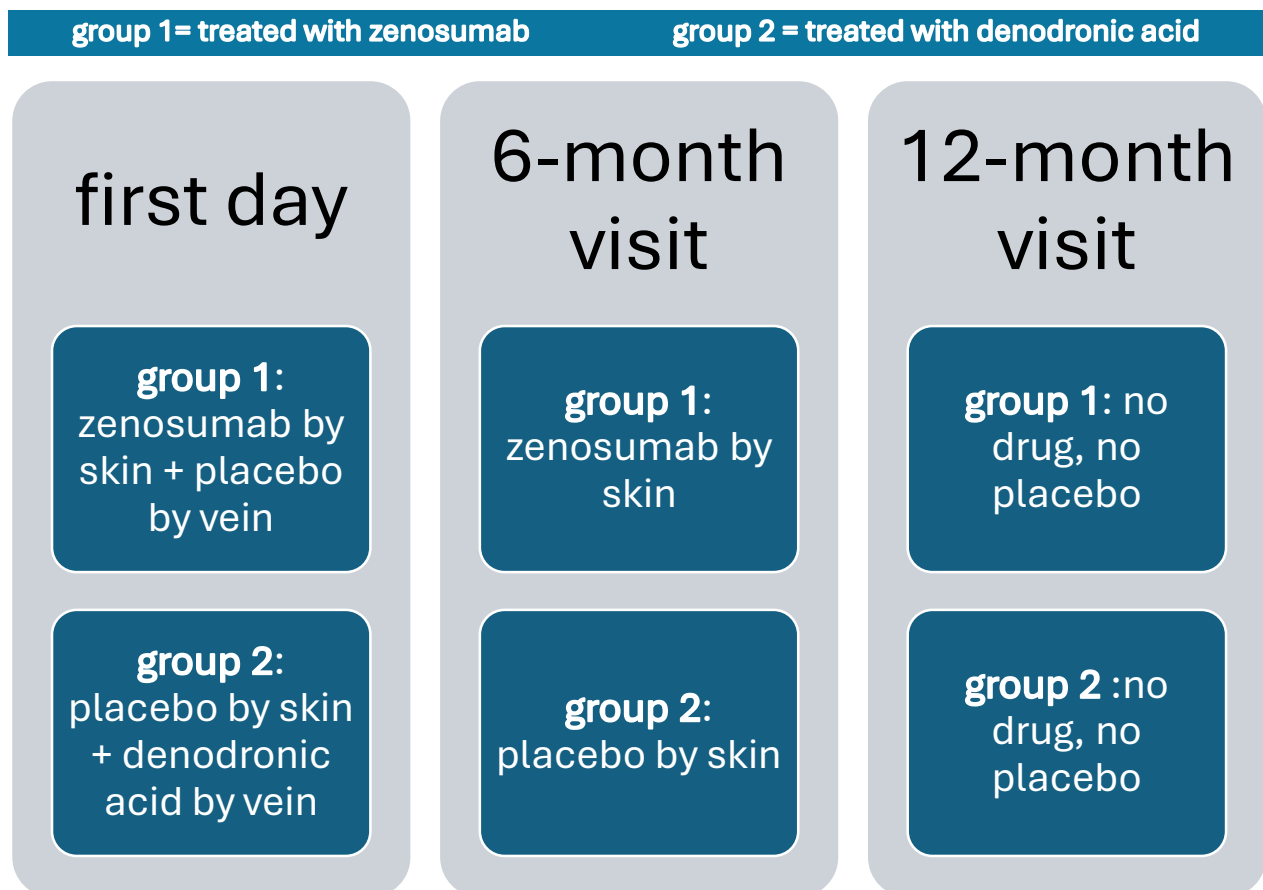


Volunteers were separated into groups.

- In group 1 — 321 volunteers received zenosumab.
- In group 2 — 322 volunteers received denodronic acid.
- 117 volunteers agreed to have blood drawn every 2 to 4 months to measure BTMs.
- All volunteers agreed to have a DEXA scan before and after treatment to measure bone thickness.

How was denosumab and zoledronic acid given to the volunteers?

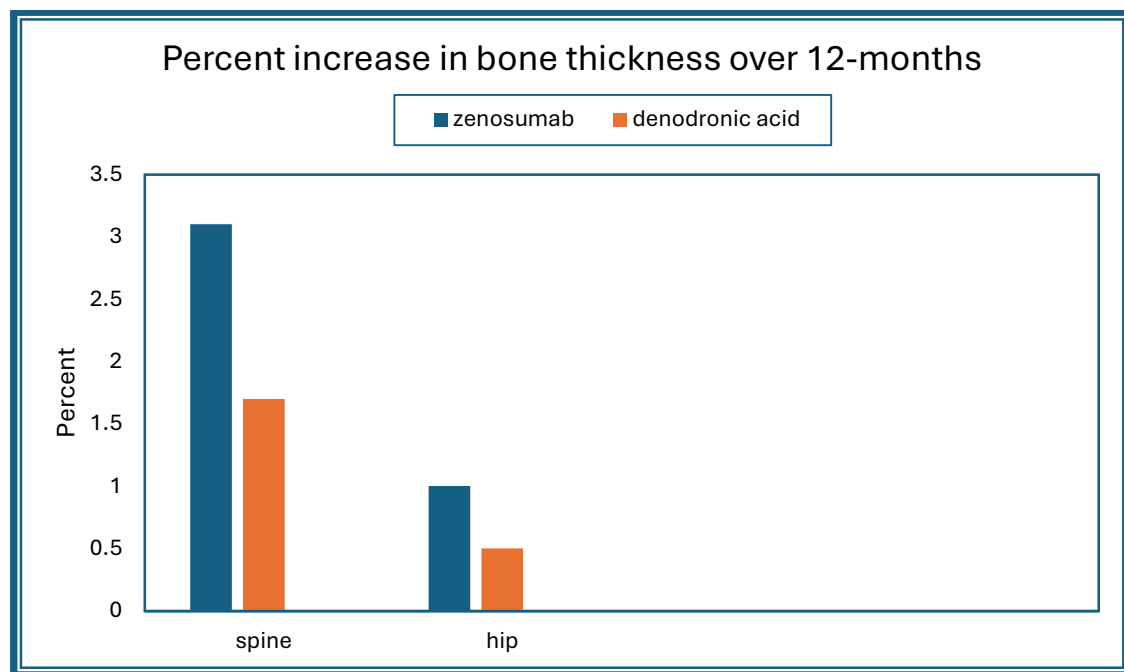
- On day 1 only, researchers gave volunteers placebo or denodronic acid directly into a vein using a catheter.
- On day 1 and at the 6-month visit, researchers gave volunteers a small needle injection under the skin of either placebo or zenosumab.
- At the 12-month visit, volunteers were given no drug and no placebo.



What were the results of the study?

Which drug worked better to treat osteoporosis— zenosumab or denodronic acid?

Zenosumab worked better to treat osteoporosis. In the zenosumab group, the DEXA scan results showed that bone thickness increased more than in the denodronic acid group. This means volunteers in the zenosumab group had less bone loss than volunteers in the denodronic acid group. We also found that BTMs were lower in the volunteers that took zenosumab compared to the denodronic acid group.



Did any patients have side effects?

Both groups had the same number of volunteers who experienced side effects (199 volunteers in each group). In the zenosumab group, 4 volunteers left the study because of side effects. In the denodronic acid group, 9 volunteers left the study because of side effects.

Did any patients have serious side effects?

A side effect is serious if it results in death, long-term illness, or time in the hospital. In the denodronic acid group, 25 out of 320 volunteers had serious side effects, and one volunteer died. In the zenosumab group, 29 out of 320 volunteers had serious side effects, and no one died. The most important side effects are shown in the table below. This table shows the number of patients with side effects out of 320 volunteers for each drug group.

Table 1. Number of Volunteers who experienced side effects

Side effect	Zenosumab (320 volunteers)	Denodronic acid (320 volunteers)
Total # side effects	199	199
Serious side effects	29	25
Vein problems	13	16
Muscle pains	43	63
Cancer	5	8
Rash	5	1
Heart problems	29	25
Infection	5	6
Death	0	1
Left study	4	9

What do the results of this study mean for me?

This clinical trial showed that zenosumab was superior to denodronic acid in treating osteoporosis, but this is only one trial. Further studies are needed to confirm these results and to give a more complete picture of who might benefit from treatment with zenosumab. Please consult with your doctor to determine which medical regimen is best for you.

Where can I learn more about this study?

You can read the full scientific report at clinicaltrials.gov. It can be found under the trial registration number PML07723710. You may also contact the staff at your study site. Again, thank you for volunteering.