Clinical Study Results

1. Study name

What does this summary cover?

This summary shows the main results from a clinical study which compared two medicines for osteoporosis. The results shown are only for one study. Researchers and/or registration and health authorities look at the results of many studies to decide which medicines work best and are safest for patients.

Title of the study:	A Randomized Double-blind Study to Evaluate the Safety and Efficacy of Denosumab Compared With Zoledronic Acid in Postmenopausal Women With Osteoporosis Previously Treated With Oral Bisphosphonates
Brief Title:	Safety and Efficacy Study to Evaluate Denosumab Compared With Zoledronic Acid in Postmenopausal Women With Osteoporosis
Protocol Number:	20110153
EU Trial Number	2012-001821-28
Other Identifiers	NCT01732770
Date of This Summary	15 Dec 2016

2. Who sponsored this study?

Who was the sponsor of the study?

Amgen Inc.

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Thousand Oaks, CA 91320-1799 USA

Phone (United States): +1 805-447-1000

Phone (Australia): 1800 803 638

Amgen Inc is the manufacturer of denosumab, which is one of the drugs included in the study.

Amgen would like to thank everyone who participated in this study and feels that it is important to share the study results.

3. General information about the clinical trial

What is osteoporosis?

- Osteoporosis is a disease that weakens your bones and makes them more likely to fracture or break. Osteoporosis is common in older women who are postmenopausal (i.e. the time in a woman's life after her period stops). This type of osteoporosis is called postmenopausal osteoporosis (PMO).

How is osteoporosis treated?

- People with osteoporosis often take a medicine called a bisphosphonate in tablet (oral) form. Because of the way these tablets have to be taken and the side effects they can cause, people often stop taking them and need to start another medicine for their osteoporosis.
- Zoledronic acid is another type of bisphosphonate and is administered as an infusion into a vein once a year. Zoledronic acid is a common treatment for women with postmenopausal osteoporosis who have stopped taking oral bisphosphonates.
- Denosumab is another treatment for women with postmenopausal osteoporosis and is administered as an injection under the skin every six months.

Where and when was the study done?

- This study took place in Belgium, Denmark, Poland, Spain, Canada, the United States and Australia.
- The study began on 07 November 2012 and ended on 09 January 2015.
- The study was completed as planned.

Why was the study done?

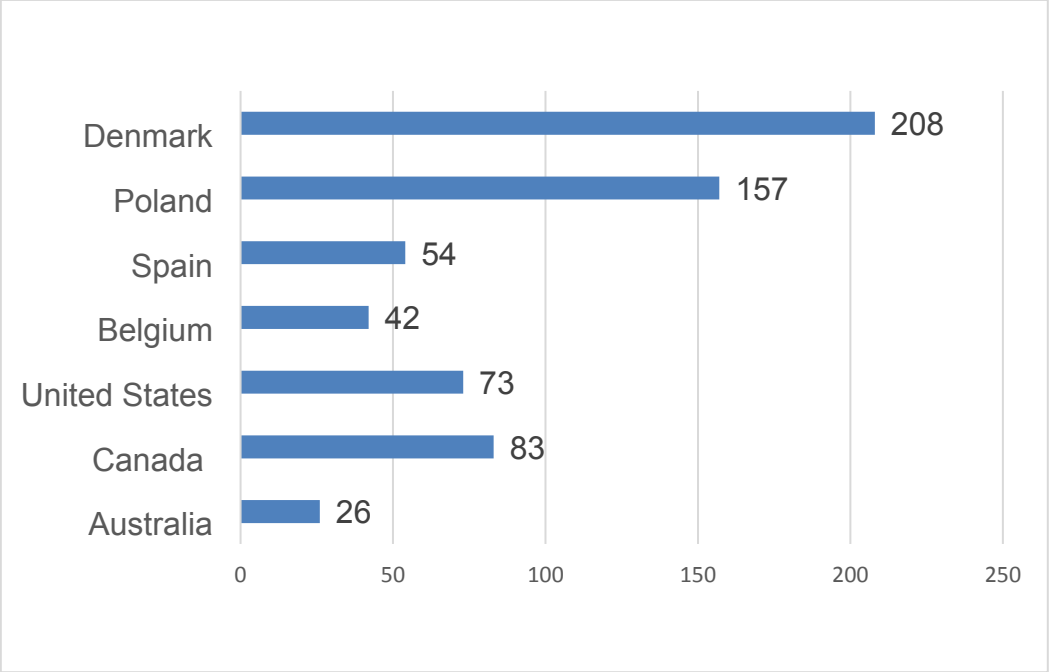
- This was a phase 4 clinical study, which is a study carried out after a medicine has been approved by a government health authority for doctors to prescribe to patients.
- Previous clinical studies of denosumab in women with postmenopausal osteoporosis showed it was better than receiving no medicine (placebo).

- Because women with postmenopausal osteoporosis often receive a medicine called zoledronic acid (after stopping oral bisphopshonates), researchers were interested in how denosumab compared to zoledronic acid.
- In this study, researchers compared denosumab with zoledronic acid in women with postmenopausal osteoporosis who had been taking an oral bisphosphonate. The effectiveness and safety of these two medicines were compared over 12 months.
- The first patient entered the study on November 7th, 2012 and the last patient finished the study on January 9th, 2015. Each participant was to stay in the study for up to 12 months.

4. What patients/people were included in this study?

- 643 women with postmenopausal osteoporosis took part in this study, including:
  - 461 women (72%, or about 72 out of 100) from the European Union
  - 156 women (24%, or about 24 out of 100) from North America
  - 26 women (4%, or about 4 out of 100) from Australia

Figure 1. How many women took part in the study?



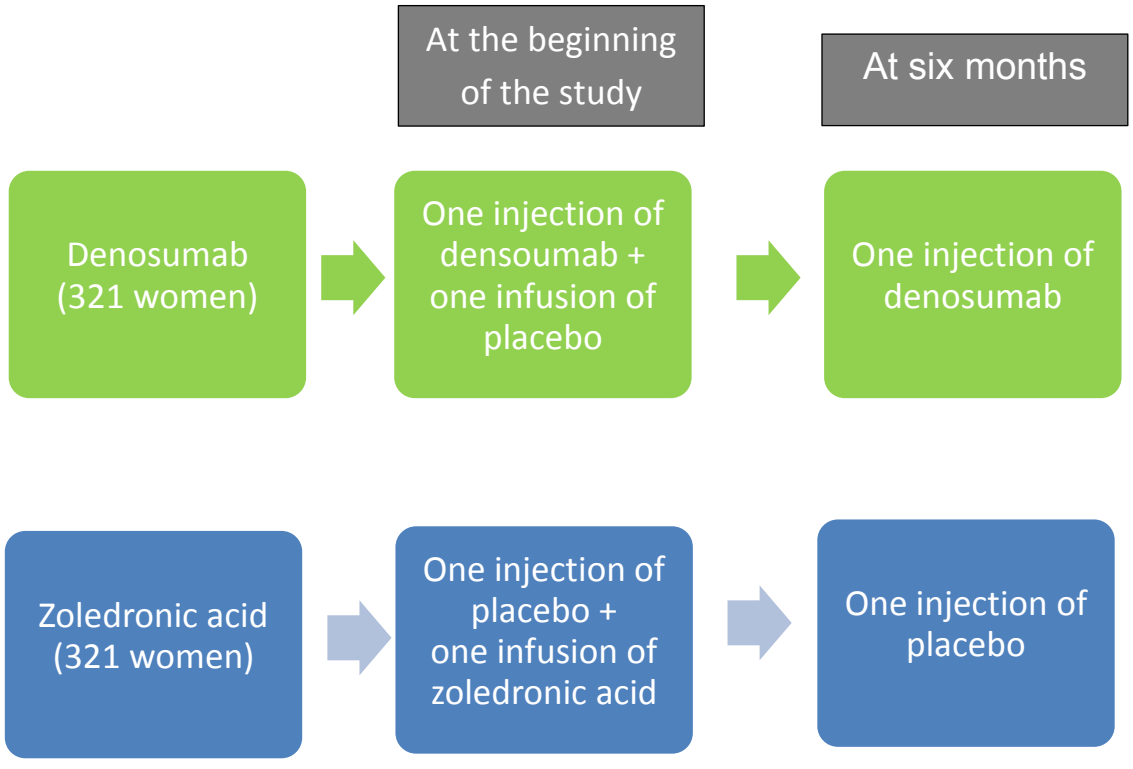
- This study was for postmenopausal women aged 55 years or older, who
  - Had been taking oral bisphosphonates for at least 2 years **and**
  - Had osteoporosis at the lower spine (also called the 'lumbar spine'), hip or femoral neck (a part of the hip bone).
- Women taking part in this study were between 55 and 91 years old; 152 (24%, or about 1 out of 4) women were 75 years or older.
- No men took part in this study.

5. Which medicines [or vaccines] were studied?

What medicinal products were studied?

- Patients received denosumab as an injection under the skin or zoledronic acid given as an infusion into a vein.
- Neither the patient nor the study doctor could choose whether they received denosumab or zoledronic acid. Patients agreed to be put into one of two treatment groups (the denosumab group or the zoledronic acid group) by chance (randomised). This is like flipping a coin or drawing numbers out of a hat, and there is an equal chance of being placed in either group.
- The different ways denosumab and zoledronic acid are given (denosumab as an injection under the skin and zoledronic acid as an infusion into a vein) would have told the patient, the study doctor and the study staff which treatment the patient was being given.
- If the patient, the study doctor or the study knew which treatment the patient was being given they might have changed their behaviour on the study. This could have influenced the results of the study.
- To stop this from happening, patients randomised to receive denosumab also received a placebo infusion (which did not contain any medicine), and patients randomised to receive zoledronic acid also received a placebo injection (which did not contain any medicine). This is shown in Figure 2.
- These steps ensured that neither the patient nor the study doctor nor his/her study staff knew which treatment the patient was receiving until after the study was over.

Figure 2. What medicines did the participants receive?



6. What were the side effects?

What are side effects (sometimes called adverse reactions)?

- All medicines can cause side effects (unwanted or unpleasant events that happen when you take the medicine).
- In a clinical study, the study doctor records side effects which they think might be associated with the study treatment a patient is receiving. These are also called "adverse reactions". Researchers analyse how many "adverse reactions" are recorded for each medicine being studied.

What adverse reactions were seen in this study of denosumab and zoledronic acid?

- When recording side effects in this study, neither the study doctor nor his/her study staff knew whether the patient was receiving denosumab (and placebo infusion) or zoledronic acid (and placebo injection).
- Only side effects the study doctor or study staff thought may be related to the study treatment a patient was receiving, also called "adverse reactions", are reported here.
- Not all women in this study experienced adverse reactions. No women died due to an adverse reaction.
- An adverse reaction was recorded as 'serious' if the event caused death, was life-threatening, required a stay in hospital, resulted in persistent or significant disability, caused a birth defect or caused another medically important serious event.
- Researchers calculated the percentage of women experiencing adverse reactions in each treatment group and compared these. Two women enrolled into the study but did not receive any study medication. These women were not included in the analysis of adverse reactions.
- The number and percentage of women in each treatment group with adverse reactions are shown in Table 1.

Table 1. How many women experienced adverse reactions?

	Denosumab (and placebo infusion) (N = 320)	Zoledronic acid (and placebo injection) (N = 320)
Any adverse reaction *(including serious adverse reactions)*	25 women (7.8%, or about 78 out of 1,000)	39 women (12.2%, or about 122 out of 1,000)
Serious adverse reactions	3 women (0.9%, or about 9 out of 1,000)	4 women (1.3%, or about 13 out of 1,000)
Study treatment stopped early because of adverse reactions	1 woman (0.3%, or about 3 out of 1,000)	6 women (1.9%, or about 19 out of 1,000)

- Adverse reactions that happened in at least 3 women in either treatment group are shown in Table 2. Calculated as a percentage, 3 women in each treatment group is the same as 0.9%. This means that if 1,000 women took the study medicine, about 9 would experience the event.

Table 2. What were the most common adverse reactions?

	Denosumab (and placebo infusion) (N = 320)	Zoledronic acid (and placebo injection) (N = 320)
Influenza-like illness (flu-like symptoms)	3 women (0.9%, or about 9 out of 1,000)	5 women (1.6%, or about 16 out of 1,000)
Myalgia (pain in a muscle or a group of muscles)	2 women (0.6%, or about 6 out of 1,000)	3 women (0.9%, or about 9 out of 1,000)
Arthralgia (joint pain)	1 woman (0.3%, or about 3 out of 1,000)	9 women (2.8%, or about 28 out of 1,000)
Back pain	1 woman (0.3%, or about 3 out of 1,000)	3 women (0.9%, or about 9 out of 1,000)
Bone pain	No women reported this event	3 women (0.9%, or about 9 out of 1,000)

What serious adverse reactions were seen in this study of denosumab and zoledronic acid?

- The number and percentage of women in each treatment group with serious adverse reactions are shown in Table 3.

Table 3. How many women experienced serious adverse reactions?

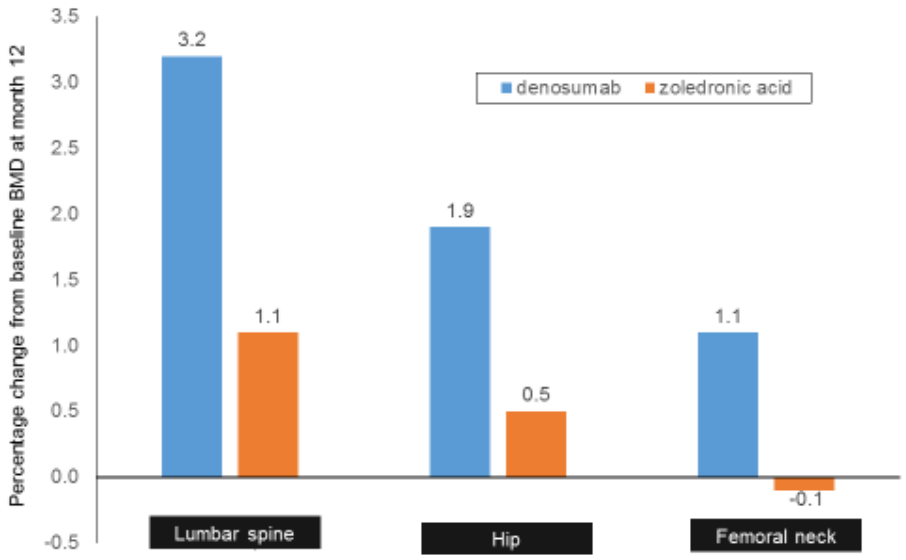
	Denosumab (and placebo infusion) (N = 320)	Zoledronic acid (and placebo injection) (N = 320)
Femur fracture (fracture of the thigh bone)	2 women (0.6%, or about 6 out of 1,000)	2 women (0.6%, or about 6 out of 1,000)
Cerebrovascular accident (damage to the brain)	1 woman (0.3%, or about 3 out of 1,000)	No women reported this event
Transient ischaemic attack (a mini stroke lasting only a few minutes)	No women reported this event	1 woman (0.3%, or about 3 out of 1,000)
Autoimmune hepatitis (inflammation in the liver)	No women reported this event	1 woman (0.3%, or about 3 out of 1,000)
Hepatic failure (liver failure)	No women reported this event	1 woman (0.3%, or about 3 out of 1,000)

7. What were the overall results of the study?

Did the medicines increase the patient's bone mineral density?

- Your bones are made up of lots of minerals which make them strong. Doctors can measure the amount of minerals in your bones, also called "bone mineral density" (BMD), using a special machine called a DXA (dual-energy x-ray absorptiometry) scanner.
- Women taking part in this study had the BMD at their lower spine (also called the "lumbar spine"), hip and femoral neck (a part of the hip bone) measured at the start and the end of the study.
- For each woman in the study, researchers calculated how much the BMD at the lower spine, hip and femoral neck changed between the start of the study (baseline) and the end of the study (month 12). The size of this change was calculated as a percentage relative to baseline.
- Researchers then compared the average increase in BMD over 12 months, at the lower spine, hip and femoral neck, in each treatment group (denosumab and zoledronic acid).

Figure 3. Denosumab increased BMD more than zoledronic acid



8. How has this study helped patients and researchers?

What is important to know about these results?

- In this clinical study, denosumab increased the density of bones in the lower spine, hip and femoral neck (measured by a DXA scanner) more than zoledronic acid over 12 months. Increased bone density is associated with stronger bones.
- Side effects (which the study doctor thought could have been associated with the study treatment, also known as 'adverse reactions') were also seen. For each of the treatment groups (denosumab and placebo, or zoledronic acid and placebo), no serious side effects occurred in more than 2 women. Calculated as a percentage, this is the same as 0.6%. This means that if 1,000 women took the study medicine, about 6 would experience the event.
- These results are only for this clinical study, which looked at a sample of 643 women with postmenopausal osteoporosis. The results for any woman taking part in this study could have been better or worse than the average results for the treatment group they were in. No single clinical study can give a complete picture of the benefits and risks of a medicine and this single study does not give a complete picture of how denosumab compares to zoledronic acid. Other studies may find different results.

9. Are there plans for further studies?

Will there be more studies with denosumab?

If more clinical studies are done, they may be listed on public websites, such as those below. These studies can be searched for using the following names:

AMG 162, denosumab, Prolia®.

- [*after implementation:* EU Clinical Trials database general URL]
- www.clinicaltrials.gov
- www.clinicaltrialsregister.eu
- amgentrials.com

10. Where can I find more information about this study?

Where can I learn more?

Amgen has committed to make research results available to the public. This summary has been provided as part of that commitment and should not be used for any other purpose. It should not be considered to make a claim for any product or to guide treatment decisions.

Some information in this summary may be different from the approved labelling for denosumab. Please refer only to the full prescribing information for proper use of denosumab.

To find out more about this study, please check these websites:

- www.clinicaltrials.gov. Use the study identifier NCT01732770.
- www.clinicaltrialsregister.eu. Use the study identifier 2012-001821-28.
- [*after implementation:* EU Clinical Trials database URL and identifier]
- http://press.endocrine.org/doi/10.1210/jc.2016-1801?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed

If you took part in this study and have questions about the results, the doctor or staff at your study site may be able to answer them.