# Clinical Study Results

## 1. Study Name

| | |
|---|---|
| Title of the study: | A Randomized, Double-Blind, Multicenter Study of Denosumab Compared With Zoledronic Acid in the Treatment of Bone Disease in Subjects With Newly Diagnosed Multiple Myeloma |
| Brief Title: | Denosumab Compared to Zoledronic Acid in the Treatment of Bone Disease in Patients With Multiple Myeloma |
| Protocol Number: | 20090482 |
| EU Trial Number: | 2010-020454-34 |
| Other Identifiers: | NCT01345019 (Clinicaltrials.gov identifier) |
| Date of This Summary: | 25 November 2020 |

# What does this summary cover?

This summary shows the main results from one clinical study. The results are only for this study. Other studies may find different results. Researchers and health authorities look at the results of many studies to decide which medicines work best and are safest for patients.

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. Your healthcare professional should refer to the full prescribing information for proper use of denosumab.

## 2. Who Sponsored This Study?

Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799 USA
Phone (United States): +1 805-447-1000

Amgen Inc. is the sponsor of the study who made denosumab, the medicine(s) still being tested in the study. Daiichi Sankyo is the local sponsor of the study in Japan. Amgen would like to thank everyone who participated in this study and feels it is important to share the results of this study.

## 3. General Information About the Clinical Trial

### *Where and when was the study done?*

- This study took place in France, Russian Federation, Greece, Italy, Bulgaria, Poland, Czech Republic, Spain, Ukraine, Hungary, Turkey, United Kingdom, Lithuania, Austria, Portugal, Switzerland, Ireland, Slovakia, Germany, United States, Canada, Republic of Korea, Australia, Japan, Taiwan, Singapore, Malaysia, Hong Kong, and New Zealand.
- The study began in May 2012 and ended in March 2019.
- The study was completed as planned.

### *Why was the study done?*

Multiple myeloma is cancer that begins in the plasma cells, which are a type of white blood cell. White blood cells are part of the body's immune system. Patients with multiple myeloma may have problems with their bones, such as bone lesions (spots of bone damage), frequent broken bones, bone pain, and pressure on the spinal cord. They may also feel very tired and have frequent infections.

Patients with multiple myeloma may need radiation therapy or surgery to treat their bone complications. Medicines can also be prescribed to prevent bone

complications. Denosumab is currently approved in some countries for the prevention of bone complications in adults who have multiple myeloma with bone lesions.

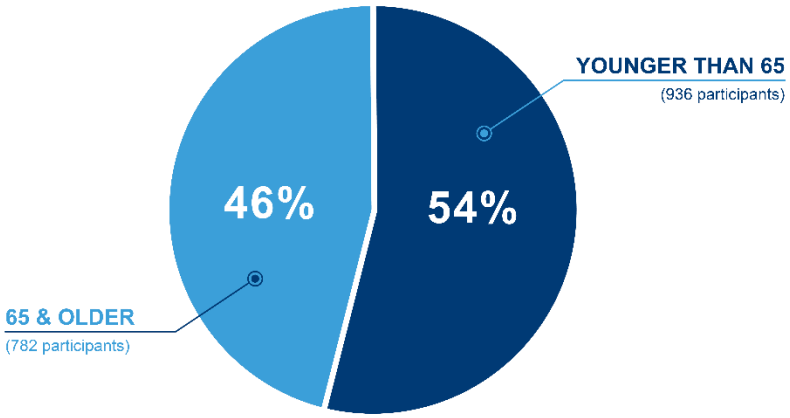
This was a phase 3 study, which is in the late stage of the development process of medicines for humans. Researchers compared denosumab to zoledronic acid, which is a type of bisphosphonate medicine. It is a standard treatment used for preventing bone complications in patients with multiple myeloma.

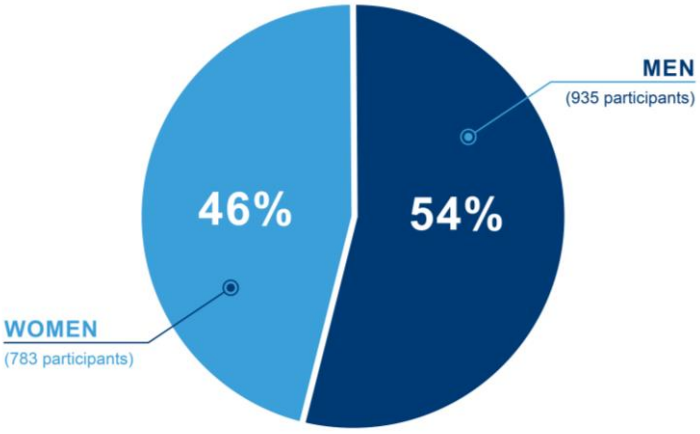
The main purpose of this study was to show that denosumab was not worse than zoledronic acid at preventing bone complications in patients with multiple myeloma. To do so, researchers looked at how many days participants who took denosumab went without a bone complication, compared to participants who took zoledronic acid.

## 4. Who Was Included in This Study?

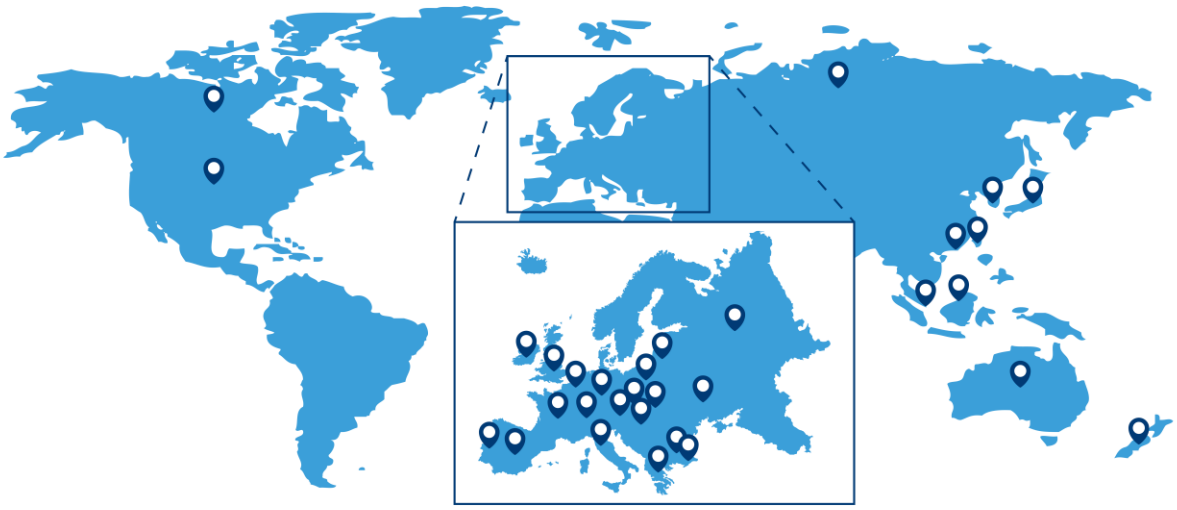
### *Who took part in the study?*

This study included 1718 participants with multiple myeloma and bone lesions. 935 participants (54%, or about 54 out of 100) were men and 783 participants (46%, or about 46 out of 100) were women. They ranged in age from 29 to 91 years. 936 participants (54%, or about 54 out of 100) were younger than 65 years old, and 782 participants (46%, or about 46 out 100) were 65 and older.




This study took place at 259 study centers across France, Russian Federation, Greece, Italy, Bulgaria, Poland, Czech Republic, Spain, Ukraine, Hungary, Turkey, United Kingdom, Lithuania, Austria, Portugal, Switzerland, Ireland, Slovakia, Germany, United States, Canada, Republic of Korea, Australia, Japan, Taiwan, Singapore, Malaysia, Hong Kong, and New Zealand. The numbers of participants in each country are shown below:



**ASIA**
Hong Kong: 9
Japan: 42
Malaysia: 14
Republic of Korea: 84
Singapore: 21
Taiwan: 26

**AUSTRALIA**
Australia: 46
New Zealand: 9

**NORTH AMERICA**
Canada: 121
United States: 324

**EUROPE**
Austria: 26
Bulgaria: 81
Czech Republic: 75
France: 125
Germany: 6
Greece: 94
Hungary: 47
Ireland: 14
Italy: 92
Lithuania: 27
Poland: 77
Portugal: 25
Russia: 110
Slovakia: 7
Spain: 66
Switzerland: 15
Turkey: 42
Ukraine: 60
United Kingdom: 33

Participants were examined by a study doctor and chosen to be in the study if they:

- provided their informed consent
- were adults
- were newly diagnosed with multiple myeloma and had bone lesions in one or more places
- had received treatment for multiple myeloma for no more than 30 days
- had received no more than 1 dose of bisphosphonate medicine by IV infusion (in the vein)
- were able to walk and care for themselves
- had adequate organ function (body organs were working well enough)

## 5. Which Medicines Were Studied?

In this study, denosumab was compared to zoledronic acid. Participants had an equal chance of receiving either treatment.

Neither the participants nor the study doctors could choose which treatment participants were given. Participants agreed to be put into a treatment group by chance ("randomized") using an automated computer system. This is like flipping a coin or drawing numbers out of a hat.

During the first part of the study, neither the participants nor the doctors knew which treatment each participant was given until after the study was over. This was done to make sure the study results were not influenced in any way. This was known as the double-blinded part of the study. Each participant would receive one of the following combinations every 4 weeks:

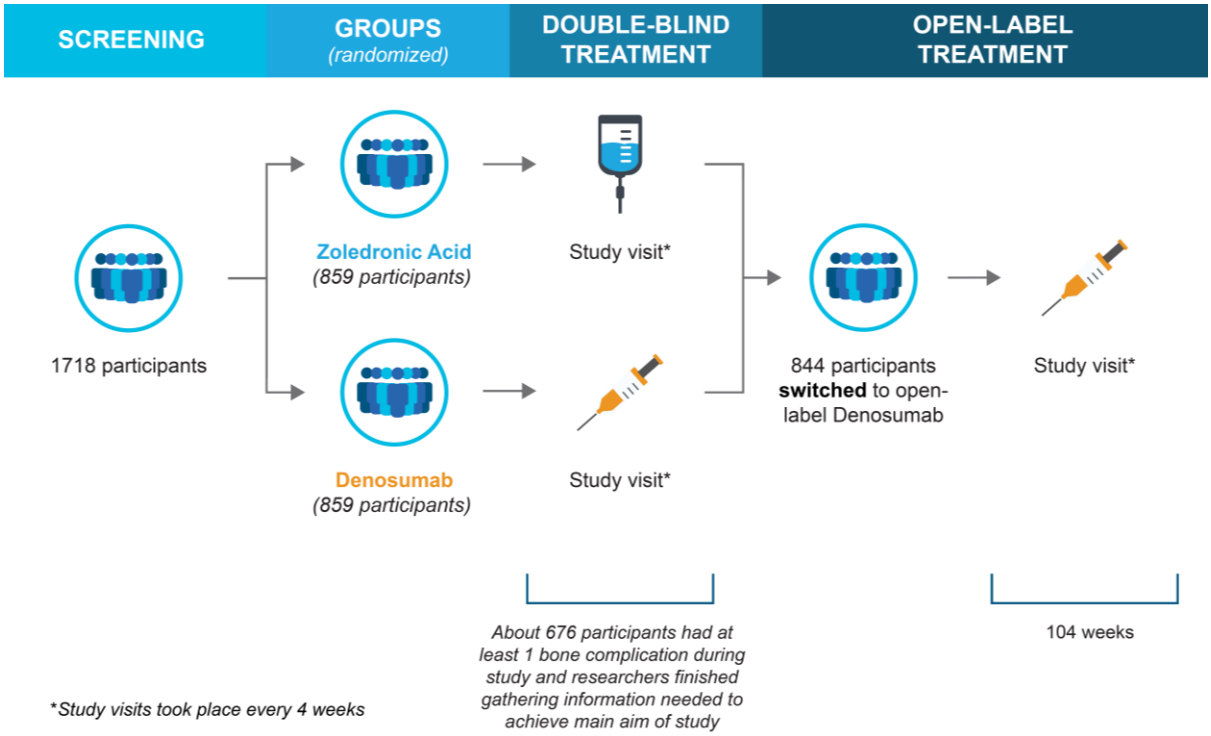
- An injection of denosumab 120 milligrams, and an IV infusion of placebo

or

- An injection of placebo and an IV infusion of zoledronic acid 4 milligrams

A placebo does not contain any medicine but looks like the study medicine. Participants also received standard treatment for multiple myeloma.

Participants were checked by the study doctor every 4 weeks. Participants were expected to continue receiving study treatment until about 676 participants had at least 1 bone complication during the study, and the researchers had finished gathering the information needed to achieve the main aim of the study. Based on a review of the data collected during this part of the study, participants who were still on double-blinded treatment at this time were then offered to switch to open-label denosumab for up to 2 years. Open-label means that both the participants and the study doctors knew what treatment the participants received.




## 6. What Were the Side Effects?

### *What is a side effect?*

All medicines can cause side effects, or unwanted medical problems that may happen when you take a medicine. In this study, doctors reported all the medical problems participants had. Doctors believed some of the problems could have been caused by the study treatment(s). These possible side effects are listed below.

### *What side effects were seen?*

When reporting side effects in this study, the study doctor did not know which treatment a participant was receiving.

The tables below show how many participants had side effects that could have been caused by the study treatment(s).

**Side Effects During the Double-Blinded Part of Study**

| | Zoledronic Acid (852 participants) | Denosumab (850 participants) |
|---|---|---|
| **How many participants had serious side effects?** | 34 participants (4%) | 34 participants (4%) |
| **How many participants had non-serious side effects?** | 221 participants (26%) | 230 participants (27%) |
| **How many participants died from side effects?** | 1 participant (less than 1%) | 0 participants (0%) |
| **How many participants stopped taking the study medicine because of side effects?** | 49 participants (6%) | 52 participants (6%) |

**Side Effects During the Open-Label Part of Study**

| | Zoledronic Acid Switched to Denosumab (418 participants) | Denosumab During Both Parts of Study (426 participants) |
|---|---|---|
| **How many participants had serious side effects?** | 13 participants (3%) | 13 participants (3%) |
| **How many participants had non-serious side effects?** | 70 participants (17%) | 69 participants (16%) |
| **How many participants died from side effects?** | 0 participants (0%) | 0 participants (0%) |
| **How many participants stopped taking the study medicine because of side effects?** | 20 participants (5%) | 36 participants (8%) |

If a participant had to stay in the hospital or died because of a side effect, the doctor reported that the side effect was serious.

The tables below show the serious side effects that occurred in at least 1% of participants (or about 1 out of 100).

**Serious Side Effects During the Double-Blinded Part of the Study**

| Serious side effect | Zoledronic Acid (852 participants) | Denosumab (850 participants) |
|---|---|---|
| **Break down of bone cells in the jaw** | 12 participants (1%) | 18 participants (2%) |

**Serious Side Effects During the Open-Label Part of the Study**

| Serious side effect | Zoledronic Acid Switched to Denosumab (418 participants) | Denosumab During Both Parts of Study (426 participants) |
|---|---|---|
| **Break down of bone cells in the jaw** | 10 participants (2%) | 11 participants (3%) |

The tables below show the non-serious side effects that occurred in at least 2% of participants in either group (or about 2 out of 100).

**Non-serious Side Effects During the Double-Blinded Part of the Study**

| Non-serious side effect | Zoledronic Acid (852 participants) | Denosumab (850 participants) |
|---|---|---|
| **Low level of calcium in blood** | 36 participants (4%) | 61 participants (7%) |
| **Increased creatinine in blood (which may be a sign of kidney damage)** | 32 participants (4%) | 9 participants (1%) |
| **Break down of bone cells in the jaw** | 20 participants (2%) | 36 participants (4%) |

| Non-serious Side Effects During the Open-Label Part of the Study | | |
|---|---|---|
| **Non-serious side effect** | **Zoledronic Acid Switched to Denosumab (418 participants)** | **Denosumab During Both Parts of Study (426 participants)** |
| **Break down of bone cells in the jaw** | 21 participants (5%) | 29 participants (7%) |
| **Low level of calcium in blood** | 9 participants (2%) | 7 participants (2%) |

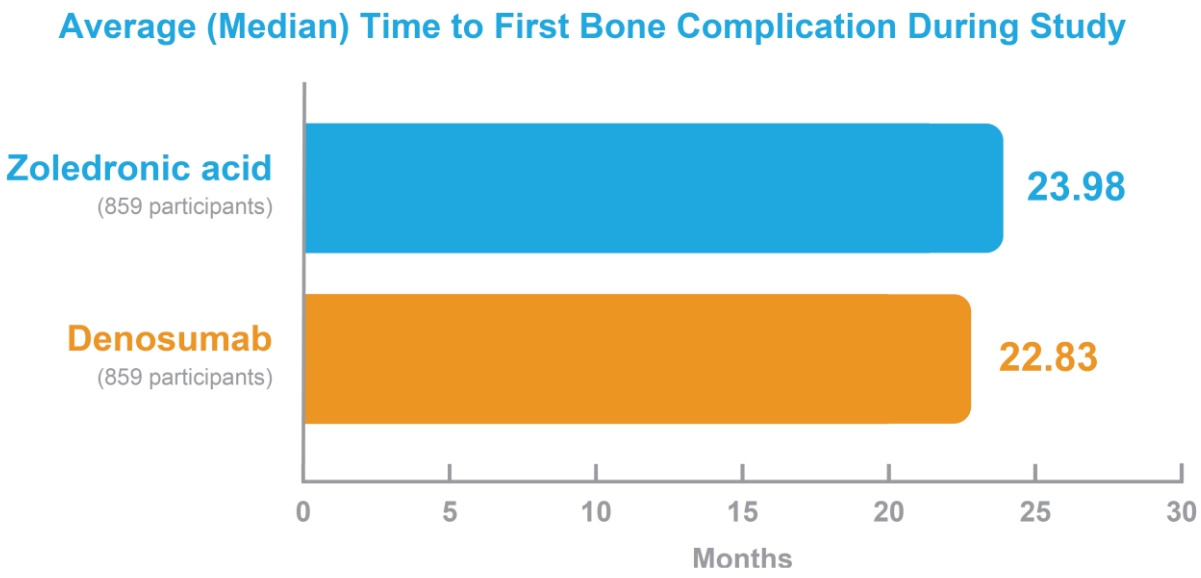
This section only shows the most often reported side effects considered by the study doctor as related to treatment. No single clinical study can give a complete picture of the benefits and risks of a medicine. Information about other side effects may be available at the websites listed at the end of this summary.

## 7. What Were the Overall Results of the Study?

**How long did participants who took denosumab go without a bone complication, compared to participants who took zoledronic acid?**

- To answer this question, the researchers looked at how long participants who took each treatment went without a bone complication. For this study, a bone complication meant a broken bone, the need for surgery or radiation therapy to the bone, or pressure on the spinal cord.
- The average (median) time from study enrollment to the first occurrence of a bone complication while participating in the study was 23.98 months for participants in the zoledronic acid group, and 22.83 months for participants in the denosumab group.
- This result showed that denosumab was not worse than zoledronic acid at preventing bone complications in patients with multiple myeloma.
- These results are based on information that was collected until the researchers had finished gathering the information needed to achieve the main aim of the study, up to 19 July 2016.

- This study was completed as planned.
- More results may be available at the websites listed at the end of this summary.




## 8. How Has This Study Helped Participants and Researchers?

**What else is important to know about these results?**

These results are only for this clinical study, which looked at a sample of 1718 people with multiple myeloma and bone lesions. Not all participants in the study had the same results. The results for any single participant could have been better or worse than the results for their group. Other studies may find different results. These results do not explain how a treatment may work in a single person. Many studies are needed to show the benefits and risks of a medicine that is still being tested. This research may help future participants and families by helping doctors understand more about the treatment being studied.

## 9. Are There Plans for Further Studies?

If more clinical studies are done, they may be listed on public websites, such as those below. Search for study medicine name denosumab (XGEVA®) on the websites below.

## 10. Where Can I Find More Information About This Study?

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

- www.clinicaltrials.gov. Use the study identifier NCT01345019
- www.clinicaltrialsregister.eu. Use the study identifier 2010-020454-34
- Raje N, Terpos E, Willenbacher W, et al. Denosumab versus zoledronic acid in bone disease treatment of newly diagnosed multiple myeloma: an international, double-blind, double-dummy, randomised, controlled, phase 3 study. *Lancet Oncol*. 2018;19(3):370-381. doi: 10.1016/S1470-2045(18)30072-X.

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