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Plain language summary of publication to understand the ROSALIA study: a new biosimilar denosumab for bone health

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Summary

What is this summary about?

This plain language summary describes the results of a clinical study, **ROSALIA**, which was published in the *Journal of Bone and Mineral Research* in 2024. The **ROSALIA** study looked at whether biosimilar **denosumab** has the same outcomes as the original-brand reference **denosumab** for treatment in women with postmenopausal **osteoporosis**.

How to say. . .

- **Denosumab:** Den-OH-sue-mab
- **Osteoporosis:** Os-tee-oh-puh-ROH-sis
- **ROSALIA:** Ro-zay-LEE-a
- **Randomized:** RAND-uh-myzd
- **Immunogenicity:** Im-myun-oh-jen-IS-uh-tee
- **Neutralizing:** NYOO-truh-lyz-ing
- **Hypocalcemia:** High-poh-kal-SEE-mee-uh
- **Nasopharyngitis:** Nay-zoh-fah-RIN-jy-tis

Why was the ROSALIA study done?

The **ROSALIA** study compared how well biosimilar **denosumab** works in comparison to reference **denosumab** in increasing bone density in women with postmenopausal **osteoporosis**. **ROSALIA** also looked at how these medicines affect the body and the immune system, their safety, and the results of switching from treatment with reference **denosumab** to biosimilar **denosumab**. The study builds on evidence from previous clinical and non-clinical studies comparing the two medicines.

Where can I find the original article on which this summary is based?

You can read the original article published in the *Journal of Bone and Mineral Research* at http://dx.doi.org/10.1093/jbmr/zjae016.

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The main results and what they mean

The **ROSALIA** study showed that biosimilar **denosumab** increased bone density, thus reducing the risk of fractures, to the same degree as reference **denosumab**. Adverse events, which describe reactions to a medicine outside of the expected treatment effects, were similar in incidence for both treatments and mostly mild to moderate. The presence of "anti-drug" antibodies (caused by the immune system trying to neutralize the treatment) was the same in both treatment groups. Both medicines were shown to be processed by the body in the same way. Changing treatment from reference **denosumab** to biosimilar **denosumab** did not change how the body reacted to treatment. The results from **ROSALIA** show that biosimilar **denosumab** matched reference **denosumab** and can be used in the same way as reference **denosumab** for postmenopausal **osteoporosis**. Furthermore, patients on reference **denosumab** can be switched to biosimilar **denosumab** with no issues.

Who should read this summary?

The summary is intended to provide education about biosimilar **denosumab** to healthcare professionals, patient advocacy groups, and people who have been prescribed Sandoz **denosumab**.

Keywords: biosimilar, bone cancer, **denosumab**, extrapolation, **osteoporosis**

What's in a name?

All medicines have a "non-proprietary" name; that is, an unbranded name for the active ingredient. **Denosumab** is a non-proprietary name. Brand names may be familiar to the patients who use the medicine but are not used in this summary (except in this box).

Reference **denosumab** is marketed by Amgen using two brand names. Prolia® is used for women with postmenopausal **osteoporosis** and men at high risk of fractures. Xgeva® is used for preventing skeletal-related events (SREs) in patients with bone metastases from solid tumors (such as breast cancer and prostate cancer), SREs in patients with multiple myeloma, and to treat giant cell tumor of bone. Prolia was used as the "comparator" in the **ROSALIA** study. Acronyms for reference **denosumab** may include REF-DMAB or REF-deno.

Sandoz **denosumab** is the first biosimilar **denosumab**. Before approval, it was referred to as "GP2411," which is how it is named in the **ROSALIA** study publication. This developmental code has now been retired. Sandoz **denosumab** is approved in the treatment of **osteoporosis** under the brand name Jubbonti® (60 mg), and for the prevention of bone complications in patients with cancer as Wyost® (120 mg). "Biosimilar **denosumab**" is used in this publication to refer to Sandoz **denosumab**, which you may see elsewhere shortened to SDZ-DMAB or SDZ-deno.

Key points

Biosimilar medicines are medicines designed to match an already approved biologic medicine (reference medicine), which are approved for use after confirmation of similarity to the reference medicine.

Biosimilar medicines undergo a rigorous testing process to show they have the same effect as the reference medicine. Evidence that supports use of the reference medicine can then also be applied to the biosimilar medicine. Overall, fewer expensive clinical trials are required and biosimilar medicines usually cost less. More people can afford the treatment and healthcare systems can afford to treat more people, helping more patients get the care they need.

The *totality of evidence* is submitted to regulatory authorities to prove that a biosimilar medicine is the same as its reference medicine based on an indistinguishable structure, equivalent efficacy, and comparable safety, using:

- *Analytical studies*, which assess the quality, structure, and function of medicines
- *Pharmacokinetic* (PK) studies, which examine what the body does to a medicine after it is taken; for example, how quickly it is absorbed and excreted
- *Pharmacodynamic* (PD) studies, which focus on what the medicine does to the body, such as how it interacts with target cells or receptors, and what effects are produced
- *Equivalence studies*, which are large clinical studies that are done to check if a new biosimilar medicine works as well as the reference medicine. These studies measure outcomes in a way that can clearly show any differences between the two medicines, while reducing the impact of individual patient differences or variations in the disease

If the biosimilar medicine proves to have a similar efficacy and safety profile to the reference medicine in the treatment of one disease, it can then be approved to be used for other diseases in which the reference medicine is already approved. This approach of *extrapolation* helps provide cost savings and faster availability to wider groups of patients.

How is a *biosimilar medicine* different to a *generic* medicine?

Biosimilars and generics are both copies of reference medicines that have come off patent. Some medicines are simple chemicals that can be copied exactly. These generic copies are manufactured by chemical processes in factories. Biosimilars are complex biologic medicines that have to be produced in living systems such as cells. Biologic medicines, including biosimilars, may have minor differences between batches and/or compared with the reference medicine that do not impact their clinical efficacy and safety. The testing process for a biosimilar medicine to be approved for use (described above) is much more rigorous than for a generic.

ROSALIA was an equivalence study of biosimilar denosumab

The **ROSALIA** study was an *integrated Phase I/Phase III clinical study* comparing biosimilar **denosumab** and reference **denosumab** in women with postmenopausal **osteoporosis**. The findings of **ROSALIA** add to the "*totality of evidence*" for biosimilar **denosumab**.

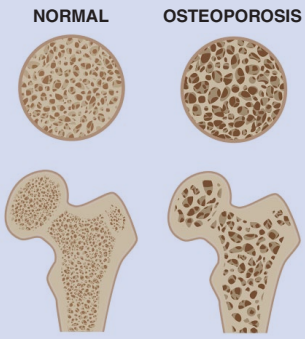
Phase I studies are the first stage of testing a new medicine to identify any side effects associated with the dosage of the new medicine. How the body reacts to the new medicine is also monitored.

Phase III studies are conducted to evaluate the efficacy and safety of the new medicine in large group of patients.

Integrated Phase I/III clinical studies combine the early and late testing phases to evaluate the safety and efficacy of the new medicine in treating a specific condition. They also look at how the medicine is processed in the body, how it affects the body, and how the immune system responds to it.

The women in ROSALIA had postmenopausal osteoporosis; what does that mean?

Osteoporosis, meaning "porous bone," happens when the process of breaking down bone outweighs the process of building new bone, reducing bone mineral density (*BMD*) and leaving bones fragile and more susceptible to fracture.



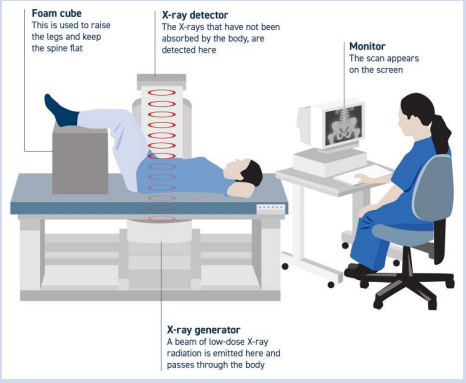
Osteoporosis develops slowly over time as *BMD* is progressively lost. It is often diagnosed for the first time only when a person suffers a fracture.

Hormonal changes during menopause can speed up the development of **osteoporosis**, meaning that it occurs in postmenopausal women more often than it occurs in men.

Osteoporosis is usually diagnosed based on a dual-energy X-ray absorptiometry (DXA) scan, which measures *BMD* in a *T*-score:

- Normal—*T*-score of ⩾−1.0
- Low bone mass—*T*-score between −1.0 and −2.5
- **Osteoporosis**—*T*-score ⩽−2.5

BMD, bone mineral density, is a measurement of how dense bones are



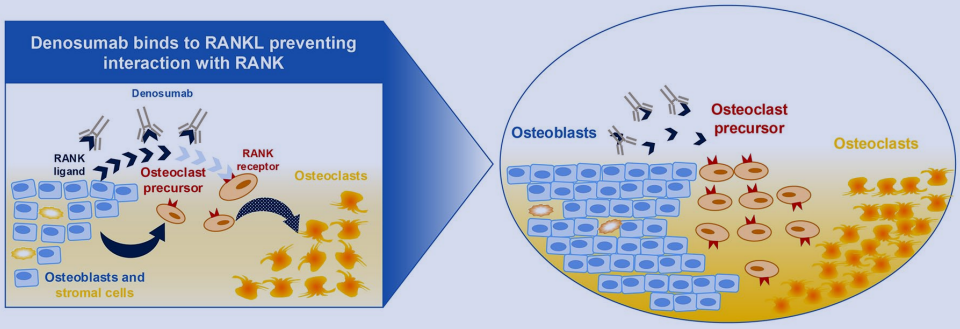
The role of denosumab in bone management

Denosumab *is a human monoclonal antibody that blocks a protein called RANKL. RANKL binds to RANK receptors on the surface of a type of immature cell called an osteoclast precursor, signaling them to develop into osteoclasts. By binding to RANKL,* ***denosumab*** *prevents this process, stopping bone breakdown. Osteoblasts can then more effectively maintain bone strength.*

A *monoclonal antibody* is a laboratory-made antibody. Antibodies are proteins that the body naturally produces to fight off infection or disease. They attach to specific parts of disease-causing agents such as bacteria or cancer cells, and help the immune system to recognize and attack them

Osteoclasts are specialized cells that are responsible for bone resorption; that is, breaking down bone

Osteoblasts are bone-building cells



Overview of the ROSALIA study

ROSALIA study was a *double-blind*, ***randomized***, 2-arm, *parallel group, integrated Phase I/III study*. It aimed to compare the efficacy, PK, PD, ***immunogenicity***, and safety of biosimilar **denosumab** and reference **denosumab** in women with postmenopausal women. The impact of switching from treatment with reference **denosumab** to biosimilar **denosumab** was also evaluated.

Double-blind means neither the participants nor the researchers know which treatment is being given. This prevents bias in a study

Randomized means participants are assigned to different groups by chance to ensure fairness in a study

A *parallel group* design means different groups of participants receive different treatments for comparison

Immunogenicity is the ability of a treatment to provoke an immune response in the form of anti-drug antibodies (ADAs), which can prevent the medicine from working effectively

Who took part in the study?

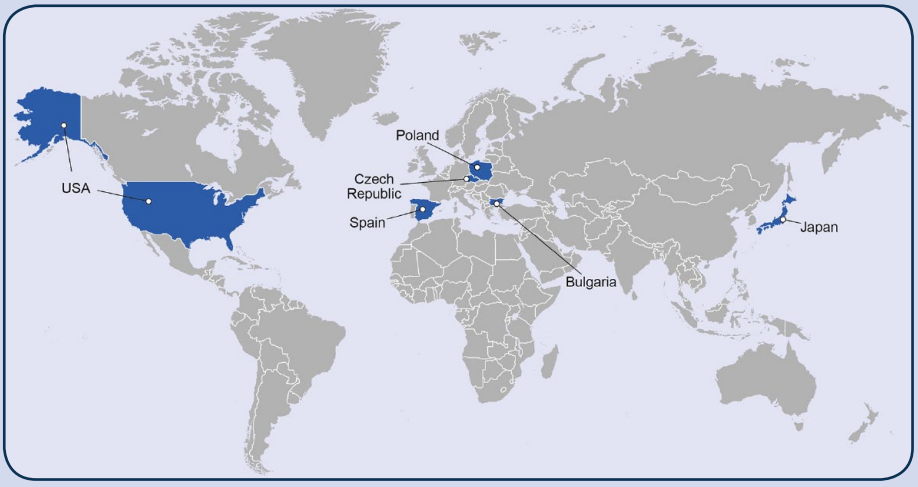
527 women took part in this study based on specific requirements:

55–80 years

50–90 kg

Osteoporosis
(DXA *T*-score of −2.5 to −4)

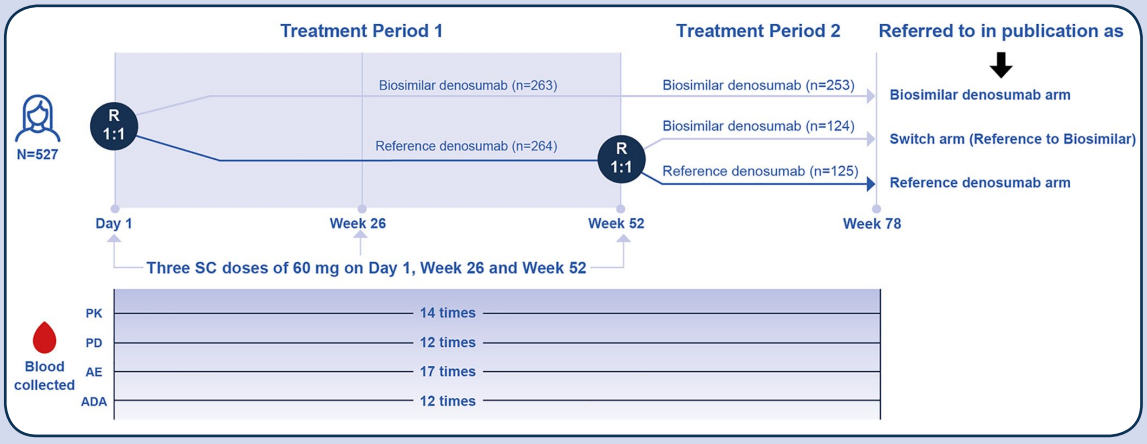
Women participating in the study were enrolled at 46 centers in the following countries:



In the first part of the study (Weeks 0–52, treatment period 1), patients were randomly assigned to receive two 60 mg *subcutaneous* (SC) injections of either biosimilar **denosumab** or reference **denosumab**, with the first dose on the first day of the study and the second dose at Week 26.

Subcutaneous means to inject just under the skin

In the second part of the study (Weeks 52–78, treatment period 2), those who had been receiving reference **denosumab** were randomly assigned again at Week 52 to either continue with reference **denosumab** or switch to biosimilar **denosumab**. Those who had been receiving biosimilar **denosumab** continued biosimilar **denosumab**. All patients received their third dose at Week 52 and were monitored until Week 78.



The patients had similar characteristics when entering in the study, so any observed differences seen are more likely to be due to the treatments than difference between patients. Other parameters, such as *T*-score, levels of markers to measure bone change, and prevalent fractures were also similar between the treatment groups.

Biosimilar denosumab (n=263)	Reference denosumab (n=264)
64.0 Median age (years)	64.0 Median age (years)
90.9 90.9% White	90.9 90.9% White
62.3 Average weight: 62.3 kg	63.4 Average weight: 63.4 kg

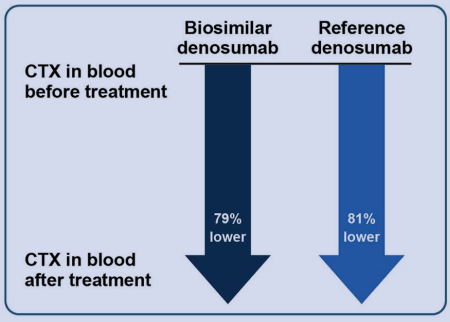
What were the results of the study?

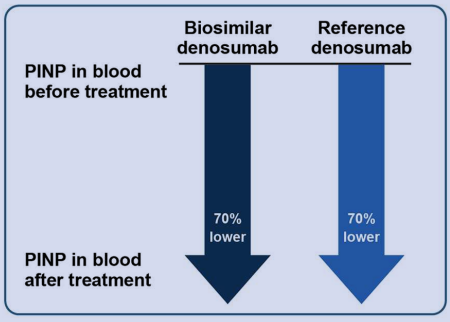
The way the two treatments behaved in the body was assessed by measuring proteins in the blood that are found when bone is broken down and re-built. The change in amount of *CTX* and *PINP* in participants' blood was similar for each treatment group after 6 months of treatment.

CTX is collagen C-terminal telopeptide, which is a protein marker found in blood that measures breakdown in bones

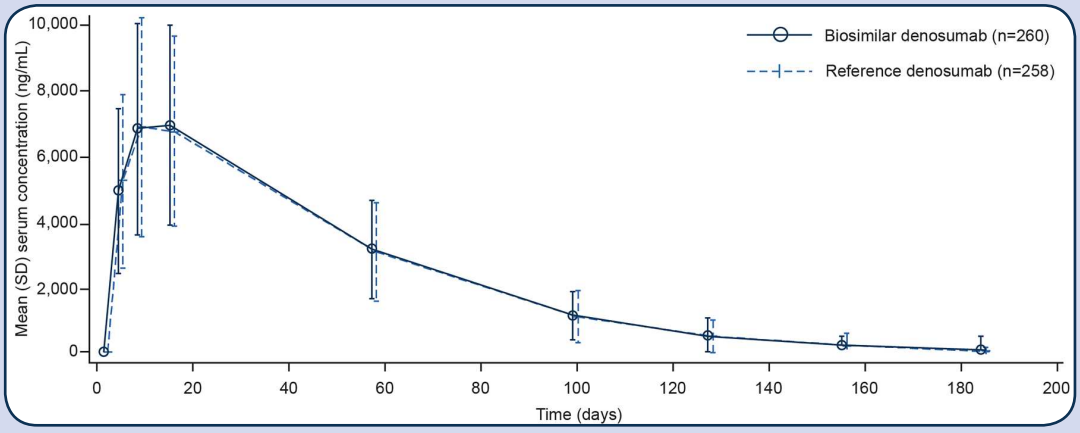
PINP is procollagen type-I N-terminal propeptide, which is a protein marker in the blood that reflects the formation of new bone tissue

These bone turnover markers are recommended as reference markers by the International **Osteoporosis** Foundation and the International Federation of Clinical Chemistry and Laboratory Medicine





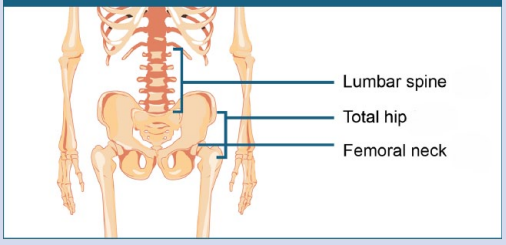
The same amounts of biosimilar **denosumab** and reference **denosumab** were measured in the blood over 26 weeks, as can be observed with the overlapping lines on the graph:



How effective was biosimilar denosumab in increasing BMD?

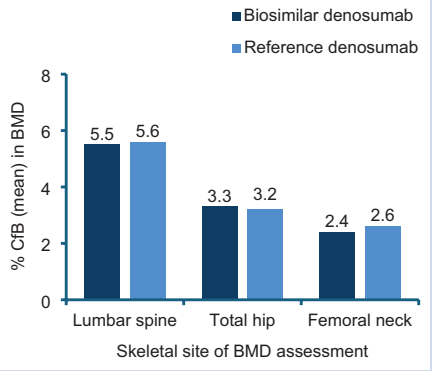
- Biosimilar **denosumab** demonstrated equivalent efficacy to reference **denosumab** based on the measurement of percentage change from baseline (*%CfB*) in *BMD* at the lumbar spine, hip, and femoral neck toward the top of the thigh bone at all timepoints
- Switching from reference **denosumab** to biosimilar **denosumab** at Week 52 did not result in any difference in *%CfB* at all skeletal sites assessed at Week 78
- These results, as shown in the graphs, indicate that biosimilar **denosumab** increases BMD in a similar way to reference **denosumab**:

Three skeletal sites assessed

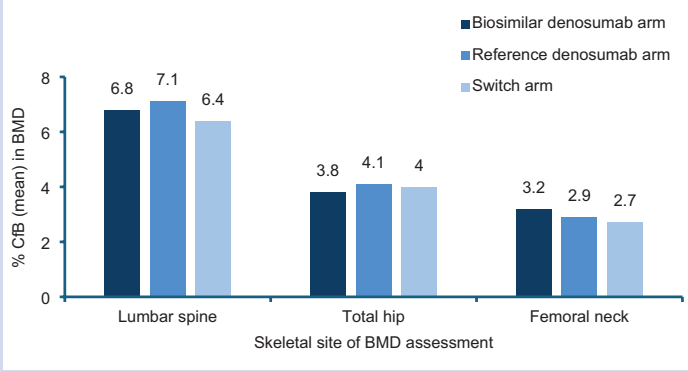


%CfB shows how much a value has increased or decreased compared to its initial measurement, expressed as a percentage

Week 52



Week 78



What were the adverse events with biosimilar denosumab?

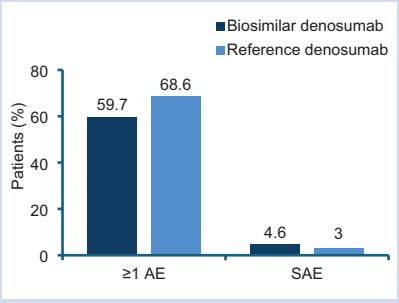
- The occurrence and seriousness of *AE*s were similar between biosimilar **denosumab** and reference **denosumab**; most were described as "mild" or "moderate"
- The incidence of *SAE*s was similar between treatment groups ($n = 12$ in biosimilar **denosumab** group and $n = 8$ in reference **denosumab** group)
- There were no deaths reported because of treatment with biosimilar **denosumab** and reference **denosumab**

AE, Adverse Event, refers to any medical condition that occurs when taking a treatment (it may or may not be related to the treatment)

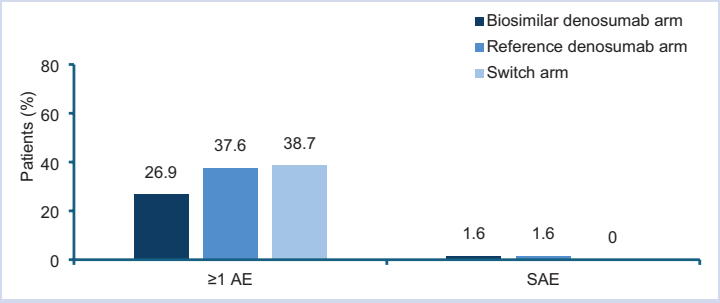
SAE, Serious Adverse Event, is an AE that poses a significant risk to health or requires medical attention

- There was no increase in the occurrence of AEs or SAEs after switching from reference **denosumab** to biosimilar **denosumab**

Weeks 0–52



Weeks 52–78



- Six patients left the study early because of an AE:

3 patients in each group discontinued the study due to an AE from the start of the study to Week 52

0 patient discontinued the study due to an AE from Weeks 52 to 78 following the treatment switch

What were the most common AEs with biosimilar denosumab?

Hypocalcemia (10%–11%)

Nasopharyngitis (6%–13%)

COVID-19 (6%–10%)

- **Hypocalcemia** is a low level of blood calcium. This event was mild and short-lived in **ROSALIA** (found at 1–2 weeks after the injection). The condition was managed according to the participating physician's judgment, by adjusting the doses of calcium and vitamin D supplementation that were being used in the study
- **Nasopharyngitis** is also known as a head cold and is not a recognized effect of **denosumab**. It was common in the study because colds are common
- COVID-19 was common as the study occurred during the world pandemic of COVID-19
- There were no clinically important differences between groups in the overall occurrence and seriousness of new vertebral fractures

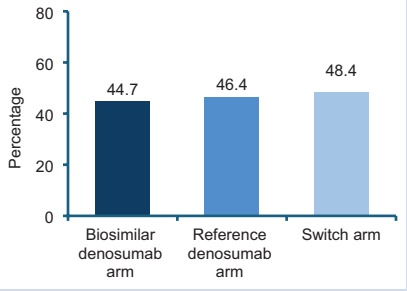
What were immune responses with biosimilar denosumab?

- A similar occurrence of positive ADAs, which might prevent the medicine from working effectively, was observed across the treatment groups throughout the study
- Only 13 out of 513 patients in the study had a measurable *persistent* ADA response
- Incidence of *NAbs* was also very low and similar across treatment groups (0.8% in each group)
- The low incidence of ADAs and *NAbs* indicates low ***immunogenicity*** of the treatment, meaning it is unlikely that the immune system will block its effectiveness

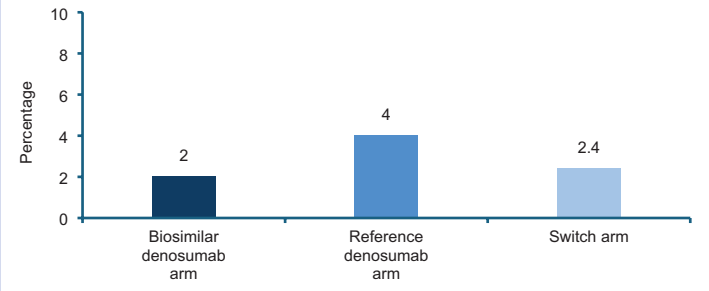
Persistent means a patient tested positive for ADA (see ***immunogenicity***, above) at their last visit and had positive results in at least two consecutive tests before that

NAbs, **Neutralizing** antibodies are a type of ADA that can block or neutralize a medicine's effectiveness

ADA positive (Week 78)



Persistent ADA (Week 78)



- Overall, neither treatment was shown to cause a significant immune response that would be expected to affect how the treatment worked, as shown by the very low reported levels of ADAs and *NAbs*. Additionally, switching from reference **denosumab** to biosimilar **denosumab** did not significantly impact immune responses

What were the main conclusions reported by the researchers?

The **ROSALIA** study, as part of the totality of evidence for biosimilar **denosumab**, showed that biosimilar **denosumab** behaves in the same way as reference **denosumab**. This conclusion was established based on measures of:

- *PK/PD*: Biosimilar **denosumab** showed similar decreases in bone markers and drug concentration to reference **denosumab**, suggesting that both drugs work in the same way
- *Efficacy*: Biosimilar **denosumab** demonstrated similar efficacy to reference **denosumab** in increasing BMD at all skeletal sites in postmenopausal women with **osteoporosis**
- *Safety*: Biosimilar **denosumab** had a similar safety profile to reference **denosumab** with comparable rates of AEs between the two medicines, with most being mild to moderate
- *Immunogenicity*: Incidence of *NAbs* and persistent ADAs was low for both biosimilar **denosumab** and reference **denosumab**
- *Treatment switch*: Changing from reference **denosumab** to biosimilar **denosumab** did not affect the treatment's effectiveness or safety

What do the results of this study mean?

The results from **ROSALIA** study show that biosimilar **denosumab** can be used in the same way as reference **denosumab** to manage bone density in postmenopausal **osteoporosis**, and that patients could be switched from reference **denosumab** to biosimilar **denosumab** without affecting treatment outcomes. Also, under the concept of extrapolation, the evidence from **ROSALIA** and postmenopausal **osteoporosis** can be extrapolated to assume similarity of biosimilar **denosumab** for all other indications of reference **denosumab**.

Where can you find the original article on which this summary is based?

- Original publication citation: Jeka S, Dokoupilová E, Kivitz A, *et al*. Equivalence trial of proposed denosumab biosimilar GP2411 and reference denosumab in postmenopausal osteoporosis: the ROSALIA study. *J Bone Miner Res*. 2024;39(3):202–210.
- Further details about ROSALIA study can be found at NCT03974100
- This study was conducted between June 14, 2019 and April 22, 2022

Declarations

Ethics approval and consent to participate

The study protocol was approved by the ethics committee or institutional review board for each site. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, and all participants provided written informed consent.

Consent for publication

The informed consent provided by all study participants included publication of the results.

Author contributions

Richard Eastell: Writing – original draft; Writing – review & editing.

Sławomir Jeka: Writing – review & editing.

Maryam Lustberg: Writing – review & editing.

Colin Edgerton: Writing – review & editing.

Paweł Żuchowski: Writing – review & editing.

Barbara Vogg: Writing – original draft; Writing – review & editing.

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Competing interests

R.E. has received consultancy funding from Biocon, CL Bio, CureTeQ, Immunodiagnostic Systems, Samsung, Sandoz, Takeda, UCB; has given meeting presentations for Pharmacosmos, Alexion, Amgen, and UCB; has received support for attending meetings from CL Bio and Samsung; has received grant funding from Alexion and Osteolabs; and has chaired a Data Safety Monitoring Board or Advisory Board for Biocon, CuRaTEQ, and STOPFOP. S.J. has received lecturer and speaker fees from UCB, Gilead, AbbVie, Eli Lilly, Novartis, Pfizer, Sandoz, Jansen, Medac, Egis, and Sobi. M.L. has been a consultant to Gilead, AstraZeneca, Pfizer, Menarini, and Lilly. C.E. has performed consulting for Sobi and Amgen, and educational activities for the Immunoglobulin National Society. P.Ż. has received accommodation and expenses during a conference from Sandoz. B.V. is an employee of Hexal AG (a Sandoz company).

Availability of data and materials

Further information on osteoporosis can be found at Porter and Varacallo[1] and Chitra and Sharon.[2]

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