Head-to-head trial of pegunigalsidase alfa versus agalsidase beta in patients with Fabry disease and deteriorating renal function: results from the 2-year randomized Phase 3 BALANCE study

Supplemental information to Wallace EL et al. *Journal of Medical Genetics*. 2023.

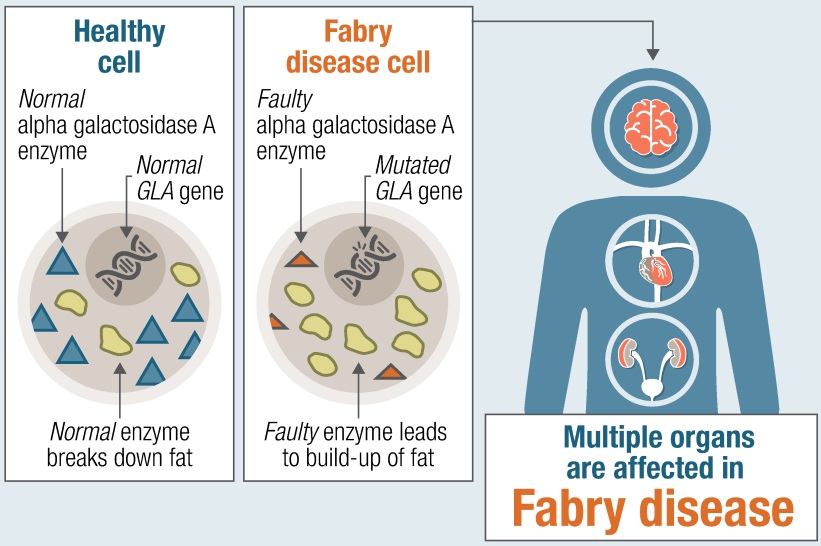
This is a plain language summary of an article about the BALANCE study, published in the *Journal of Medical Genetics* in 2023.

How to say...

Pegunigalsidase alfa: "peh-GOO-nih-GAL-sud-ace AL-fuh"
Agalsidase beta: "AY-gal-suh-days bay-tuh"
Alpha galactosidase: "al-fuh guh-lak-tow-suh-days"
Fabry: "FAB-ree"

What is Fabry disease?

Fabry disease is a rare disease that occurs in men and women when defects in a gene called *GLA* lead to the formation of a faulty enzyme called **alpha galactosidase A**. This enzyme is responsible for breaking down certain fats in the body. For a person with Fabry disease, the faulty enzyme leads to a build-up of fats such as Gb3 and lyso-Gb3 in their blood and throughout their body. This build-up can damage multiple organs, including the kidneys. This damage reduces kidney function and may worsen to kidney failure.



One way to treat Fabry disease is with an enzyme produced in a laboratory to replace the faulty enzyme. Usually, these **enzyme replacement therapies** are given through a needle into a vein, called an **intravenous infusion**, so that the enzyme goes straight into the bloodstream. **Agalsidase alfa** and **agalsidase beta** are two such treatments that replace the faulty enzyme so that people with Fabry disease can break down Gb3. Although these drugs can help control some symptoms, they do not help with all symptoms or fully prevent Fabry disease from getting worse. In addition, some people receiving enzyme replacement therapy may have an **infusion-related reaction** while receiving the treatment or shortly after. This happens when the body's immune system overreacts to the enzyme, resulting in immune responses that could be mild, moderate, or severe.

Pegunigalsidase alfa is an enzyme replacement therapy that has been recently approved to treat people with Fabry disease. It is well tolerated, lasts longer in the blood than other enzyme replacement therapies and reduces how much lyso-Gb3 builds up in their blood.

Why was the study done?

The **BALANCE** study looked at how effective and safe pegunigalsidase alfa is compared with agalsidase beta when used to treat people with Fabry disease who have worsening kidney function. Everyone in the study had been previously treated with agalsidase beta for an average of 6 years. This study was designed to determine whether pegunigalsidase alfa works comparably to agalsidase beta to slow the decline in kidney function. Researchers can use these kinds of studies to learn whether new treatments might offer some patients different options for their care.

What did the researchers want to find out in this study?

- How did the two drugs—pegunigalsidase alfa and agalsidase beta—affect how well the kidneys filter blood?
- Were any changes seen in lyso-Gb3 levels with pegunigalsidase alfa or agalsidase beta treatment?
- What were the safety results of this study?

What was the study plan?

The BALANCE study included 78 people with Fabry disease. One participant withdrew before the study started. 52 people were given pegunigalsidase alfa and 25 were given agalsidase beta as intravenous infusions once every 2 weeks for 2 years. At the start of the study, participants were between 18 and 60 years old and the average age was 44 years. There were 30 women and 47 men.

BALANCE was a **head-to-head study**, which means that pegunigalsidase alfa was directly compared with another treatment, agalsidase beta. This study was also **double-blind**, meaning neither the researchers nor the participants knew which treatment each participant received. This study was **randomized**, meaning the researchers used a computer program to randomly choose which of the two treatments each participant was given. After BALANCE, the majority of participants joined an open-label extension study called BRILLIANCE, in which they knew what treatment they were getting. In BRILLIANCE, participants who were treated with pegunigalsidase alfa in BALANCE continued to get it, while those treated with agalsidase beta switched to pegunigalsidase alfa.

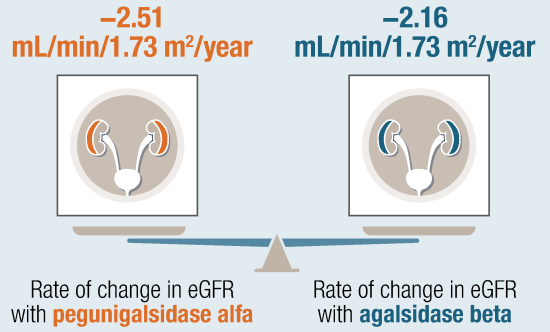
What did the results show?

How did the two drugs—pegunigalsidase alfa and agalsidase beta—affect how well the kidneys filter blood?

Researchers used a blood test to measure the estimated glomerular filtration rate, which is also called eGFR. This number shows how much blood the kidneys filter each minute and is based on factors such as people's age, sex, and body size.

As kidney disease gets worse in people with Fabry disease, eGFR may decrease over time. This study looked at how much eGFR changed over 2 years to compare how effectively the two treatments prevent kidney function from getting worse. To measure this change, blood tests before treatment started and then monthly over 2 years of treatment were used to calculate the rate at which eGFR changed. The rate at which eGFR changes is calculated over a year and the units used to describe this change are milliliters of blood per minute per 1.73 meter squared per year, which is written as mL/min/1.73m^2/year.

The rates of change in eGFR were –2.51 mL/min/1.73 m^2/year with pegunigalsidase alfa and –2.16 mL/min/1.73 m^2/year with agalsidase beta after 2 years. The difference between these two rates was –0.36 mL/min/1.73m^2/year. This value was small enough to show that pegunigalsidase alfa was comparable to agalsidase beta.



Both treatments were similar in how they affected the kidneys' ability to filter blood

Were any changes seen in lyso-Gb3 levels with pegunigalsidase alfa or agalsidase beta treatment?

The researchers regularly took samples of blood from participants to measure the amount of lyso-Gb3. Lyso-Gb3 levels remained **stable** among men and women and were higher in males throughout the study in both treatment groups. "Stable" means that lyso-Gb3 levels did not change significantly after 2 years of treatment, compared to the levels before the study started.

What were the safety results of this study?

Any side effects that participants may have during a clinical study, whether they are related to study treatment or not, are called **adverse events**. All treatments can have adverse events. Adverse events are considered serious when they are life-threatening, cause lasting problems, or need hospital care.

Most participants taking either treatment had at least 1 adverse event at some point during the study. Overall, **participants taking agalsidase beta had a 3.6-fold higher rate of adverse events related to treatment than participants taking pegunigalsidase alfa.**

How many participants had…	Number of participants affected after taking… Pegunigalsidase alfa (out of 52 participants)	Agalsidase beta (out of 25 participants)
any adverse events?	47 (90%)	24 (96%)
serious adverse events that may be related to treatment received?	1 (2%)	0 (0%)
adverse events that may be related to treatment received leading to withdrawal?	1 (2%)	0 (0%)

Infections were the most common adverse event for participants treated with either pegunigalsidase alfa or agalsidase beta. Two participants treated with pegunigalsidase alfa had adverse events leading them to withdraw from the study. One of the participants withdrew because they needed a kidney transplant. The other had a serious adverse event that was an infusion-related reaction, which was considered to be related to pegunigalsidase alfa treatment. No participants died during the study.

Overall, pegunigalsidase alfa was well tolerated. The proportion of participants having infusion-related reactions was similar in both treatment groups. However, **participants taking pegunigalsidase alfa experienced infusion-related reactions less often than those taking agalsidase beta**. In both treatment groups, a larger proportion of men had infusion-related reactions compared with women.

What did this study tell us and why is it important?

BALANCE is the first and only head-to-head study in Fabry disease comparing pegunigalsidase alfa with agalsidase beta. The study showed that pegunigalsidase alfa was comparable to agalsidase beta in how it affected the rate at which kidneys filter blood in people with Fabry disease. Overall, pegunigalsidase alfa was well tolerated. A similar proportion of participants experienced adverse events in both treatment groups, although participants treated with pegunigalsidase alfa had lower rates of adverse events that may have been related to treatment. Therefore, pegunigalsidase alfa may be a new treatment option for adults with Fabry disease who have worsening kidney function.

More information

This summary is based on the article called "Head-to-head trial of pegunigalsidase alfa versus agalsidase beta in patients with Fabry disease and deteriorating renal function: results from the 2-year randomized Phase 3 BALANCE study", published in *Journal of Medical Genetics* in 2023. Read more about this phase 3 study at https://clinicaltrials.gov/ct2/show/NCT02795676.

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