Extended long-term efficacy and safety of velmanase alfa treatment up to 12 years in patients with alpha-mannosidosis

Supplement information to Guffon et al. *The Journal of Inherited Metabolic Disease* 2024.

This is a summary of an article about the combined results of two clinical studies, named rhLAMAN-07 and rhLAMAN-09, in patients with alpha-mannosidosis. This article was published in *The Journal of Inherited Metabolic Disease* in 2024.

How to say...

Alpha-mannosidosis: "all-fuh mann-oh-suh-doh-sis"
Enzyme: "en-sime"
Immunoglobulin G: "im-mun-o-globulin G"
Oligosaccharide: "all-ee-go-sack-uh-ryed"
Velmanase alfa: "vell-muh-nays-al-fuh"

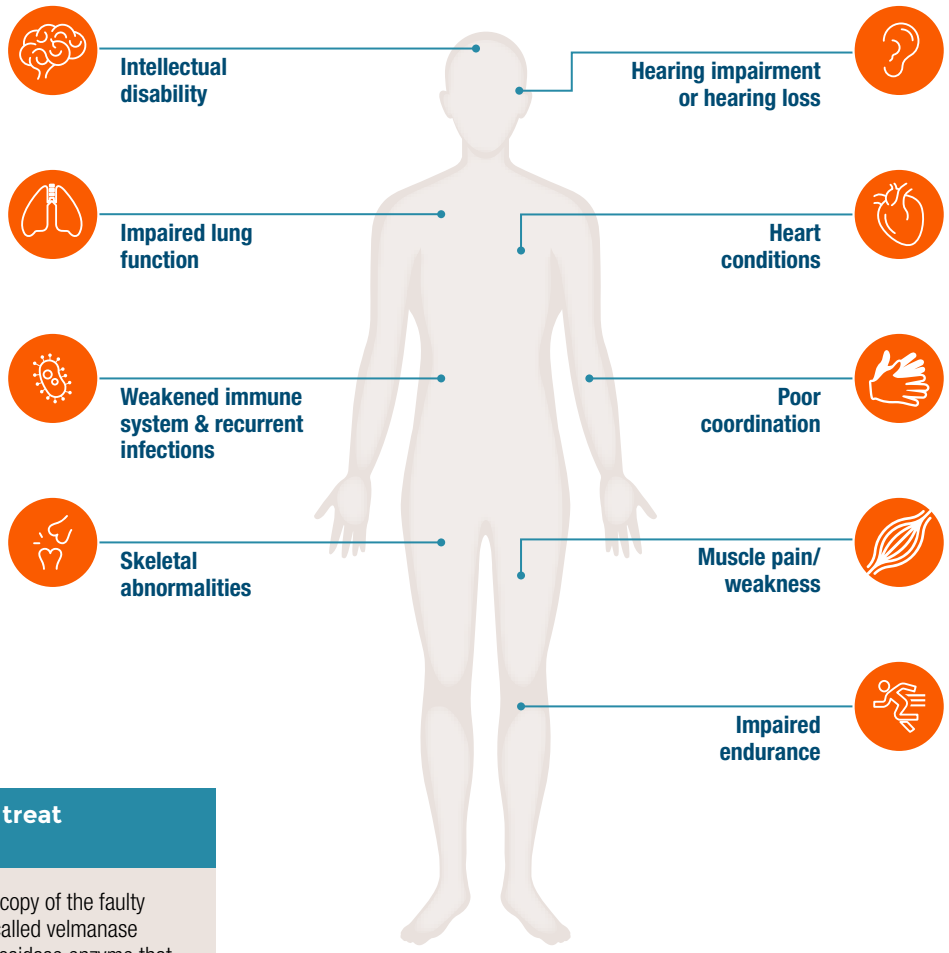
What is alpha-mannosidosis?

Alpha-mannosidosis is an extremely rare, inherited condition in which the enzyme called alpha-D-mannosidase does not work properly. The enzyme helps to clear waste deposits in our cells. Without this enzyme, **oligosaccharides** build up, affecting the cell's ability to function effectively. Over time, the high levels of **oligosaccharides** in tissues such as the liver, kidney, spleen, and brain cause a range of symptoms *(Figure 1)*. Most people experience their first symptoms during childhood, and as the disease progresses, symptoms may get worse. Whereas some people have mild symptoms, others have moderate or severe symptoms.

While there is no cure for alpha-mannosidosis, treatment options such as HSCT (hematopoietic stem cell transplantation) and ERT (enzyme replacement therapy) can help with symptom management, slow progression of the disease, and improve quality of life. This paper focuses on outcomes of long-term treatment with ERT.

Oligosaccharides: Complex sugar molecules

Figure 1 Symptoms of alpha-mannosidosis.



What is ERT and how does it help treat alpha-mannosidosis?

ERT works by providing the body's cells with a functional copy of the faulty enzyme. The ERT for people with alpha-mannosidosis is called velmanase alfa, which provides a working version of the alpha-mannosidase enzyme that breaks down **oligosaccharides** and improves disease symptoms. Velmanase alfa is given to patients by **intravenous infusions**, which are repeated every week to maintain high enough enzyme levels in the blood.

Intravenous infusion: Velmanase alfa is injected through the blood vessels (veins) into the bloodstream, which transports the enzyme to organs around the body. Velmanase alfa is too big to cross the protective barrier of the brain and so does not relieve brain symptoms

Why were these studies done?

Previous studies with treatment durations of up to 4 years have shown that velmanase alfa may be effective in treating patients with alpha-mannosidosis, with manageable side effects. However, as patients require continuous long-term treatment, further information was needed about how effective and safe velmanase alfa is when patients are treated for many years. Two long-term studies named rhLAMAN-07 and rhLAMAN-09 were carried out to examine the **efficacy** and safety of treating patients with alpha-mannosidosis with velmanase alfa for up to 12 years.

Efficacy: Effectiveness of treatment

What did the researchers want to find out?

What is the effect of long-term treatment with velmanase alfa on patients':

- Physical measures, like endurance (measured by exercise tests) and lung function
- Levels of **oligosaccharides**
- **Immune function**
- Side effects

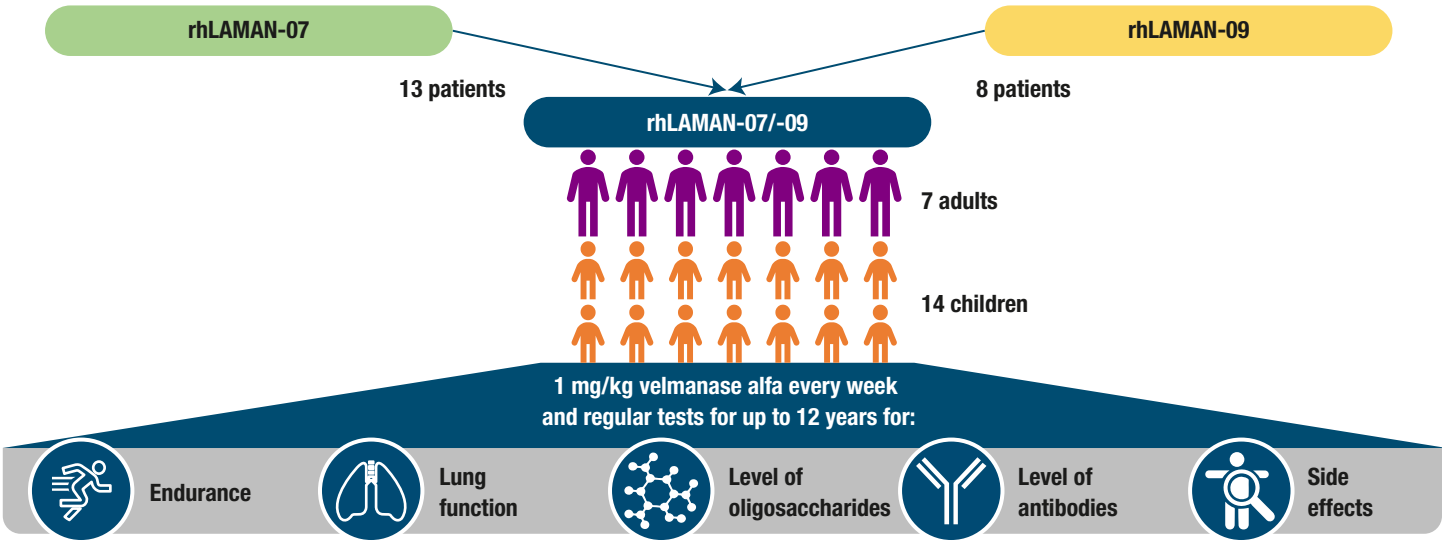
Immune function: The body's defense against infections, which includes antibodies and white blood cells

What was the study plan?

21 patients participated in the studies. Patients were divided by age (at the start of treatment) into two groups: children aged 4–15 years and adults aged 18–36 years. All patients were treated with 1 mg velmanase alfa per 1 kg of bodyweight once every week for up to 12 years *(Figure 2)*.

Two of the 21 patients dropped out of the studies; one patient after ~1 month because they joined a local aftercare program, and the other patient after ~4.5 years based on their parent's decision because the patient had mild or moderate side effects during or shortly after infusions.

Figure 2 Overview of the study plan.



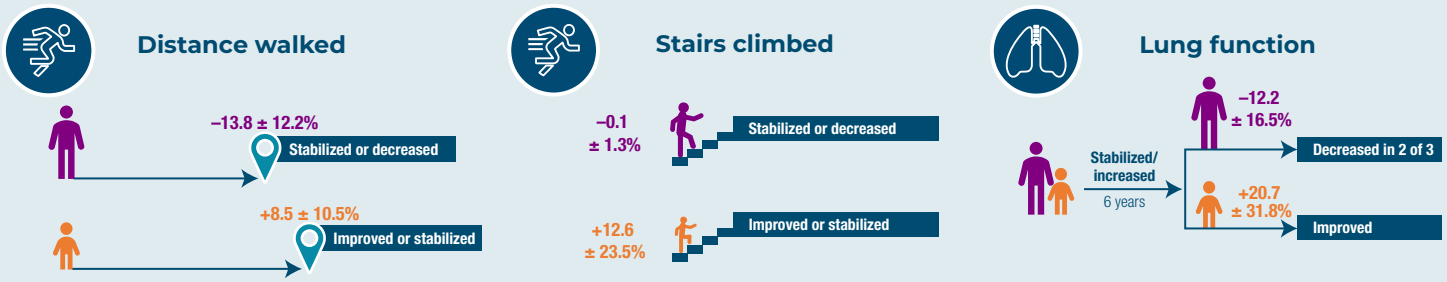
For up to 12 years, patients were regularly tested for their:

- Endurance – by measuring distance walked within 6 minutes (6MWT) and number of stairs climbed within 3 minutes (3MSCT)
- Lung function – by measuring the amount of air that can be forcibly exhaled from the lungs following a deep breath, which is called forced vital capacity (FVC)
- **Oligosaccharide** levels – by measuring the amount of complex sugars in the blood
- Antibody levels – by measuring how much of a type of antibody called **immunoglobulin G** is in the blood
- Side effects – by collecting the number of any unwanted effects that occur in patients during a study. The term is used here regardless of whether the side effect may or may not be related to the study drug. The severity of side effects can range from mild to severe. If these effects are life-threatening or medically important, cause disability, or require hospital care, they are defined as serious.

Immunoglobulin G is important for fighting infections caused by bacteria and viruses. People with alpha-mannosidosis typically have lower levels of this antibody, which impairs their ability to fight infections

What did the results show in adults and children?

Figure 3 Endurance (walking and climbing tests) and lung function.



The distance walked within 6 minutes improved or stabilized (stayed the same) in all children up until the last measurement. In adult patients, the distance either stayed the same or slightly decreased. One adult showed a marked decrease.

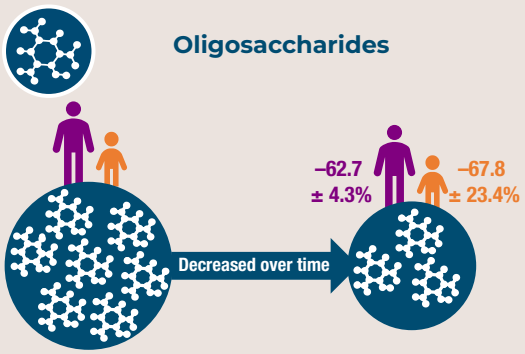
Children improved in the 3-minute stair climb test within the first 12–27 months and then stabilized. In adults the number of climbed stairs either stabilized or slightly decreased.

Within the first 6 years, lung function stabilized or improved in all patients. After 6 years, lung function further improved in children, while two of the three adults of whom values were available until 12 years of treatment experienced a drop.

The purple and orange numbers show the changes with treatment for adults and children, respectively (average percent changes from treatment start to 8 years of treatment ± **standard deviation**).

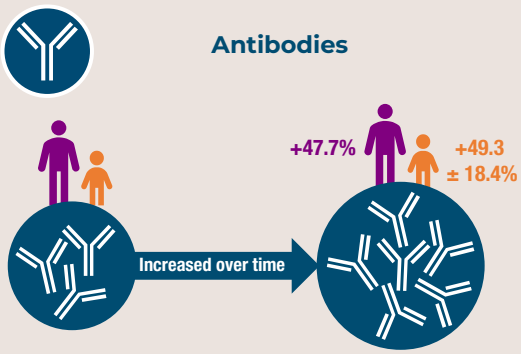
Standard deviation: A measure to look at how individual scores differ from the average

Figure 4 Levels of **oligosaccharides.**



Increased **oligosaccharide** levels in the blood of both children and adults dropped to lower levels and remained low throughout the study.

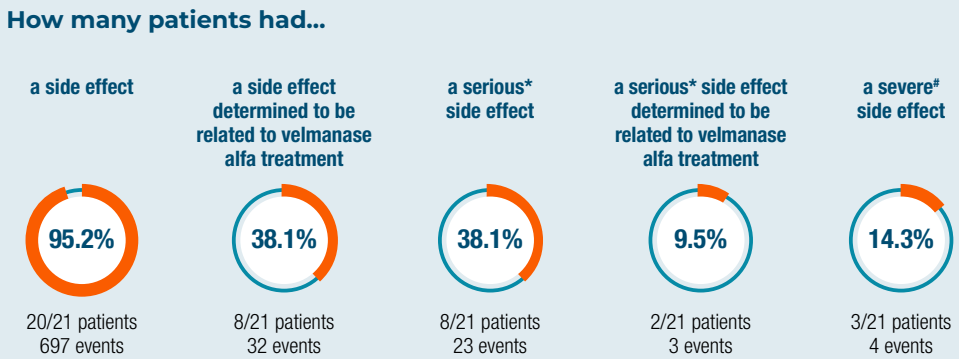
Figure 5 Levels of **immunoglobulin G.**



Immunoglobulin G levels were looked at in three children and one adult for up to 2.5 years. In all patients, **immunoglobulin G** levels increased close to or back to normal ranges that are seen in healthy people. The levels stabilized over 2.5 years, suggesting that the patients' **immune function** improved.

The purple and orange numbers show the changes with treatment for adults and children, respectively (average percent changes from treatment start to 10 years of treatment ± **standard deviation**).

Figure 6 Side effects during the studies.



Most patients given velmanase alfa had at least one side effect at some point during the studies. Most of these were mild or moderate and were easily treated and managed. In total, 8 of the 21 patients reported 32 events that were considered by the researchers to be related to velmanase alfa treatment (Figure 6). Only two patients reported three serious side effects related to the treatment – one patient had diarrhea and **hypokalemia**, and the other experienced vomiting. However, the events disappeared in both patients on the same day or the day after treatment.

The study results showed that long-term treatment did not lead to any new safety concerns when compared with earlier, shorter studies of velmanase alfa in patients with alpha-mannosidosis.

The researchers therefore concluded that velmanase alfa was a tolerable treatment.

Hypokalemia: too low level of the electrolyte potassium in the blood which can lead to problems with the heart amongst other issues

*Serious side effects are life-threatening or medically important, cause disability, or require hospital care. #Severe side effects are events of severe intensity.

What did these studies tell us and why is it important?

This study suggests that treatment benefits were maintained for up to 12 years in both children and adults with alpha-mannosidosis and supports long-term use of velmanase alfa. Most patients stabilized or even improved in walking, stair climbing ability and lung function. Increased levels of **oligosaccharides** in the patients' blood could be reduced and their **immune function** enhanced. The researchers concluded, although based on data of only a few patients, that treatment with velmanase alfa may slows down disease progression. This is important as the disease progresses with age and symptoms can get worse when untreated.

More information

This summary is based on the article called "Extended long-term efficacy and safety of velmanase alfa treatment up to 12 years in patients with alpha-mannosidosis" which was published in *The Journal of Inherited Metabolic Disease* in 2024. To find out more about the individual trials please check https://classic.clinicaltrials.gov/ct2/show/NCT01908712 for rhLAMAN-07 and https://classic.clinicaltrials.gov/ct2/show/NCT01908725 for rhLAMAN-09.

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