Plain Language Clinical Study
Summary

This summary reports the results of only one study. Researchers must look at the results of many types of studies to understand if a study medicine works, how it works, and if it is safe to prescribe to patients. The results of this study might be different than the results of other studies that the researchers review.

Sponsor: Pfizer Inc.

Medicine Studied: Oxbryta® (voxelotor, also known as PF-06759497 or GBT440)

Protocol Number: C5341026 (GBT440-042)

Dates of Study: 30 May 2022 to 22 October 2024

Title of this Study: **Res**olution **o**f Sickle Cell **L**eg Ulcers With **V**ox**e**lotor (RESOLVE)

[A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy of Voxelotor for the Treatment of Leg Ulcers in Patients With Sickle Cell Disease]

Date of this Report: 25 June 2025

– Thank You –

If you or your child participated in this study, Pfizer, the Sponsor, would like to thank you for your participation.

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This summary will describe the study results. Do you have any questions about the study or the results? If so, please contact the doctor or staff at your or your child's study site.

Why was this study done?

What is sickle cell disease?

Sickle cell disease (SCD) is a condition where red blood cells are shaped like a "sickle" (crescent moon) instead of being round. These sickle cells break down more quickly asnd can block blood flow. This makes it harder for the blood to carry oxygen around the body, leading to problems such as anemia (low levels of red blood cells). A complication of SCD includes open sores ("ulcers") on the legs, likely due to poor blood flow and the breakdown of red blood cells.

Leg ulcers are very painful, heal slowly, and even after they heal, often come back again. No therapies are available for treating or managing leg ulcers caused by SCD.

What is voxelotor?

Voxelotor (VOX-el-oh-tor), also known as Oxbryta®, is a study medicine given as a tablet.

Researchers wanted to learn if voxelotor might help treat leg ulcers caused by SCD. Voxelotor is designed to prevent the formation of sickle cells, which may help to improve blood flow and reduce the breakdown of red blood cells.

What was the purpose of this study?

The main purpose of this study was to find out whether voxelotor could help treat leg ulcers in participants with SCD compared to placebo. A placebo does not have any medicine in it, but it looks just like voxelotor.

Researchers wanted to know:

- **Can voxelotor help treat leg ulcers compared to placebo after 12 weeks of treatment?**
- **What medical problems did participants have during the study?**

This study stopped early and was not completed as planned.

What happened during the study?

How was the study done?

Screening and Run-in Periods

During the **Screening Period**, researchers checked the participants' health to make sure they could join the study.

After the Screening Period, participants entered the 2-week **Run-in Period**, wherein researchers checked the participants' leg ulcers. During this period, participants started wound care for their leg ulcers according to the study plan.

Double-blind Period

Researchers used a computer program to randomly divide the participants into 2 groups.

- **Voxelotor Group**: Participants took voxelotor tablets once per day.
- **Placebo Group**: Participants took placebo tablets once per day.

Participants took voxelotor or placebo for 12 weeks while continuing wound care for their leg ulcers according to the study plan. During this period, the participants and researchers did not know to which treatment group the participants were assigned. This is known as the "**Double-blind**" **Period**. During this period, researchers looked at the participants' leg ulcers to answer the main question of the study.

Open-label Period

After the 12-week Double-blind Period, participants entered the "**Open-label**" **Period**. During this period, the participants and researchers knew that all participants were taking voxelotor.

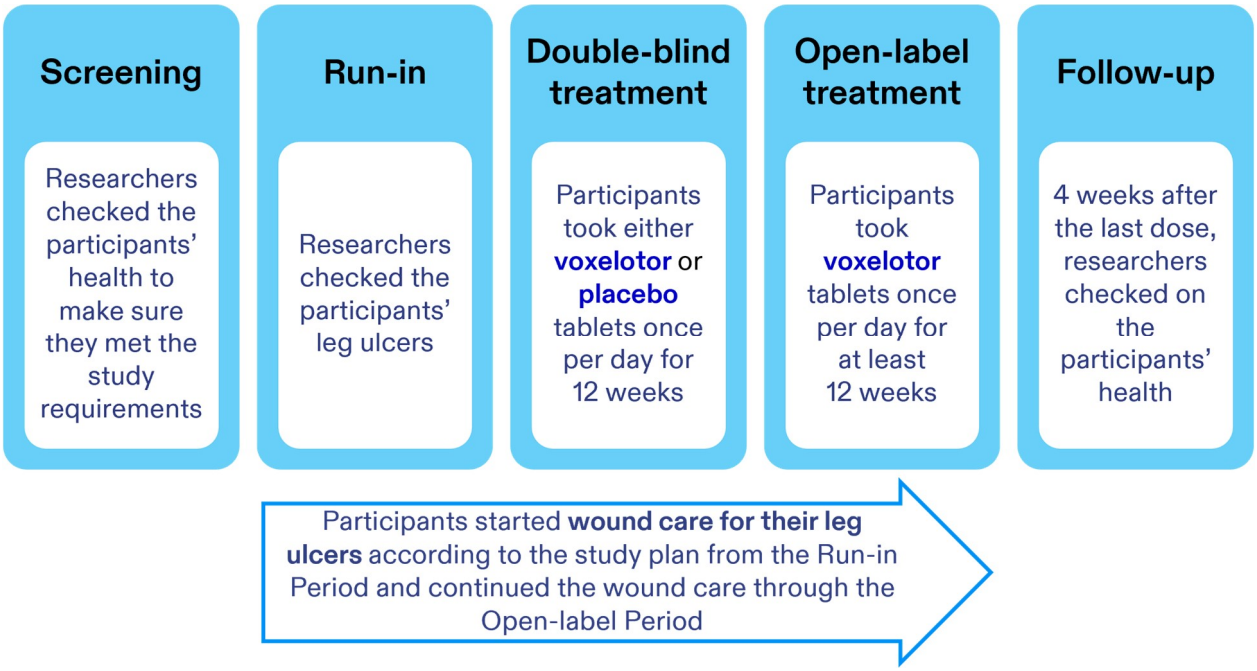
- **Voxelotor Group:** Participants who took voxelotor in the Double-blind Period continued to take voxelotor.
- **Delayed Voxelotor Group:** Participants who took placebo during the Double-blind Period were switched to start voxelotor.

Participants took voxelotor for at least 12 weeks while continuing wound care for their leg ulcers according to the study plan. Participants who completed the 12-week treatment in the Open-label Period could keep taking voxelotor as long as they were receiving clinical benefit as observed by the researchers.

Throughout the study, researchers checked on the participants' health and asked them how they were feeling.

The figure below shows how the study was done.

Figure 1. How was the study done?



Where did this study take place?

The Sponsor ran this study at 19 locations in 3 countries: Brazil, Kenya, and Nigeria.

When did this study take place?

It began on 30 May 2022 and ended on 22 October 2024.

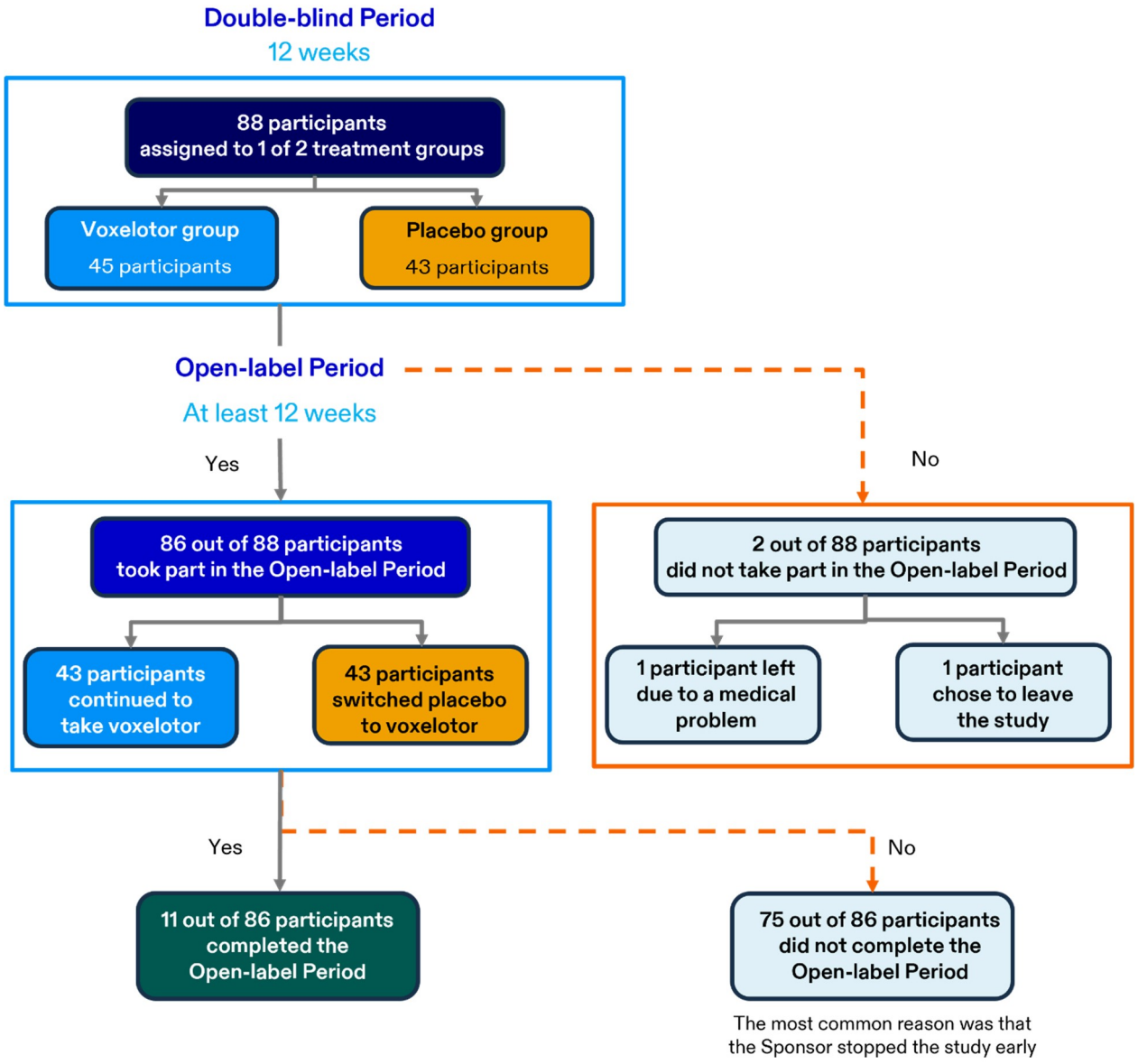
Who participated in this study?

The study included participants who were at least 12 years old with SCD and had at least 1 leg ulcer.

- A total of 50 boys/men and 38 girls/women participated.
- All participants were between the ages of 12 and 54 years.

The figure below shows the number of participants who took part in the study.

Figure 2. How many participants took part in the study?



How long did the study last?

Study participants were in the study for about 34 weeks (8 months). The study ran for about 2 years and 4 months before the Sponsor stopped the study. This study stopped early and was not completed as planned.

In May 2024, the Sponsor and researchers decided to pause voxelotor treatment in the study to review all the collected information, including the deaths in the study.

> Overall, 11 participants died in the study. None of the deaths were considered related to voxelotor.

In September 2024, the Sponsor decided to stop this study early because, after reviewing all information from studies on voxelotor, the benefits of voxelotor no longer outweighed the risks. Starting in September 2024, the Sponsor decided that voxelotor would no longer be available in all markets where it was previously approved. The Sponsor also stopped all ongoing clinical studies on voxelotor.

When the study ended in October 2024, the Sponsor began reviewing the information collected. The Sponsor then created a report of the results. This is a summary of that report.

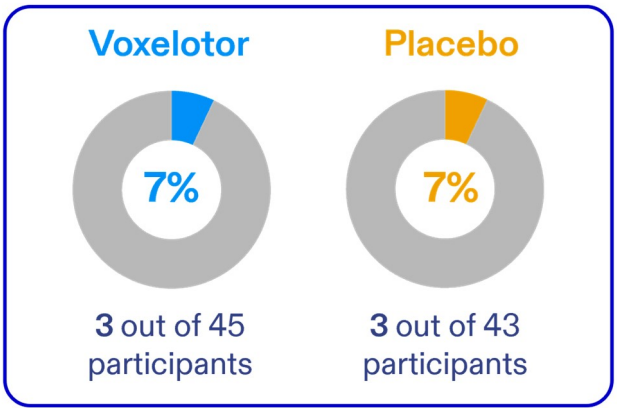
What were the results of the study?

Can voxelotor help treat leg ulcers compared to placebo after 12 weeks of treatment?

To answer this question, researchers counted the number of participants whose leg ulcers healed after 12 weeks of treatment while continuing wound care for their leg ulcers in the Double-blind Period. They then compared the results between participants who took voxelotor and those who took a placebo.

The figure below shows the number of participants whose leg ulcers healed after 12 weeks of treatment in the Double-blind Period.

Figure 3. Number of participants with healed leg ulcers after 12 weeks of treatment in the Double-blind Period



Based on these results, the study did not show that 12-week treatment with voxelotor had a greater effect than placebo at healing leg ulcers caused by SCD.

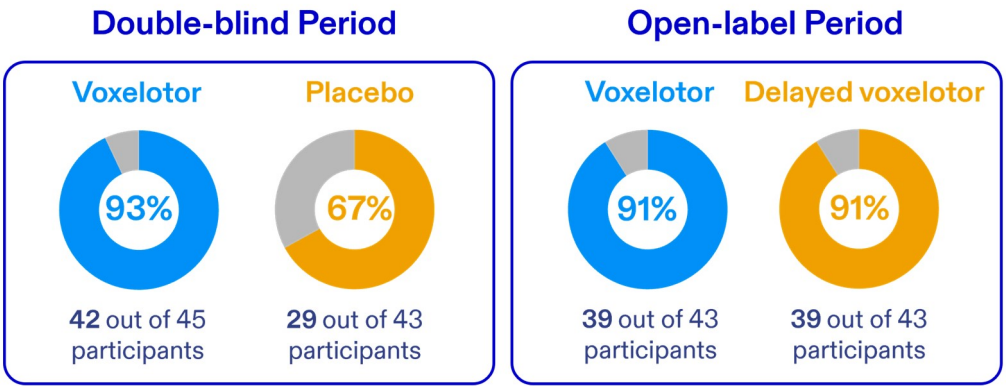
This does not mean that everyone in this study had these results. This is a summary of just some of the main results of this study. Other studies may have different results.

What medical problems did participants have during the study?

The researchers recorded any medical problems the participants had during the study. Participants could have had medical problems for reasons not related to the study (for example, caused by an underlying disease or by chance). Or, medical problems could also have been caused by a study treatment or by another medicine the participant was taking. Sometimes the cause of a medical problem is unknown. By comparing medical problems across many treatment groups in many studies, doctors try to understand what effects a study medicine might have on a participant.

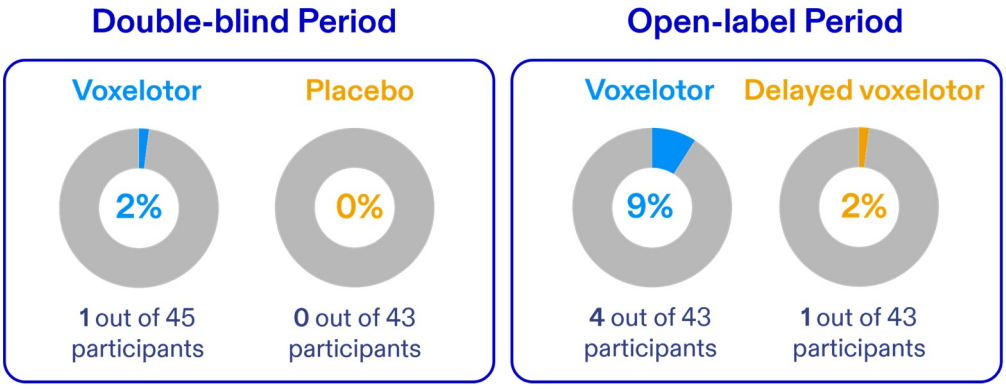
The figure below shows the number of participants who had at least 1 medical problem in the study.

Figure 4. How many participants had medical problems?



The figure below shows the number of participants who left the study because of medical problems.

Figure 5. How many participants left the study because of medical problems?



The table below shows the most common medical problems in the **Double-blind Period** – those reported by more than 15% of participants in either group.

Below are instructions on how to read Table 1.

Instructions for Understanding Table 1.

- The **1st** column lists the commonly reported medical problems in the **Double-blind Period**. All medical problems were reported by more than 15% of participants in either group.
- The **2nd** column shows the total number and percentage of participants in the **Voxelotor group** who reported each medical problem.
- The **3rd** column shows the total number and percentage of participants in the **Placebo group** who reported each medical problem.

Table 1. Commonly reported medical problems in the Double-blind Period		
Medical Problem	**Voxelotor (45 Participants)**	**Placebo (43 Participants)**
Sickle cell anemia with crisis	20 out of 45 participants (44%)	11 out of 43 participants (26%)
Skin ulcer	9 out of 45 participants (20%)	10 out of 43 participants (23%)
Joint pain	8 out of 45 participants (18%)	1 out of 43 participants (2%)
Pain in arms or legs	8 out of 45 participants (18%)	1 out of 43 participants (2%)
Malaria (a disease caused by parasites from infected mosquitoes)	7 out of 45 participants (16%)	8 out of 43 participants (19%)
Anemia	5 out of 45 participants (11%)	8 out of 43 participants (19%)

> People with SCD can develop a sudden pain crisis called "**sickle cell anemia with crisis**." This happens when the sickled red cells in blood vessels lead to a blockage. As a result, the blood flow and oxygen delivery to areas of the body is prevented, causing painful crises.

The table below shows the most common medical problems in the **Open-label Period** – those reported by more than 15% of participants in either group.

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Below are instructions on how to read Table 2.

Instructions for Understanding Table 2.

- The **1st** column lists the commonly reported medical problems in the **Open-label Period**. All medical problems were reported by more than 15% of participants in either group.
- The **2nd** column shows the total number and percentage of participants in the **Voxelotor group** who reported each medical problem.
- The **3rd** column shows the total number and percentage of participants in the **Delayed Voxelotor group** who reported each medical problem.

Table 2. Commonly reported medical problems in the Open-label Period

Medical Problem	Voxelotor (43 Participants)	Delayed Voxelotor (43 Participants)
Sickle cell anemia with crisis	26 out of 43 participants (61%)	23 out of 43 participants (54%)
Malaria	16 out of 43 participants (37%)	13 out of 43 participants (30%)
Joint pain	7 out of 43 participants (16%)	6 out of 43 participants (14%)
Anemia	5 out of 43 participants (12%)	7 out of 43 participants (16%)

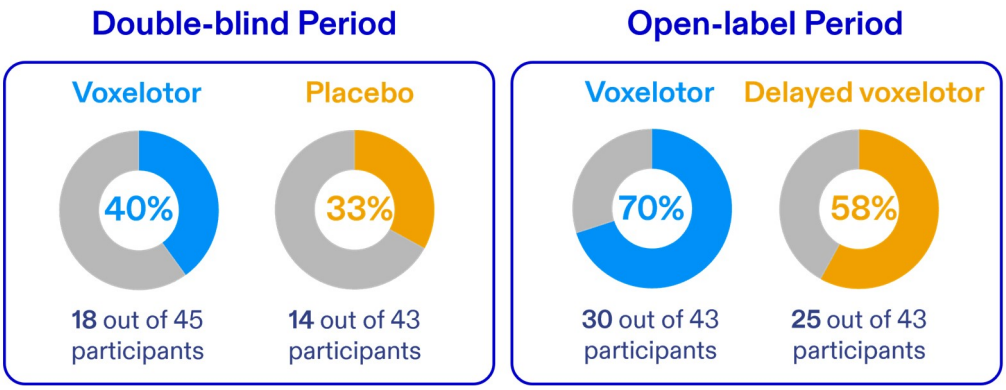
Table 2. Commonly reported medical problems in the Open-label Period		
Medical Problem	**Voxelotor (43 Participants)**	**Delayed Voxelotor (43 Participants)**
Skin ulcer	4 out of 43 participants (9%)	12 out of 43 participants (28%)

Did study participants have any serious medical problems?

A medical problem is considered "serious" when it is life-threatening, needs hospital care, or causes lasting problems.

The figure below shows the number of participants who had at least 1 serious medical problem in the study.

Figure 6. How many participants had serious medical problems?



The table below shows the most common serious medical problems in the **Double-blind Period** – those reported by more than 10% of participants in either group.

Below are instructions on how to read Table 3.

Instructions for Understanding Table 3.

- The **1st** column lists the commonly reported serious medical problems in the **Double-blind Period**. All serious medical problems were reported by more than 10% of participants in either group.
- The **2nd** column shows the total number and percentage of participants in the **Voxelotor group** who reported each serious medical problem.
- The **3rd** column shows the total number and percentage of participants in the **Placebo group** who reported each serious medical problem.

Table 3. Commonly reported serious medical problems in the Double-blind Period

Serious Medical Problem	Voxelotor (45 Participants)	Placebo (43 Participants)
Sickle cell anemia with crisis	13 out of 45 participants (29%)	9 out of 43 participants (21%)
Anemia	4 out of 45 participants (9%)	7 out of 43 participants (16%)

The table below shows the most common serious medical problems in the **Open-label Period** – those reported by more than 10% of participants in either group.

Below are instructions on how to read Table 4.

Instructions for Understanding Table 4.

- The **1st** column lists the commonly reported serious medical problems in the **Open-label Period**. All serious medical problems were reported by more than 10% of participants in either group.
- The **2nd** column shows the total number and percentage of participants in the **Voxelotor group** who reported each serious medical problem.
- The **3rd** column shows the total number and percentage of participants in the **Delayed Voxelotor group** who reported each serious medical problem.

Table 4. Commonly reported serious medical problems in the Open-label Period

Serious Medical Problem	Voxelotor (43 Participants)	Delayed Voxelotor (43 Participants)
Sickle cell anemia with crisis	23 out of 43 participants (54%)	18 out of 43 participants (42%)
Malaria	10 out of 43 participants (23%)	9 out of 43 participants (21%)
Anemia	5 out of 43 participants (12%)	7 out of 43 participants (16%)

During the study, a total of 11 participants died. None of the deaths were considered related to voxelotor. Of these 11 participants:

- 1 participant who received voxelotor during the **Double-blind Period** died because of sickle cell anemia with crisis.
- 8 participants died because of medical problems during the **Open-label Period** or **Follow-up Period**.
    - 5 participants in the **voxelotor group**: The medical problems were gallstones, bacteria present in the blood, malaria, sepsis (a condition wherein the body responds improperly to an infection), clot in a blood vessel in the lungs, "hypovolemic shock" (a condition wherein the body loses too much blood and fluid), and sickle cell anemia with crisis.
    - 3 participants in the **delayed voxelotor group**: The medical problems were "dengue hemorrhagic fever" (fever and bleeding in the body caused by a virus that is spread by mosquitoes), high levels of potassium, and fluid in the lungs.
- 2 participants died after the pause of voxelotor treatment in the study, so they were no longer taking voxelotor. They died because of medical problems of "complicated malaria" (a serious type of malaria that needs urgent hospital care), sepsis caused by bacterial infection, injury to the leg, and sickle cell anemia with crisis.

Where can I learn more about this study?

If you have questions about the results of your study, please speak with the doctor or staff at your study site.

For more details on your study protocol, please visit:

www.pfizer.com/research/research_clinical_trials/trial_results

Use the protocol number **C5341026**

The full scientific report of this study is available online at:

www.clinicaltrials.gov

Use the study identifier **NCT05561140**

Please remember that researchers look at the results of many studies to find out which medicines can work and are safe for patients.

Again, if you or your child participated in this study, **thank you** for volunteering. We do research to try to find the best ways to help patients, and you helped us to do that!

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