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: C5341021 (GBT440-032)

Dates of Study: 11 November 2020 to 06 November 2024

Title of this Study: Study to Evaluate the Effect of GBT440 on TCD in Pediatrics With Sickle Cell Disease (HOPE Kids 2)

[A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Voxelotor (GBT440) in Pediatric Participants With Sickle Cell Disease (HOPE Kids 2)]

Date of this Report: 28 July 2025

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– Thank You –

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

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 and 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 hemoglobin). Hemoglobin is a protein in the red blood cells that carries oxygen throughout the body.

What is voxelotor?

Voxelotor (VOX-el-oh-tor), also known as Oxbryta®, is a study medicine given by mouth. In this study, voxelotor was given as a tablet for participants 12 years and older and suspension for participants below 12 years old. Suspension is a liquid with solid particles of the medicine (not completely dissolved in the liquid). Voxelotor is designed to prevent the formation of sickle cells.

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What was the purpose of this study?

Patients with SCD and normal blood flow in the brain are less likely to have a stroke than those with faster-than-normal blood flow. The main purpose of this study was to find out whether voxelotor could slow down the brain's blood flow in participants with SCD.

Researchers wanted to know:

- **Did voxelotor slow down the brain's blood flow after 24 weeks?**
- **What medical problems did participants have during the study?**

This study stopped early and was not completed as planned. This was because of safety concerns about voxelotor.

What happened during the study?

How was the study done?

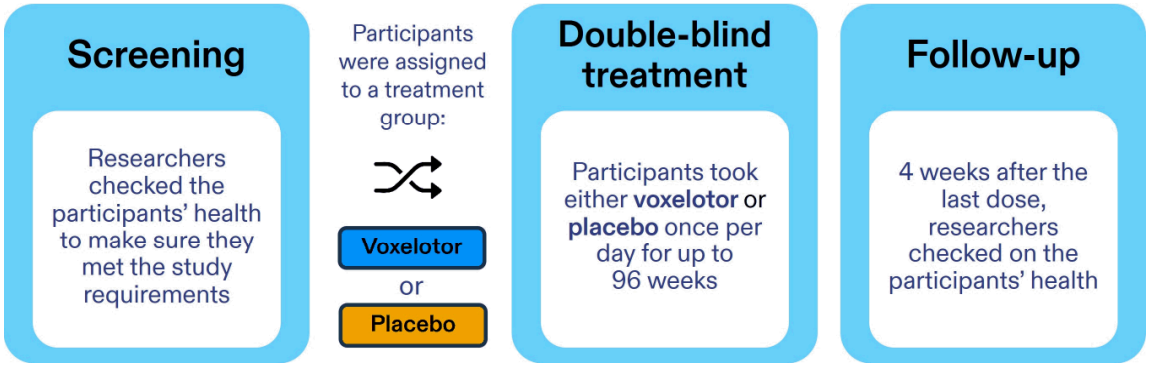
Researchers used a computer program to assign participants to a treatment group (voxelotor or placebo) at random. A placebo does not have any medicine in it, but it looks just like the study medicine.

- **Voxelotor group:** Participants in this group took voxelotor once per day for up to 96 weeks. For participants at least 12 years old, their dose of voxelotor was 1500 mg. For participants under 12 years old, their dose of voxelotor was based on how much they weighed.
- **Placebo group:** Participants in this group took a placebo once per day for up to 96 weeks.

The participants and researchers did not know to which treatment group the participants were assigned. This is known as a "double-blind" study.

Figure 1 below shows how the study was done.

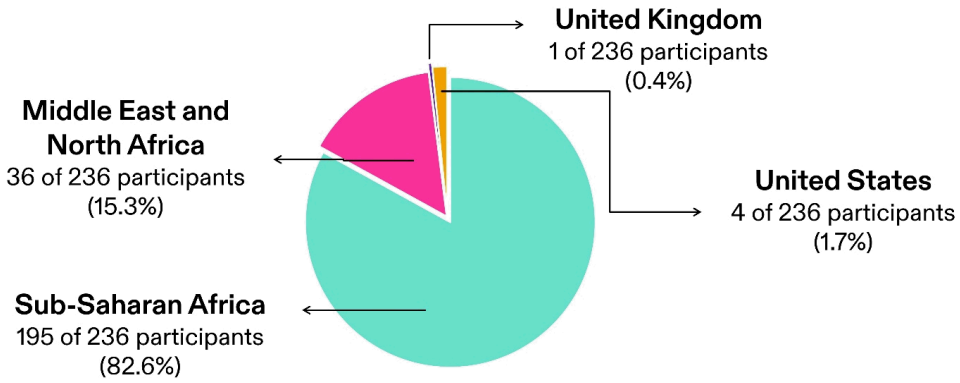
Figure 1. How was the study done?



Where did this study take place?

The Sponsor ran this study at 29 locations in the Middle East and North Africa, Sub-Saharan Africa, the United States, and the United Kingdom. Figure 2 below shows the number of participants in the study by region.

Figure 2. Number of participants by region



When did this study take place?

It began on 11 November 2020 and ended on 06 November 2024 when the final results were collected.

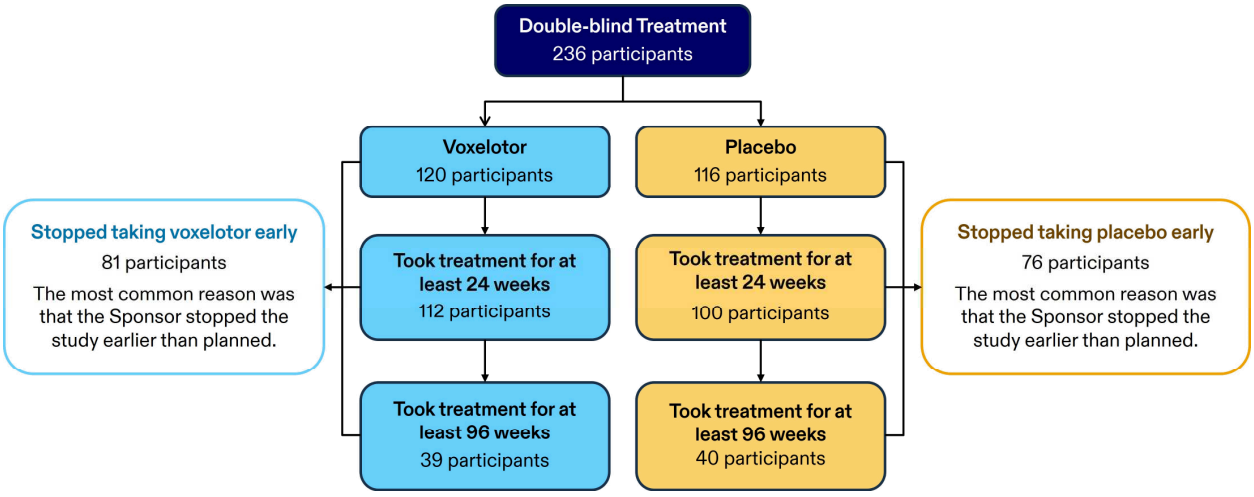
Who participated in this study?

The study included children and teenagers with SCD. Participants in the study had a fast brain blood flow of 170 centimeters/second (cm/sec) to less than 200 cm/sec. The normal speed of the brain's blood flow is below 170 cm/sec.

- A total of 114 boys and 122 girls participated.
- All participants were between the ages of 2 and 14 years.

Figure 3 below shows how many participants took part in the study.

Figure 3. How many participants took part in the study?



How long did the study last?

Study participants were planned to be in the study for about 2 years. The study ran for about 4 years and was not completed as planned because the Sponsor stopped the study early.

On 01 May 2024, the Sponsor and researchers paused dosing of voxelotor in the study due to safety concerns. This pause allowed time for a review of the collected information, including the deaths in the study. Even though dosing of voxelotor was paused, participants continued having their check-ups at the study site so that the study doctor could monitor the participants and collect safety information.

On 25 September 2024, the Sponsor decided that voxelotor would no longer be available where it was previously approved. The Sponsor also stopped this study and all ongoing clinical studies on voxelotor. This decision was due to safety concerns based on the information available at that time from this study and from other voxelotor studies.

Following the decision to stop all clinical studies on voxelotor, this study ended in November 2024, when all final results were collected. The Sponsor reviewed the information collected and then created a report of the results. This is a summary of that report.

What were the results of the study?

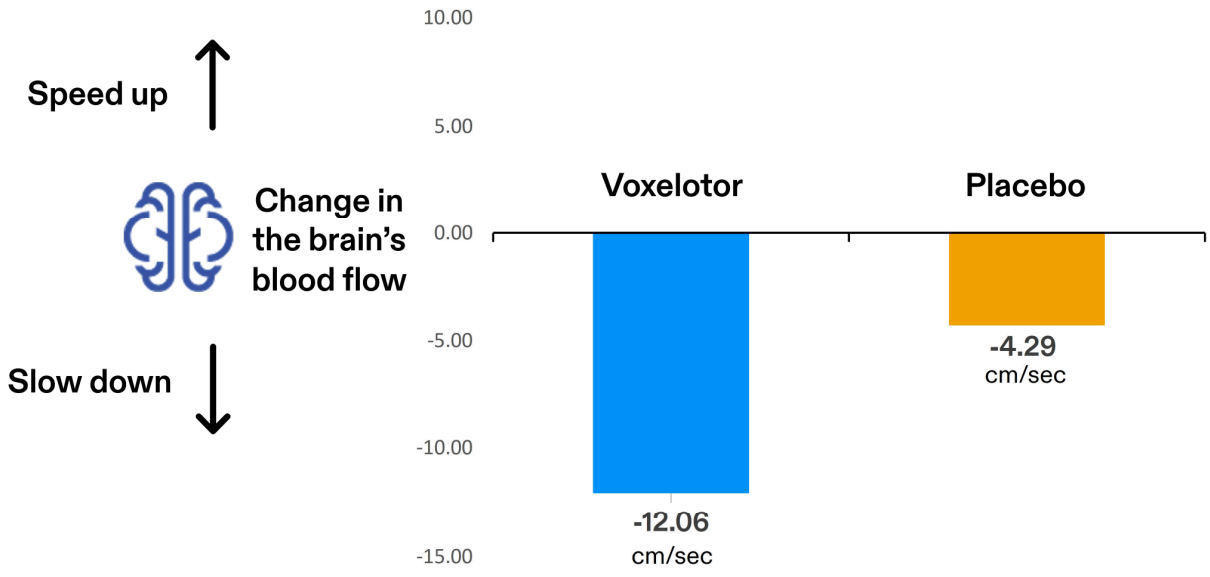
Did voxelotor slow down the brain's blood flow after 24 weeks?

To answer this question, researchers used a tool called Transcranial Doppler (TCD) to measure the brain's blood flow. The TCD uses sound waves to measure the speed and direction of the brain's blood flow. A faster-than-normal brain blood flow means a greater risk of stroke.

Researchers compared the TCD results of participants before the treatment started and 24 weeks after the treatment began. A decrease in TCD result indicates that the brain's blood flow is moving more slowly.

Figure 3 below shows the effect on the brain's blood flow based on the TCD results after 24 weeks of taking voxelotor or placebo.

Figure 3. The effect of voxelotor on the brain's blood flow compared to placebo



Based on these results, the researchers have concluded that the results are not likely the result of chance. Among participants with fast blood flow in the brain due to SCD, taking voxelotor for 24 weeks may help slow down the brain's blood flow.

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.

Figure 4 below shows the number of participants who had at least 1 medical problem in the study.

Figure 4. How many participants had medical problems?

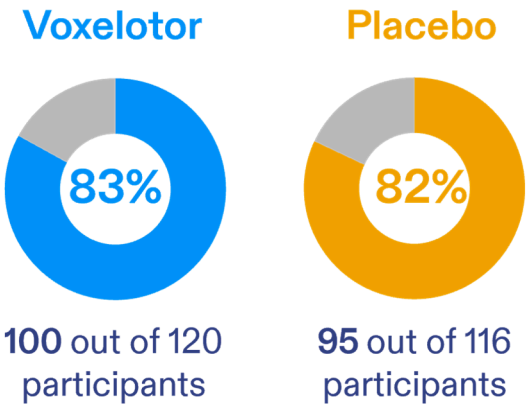


Figure 5 below shows the number of participants who stopped taking the study treatment because of medical problems.

Figure 5. How many participants stopped taking the study treatment because of medical problems?

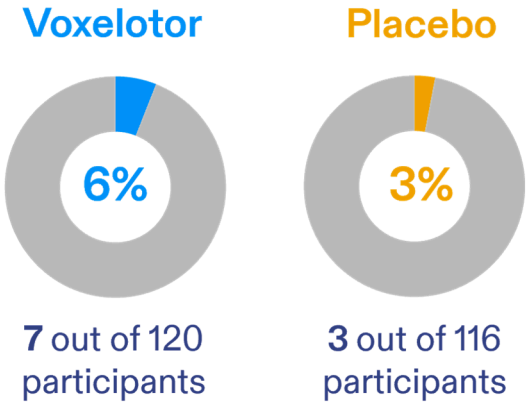


Table 1 below shows the most common medical problems in the study – those reported by more than 10% of participants in either group.

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 study. These 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 medical problem.
- The **3rd** column shows the total number and percentage of participants in the **placebo group** who reported each medical problem.
- Using these instructions, you can see that 71 out of the 120 participants (59%) who took voxelotor and 44 out of the 116 participants (38%) who took placebo reported sickle cell anemia with crisis.

> 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 are prevented, causing painful crises.

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Table 1. Commonly reported medical problems by study participants		
Medical Problem	**Voxelotor (120 Participants)**	**Placebo (116 Participants)**
Sickle cell anemia with crisis	71 out of 120 participants (59%)	44 out of 116 participants (38%)
Fever	37 out of 120 participants (31%)	15 out of 116 participants (13%)
Malaria (a disease caused by parasites from infected mosquitoes)	33 out of 120 participants (28%)	28 out of 116 participants (24%)
Anemia	16 out of 120 participants (13%)	19 out of 116 participants (16%)
Infection of the nose and throat	15 out of 120 participants (13%)	7 out of 116 participants (6%)

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.

Figure 6 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?

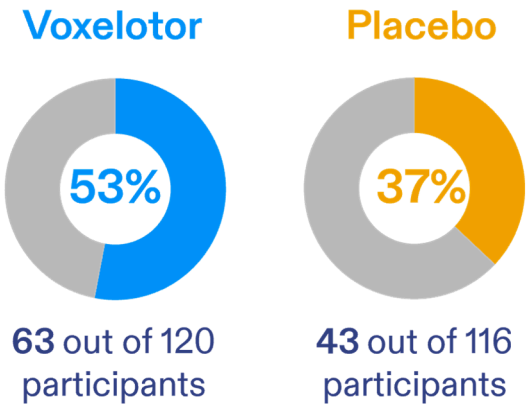

Table 2 below shows the most common serious medical problems in the study – those reported by more than 10% of participants in either group.

Below are instructions on how to read Table 2.

Instructions for Understanding Table 2.

- The **1st** column lists the commonly reported serious medical problems in the study. These 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.
- Using these instructions, you can see that 44 out of the 120 participants (37%) who took voxelotor and 18 out of the

116 participants (16%) who took placebo reported sickle cell anemia with crisis.

Table 2. Commonly reported serious medical problems by study participants

Serious Medical Problem	Voxelotor (120 Participants)	Placebo (116 Participants)
Sickle cell anemia with crisis	44 out of 120 participants (37%)	18 out of 116 participants (16%)
Malaria	20 out of 120 participants (17%)	16 out of 116 participants (14%)
Fever	19 out of 120 participants (16%)	5 out of 116 participants (4%)
Anemia	12 out of 120 participants (10%)	13 out of 116 participants (11%)

A total of 10 participants died because of medical problems during the study. Of these 10 participants:

- 8 participants in the voxelotor group died. The most common medical problems that the study doctors thought might have led to the participants' deaths were sickle cell anemia with crisis (6 participants), anemia (2 participants), and fever (2 participants).
- 2 participants in the placebo group died. One (1) participant died because of anemia, "cardiac failure" (when the heart is too weak or damaged to pump blood properly), and malaria, and 1 participant died because of stroke.

None of the deaths were considered by the study doctors as related to voxelotor.

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 **C5341021 (GBT440-032)**

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

www.clinicaltrials.gov	Use the study identifier **NCT04218084**
https://euclinicaltrials.eu	Use the study identifier **2017-000903-26**

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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