Clinical Study Results

A Study to Compare Sepiapterin and Sapropterin as Treatments for Phenylketonuria (PKU)

Experimental Drug Studied: Sepiapterin

Sponsor: PTC Therapeutics, Inc.

Thank you!

PTC Therapeutics, Inc., the sponsor of this clinical study, would like to thank the participants who helped make this research possible. Their commitment helped researchers learn more about a drug called sepiapterin as a treatment for PKU.

This is a summary of the study results. PTC created this summary to share these results with the participants, their families and caregivers, and the general public.

It is important to note that this is a summary of the overall study results. Individual participants might have had different results.

It is also important to note that these are results from a single study. Other studies might have different results. It typically takes results from more than 1 study to understand how a new drug works, how well it works, and how safe it is.

You can find more information about this study, including the full study title, at the end of this summary.

Topics

Why was the research needed?

Researchers are looking for better ways to treat **phenylketonuria**, also known as **PKU**. PKU is a rare inherited disorder that affects the brain. People with PKU have a genetic mutation that limits their ability to break down a substance called **phenylalanine**, or **Phe** for short. Phe is an amino acid (a protein "building block") found in foods that contain protein, such as meat, eggs, and nuts. When someone is unable to break down this amino acid, high levels of it can build up in the body. This can cause serious medical problems, including severe and permanent intellectual disability, seizures, delayed development, memory loss, and behavioral and emotional problems.

PKU is usually diagnosed soon after birth with a blood test. Infants with PKU typically start showing symptoms within a few months. If left untreated, these symptoms get worse with time. There is currently no cure for PKU. Treatment usually involves a low-protein diet as well as medicines that help lower Phe levels.

Sepiapterin was developed to help people with PKU break down Phe.

The main goal of this study was to learn whether sepiapterin helped lower Phe levels in people with PKU better than another PKU treatment called **sapropterin**.

Another main goal of the study was to learn about the safety of sepiapterin as a treatment for PKU. Learning about the safety of a drug means learning about possible health risks associated with taking it, including possible side effects.

When this study was being done, sepiapterin was an experimental treatment for PKU. "Experimental" means it had not yet been approved by a health authority such as the European Medicines Agency and Food and Drug Administration. Soon after this study ended, sepiapterin was approved as a treatment for high levels of Phe in patients with PKU in the European Union, the United States, Australia, and Switzerland.

Who took part in this study?

This study included 82 participants with PKU. There were 43 females and 39 males who were 2 to 66 years old when they joined the study. The average age of the participants was 15 years.

The participants were from these countries:

- Australia (21 participants)
- Canada (9 participants)
- Denmark (8 participants)
- Netherlands (5 participants)
- Italy (3 participants)
- Slovenia (2 participants)
- Poland (10 participants)
- Czech Republic (8 participants)
- United Kingdom (8 participants)
- Spain (3 participants)
- France (3 participants)
- Germany (2 participants)

Of these 82 participants, there were 38 who were taking sapropterin when they joined this study. These participants agreed to stop taking sapropterin 1 week before starting treatment in this study.

What treatments did the participants take?

This study was done in 2 parts.

In Part 1, participants were assigned to take sepiapterin.

In Part 2, the participants were assigned to take these treatments:

- Sepiapterin
- Sapropterin

The participants took both of these treatments in Part 2, but not at the same time. The next section has more information about how the participants took each of these treatments.

Sepiapterin is a powder that participants took once a day by mixing it into water, apple juice, or soft foods, such as apple sauce or strawberry jam. The amount (dose of the drug) that participants took depended on how much they weighed. Participants took 60 milligrams (mg) of sepiapterin every day for every kilogram (kg) of their body weight, so the daily dose was 60 mg/kg.

Sapropterin was taken by mouth once a day as tablets. The daily dose of sapropterin that was used in this study (20 mg/kg) is the highest dose that is recommended as a treatment for PKU.

What happened during the study?

In Part 1, all 82 participants were assigned to take sepiapterin every day for 2 weeks. Study doctors collected blood samples to measure Phe levels during treatment. If participants did not show at least a 20% drop in Phe levels, on average, during treatment, they could not move on to Part 2.

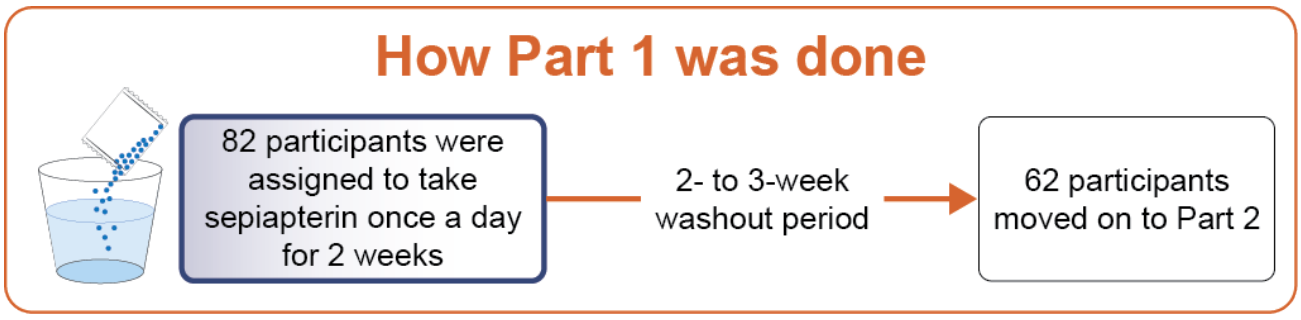
Of the 82 participants in Part 1, 67 (82%) had at least a 20% drop in Phe levels during treatment. Among these 67 participants, Phe levels dropped, on average, 59% during treatment with sepiapterin in Part 1 (compared with levels measured just before they started treatment in Part 1).

Among the 38 participants who had been taking sapropterin before they joined this study, Phe levels dropped, on average, 54% during treatment with sepiapterin in Part 1 (compared with levels measured just before they started treatment in Part 1, which was about 1 week after they had stopped their regular treatment with sapropterin).

Of the 67 participants who had at least a 20% drop in Phe levels in Part 1, 62 moved on to Part 2. These participants were asked to wait 2 to 3 weeks after they finished treatment in Part 1 before starting treatment in Part 2. This waiting period is called a **washout period**.

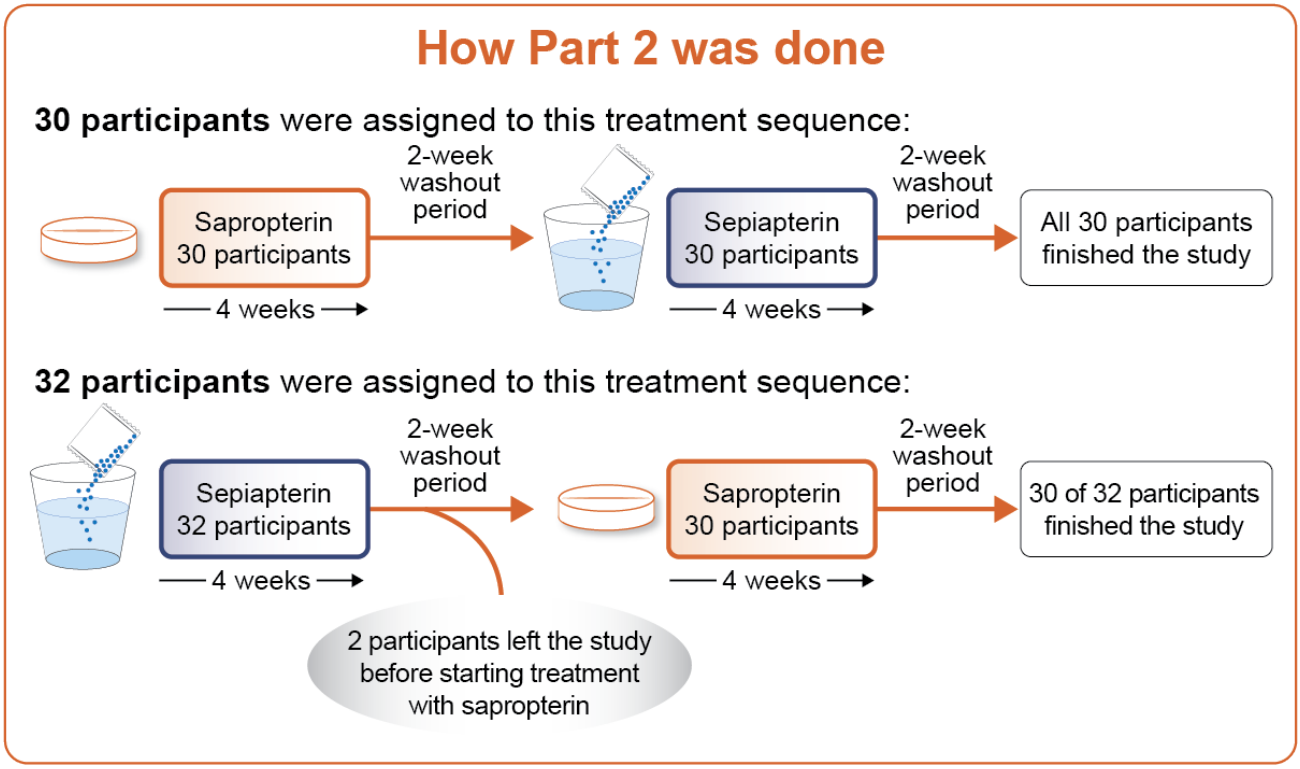
Washout periods are often used in clinical studies when more than 1 treatment is being tested. They help make sure that one medicine has fully "washed out" of a participant's system before they start the next one. In this case, the washout period helped make sure that treatment with sepiapterin in Part 1 would not affect any of the results measured in Part 2.

The figure below shows how Part 1 was done.



In Part 2, participants took 1 treatment (sepiapterin or sapropterin) every day for 4 weeks. Then they had a 2-week washout period before switching over to the other treatment for 4 weeks.

The order in which each participant received the 2 treatments was assigned randomly by a computer program. The figure below shows how Part 2 was done.



All 62 participants in Part 2 received 4 weeks of treatment with sepiapterin, either in the first or second treatment sequence.

Only 60 of 62 participants received 4 weeks of treatment with sapropterin because 2 participants left the study early.

During the study, the participants:

- Followed their usual diet, making sure not to change how much protein they ate,
- Kept a log of their diet so that a dietician could review it and help monitor how much protein they were eating,
- Gave blood and urine samples,
- Had their heart health checked with a machine called an **electrocardiogram**, and
- Told study doctors and other members of the study team about how they were feeling, what other medications they were taking, and if they were having any new or worsening medical problems.

Participants who completed both Part 1 and Part 2 were in the study for up to about 5.5 months. The study started in April 2024 and ended in March 2025.

What were the results of the study?

This section summarizes the overall study results. Individual participants might have had different results.

This section only summarizes the results of the main research question asked in this study. There were other research questions. You can find more information about the other results of this study on the website listed at the end of this summary.

Did sepiapterin lower Phe levels more than sapropterin in Part 2?

Yes.

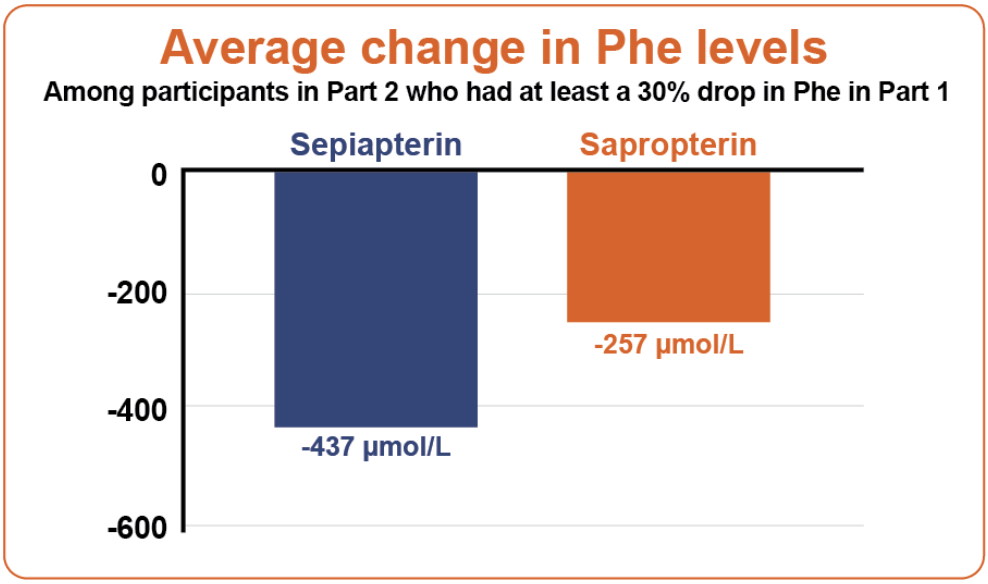
Researchers looked at the participants' Phe levels right before they started a 4-week treatment period. Then they looked at how Phe levels changed, on average, from before treatment to the last 2 weeks of the treatment period.

They compared the results seen with sepiapterin to the results seen with sapropterin.

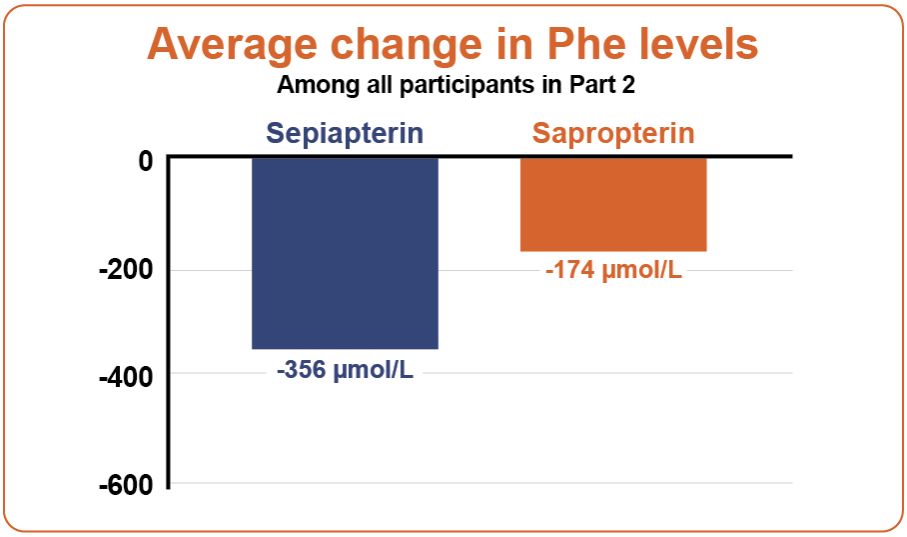
To measure participants' Phe levels during the study, the study team collected small samples of blood. Using these samples, researchers could learn how much Phe was in the participant's blood when each blood sample was drawn. The results were recorded as the amount of Phe (measured with a unit called a micromole, or µmol for short) that would be in a liter (L) of blood, or **µmol/L** for short.

The main analysis of the study focused on participants in Part 2 who had at least a 30% drop in Phe levels during Part 1. There were 58 participants who contributed to these results.

The figure below shows how Phe levels changed, on average, for these participants with each treatment.



A second analysis was done to look at the results for all 62 participants in Part 2. As with the first analysis, Phe levels dropped more with sepiapterin than with sapropterin. The figure below shows how Phe levels changed, on average, with each treatment.



What possible side effects did the participants have during the study?

During the study, doctors kept track of any new or worsening medical problems that the participants had. In particular, they looked at any new or worsening medical problems the participants had that the study doctors thought might be related to the treatment the participant was taking in the study. These medical problems are called **adverse reactions**.

Think of an adverse reaction as a possible side effect of an experimental drug. Adverse reactions may or may not be true side effects. Usually, multiple studies are needed to fully understand a drug's side effects.

Some adverse reactions are considered "serious". Examples of serious adverse reactions are those that are life-threatening, have long-term complications, or need hospital care for treatment.

Did the participants have any serious adverse reactions?

None of the participants in this study had a serious adverse reaction.

Did the participants have any non-serious adverse reactions? If so, what were they?

In Part 1, 17 of 82 participants (21%) had at least 1 non-serious adverse reaction. The table below shows the most common adverse reactions in Part 1. There were other adverse reactions in Part 1, but they happened to fewer participants.

These were the adverse reactions that affected more than 2 participants in Part 1

	Out of 82 participants who took sepiapterin
Diarrhea	5 participants (6%)
Abdominal (belly) pain	3 participants (4%)
Headache	3 participants (4%)

In Part 2:

- Of the 62 participants who took sepiapterin in Part 2, 9 (15%) had at least 1 adverse reaction that study doctors thought might be related to sepiapterin.
- Of the 60 participants who took sapropterin in Part 2, 4 (7%) had at least 1 adverse reaction that study doctors thought might be related to sapropterin.

The table below shows the most common adverse reactions with each treatment in Part 2. There were other adverse reactions in Part 2, but they happened to fewer participants.

These were the adverse reactions that affected more than 2 participants in Part 2

	Sepiapterin Out of 62 participants	**Sapropterin Out of 60 participants**
Diarrhea	5 participants (8%)	0 participants
Nausea	3 participants (5%)	1 participant (2%)

None of the participants stopped treatment in this study because of an adverse reaction.

How has this study helped?

The results of this study helped researchers learn more about sepiapterin as a treatment for PKU.

This summary only shows the main results from a single study. Other studies might have different results. Researchers and health authorities typically look at the results of multiple studies to decide how a drug works, how well it works, and how safe it might be for patients.

Additional clinical studies with sepiapterin are ongoing.

Where can I learn more about this study?

You can find more information about this study on the website listed below.

https://ema.europa.eu

Type **2023-506238-61-00** into one of the search boxes, scroll down, and click "Search".

Full title of the study: A Phase 3, Randomized, Crossover, Open-Label, Active-Controlled Study of Sepiapterin Versus Sapropterin in Participants With Phenylketonuria ≥2 Years of Age

Protocol number: PTC923-PKU-301

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Thank you!

PTC Therapeutics would like to thank the participants and their families for their time and their commitment to clinical research. Clinical study participants help researchers and health authorities find answers to important health questions and discover new treatments.