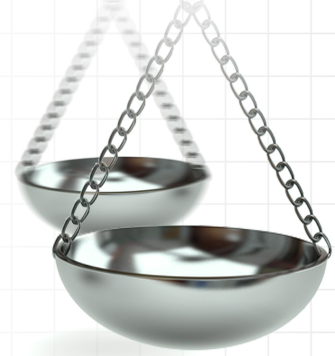
Plain Language Summary of Publication

Sepiapterin as a treatment for people living with phenylketonuria: a plain language summary of the APHENITY trial



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Summary

What is this summary about?
This plain language summary is based on an article about the APHENITY trial that was published in *The Lancet* journal in October 2024. The APHENITY trial was a phase 3 clinical trial to find out whether sepiapterin helped people living with phenylketonuria (PKU) and to learn more about its safety. PKU is a rare, genetic condition that causes high levels of phenylalanine (Phe) to build up in the body. High levels of Phe in the body can cause symptoms such as seizures, rashes, and problems with movement, and can also affect brain development, thinking skills, and behaviour. These symptoms can have an impact on people's health-related quality of life.

What happened in the APHENITY trial?
Previous studies have shown that sepiapterin is able to decrease Phe levels in the blood. In the APHENITY trial, the researchers wanted to learn more about the efficacy and safety of sepiapterin in a large group of people living with PKU over the course of 8 weeks of treatment. The researchers wanted to:

- Assess the efficacy of sepiapterin by seeing whether sepiapterin decreased Phe levels in the blood compared with a placebo
- Assess the safety of sepiapterin by seeing how many health complaints the participants who took sepiapterin had compared with those who took the placebo

The APHENITY trial was carried out in two parts:

- During Part 1, the participants took sepiapterin for 2 weeks to find out if it decreased their Phe levels
- During Part 2, the participants who benefitted from sepiapterin during Part 1 were randomly assigned to either continue taking sepiapterin or start taking a placebo for a further 6 weeks

What were the results?
During Part 1, the researchers found that 114 out of 156 participants benefitted from sepiapterin. This was 73% or about 7 in 10 participants.

During Part 2, the researchers found that the participants who took sepiapterin had reduced blood Phe levels compared with those who took the placebo. The researchers also found that compared with those who took the placebo, more of the participants who took sepiapterin reduced their blood Phe levels to within the ranges recommended by treatment guidelines.

For both parts of the trial, the participants did not have any serious health complaints. So, the researchers concluded that no safety concerns were seen with sepiapterin in this trial.

What do the results of the trial mean?
These results showed that sepiapterin helped to reduce blood Phe levels in the participants, and there were no unexpected safety concerns in people living with PKU.

Becaris PUBLISHING

Who sponsored this trial?

This trial was **sponsored** by PTC Therapeutics.

Sponsor: the organization or individual who is responsible for starting, managing, financing, and overseeing a clinical trial.

Where can readers find more information?

The original article discussed in this summary was published in the journal *The Lancet* and is called "Effects of oral sepiapterin on blood Phe concentration in a broad range of patients with phenylketonuria (APHENITY): results of an international, phase 3, randomised, double-blind, placebo-controlled trial". You can read the original article here: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(24)01556-3/abstract.

How to say (double click on the sound icon to play the sound)

APHENITY: uh-FEN-uh-tee
Pegvaliase: pehg-VAL-ee-ays
Phenylalanine hydroxylase: fee-nile-AL-uh-neen high-DROK-suh-lays
Phenylketonuria: fee-nile-kee-toh-NYOO-ree-uh
Placebo: pluh-SEE-boh
Sapropterin dihydrochloride: sahp-pro-tare-rin dai-hai-druh-klaw-ride
Sepiapterin: see-pee-ah-tare-rin
Tetrahydrobiopterin: tet-ruh-HY-droh-BY-op-ter-in
Tyrosine: TAI-roh-seen

Who is this article for?

This summary may be helpful for people living with PKU, the caregivers and families of people living with PKU, and non-specialist audiences.

What is phenylketonuria?

Phenylketonuria (PKU) is a rare genetic condition that causes high levels of **phenylalanine (Phe)** to build up in the body. If people living with PKU are not treated, high levels of Phe in the body can affect brain development, thinking skills, and behaviour and may cause symptoms such as seizures, rashes, and problems with movement.

PKU is an inherited condition and is caused by changes in a **gene** that is passed down from both parents. A change in a gene is called a **variant**. People living with PKU have variants in the gene that make a protein called **phenylalanine hydroxylase (PAH)**. PAH is an **enzyme** that breaks down Phe in the body.

Phe is an **amino acid**, which are the building blocks that make up **proteins**. There are many different amino acids that can be joined together to make a protein. Amino acids can be found in lots of foods such as milk, eggs, cereals, vegetables, and meat. Phe is an **essential amino acid**, which means that it cannot be made by the body and must instead come from eating certain foods.

Phe is broken down by PAH in the body to make another amino acid called **tyrosine (Tyr)**. The PAH enzyme does not work properly in people living with PKU. As a result, people living with PKU have high levels of Phe and low levels of Tyr.

There are a few different types of PKU. The most severe form of PKU is called **classic PKU**. People living with classic PKU have PAH that works very poorly or PAH that does not work at all. So, people living with classic PKU have very high levels of Phe. People living with less severe forms of PKU have PAH that works a little, but not completely. These patients still have higher than normal blood Phe levels, but not as high as those with classic PKU.

Phenylketonuria (PKU): A rare, genetic condition that causes high levels of phenylalanine to build up in the body. High levels of phenylalanine in the body can cause seizures, rashes, and problems with movement, and can affect brain development, thinking skills, and behaviour.

Phenylalanine (Phe): An essential amino acid that the body needs to make proteins and other important molecules. Phenylalanine levels are high in people living with phenylketonuria and this can be harmful.

Genes: Parts of DNA that contain instructions for making proteins. Genes are passed down from parents to their children and they affect how the body works.

Variants: Changes in genes that can cause disease. They are also sometimes called mutations.

Phenylalanine hydroxylase (PAH): An enzyme that breaks down phenylalanine into another amino acid called tyrosine.

Enzymes: Proteins that speed up chemical reactions in the body.

Amino acids: The building blocks of proteins.

Proteins: Large, biological molecules with many important roles in the body. Proteins are essential for the structure, function, and regulation of tissues and organs throughout the body.

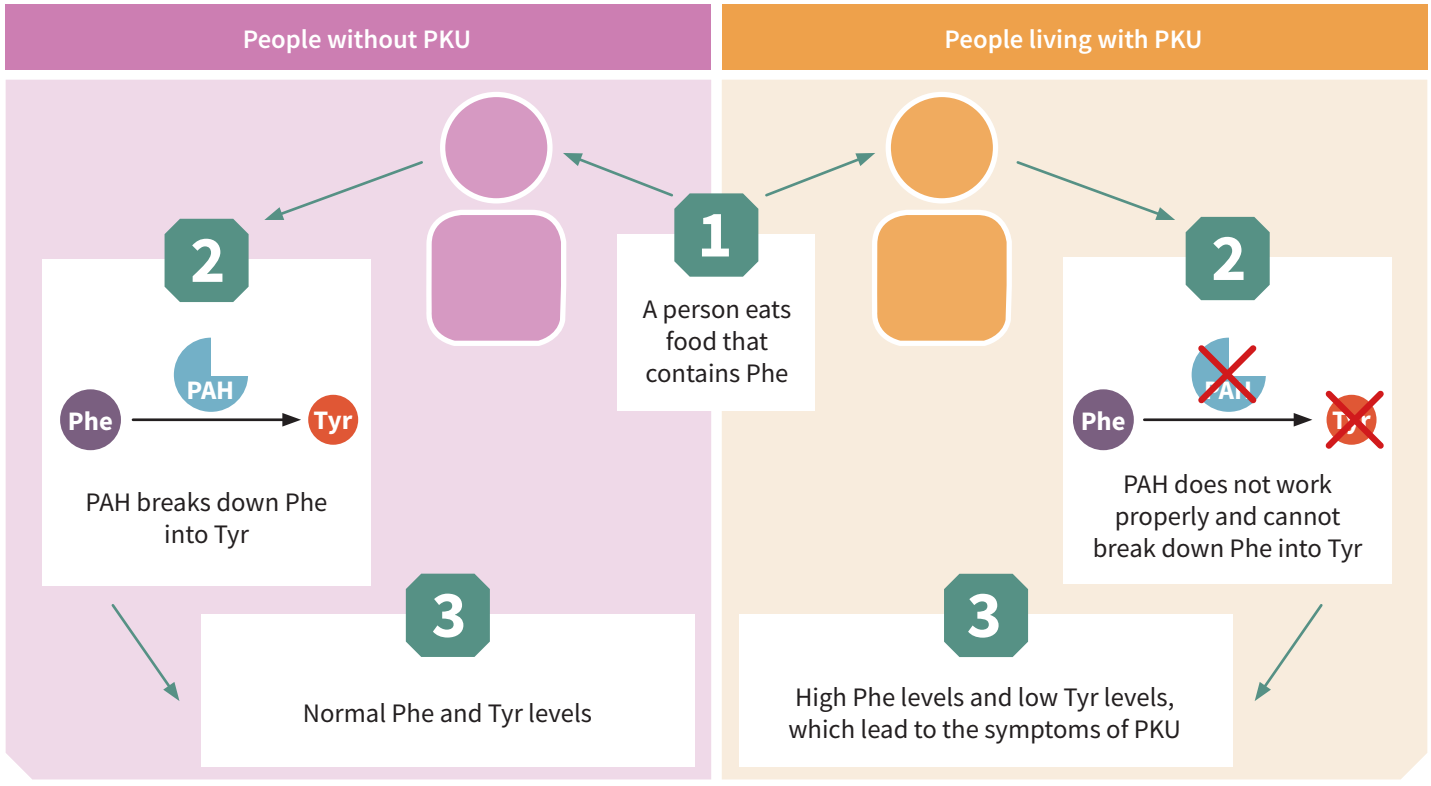
Essential amino acids: Amino acids that the body cannot make itself and must instead come from eating certain foods.

Tyrosine (Tyr): An amino acid that is made by breaking down phenylalanine.

Classic phenylketonuria: The most severe type of phenylketonuria where people have phenylalanine hydroxylase that works very poorly or not at all. People living with classic phenylketonuria have very high levels of phenylalanine.

Health-related quality of life: Refers to how any health issues that a person has can affect their daily life and activities.

What happens to Phe in the body?



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Treatment and management of PKU

Current treatment options

There is currently no cure for PKU. **Sepiapterin** was approved in several places including Australia, the EU, and the USA in 2025, as a treatment to help people living with PKU to control their Phe levels.

There are other treatments available, called **sapropterin dihydrochloride** and **pegvaliase**, but these treatments only benefit some people living with PKU because they:

- Are only approved for people of certain ages, and/or
- Have limited response rates, meaning that many people do not benefit from treatment, and/or
- Have side effects (including serious side effects such as allergic reactions in some people who take pegvaliase)

Sepiapterin: An approved treatment for people living with phenylketonuria of all ages (or from 1 month of age, depending on the country), that helps to control blood phenylalanine levels.

Sapropterin dihydrochloride: An approved treatment for people living with phenylketonuria of all ages.

Pegvaliase: An approved treatment for people living with phenylketonuria aged 15 years or older, depending on the country.

Dietary management of PKU

People living with PKU must eat a restrictive, very low-protein diet. This means avoiding or eating less of certain foods containing natural protein, such as milk, eggs, cereals, and meat.

People living with PKU often need to eat and drink specially made medical food and drinks that do not contain Phe but still provide vitamins, minerals, and other amino acids that may be missing from their diet. But a low protein diet can be difficult to follow over long periods of time and can impact the quality of life of people living with PKU.

So, there is a need for new and different ways to help to control high Phe levels and treat people living with PKU.

What is sepiapterin?

Sepiapterin is an oral drug that helps to control blood Phe levels and treat people living with PKU.

How does sepiapterin work?

Sepiapterin works by helping the PAH enzyme to break down Phe in the body, which helps to decrease Phe levels in the blood. Sepiapterin works in two ways to help the PAH enzyme to break down Phe in the body more efficiently:

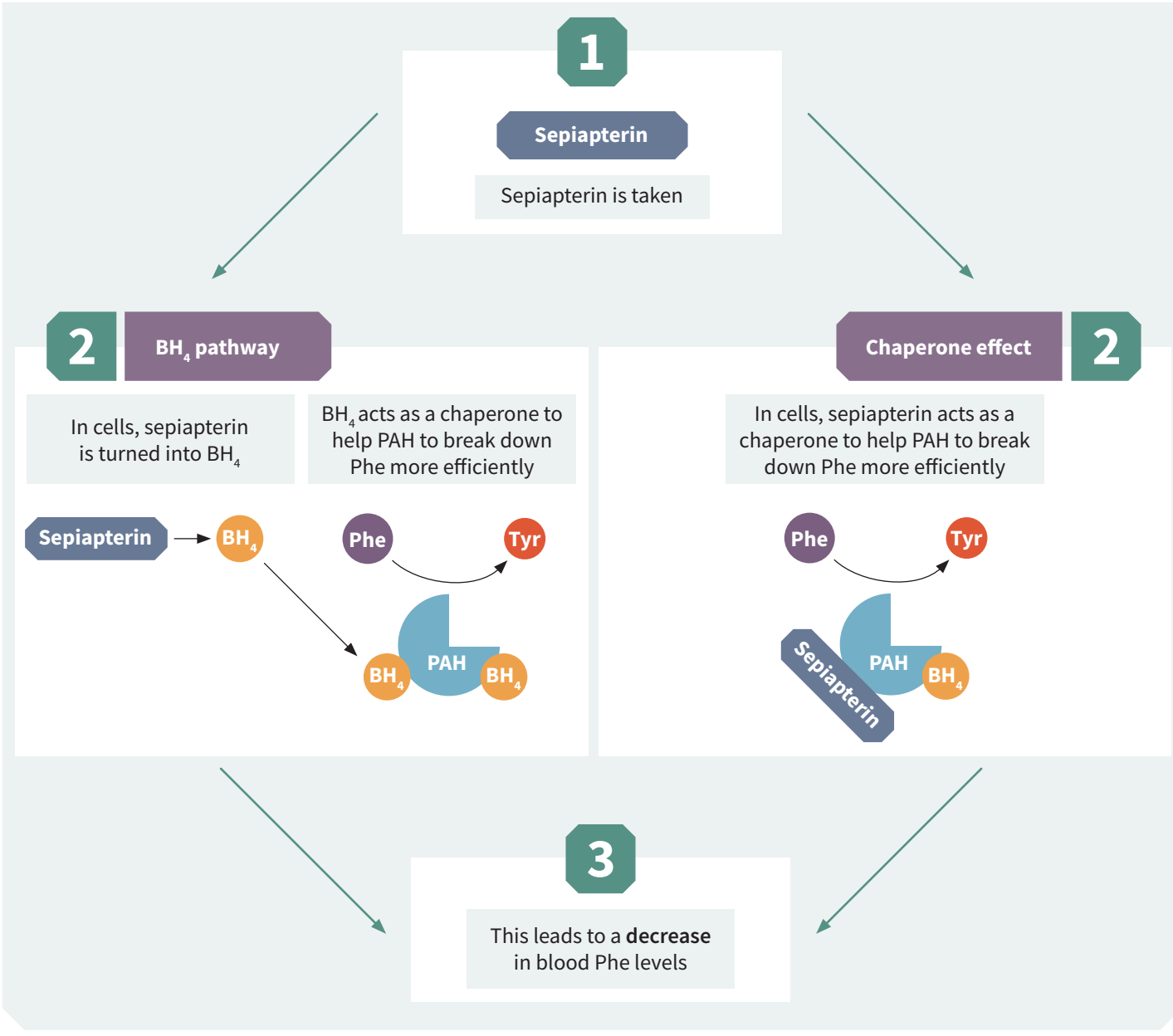
1. Sepiapterin can turn into a substance called **tetrahydrobiopterin (BH_4)** soon after it is taken. BH_4 acts as a **chaperone**, which means it helps PAH to fold into the correct shape to break down Phe in the body
2. Sepiapterin can also work directly with PAH without being turned into BH_4. This is because sepiapterin can act directly as a chaperone to PAH

Sepiapterin helps people living with PKU to control their blood Phe levels and could help to reduce the symptoms of PKU. Researchers also hope that it may allow people living with PKU to eat more protein.

Tetrahydrobiopterin (BH_4): A substance in the body that helps certain enzymes, such as phenylalanine hydroxylase, to work properly.

Chaperones: Biological substances that help proteins to fold into the correct shapes so that they can work properly.

How does sepiapterin work?



How is sepiapterin taken?

Sepiapterin is a powdered drug that is taken once a day by mouth. The powder is mixed with water, apple juice, or soft foods like apple sauce or strawberry jam. The amount of sepiapterin that is taken is based on the person's weight.

Author's note: The **"What is phenylketonuria?"** and **"What is sepiapterin?"** sections of this summary provide information on PKU and sepiapterin as context for the results of the **APHENITY** trial. The sources for this information are listed in the "Further reading" section of this summary.

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APHENITY: The name of the phase 3 clinical trial of sepiapterin for people living with phenylketonuria.

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The APHENITY trial

Why was the APHENITY trial carried out?

In the APHENITY trial, the researchers wanted to learn more about how well sepiapterin works and about its **safety** in a large group of people living with PKU of all ages.

In an earlier trial, researchers found that treatment with sepiapterin decreased blood Phe levels in people living with PKU.

Who took part in the APHENITY trial?

People of any age with PKU were able to join this trial if they:

- Had high blood Phe levels at the beginning of the trial
- Had no other medical conditions that may affect how well sepiapterin works
- Did not take certain other medications during the trial
- Were willing to stop using other medications for PKU called sapropterin dihydrochloride and pegvaliase

The participants stopped taking other medications for PKU before starting treatment with sepiapterin. This was done to make sure that those medications were cleared from their bodies and would not affect the results of the trial.

All of the participants, or their caregivers, provided written agreement to take part in the trial before it started. This is called **informed consent**.

Some of the key information about the participants at the beginning of the trial is shown in the figure below. Blood Phe levels are measured in **micromoles per litre** (µmol/l) of blood or **milligrams per decilitre** (mg/dl) of blood.

Safety: How safe a drug is in terms of adverse events or adverse reactions.

Informed consent: The consent voluntarily given by a study participant or caregiver to take part in a study after being fully informed about the study's details, risks, and benefits.

Micromoles per litre (µmol/l): A way of measuring the amount of a substance.

Milligrams per decilitre (mg/dl): A way of measuring the amount of a substance.

Key information about the APHENITY trial participants

Average age:
17.7 years

Average blood Phe level:
712.2 µmol/l

Recommended blood Phe levels:

US guidelines:
360 µmol/l or below

European guidelines:
For children up to 12 years old and pregnant women: 120–360 µmol/l

For children over 12 years old and adults: 120–600 µmol/l

36 out of 157 participants had **classic PKU**

This was 23% or about 2 in 10 participants

56 out of 157 participants had **previously not responded to treatment with sapropterin dihydrochloride**

This was 36% or nearly 4 in 10 participants

How was this trial carried out?

The APHENITY trial was a **phase 3 clinical trial** that was carried out between September 2021 and April 2023.

In phase 3 clinical trials, researchers try to learn more about how well a treatment works, usually compared with a **placebo**, and about its safety in a large group of participants.

The participants stayed on their usual diet during the trial.

Clinical trial: A research study that tests a treatment to check whether there are any safety concerns and how well it works in people.

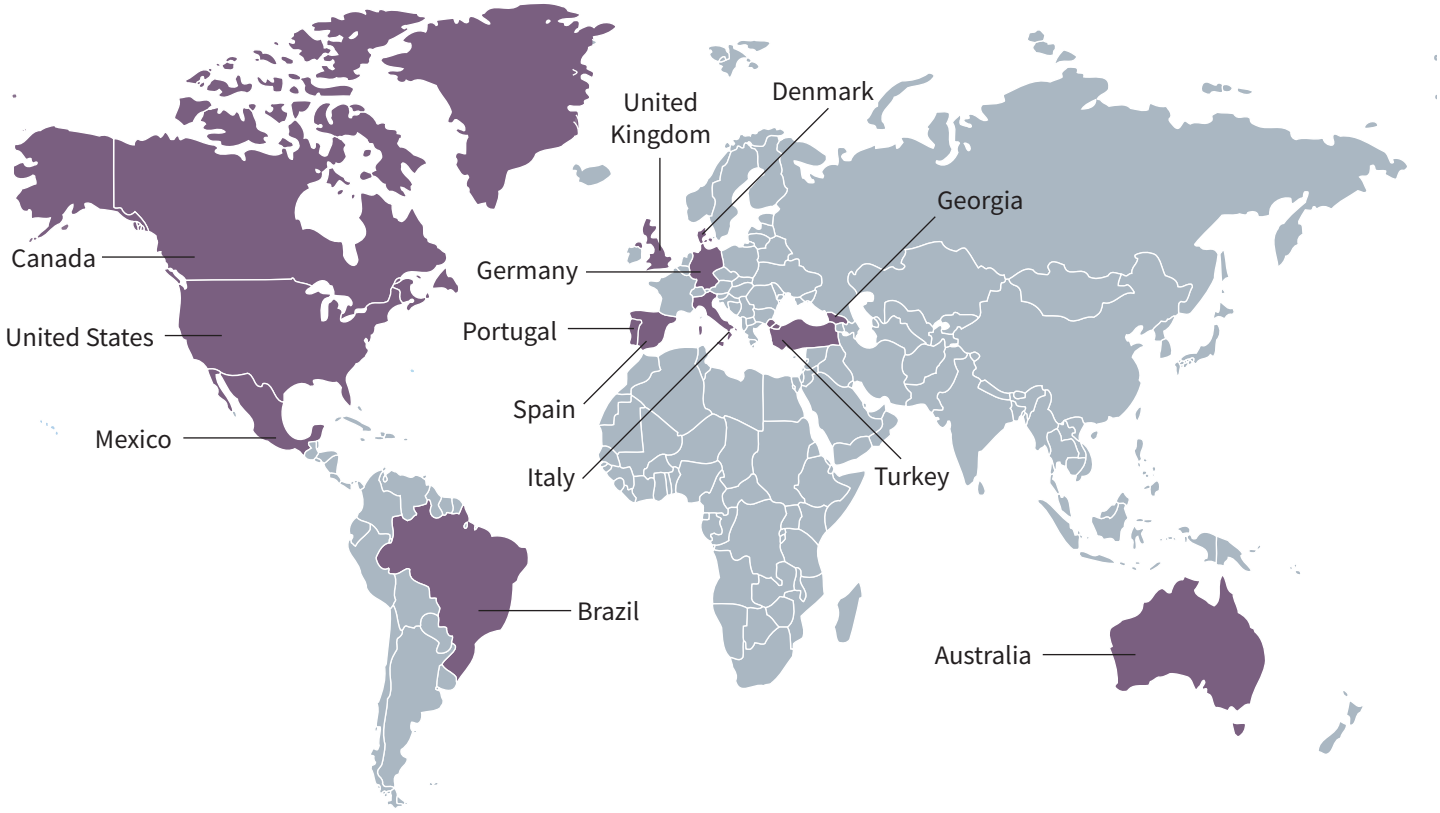
Phase: The stage of a clinical trial for a new treatment. It ranges from phases 0 and 1 (earlier, smaller trials) to phases 3 and 4 (later, larger trials).

Phase 3 clinical trial: A large clinical trial that compares a new treatment with either a placebo or current, standard treatments.

Placebo: A substance that looks like a medicine but has no medicine in it. Researchers use placebos in clinical trials to check how safe a new treatment is and how well it works compared with the placebo.

The APHENITY trial was carried out in two parts.

The trial was carried out at 34 sites across 13 countries



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Part 1

What was the purpose of Part 1 of the trial?

In Part 1 of the APHENITY trial, the researchers wanted to identify which participants benefitted from sepiapterin. A participant was considered to have benefitted from sepiapterin if their blood Phe levels decreased by at least 15% after taking sepiapterin for 2 weeks when compared with their blood Phe levels at the beginning of the trial. These participants were considered responders. The researchers also wanted to learn more about the safety of sepiapterin.

What did the participants take during Part 1 of the trial?

During Part 1, all of the participants took sepiapterin once a day for 2 weeks. They took it by mouth as a powder mixed into water, apple juice, or soft foods like apple sauce or strawberry jam.

Part 1 of the trial was **open-label**. This meant that the participants, researchers, trial doctors, and other trial staff knew that the participants were taking sepiapterin.

Open-label trial: A way of carrying out a clinical trial where the participants, researchers, trial doctors, and other trial staff know what treatment the participants are taking.

Dried blood samples: Small drops of blood that are collected from participants and dried, which can then be used for various tests and research purposes.

What was carried out during Part 1 of the trial?

To check whether a participant benefitted from sepiapterin, the researchers collected **dried blood samples** from the participants throughout Part 1 of the trial. The researchers then measured the levels of Phe in these samples.

Overall, **157** participants took part in Part 1 of this trial. One participant left the trial before the researchers could test their response to sepiapterin. So, the results in the section below include only **156** participants.

What were the results of Part 1 of the trial?

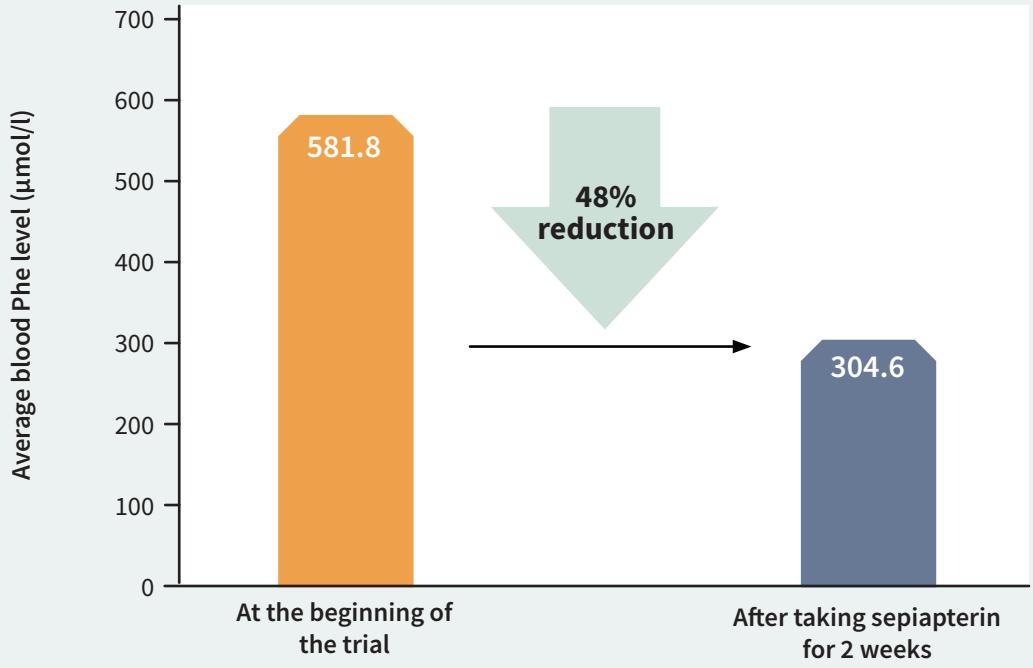
During Part 1, the researchers found that sepiapterin reduced blood Phe levels by at least 15% after 2 weeks in 114 out of 156 participants.

This means that **73%** of participants, or about **7 in 10** participants, benefitted from sepiapterin during Part 1.

The researchers also wanted to see if taking sepiapterin reduced blood Phe levels in participants who had been taking a medication for PKU called sapropterin dihydrochloride at the beginning of the trial.

In the 27 participants who were taking sapropterin dihydrochloride at the beginning of the trial, the **average blood Phe levels decreased by an additional 48%** after taking sepiapterin for 2 weeks from when they were taking sapropterin dihydrochloride.

Change in average blood Phe levels in the participants who had been taking sapropterin dihydrochloride at the beginning of the trial



The participants who benefitted from sepiapterin in Part 1 and were at least 2 years old could join Part 2 of this trial. The participants who were younger than 2 years old could join a different trial.

In total, **110 out of the 157** participants who started the trial joined Part 2.

Before starting Part 2, the participants did not take any treatment for at least 2 weeks. This was done to make sure that the sepiapterin taken during Part 1 had been cleared from their bodies and would not affect the results of Part 2.

Part 2

What was the purpose of Part 2 of the trial?

In Part 2 of the APHENITY trial, the researchers wanted to learn more about the effects of sepiapterin on the participants' blood Phe levels. They also wanted to learn more about the safety of sepiapterin.

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What did the participants take during Part 2 of the trial?

During Part 2, the participants either continued taking sepiapterin or started taking a placebo. They took these treatments every day by mouth for 6 weeks.

Each participant's treatment was chosen at random by a computer. About half of the participants took sepiapterin and the other half took the placebo.

Double-blind trial: A way of carrying out a clinical trial where none of the participants, researchers, trial doctors, or other trial staff know which treatment each participant is taking.

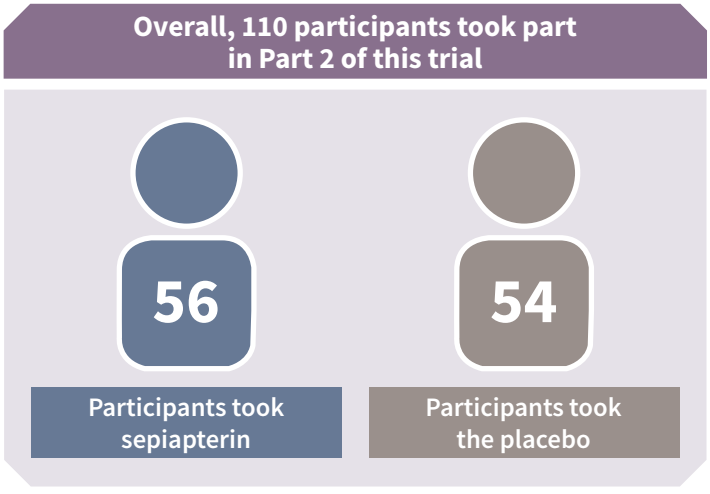
Part 2 of this trial was **double-blind**. This meant that none of the participants, researchers, trial doctors, or other trial staff knew which treatment each participant was taking. Some trials are carried out this way because knowing which treatment each participant is taking can affect the results of the trial.

All of the participants taking sepiapterin took the same dose. This dose was increased every 2 weeks until the trial finished to see which dose of sepiapterin was the best at lowering blood Phe levels while not causing any safety concerns.

What was carried out during Part 2 of the trial?

To measure the effect of sepiapterin on the participants' blood Phe levels, the researchers collected dried blood samples from the participants throughout Part 2 of the trial. The researchers then measured the levels of Phe in these samples.

The researchers calculated the average change in blood Phe levels after taking sepiapterin or placebo for 6 weeks when compared with the start of Part 2 of the trial.



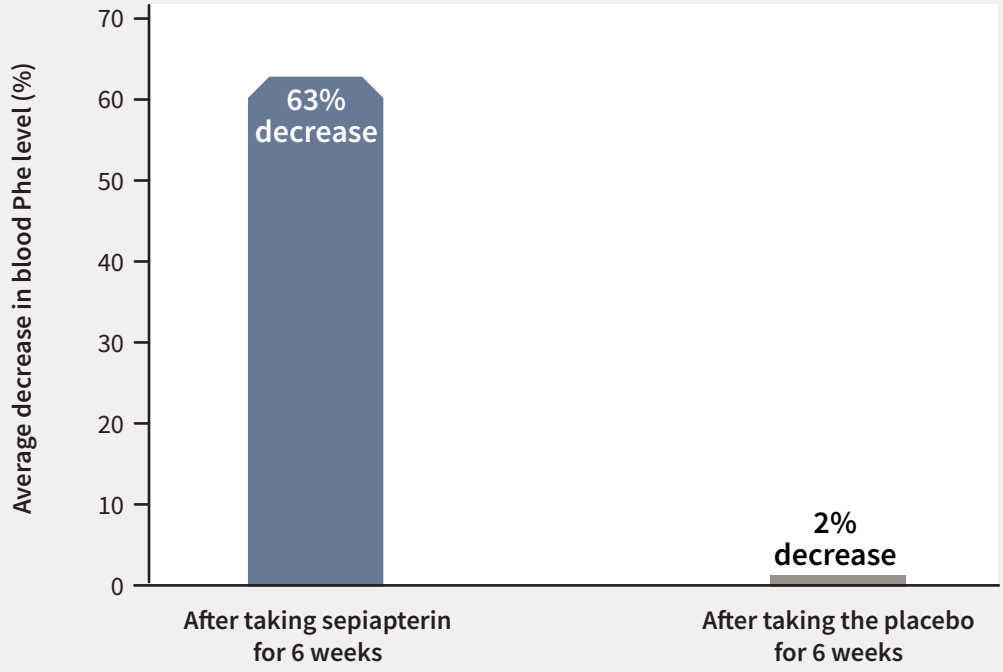
To be included in the results for measuring the effect of sepiapterin on blood Phe levels during Part 2, the participants needed to have had at least a **30% decrease** in their blood Phe levels during Part 1 of the trial.

- In the sepiapterin group, 1 participant left the trial before the researchers could collect enough blood samples, and 6 participants did not have at least a 30% decrease in blood Phe levels during Part 1. So, the results in the section below for this group include only **49** participants.
- In the placebo group, 5 participants did not have at least a 30% decrease in blood Phe levels during Part 1. So, the results in the section below for this group include only **49** participants.

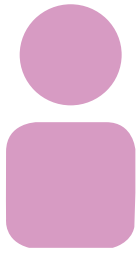
What were the results of Part 2 of the trial?

Overall, the researchers found that there was a greater decrease in blood Phe levels in the participants who took sepiapterin (−410.1 µmol/l) than in those who took the placebo (−16.2 µmol/l) after 6 weeks of treatment from the beginning of Part 2.

Average decrease in blood Phe levels in participants who took either sepiapterin or the placebo for 6 weeks from the beginning of Part 2



The researchers also looked at how much blood Phe levels decreased in three specific groups of participants. These groups were as follows:



Participants with classic PKU: The researchers looked at this group to see whether sepiapterin worked in people living with the most severe form of PKU and the highest levels of Phe in the blood.

Participants who did not benefit from sapropterin dihydrochloride before the trial: The researchers looked at this group to see whether sepiapterin worked in people who had not benefitted from other treatments for their PKU in the past.

Participants who were taking sapropterin dihydrochloride at the start of the trial: The researchers looked at this group to see whether sepiapterin worked even in people who were taking a PKU treatment at the beginning of the trial.

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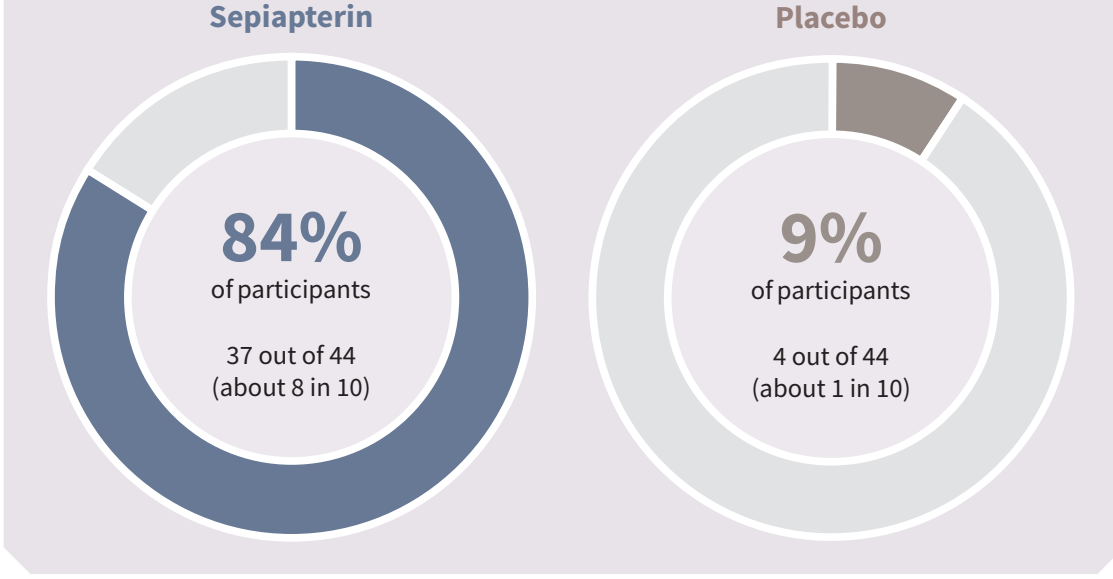
In all of the three groups, the participants who took sepiapterin had a greater decrease in blood Phe levels than those who took the placebo.

The researchers also looked at how many of the participants who had high blood Phe levels (above 360 µmol/l or 6 mg/dl) at the beginning of Part 2 of the trial met the recommended blood Phe levels in US treatment guidelines (below 360 µmol/l or 6 mg/dl) after taking sepiapterin or the placebo for 6 weeks.

The researchers found that more participants in the sepiapterin group achieved blood Phe levels below 360 µmol/l or 6 mg/dl after 6 weeks of treatment compared with the participants in the placebo group.

The number of participants who achieved blood Phe levels below 360 µmol/l (6 mg/dl) in Part 2 of the trial



What did the researchers learn about the safety of sepiapterin?

In both Part 1 and Part 2 of the APHENITY trial, the researchers also looked at the safety of sepiapterin.

The researchers kept track of all the health complaints that the participants had during the trial. Any health complaints that occur during clinical trials are called **adverse events**. Adverse events may or may not be caused by the treatments being investigated in the trials.

Adverse event: Any health complaint that occurs during a clinical trial regardless of whether it is related to a trial treatment or not.

An adverse event is considered serious when it is life-threatening, causes lasting problems, or requires hospital care.

Part 1

Participants during Part 1 of this trial were treated with open-label sepiapterin for 2 weeks.

Adverse reaction: Any health complaint that occurs during a clinical trial that the trial doctors have reported as possibly being related to a trial treatment.

During Part 1, 28 out of 157 participants had at least 1 adverse event that the trial doctors thought was related to sepiapterin. This was 18% or about 2 in 10 participants. An adverse event that is thought to be related to the trial treatment is called an **adverse reaction**.

The most common adverse reaction during Part 1 was diarrhoea. This adverse event was experienced by 6 out of 157 participants. This was 4% or about 4 in 100 participants.

The table below shows the number of participants who had different types of adverse events during Part 1.

	Sepiapterin (out of 157 participants)
How many participants had an adverse event?	68 participants (43% or about 4 in 10)
How many participants had an adverse event that was thought to be related to sepiapterin (adverse reaction)?	28 participants (18% or about 2 in 10)
How many participants had a serious adverse event?	None
How many participants stopped taking sepiapterin because of an adverse event?	1 participant (fewer than 1% or fewer than 1 in 100)
How many participants left the trial because of an adverse event?	2 participants (1% or about 1 in 100)

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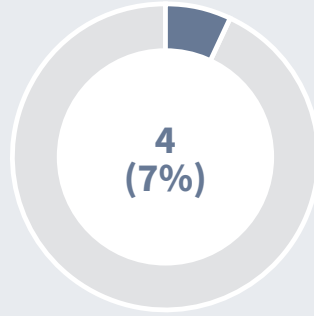
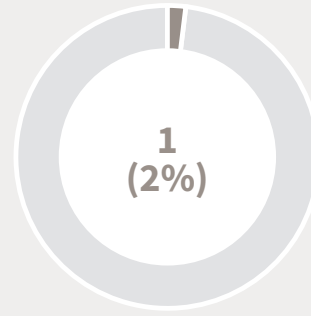
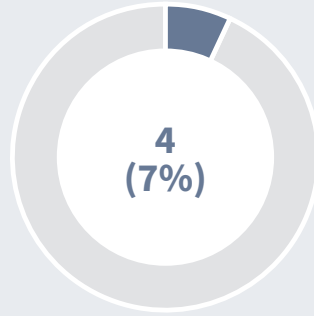
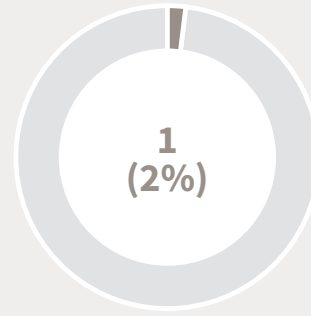
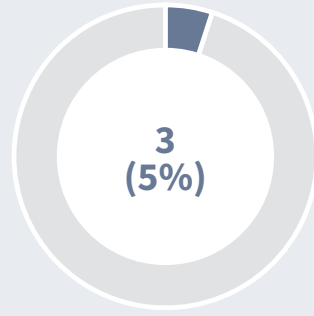
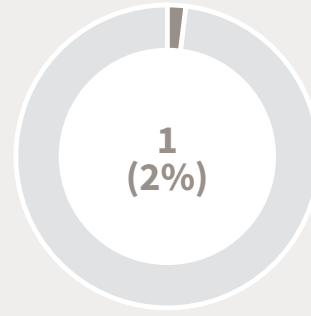
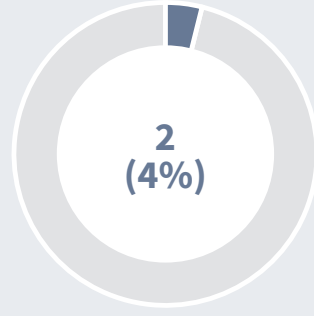
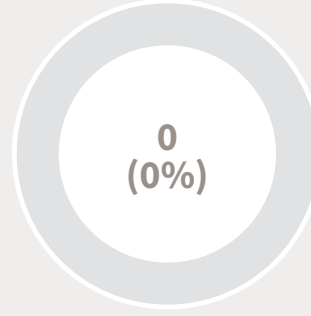
Part 2

Participants during Part 2 of this trial were treated with double-blind sepiapterin or a placebo for 6 weeks.

The most common adverse events during Part 2 were diarrhoea and headache. The most common adverse events during Part 2 are shown in the table below:

Most common adverse events	Sepiapterin (out of 56 participants)	Placebo (out of 54 participants)
Diarrhoea		
Headache		
Infection in the nose, sinuses, throat, or voice box		
Poo that looks a different colour than usual		

During Part 2, 33 out of the 56 participants who took sepiapterin had at least 1 adverse event. This was 59% or about 6 in 10 participants.

For the participants who took the placebo, 18 out of 54 participants had at least 1 adverse event. This was 33% or about 3 in 10 participants.

The table below shows the number of participants who had different types of adverse events during Part 2.

	Sepiapterin (out of 56 participants)	**Placebo** (out of 54 participants)
How many participants had an adverse event?	33 participants (59% or about 6 in 10)	18 participants (33% or about 3 in 10)
How many participants had a serious adverse event?	None	None
How many participants stopped taking the trial treatment because of an adverse event?	None	None
How many participants left the trial because of an adverse event?	None	None

What do the results of this trial mean?

Participants who took **sepiapterin** had a greater reduction in blood Phe levels than those who took the placebo

There were **no safety concerns** seen with sepiapterin in participants living with PKU in this trial

Efficacy: How well a drug is able to do its intended and expected function. For instance, for sepiapterin, this would be how well sepiapterin is able to reduce phenylalanine levels in the blood.

The APHENITY trial showed that sepiapterin helped to lower blood Phe levels and there were no safety concerns seen, even for participants with classic PKU and for those who had not benefitted from other medications for PKU.

Longer trials are needed to learn more about the long-term **efficacy** and safety of sepiapterin. A longer trial is currently looking at whether sepiapterin will allow people living with PKU to eat a wider variety of foods that include more natural protein.

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What does this trial mean for people living with PKU and caregivers?

This section has been answered by the caregiver author.

Better Phe control

People living with PKU who have not been able to reduce their blood Phe levels before may be able to do so with sepiapterin. Achieving blood Phe levels that fall within normal ranges has been shown to improve the quality of life of people living with PKU by reducing or preventing the problems associated with increased blood Phe levels, such as brain development, thinking skills, and behaviour.

Less restrictive diets

People living with PKU and their caregivers may benefit from sepiapterin as an oral treatment option that could reduce the burden associated with the restrictive medical diets that are currently used in the treatment of PKU.

Improved quality of life

An alternative to restrictive, low-Phe diets could improve the quality of life for both people living with PKU and their caregivers by allowing them to participate more fully in social, educational, and family activities. This could improve their mental health and reduce feelings of isolation and frustration.

Improved emotional health

Sepiapterin may help people living with PKU and their caregivers to experience better emotional health and increased self-esteem, both through the reduction of blood Phe levels and through a reduction in the emotional load associated with the management of PKU.

More treatment options

For some people living with PKU, especially younger people who do not benefit from sapropterin dihydrochloride, sepiapterin may be the only current alternative to restrictive medical diets.

Where can readers find more information on this trial?

- The original article discussed in this summary was published in the journal *The Lancet* and is called "Effects of oral sepiapterin on blood Phe concentration in a broad range of patients with phenylketonuria (APHENITY): results of an international, phase 3, randomised, double-blind, placebo-controlled trial". You can read the original article here: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(24)01556-3/abstract
- You can read more about this trial here: https://clinicaltrials.gov/study/NCT05099640

Educational resources

You can find out more about PKU on the following websites:

- National Society for Phenylketonuria (NSPKU): https://nspku.org/
- National PKU Alliance (NPKUA): https://www.npkua.org/
- flok: https://flok.org/
- European Society for Phenylketonuria and Allied Disorders Treated as Phenylketonuria (E.S.PKU): https://www.espku.org/
- Canadian PKU and Allied Disorders (CanPKU+): https://www.canpku.org/

Further reading

1. The original publication of the phase 3 APHENITY trial. Available here: https://doi.org/10.1016/S0140-6736(24)01556-3. Written by Muntau AC *et al.* and published in 2024 in *The Lancet*, volume 404 (issue 10460).
2. A publication of an earlier phase 2 clinical trial of sepiapterin in PKU. Available here: https://doi.org/10.1016/j.metabol.2021.155116. Written by Bratkovic D *et al.* and published in 2022 in *Metabolism*, volume 128 (issue 155116).
3. A review of PKU and its current and future management. Available here: https://doi.org/10.1016/S0140-6736(10)60961-0. Written by Blau N *et al.* and published in 2010 in *The Lancet*, volume 376 (issue 9750).
4. Dietary guidelines for people living with PKU. Available here: https://doi.org/10.1186/s13023-020-01391-y. Written by MacDonald A *et al.* and published in 2020 in *Orphanet Journal of Rare Diseases*, volume 15 (issue 1).
5. European medical guidelines for diagnosing and treating PKU. Available here: https://doi.org/10.1016/j.ymgme.2025.109125. Written by van Wegberg AMJ *et al.* and published in 2025 in *Molecular Genetics and Metabolism*, volume 145 (issue 2).
6. A paper discussing the differences in the diagnosis, treatment, and management of PKU between Europe and the USA. Available here: https://doi.org/10.1186/s13023-020-01541-2. Written by Lowe TB *et al*. and published in 2020 in *Orphanet Journal of Rare Diseases*, volume 15 (issue 1).
7. Medical guidelines for diagnosing and managing PAH deficiency. Available here: https://doi.org/10.1016/j.gim.2024.101289. Written by Smith WE *et al.* and published in 2025 in *Genetics in Medicine*, volume 27 (issue 1).
8. A publication of clinical trial results for sepiapterin to learn how it works in the bodies of healthy people. Available here: https://doi.org/10.1002/cpdd.1363. Written by Gao L *et al.* and published in 2023 in *Clinical Pharmacology in Drug Development*, volume 13 (issue 5).
9. A review of pegvaliase for the treatment of PKU. Available here: https://doi.org/10.1177/1177392819857089. Written by Hydery T and Coppenrath VA, and published in 2019 in *Drug Target Insights*, volume 13 (issue 1).

Author contributions

All authors contributed to the drafting and revision of the manuscript.

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Competing interests disclosure

AC Muntau declares clinical trial support from BioMarin and PTC Therapeutics; has participated on advisory boards for BioMarin, Jnana Therapeutics, PTC Therapeutics, and Synlogic Therapeutics; and has consulted and lectured for BioMarin, Jnana Therapeutics, and PTC Therapeutics. S Gallagher declares no competing interests. M Lah declares clinical trial support from BioMarin and Homology Medicines; and has participated on advisory boards for BioMarin and PTC Therapeutics. A Belanger-Quintana declares clinical trial support from BioMarin, Moderna, and PTC Therapeutics; has participated on advisory boards for BioMarin, Jnana Therapeutics, Nutricia, and PTC Therapeutics; and has consulted and lectured for BioMarin, Danone, Genzyme/Sanofi, Nestlé, PTC Therapeutics, Recordati Rare Diseases, and Takeda. N Longo declares clinical trial support from BioMarin, Homology Medicines, Jnana Therapeutics, Moderna, and PTC Therapeutics; and has participated on advisory boards for Amgen/Horizon Therapeutics, Amicus Therapeutics, Audentes/Astellas, BioMarin, BridgeBio/CoA Therapeutics, Chiesi/Protalix, Genzyme/Sanofi, Hemoshear, Ipsen, Jaguar Gene Therapy, Jnana Therapeutics, Leadiant Biosciences, Moderna, Nestlé Pharma, PTC Therapeutics, Reneo, and Ultragenyx. The authors have no other competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript apart from those disclosed.

Data sharing statement

The original article discussed in this summary was published in the journal *The Lancet* and is called "Effects of oral sepiapterin on blood Phe concentration in a broad range of patients with phenylketonuria (APHENITY): results of an international, phase 3, randomised, double-blind, placebo-controlled trial". You can read the original article here: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(24)01556-3/abstract

You can read more about this trial here: https://clinicaltrials.gov/study/NCT05099640