



## The effects of elafibranor in people with primary biliary cholangitis: a plain language summary

Kris V. Kowdley, Christopher Bowlus, Cynthia Levy, Ulus S. Akarca, Mario Reis Alves-da-Silva, Pietro Andreone, Marco Arrese, Sven M. Francque, Michael A. Heneghan, Pietro Invernizzi, David Jones, Eric Lawitz, Marlyn J. Mayo, Mark G. Swain, Victor Vargas, John M. Vierling, Alejandra Villamil, Carol Addy, Julie Dietrich, Sarah Mazain, Bachirou Taddé, Benjamin Miller, Jianfen Shu, Claudia O. Zein, Carol Roberts, Gail Wright, Jörn M. Schattenberg & on behalf of the ELATIVE® Investigators' Study Group

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## The effects of elafibranor in people with primary biliary cholangitis: a plain language summary

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Author affiliations can be found at the end of this article

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### Where can I find the original article on which this summary is based?

You can read the full article called 'Efficacy and Safety of Elafibranor in Primary Biliary Cholangitis', published in the *New England Journal of Medicine*, at: <https://www.nejm.org/doi/full/10.1056/NEJMoa2306185>. Additionally, a short animated video summary is available here: <https://www.biomedicine.video/gastroenterology-hepatology/elafibranor-efficacy-and-safety-in-people-with-primary-biliary-cholangitis>.

### Summary

#### What is this summary about?

This is a plain language summary describing the **phase 3 clinical trial** called 'ELATIVE<sup>®</sup>'. Primary biliary cholangitis (PBC) is a rare disease of the liver that can get worse over time and can be potentially life threatening. Living with PBC can also reduce a person's **quality of life**. There are currently not many treatment options available for PBC. The ELATIVE<sup>®</sup> clinical trial tested how well a potential new treatment called 'elafibranor' works in treating people with PBC.










#### What was done?

The ELATIVE<sup>®</sup> clinical trial aimed to find out how well elafibranor works in treating PBC for people who did not get better with the current **first-line treatment**, called 'ursodeoxycholic acid' (UDCA). The trial also looked at what the **side effects** of elafibranor might be. 161 people with PBC took part in ELATIVE<sup>®</sup> worldwide. People were randomly split into 2 groups: 1 group took an elafibranor tablet and the other group took a tablet with no medicine, called '**placebo**'. Both tablets were taken once a day for at least a year. Most people were taking UDCA before the clinical trial started, and they continued to take this medication with elafibranor or placebo during the clinical trial.

#### What were the results?

Researchers looked at 2 substances produced by the liver and found in the blood, called **alkaline phosphatase** and **bilirubin**. People with higher amounts of these substances in their blood have worse liver health. After a year of treatment, more people taking elafibranor had lower levels of these substances in their blood than people taking placebo. This suggests that their liver condition had improved.

How to say (download PDF and double click sound icon to play sound)...

- **Primary biliary cholangitis:** prai-muh-ree bi-lee-ur-ee ko-lan-jai-tus 
- **Elafibranor:** ell-uh-fib-rah-nor 
- **Ursodeoxycholic acid:** ur-soh-dee-ox-ee-koh-lik ah-sid 
- **Pruritus:** proo-rye-tus 
- **Diarrhea:** dye-uh-ree-uh 
- **Nausea:** naw-zee-uh 
- **Creatinine:** kree-ah-tuh-neen 
- **Creatine phosphokinase:** kree-uh-teen fos-foh-ky-nayz 
- **Obeticholic acid:** oh-beh-tih-koh-lik ah-sid 

**Phase 3 clinical trial:** A study that tests the benefits and risks of a potential new treatment in people with a specific disease. It follows similar studies where the treatment has been tested in smaller groups of people.

**Quality of life:** In medical terms, a measure of how a person feels about their own physical and mental health. This takes into account how a person's daily life and wellbeing is affected by their disease, and is a useful tool for researchers who are developing potential new treatments.



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People with PBC often experience symptoms of itchy skin (often called 'pruritus') and tiredness, and current treatments do not always improve these symptoms. The effect of elafibranor on itch was looked at in people who had uncontrollable itch at the start of the clinical trial. Elafibranor treatment did not worsen pruritus. However, the 'Worst Itch Numeric Rating Scale (NRS)' was not able to demonstrate that itch improved more in people who were taking elafibranor compared with people taking the placebo. Yet, elafibranor seemed to reduce symptoms of itch when looking at the results of 2 other questionnaires, called the 'PBC-40' (itch section) and '5-dimensional (5-D) Itch' questionnaires.

A similar percentage of people taking elafibranor and taking placebo had side effects. The most common side effects of elafibranor were linked to the digestive system and included stomach pain, diarrhea, nausea, and vomiting. These side effects were experienced by about 1 in every 10 people taking elafibranor and were mostly easy to control.

### What do the results mean?

The results from this clinical trial indicate that elafibranor may be a promising treatment option for people with PBC who do not get better with the current first-line treatment. A continuation of this clinical trial, and another clinical trial called 'ELFIDENCE', are testing the effects of elafibranor over a longer time period.

**First-line treatment:** The first therapy that is recommended for a specific disease.

**Side effect:** Any unexplained or unintended effect of a medical treatment.

**Placebo:** A treatment that looks very similar to the treatment being tested, except it has no active ingredients. This means that the placebo should not bring about any effect on a person's disease or symptoms.

**Alkaline phosphatase:** A substance that can be measured in the blood. People with PBC have higher amounts of alkaline phosphatase in their blood.

**Bilirubin:** A substance found in the blood when red blood cells are broken down. People with liver disease have higher amounts of bilirubin in their blood.

## What is the purpose of this plain language summary?

The purpose of this plain language summary is to help you to understand the findings from recent research in the ELATIVE® clinical trial.

Elafibranor is used to treat the condition under study that is discussed in this summary. Approval varies by country; please check with your local provider for more details.

## Who is this article for?

This summary is intended for all general audiences, which may include people with PBC and their families and caregivers.

## Who sponsored this study?

The ELATIVE® clinical trial was **sponsored** by GENFIT; development of this PLSP was funded by Ipsen.

**Sponsor:** A company or organisation that oversees and pays for a clinical research study. The sponsor also collects and analyses the information from the study.

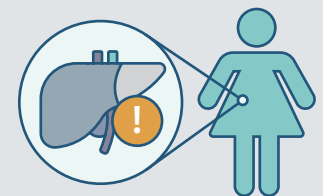
## What is PBC?

PBC is a liver disease where the immune system attacks and damages small bile ducts in the liver.

These ducts are important to carry and move bile, which helps the body remove toxic substances.

PBC is rare and mostly affects women aged 40 years or older (affecting around 1 out of every 1,000 women over the age of 40) and, more rarely, men (1 male patient for every 9 female patients). The cause of PBC is not well understood.

Despite being rare, PBC is being diagnosed more often, with growing awareness of its symptoms and features.



People with PBC may experience symptoms such as itchy skin and tiredness, which can reduce their quality of life.



In particular, itch affects around **80%** of patients and **30%** experience severe itch.



If it is not adequately treated, PBC can lead to serious scarring of the liver, the need for liver transplant, and can contribute to early death.

## What treatments are currently available?

The medicines currently recommended for PBC, referred to as 'standard of care', do not always make people better.

### First-line treatment

The current first-line treatment for PBC is ursodeoxycholic acid, or 'UDCA', taken in tablet form.

Up to **4 in 10** people taking UDCA do not see an adequate improvement in their liver condition. This group of people took part in ELATIVE® clinical trial.



### Second-line treatment

Obeticholic acid, or 'OCA', is a current second-line treatment for PBC, taken in tablet form. OCA is given together with UDCA only to people with PBC who have not seen an improvement with UDCA treatment alone, or who have side effects that prevent them from continuing with UDCA.

Up to **5 in 10** people taking OCA also do not see an adequate improvement in their liver condition.



Also, these treatments do not improve symptoms of itchy skin or tiredness for some people, and some people may even have worse itching after taking OCA. Therefore, there is a need for a new treatment option for PBC.

## What is elafibranor?



Elafibranor is a potential new treatment for people with PBC who do not get better with UDCA.



Elafibranor has been shown to improve liver health and possibly symptoms of PBC in a clinical trial.



Elafibranor has an effect on various processes throughout the body including managing fats and sugars better, improving the balance of chemicals, and reducing inflammation.

## Researchers carried out the ELATIVE® clinical trial to find out:



Does elafibranor improve liver health and symptoms of PBC?



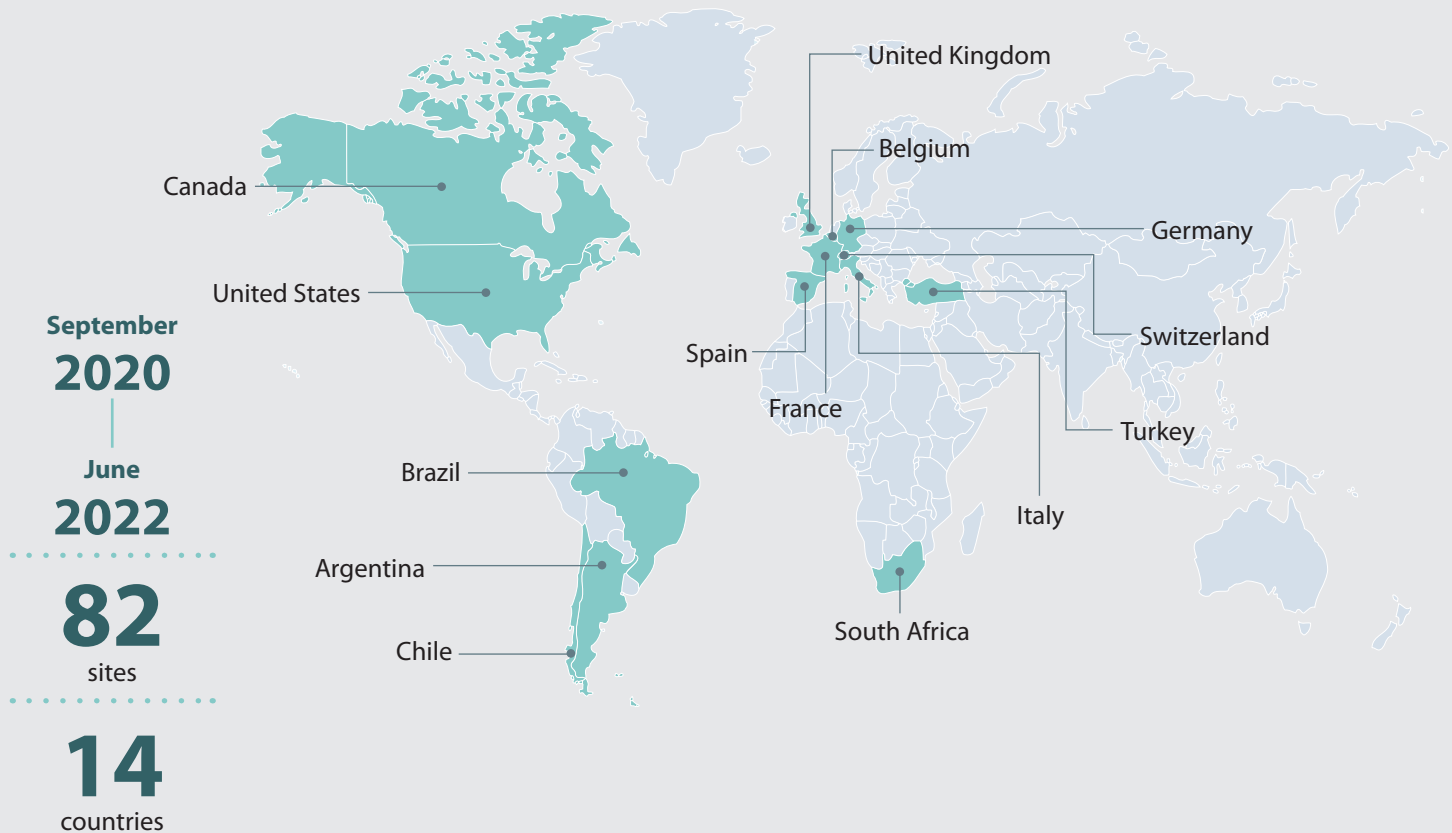
Does elafibranor have any side effects?



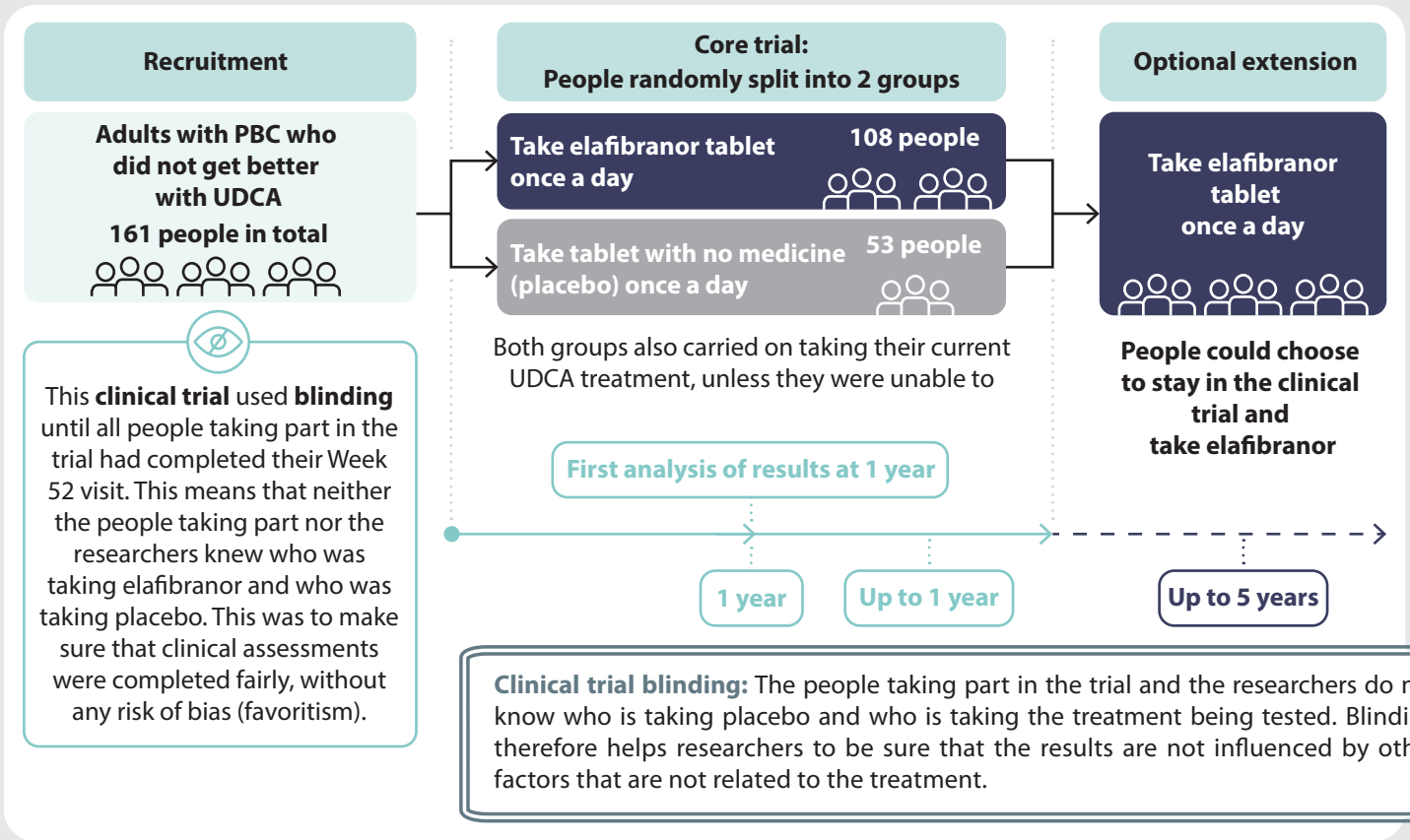
ELATIVE® is a clinical trial aiming to provide a definitive answer to the question of elafibranor's suitability to treat PBC. ELATIVE® follows a previous clinical trial that had been carried out over a shorter time period in a smaller group of people.

## How was the clinical trial designed?

People began taking part in the ELATIVE® clinical trial from September 2020 to June 2022 across 82 sites including universities, clinics, and hospitals in 14 countries.



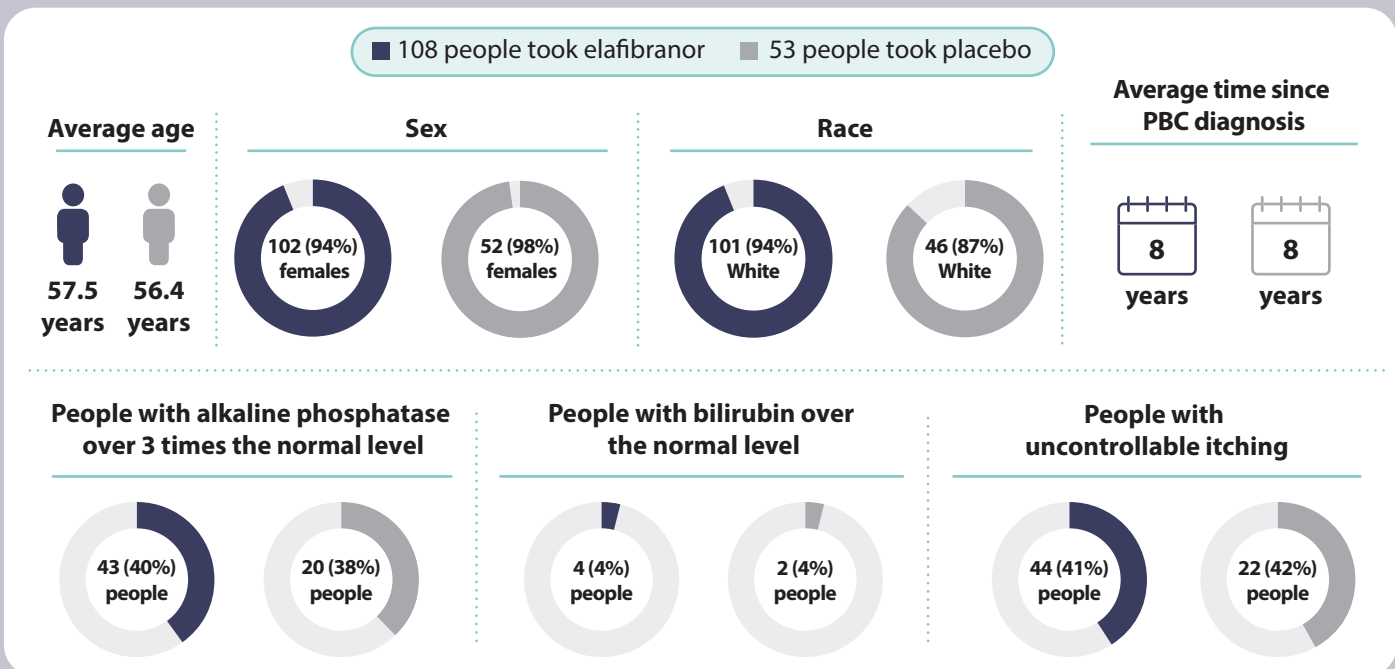
In total, 161 people with PBC were randomly split into 2 groups. In one group, 108 people took an elafibranor tablet, and in the other group, 53 people took a tablet with no medicine, called placebo. This 2:1 ratio in clinical trials means that more people get the treatment, which makes the results stronger, helps recruit volunteers, and is fairer. Each treatment was taken once a day and people stayed on treatment for at least 1 year. Once each person taking part had completed between 1 to 2 years of treatment, they could then choose to continue treatment with only elafibranor for up to 5 more years. If patients were taking UDCA before the trial, they carried on taking their usual dose of UDCA throughout the trial.



## Who took part in the clinical trial?

The people who took part in ELATIVE® were aged between 18 and 75 years old. They all had PBC and either did not get better after at least a year of UDCA treatment, meaning that they still had high levels of alkaline phosphatase in their blood, or they had too many side effects from UDCA treatment.

The characteristics of people who took part in ELATIVE® were similar between the 2 treatment groups:



## What were the overall results of the study?

The researchers in ELATIVE® measured how bad a person's liver disease was by looking at substances in the blood, called alkaline phosphatase and bilirubin. When a liver condition is worse, there are higher amounts of these substances in the blood. A positive sign that a treatment is effective for PBC is if it can lower the amounts of alkaline phosphatase and bilirubin in the blood. This was the main aim of the clinical trial.

To measure improvement in a standard way, researchers measured the levels of these substances before patients started treatment and after they had taken treatment for 1 year. These levels were then compared to the 'normal range', which is calculated by taking the lowest and highest levels of alkaline phosphatase and bilirubin that are seen in people who do not have liver disease. The highest value in this range is called the **upper limit of normal**.

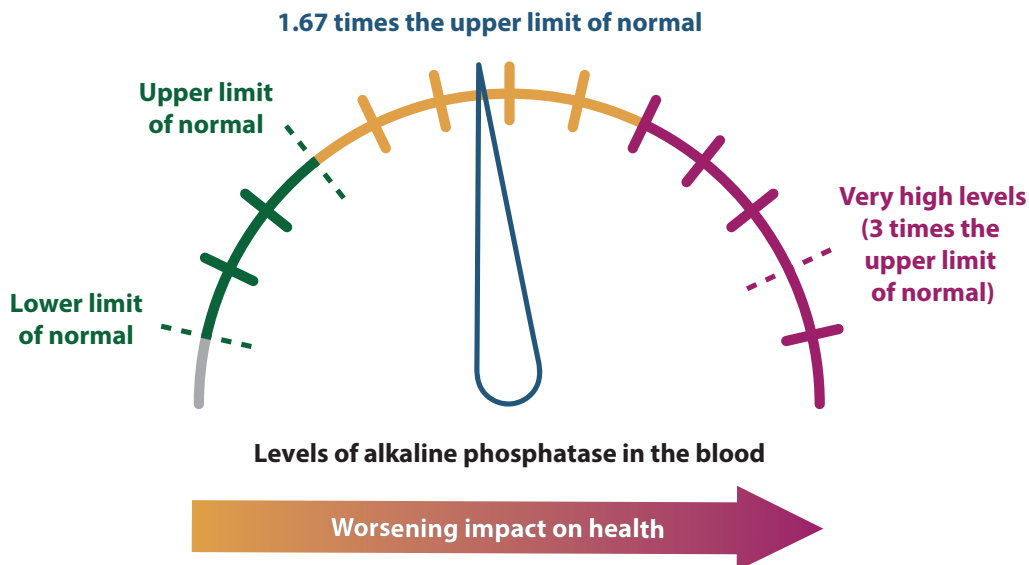
**The upper limit of normal:** The highest measurement of the 'normal range' usually seen in people who do not have liver disease. For example, the normal range for alkaline phosphatase in women is between 35 (lower limit of normal) and 104 (upper limit of normal) units per liter.

### Measurement of alkaline phosphatase levels

Levels of alkaline phosphatase and bilirubin are usually higher than the upper limit of normal in patients with PBC who have an inadequate response to current treatment.

Previous research has shown that patients are less likely to need a liver transplant if, within 1 year, their levels of alkaline phosphatase fall below 1.67 times the upper limit of normal, with their total levels of alkaline phosphatase also reducing by more than 15% at the same time.

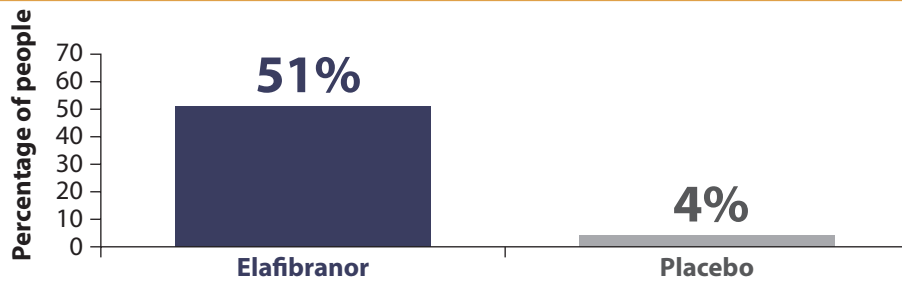
Based on this, the researchers in ELATIVE® measured alkaline phosphatase to see if patients had a positive response to treatment with elafibranor.



## What did liver tests show in people taking elafibranor?

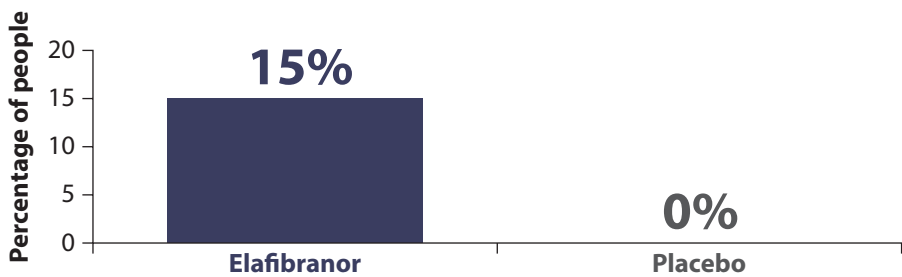
At the start of ELATIVE®, all patients had similar levels of alkaline phosphatase and bilirubin. At the end of 1 year of treatment, people taking elafibranor had lower levels of these 2 substances. This shows a positive response to treatment and an improvement in their liver condition.

### Percentage of people with a positive response to treatment after 1 year of treatment



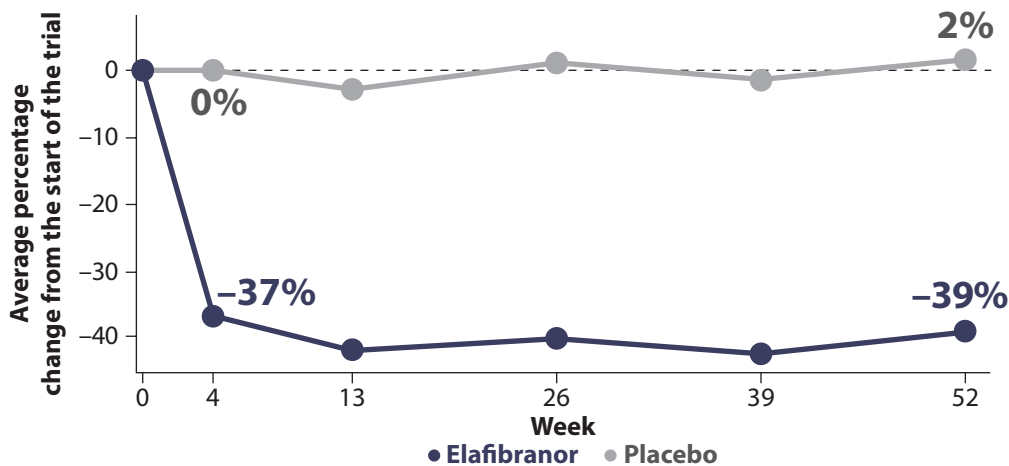
**47%** more people had improvements in these substances after taking elafibranor for 1 year versus placebo

### Percentage of people with levels of alkaline phosphatase within the normal limits after 1 year of treatment



Only people taking elafibranor had normal levels of alkaline phosphatase after 1 year of treatment

### Percentage change in levels of alkaline phosphatase over time



Patients receiving placebo had on average a **2%** increase in alkaline phosphatase levels after 1 year of treatment.

Patients receiving elafibranor had on average a **39%** decrease in alkaline phosphatase levels after 1 year of treatment.

At as early as 4 weeks of treatment, alkaline phosphatase levels were reduced by 37% in people taking elafibranor. This shows that liver health was improving quickly. By comparison, the levels did not change in people taking placebo, which was to be expected. These responses stayed mostly the same for the rest of the clinical trial.

From *N Eng J Med*, Kowdley KV, et al. Efficacy and Safety of Elafibranor in Primary Biliary Cholangitis, 2024, 390, 795–805. Copyright © 2024 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.



### What were the main questionnaires completed in the ELATIVE® clinical trial?

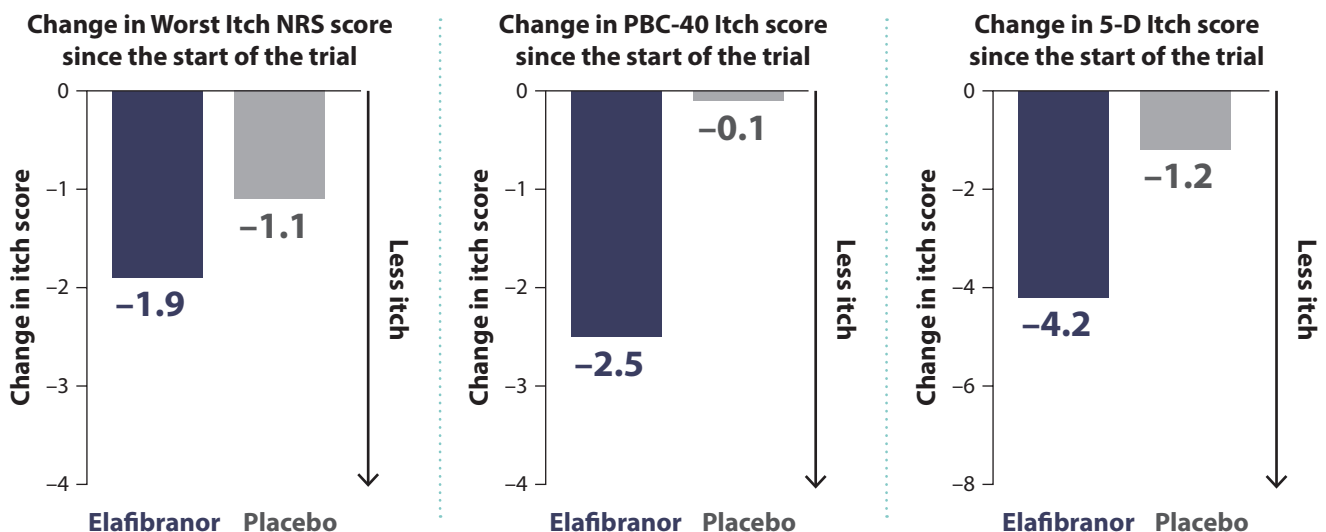
- As part of ELATIVE®, patients completed multiple questionnaires to rate their experience of PBC symptoms.
- The Worst Itch NRS is a daily questionnaire that contains 1 question where people rate how severe their itch has been on a scale of 0 (no itch) to 10 (worst itch imaginable) in the last 24 hours.
- The PBC-40 (itch section) and 5-D Itch questionnaires were completed to measure people’s quality of life at the beginning of the clinical trial and at each study visit (Weeks 4, 13, 26, 39, and 52).
  - » The PBC-40 questionnaire asks people to rate their experience of many symptoms, including those related to digestion, itch, and sleep. Statements such as “Because of PBC, I get more stressed about things than I used to,” are rated on a scale from “Not at all” to “Very much.”
  - » The 5-D Itch questionnaire measures 5 aspects of itch, including whether the itch is improving or getting worse and which parts of the body are affected.
- Other questionnaires that look at people’s overall quality of life were also completed at the beginning of the trial and at each study visit, such as the European Quality of Life 5 Dimensions (EQ-5D) questionnaire.

### How did elafibranor treatment affect symptoms of itch?

Results from the Worst Itch NRS questionnaire showed that elafibranor treatment did not significantly worsen or improve daily itch in people with PBC when compared to itch in people who were taking the placebo. Some improvements can sometimes be seen in people taking placebo. When a person thinks that they are taking a treatment, this can cause an effect in how the person sees their disease and symptoms. People taking part in a clinical trial tend to meet with their doctor more often than they usually would, which can also have a positive effect. These may be a few reasons why a possible trend for some improvement was seen in the Worst Itch NRS questionnaire among people who were taking placebo in the ELATIVE® clinical trial.

The results of 2 different questionnaires (the PBC-40 and 5-D Itch) suggested that elafibranor treatment did lead to some improvements in itch and quality of life. Further research is needed to find out more about the effect of elafibranor on itch.

### Responses to questionnaires that measure itch and its impact on quality of life suggest that elafibranor may provide some improvement after 1 year of treatment



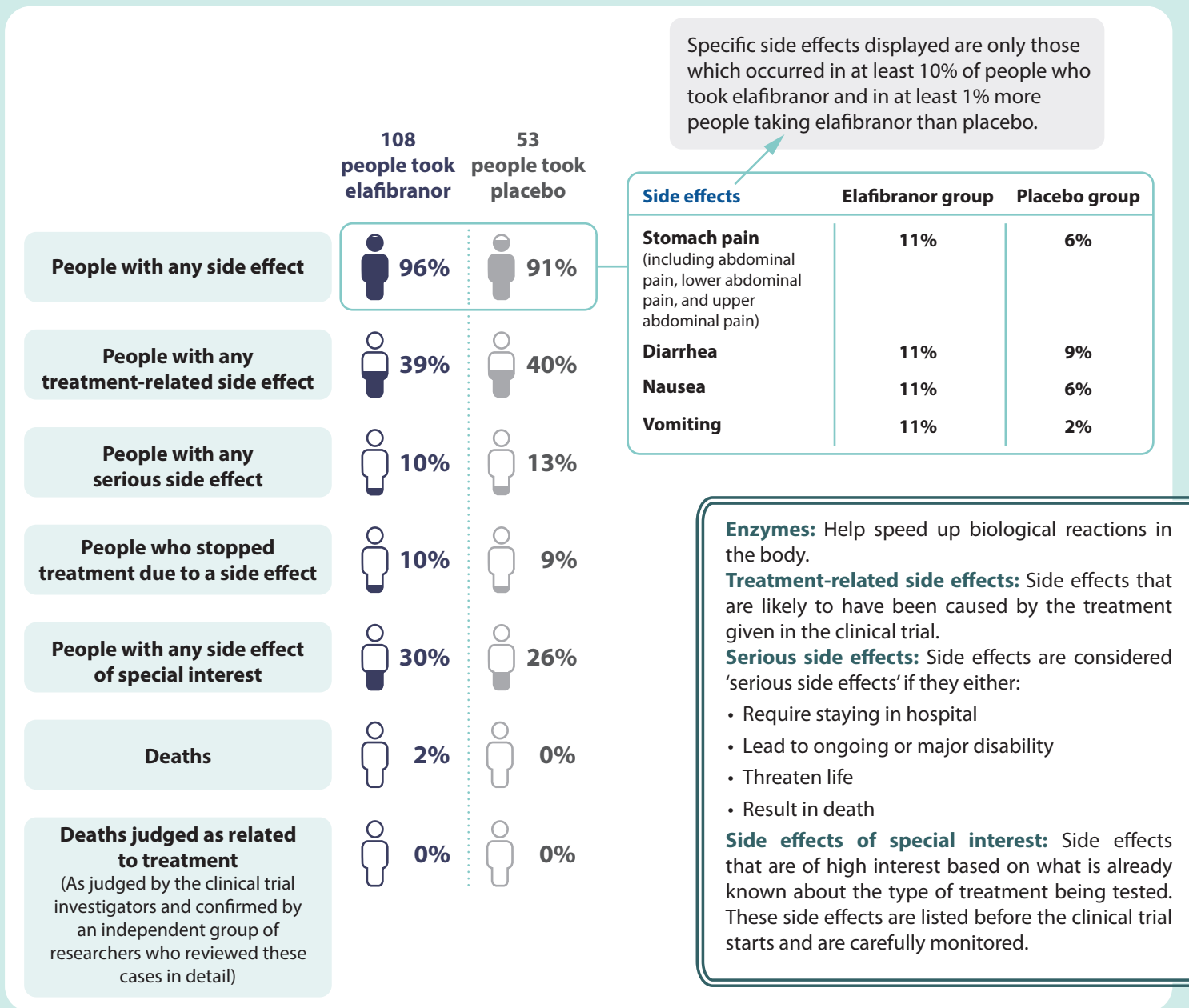
## What were the most common side effects?

A similar percentage of people taking elafibranor and taking placebo had side effects.

The most common side effects were stomach pain, diarrhea, nausea, and vomiting. These side effects each occurred in about 1 out of 10 people receiving elafibranor.

The other side effects included changes to the blood level of creatinine and changes to the blood level of an **enzyme** called creatine phosphokinase. Increases in these substances can be caused by problems with kidney function or muscle damage.

A higher proportion of people taking placebo experienced side effects of tiredness and itching. These side effects were less common among those who took elafibranor.



## What do the results of this study mean?



The results from this clinical trial suggest that elafibranor could potentially be used to treat PBC in people who do not get better with UDCA or cannot take UDCA because of its side effects.

## Study strengths and areas for future research



The people who took part in the ELATIVE® clinical trial had similar disease characteristics to people with PBC in the real-world population.



An advantage of the ELATIVE® clinical trial is that the doctors and the people with PBC taking part did not know which treatment was being taken during the clinical trial; the trial used blinding. This means that the researchers can be more confident that the changes seen were due to elafibranor treatment.



A continuation of this clinical trial and another clinical trial, ELFIDENCE, are ongoing. People continuing to take elafibranor will be assessed for up to 7 additional years to see if their disease continues to improve and if they have any new side effects. The results from ELFIDENCE will help show whether elafibranor improves liver health in the longer term and prevents the need for liver transplant and hospitalization.

## Where can readers find more information on this study?

This summary is based on the article entitled 'Efficacy and Safety of Elafibranor in Primary Biliary Cholangitis', published in the *New England Journal of Medicine* – the full text is available at: <https://www.nejm.org/doi/full/10.1056/NEJMoa2306185>.

Additional information can be found at <https://clinicaltrials.gov> for ELATIVE® (clinical trial identifier: NCT04526665) and ELFIDENCE (clinical trial identifier: NCT06016842).

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## Disclosure statement

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