# PLAIN LANGUAGE SUMMARY OF CLINICAL STUDY RESULTS

**Study Sponsor:** Gilead Sciences

**Gilead Protocol Number:** GS-US-428-4194

**Dates of Trial:** March 2019 to December 2022

**Short Study Title:** Study of Cilofexor in Adults With Primary Sclerosing Cholangitis

**Study Nickname:** PRIMIS

## Thank you

Thank you to the participants who contributed to the clinical study for **cilofexor**, also known as **GS-9674**.

Gilead Sciences sponsored this study. We believe it is important to share the results with study participants and the general public.

If you participated in the study and have questions about the results, please speak with a doctor or staff member at the study site.

Always talk to a doctor or healthcare provider before making any treatment changes.

**Date of this Report:** November 2023

The information in this summary does not include any information available after this date. This document is a short summary of this study written for a general audience. Links to scientific summaries of this study can be found at the end of this document.

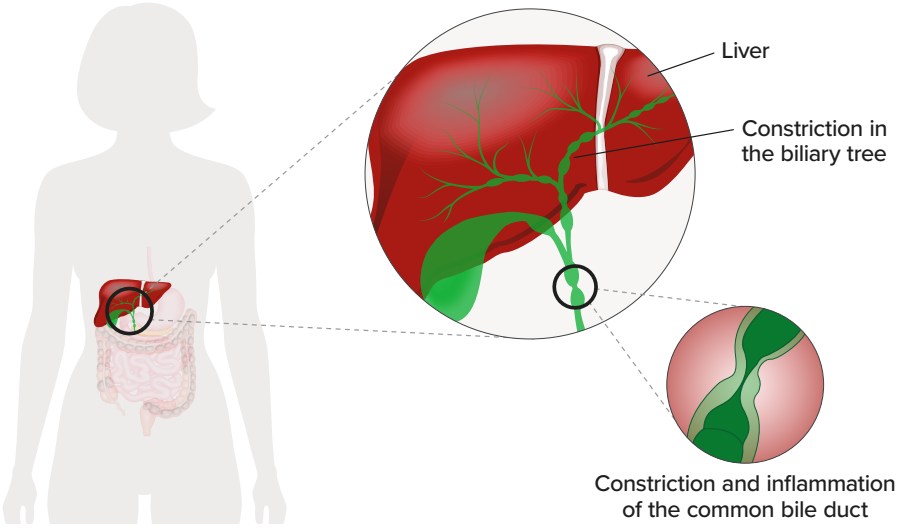
# What was the purpose of the study?

The purpose of the study was to learn if treatment with cilofexor can lower the risk of progression of liver damage in participants with **primary sclerosing cholangitis (PSC)** who were at risk of severe liver damage.

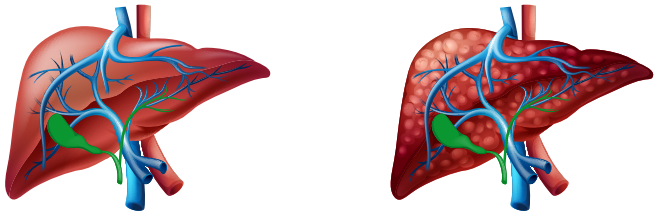
## What is PSC?

PSC is a long lasting disease that affects bile ducts. **Bile ducts** are tubes inside and outside of the liver that carry bile fluid. Bile fluid is made in the liver and aids digestion, absorption of nutrients from food, and the removal of toxins from the body. Bile ducts outside the liver carry bile fluid from the liver to the gall bladder and small intestine.

PSC is a condition in which the bile ducts get damaged. Over time, the ducts become narrow, scarred, and block the flow of bile, which causes it to build up in the liver. This causes damage to the liver. Common symptoms include itching, feeling tired, fever, diarrhea, and jaundice (yellowing of the eyes and skin).




The liver cells try to repair themselves but, in the process, form scar tissue. The scar tissue prevents the liver from working properly. The scarring of the liver is called **liver fibrosis**. As scarring gets worse, called **progression of fibrosis**, it leads to **liver cirrhosis**. Cirrhosis is a late stage of scarring of the liver, which leads to severe liver damage. People with PSC may develop complications of cirrhosis that can lead to liver failure or cancer of the bile ducts.



Normal liver | Liver with cirrhosis

Liver transplants have been effective in treating PSC where the damaged liver is removed and replaced by a healthy one from a donor. However, beyond that there are limited treatment options available for people with PSC.

In this study, researchers tested the study drug **cilofexor** in people with PSC, who did not have cirrhosis, but were at a high risk of developing cirrhosis. Cilofexor acts by reducing the amount of bile formed which could help reduce the damage to the liver in people with PSC.

This was a phase 3 clinical study, where researchers looked at how **cilofexor** worked in a large group of people with PSC.

### The main questions the researchers wanted to answer in this study were:

- How many participants had progression in liver fibrosis at Week 96 of the study, if any?
- What side effects did participants have during the study, if any?

# Who took part in the study?

- **419 participants** with PSC in **16 countries** around the world.
- 3 participants left the study before taking cilofexor or placebo and were not included in the study results.

**People could take part in the study if they:**

Were between 18 to 75 years of age

Had PSC

Had liver damage that had not progressed to cirrhosis

The participants enrolled in the study were between the ages of **18 to 74 years**.
The table below shows how many study participants were from each country.

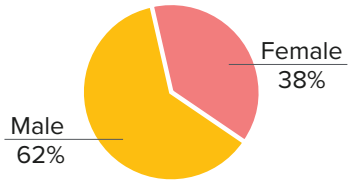
| Country | Number of participants (%) |
|---|---|
| United States | 174 (42%) |
| Canada | 38 (9%) |
| Australia | 31 (7%) |
| Japan | 27 (6%) |
| Italy | 23 (6%) |
| Finland | 19 (5%) |
| United Kingdom | 19 (5%) |
| Germany | 18 (4%) |
| Spain | 16 (4%) |
| France | 14 (3%) |
| Israel | 11 (3%) |
| Denmark | 7 (2%) |
| Belgium | 6 (1%) |
| New Zealand | 6 (1%) |
| Switzerland | 6 (1%) |
| Austria | 4 (1%) |

The tables below show the sex, race, and ethnicity of participants who were included in this study.

| Race | Number of participants (%) |
|---|---|
| White | 345 (82%) |
| Asian | 38 (9%) |
| Black or African American | 20 (5%) |
| Unknown or not reported | 11 (3%) |
| Other or more than one race | 5 (1%) |

| Ethnicity | Number of participants (%) |
|---|---|
| Not Hispanic or Latino | 391 (93%) |
| Hispanic or Latino | 14 (less than 4%) |
| Unknown or not reported | 14 (less than 4%) |

**Sex**



# What happened during the study?

At the start of the study, the study doctor checked participants to see if they could take part in the study. Each participant had suitable tests to check for PSC and the level of liver fibrosis before they received the study treatment

There were **2 parts** to this study:

**Part 1** of the study was **randomized and double blinded**.

**Randomized:** This means the researchers used a computer program to randomly choose the treatment each participant took. This helped make sure the treatments were chosen fairly.

Participants were randomized in 2:1 ratio, which means that there were twice as many participants receiving **cilofexor** treatment as those receiving the **placebo.**

**Double blinded:** This means that the participants, doctors, or other study staff, and the sponsor, i.e. Gilead personnel, did not know what study treatment each participant took. This was done to make sure that the study results were not influenced in any way.

During this part of the study, participants were randomized into 1 of the 2 treatment groups. Participants took the following treatments for up to 96 weeks:

- **Cilofexor 100 milligram (mg) tablet,** 1 time every day
  or
- **Placebo tablet,** 1 time every day

Participants visited the clinic multiple times during Part 1. Participants had tests to see if there were any changes in the severity of their PSC from the start of the study to the end of Week 96 of the study. Participants were also checked for any medical events they had during the study. About 30 days after the participants stopped taking the study treatments, they visited the study site to complete a follow-up visit.

A **placebo** looks like a treatment but does not have any active ingredient (drug) in it. Researchers use a placebo as a point of comparison to identify whether a new treatment is effective and safe. Placebo was chosen to compare with cilofexor because there is no standard treatment available for people with PSC.

**Part 2** of the study was **open label**.

**Open label:** This means the participants, doctors, and study staff knew what treatment each participant took.

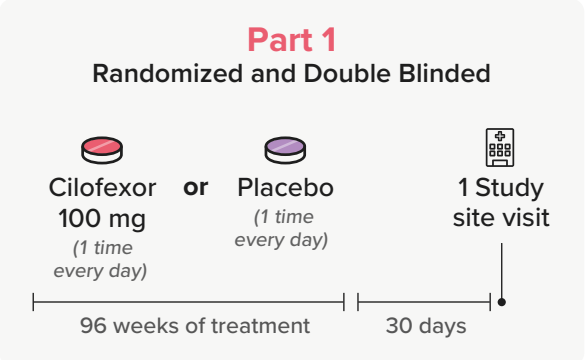
Participants who completed Part 1 and did not have cirrhosis could receive **cilofexor** during Part 2. Participants who received **placebo** during Part 1 could also receive cilofexor during this part of the study.

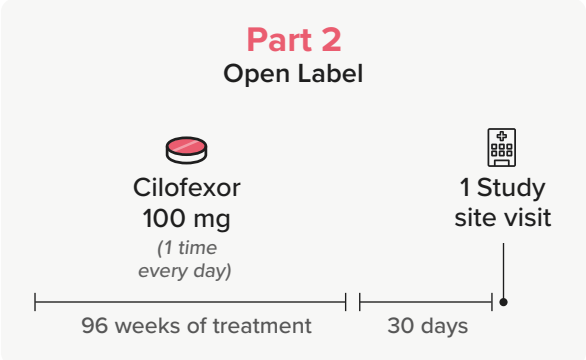
In Part 2, all the participants received:

- **Cilofexor 100 mg tablet,** 1 time every day, for up to 96 weeks

Participants visited the clinic multiple times during Part 2. During the visits, study doctors checked participants for any medical events and other health problems. About 30 days after the participants stopped taking the study treatments, they visited the study site to complete a follow-up visit.

After 160 participants were treated and evaluated at Week 96 during Part 1, the results obtained from these participants were assessed. **Gilead Sciences decided to stop the study because the study treatment did not work as expected.**



# What were the results of the study?

This is a summary of the main results from this study. The individual results of each participant might be different and are not presented in this summary. A detailed presentation of the results can be found on the websites listed at the end of this summary.

## How many participants had progression in liver fibrosis at Week 96 of the study, if any?

Researchers wanted to know the number of participants whose liver fibrosis had got worse. Worsening liver fibrosis meant there was an increase in the scarring of the liver. Researchers performed **liver biopsies** to check participants for progression in liver fibrosis from the start of the study to the end of Week 96 of the study.

A **liver biopsy** involves taking a sample of liver tissue and examining it under a microscope to determine the presence and stage of liver fibrosis.

Researchers evaluated the liver tissue samples using a system called the **Ludwig classification**. It rates the stage of liver fibrosis based on how much scarring has taken place over time. **Fibrosis is described in 5 stages**, which are given below:

### Stages of liver fibrosis according to Ludwig Classification

**F0**
Lack of scarring

**F1**
Mild scarring

**F2**
Moderate scarring

**F3**
Severe scarring

**F4**
Cirrhosis (late-stage scarring of the liver)

Participants were said to have progression of liver fibrosis if they had an increase in the scarring of the liver by one or more stages. The results included 197 participants who were evaluated at the start of the study and at Week 96.

The table below shows the number of participants who had a progression of liver fibrosis at Week 96 during Part 1 of the study.

| **Progression of liver fibrosis at Week 96** | |
|---|---|
| **Cilofexor 100 mg** (out of 133 participants) | **Placebo** (out of 64 participants) |
| **Number of participants (%)** | |
| 41 (31%) | 21 (33%) |

The difference between the cilofexor and placebo treatment groups was small. A similar percentage of participants had a progression of liver fibrosis in the cilofexor and placebo groups.

# What side effects did participants have during the study?

For the purpose of this summary, **side effects** are defined as unwanted medical events that the study doctors thought might be related to the study treatment.

A side effect is considered **serious** if it:

- results in death
- is life-threatening
- considered by the study doctor to be medically important
- causes lasting problems
- requires hospital care

The results from several studies are usually needed to help decide if a treatment actually causes a side effect.

**No participants died from any side effects.**

The table below shows how many participants had side effects during the study.

| Overall side effects | | | | |
|---|---|---|---|---|
| | Part 1 | | Part 2 | |
| | **Cilofexor 100 mg** (out of 277 participants) | **Placebo** (out of 139 participants) | **Cilofexor 100 mg** (out of 80 participants) | **Placebo to Cilofexor 100 mg** (out of 45 participants) |
| | Number of participants (%) | | | |
| How many participants had serious side effects? | 9 (3%) | 5 (4%) | 1 (1%) | 0 |
| How many participants had any side effects? | 134 (48%) | 50 (36%) | 12 (15%) | 7 (16%) |
| How many participants stopped taking study treatment because of side effects? | 18 (6%) | 3 (2%) | 2 (3%) | 1 (2%) |

The table below shows **all the serious side effects** that occurred during the study.

| Serious side effects | | | | |
|---|---|---|---|---|
| | Part 1 | | Part 2 | |
| | **Cilofexor 100 mg** (out of 277 participants) | **Placebo** (out of 139 participants) | **Cilofexor 100 mg** (out of 80 participants) | **Placebo to Cilofexor 100 mg** (out of 45 participants) |
| | Number of participants (%) | | | |
| Inflammation of the bile ducts (Cholangitis) | 1 (under 1%) | 1 (under 1%) | 0 | 0 |
| Belly pain above the belly button (Abdominal pain upper) | 0 | 0 | 1 (under 1%) | 0 |
| Increased level of liver protein in the blood (Alanine aminotransferase increased) | 0 | 1 (under 1%) | 0 | 0 |
| Stone in the bile duct (Bile duct stone) | 1 (under 1%) | 0 | 0 | 0 |
| Severe pain in the abdomen that comes and goes due to blocked bile duct (Biliary colic) | 1 (under 1%) | 0 | 0 | 0 |
| Stroke (Cerebrovascular accident) | 0 | 1 (under 1%) | 0 | 0 |
| Infection of the bile ducts (Cholangitis acute) | 1 (under 1%) | 0 | 0 | 0 |
| Sudden swelling (inflammation) of the gallbladder (Cholecystitis acute) | 1 (under 1%) | 0 | 0 | 0 |
| Formation of gallstones (Cholelithiasis) | 1 (under 1%) | 0 | 0 | 0 |
| Liver damage caused by a drug (Drug-induced liver injury) | 0 | 1 (under 1%) | 0 | 0 |
| Gallbladder cancer | 1 (under 1%) | 0 | 0 | 0 |
| Cancer of the stomach (Gastric cancer) | 0 | 1 (under 1%) | 0 | 0 |
| Yellowing of the skin (Jaundice) | 1 (under 1%) | 0 | 0 | 0 |
| Infection caused by Klebsiella bacteria (Klebsiella infection) | 1 (under 1%) | 0 | 0 | 0 |
| Collection of pus in the liver (Liver abscess) | 1 (under 1%) | 0 | 0 | 0 |
| Itching (Pruritus) | 1 (under 1%) | 0 | 0 | 0 |

The table below shows the **top 6 most common non-serious side effects** that occurred during the study. There were other side effects, but those occurred in fewer participants. Some participants may have had more than one side effect.

The most common non-serious side effects were itching, feeling tired, and belly pain above the belly button.

| Most common non-serious side effects | | | | |
|---|---|---|---|---|
| | Part 1 | | Part 2 | |
| | **Cilofexor 100 mg** (out of 277 participants) | **Placebo** (out of 139 participants) | **Cilofexor 100 mg** (out of 80 participants) | **Placebo to Cilofexor 100 mg** (out of 45 participants) |
| | Number of participants (%) | | | |
| Itching (Pruritus) | 96 (35%) | 24 (17%) | 8 (10%) | 7 (16%) |
| Feeling tired (Fatigue) | 10 (4%) | 8 (6%) | 0 | 0 |
| Belly pain above the belly button (Abdominal pain upper) | 6 (2%) | 6 (4%) | 1 (1%) | 0 |
| Feeling sick to the stomach (Nausea) | 9 (3%) | 3 (2%) | 0 | 0 |
| Belly pain (Abdominal pain) | 5 (2%) | 4 (3%) | 0 | 0 |
| Headache | 5 (2%) | 2 (1%) | 0 | 0 |

## How has this study helped researchers?

Even though the study did not continue as planned, it helped the researchers to learn how well and safe cilofexor was in people living with PSC.

The results from several studies are needed to help decide which treatments work and are safe. This summary shows only the main results from this one study. Other studies may provide new information or different results. Always talk to a doctor before making any treatment changes.

The results of this study will be used in other studies to learn if cilofexor could help people with PSC.

Gilead Sciences does not plan to have further studies with cilofexor in PSC.

## Where can I learn more about this study?

You can find more information about this study on the websites listed below:

**www.clinicaltrials.gov**

Once you are on this website, type **NCT03890120** into the search box and click **Search**

**www.clinicaltrialsregister.eu**

Once you are on the website, click **Home and Search**, then type **2019-000204-14** into the search box and click **Search**

**www.gileadclinicaltrials.com**

Once you are on the website, type **GS-US-428-4194** into the search box and click **Search Now**

**National Clinical Trials Number:** NCT03890120

**EU Clinical Trials Number:** 2019-000204-14

Please note that information on these websites may be presented in a different way from this summary.

**Full Study Title:** A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability, and Efficacy of Cilofexor in Non-Cirrhotic Subjects With Primary Sclerosing Cholangitis

For more information about clinical trials: **https://beta.clinicaltrials.gov/study-basics/learn-about-studies**

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# Thank you

Clinical study participants belong to a large community of people who take part in clinical research around the world. They help researchers answer important health questions and find medical treatments for patients.

GILEAD