

PLAIN LANGUAGE SUMMARY OF CLINICAL STUDY RESULTS

Study Sponsor: CymaBay Therapeutics (later acquired by Gilead Sciences)

Protocol Number: CB8025-32048

Dates of Trial: April 2021 to August 2023

Short Study Title: A Study of Seladelpar in People with Primary Biliary Chalangitis who didn't get Better With Ursodeoxycholic Acid

Study Nickname: RESPONSE

Date of this Report: June 2024

The information in this summary does not include any information available after this date.

Thank you

Thank you to the participants who contributed to the clinical study of **seladelpar**, also known as **MBX-8025**, **RWJ-800025**.



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 stall member at the study site.

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



What was the purpose of the study?

The purpose of this study was to find out if the experimental drug, seladelpar, was safe and could help people with a liver condition called primary biliary cholangitis (PBC), who didn't get better with the usual treatment, ursodeoxycholic acid (UDCA). Seladelpar was compared to a placebo.



Placebo: A placebo looks like a treatment but does not have any active drug in it. Researchers use a placebo as a point of comparison to identify whether the new treatment is effective and safe.

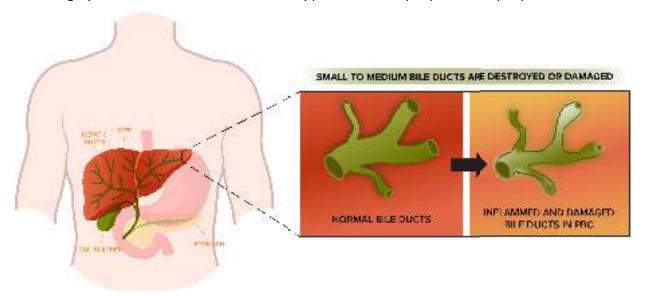
This is a Phase 3 clinical study. This means that researchers looked at how seladelpar worked in a large group of people with PBC.

What is PBC?

PBC is a liver disease that is more common in middle-aged women. In PBC, the immune system (the body's defense system) mistakenly attacks bile ducts. Bile ducts are tiny canals that carry bile, a fluid made in the liver to help with digestion and absorption of some vitamins. If the bile ducts get damaged, bile cannot flow properly to the other organs and gets stored in the liver. This causes problems in the liver and leads to a condition called PBC.

The common symptoms include pruritus (itching) and fatigue (extreme tiredness). PBC can make it hard for people to do everyday tasks and it affects their quality of life. Over time, PBC can worsen. If left untreated, it can lead to liver injury, liver fibrosis (scarring of the liver), liver cirrhosis (severe scarring of the liver), and sometimes liver failure.

The graphic below shows how bile ducts appear in normal people versus people with PBC



Common tests for checking PBC are:

Blood tests that look for levels of certain liver enzymes in the blood: The levels of alkaline phosphatase (ALP), a liver enzyme, indicate liver stress and may signal PBC. People with PBC may also show increased levels of liver substance called bilirubin.

Antimitochondrial antibody (AMA) test: The blood test checks for specific antibodies (AMAs) in the blood. Usually, antibodies are made by the body to fight-off infections. However, AMAs are formed when the body turns against its own cells, tissues, or organs. Finding AMAs in the blood suggests PBC, where the immune system harms the liver.

Imaging tests and liver biopsy: If blood tests show PBC, the researchers may do imaging tests or scans to look at the liver and biliary system. As part of a liver biopsy, the researchers take a tiny piece of liver tissue with a needle to see any changes in it under a microscope.

Currently, available treatments for PBC include UDCA. It helps maintain levels of bile in the body, thus reducing the symptoms of PBC. However, people with PBC sometimes stop responding to UDCA or are unable to tolerate it. Therefore, there is a need for new treatments for PBC that can also help reduce itching and improve the quality of life of people. In this study, the researchers wanted to see if seladelpar could help make the liver better after taking it for at least 12 months (1 year) and reduce itching after taking it for 6 months.

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

For the effectiveness of drug:

 How many participants showed response after. 1 year of treatment, based on the levels of liver. enzymes and liver substances?.

For the safety of drug:

- *How many participants had unwanted medical events during the study. If any?.
- How many participants had laboratory test. abnormalities during the study, if any?.
- What side effects did participants have during the study. If any?

The other key parameters the researchers wanted to learn about were:

- How many participants had normal levels of ALP after 1 year of freatment?
- Did participants' itching (pruritus) symptoms improve after 6 months of treatment?



Who took part in the study?

A total of 193 participants living with PBC in 24 countries around the world took part in the study.

Number of

People could take part in the study if they:



Were between the ages of 18 to 75.

Porcontago of







Were using UDCA for at least 1 year and still had increased levels of ALP. On were unable to tolerate UDCA.

The participants enrolled in the study were between the ages of 28 to 75 years.

The table below shows how many study participants were from each country.

	ercentage of participants	Number of participants
United States	32%	G1
Argentina	15%	29
Mexico	6%	12
Spain	less than 6%	11
Russia	5%	9
Italy	4%	8
Turkey	4%	8
United Kingdom	4%	8
Poland	less than 4%	7
South Korea	less than 4%	7
Israel	3%	5
Belgium	2%	3

Percentage of participants		Number of participants
Czech Republic	2%	3
Switzerland	2%	3
Australia	1%	2
Canada	1%	2
Chile	1%	2
France	1%	2
Germany	1%	2
Greece	1%	2
Hungary	1%	2
New Zealand	1%	2
Romania	1%	2
Austria	less than 1%	1

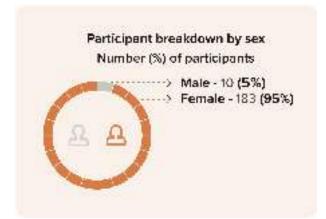
Race of participants who took part are shown below.

Percentage of participants

White
Asian

American Indian or Alaska Native
Black or African American
Unknown or Not Reported

Sex of participants who took part are shown below.



Ethnicity of participants who took part are shown below.



? What happened during the study?

The study was randomized and double-blind.



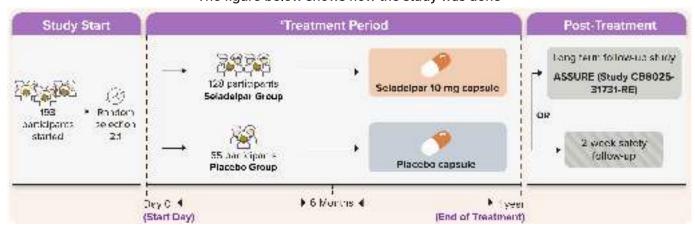
Randomized: This means that the researchers used a computer program to randomly choose the treatment each participant took. This helped make sure the treatments were chosen fairly.

Double-blind: This means none of the participants, doctors or other study staff, and the sponsor personnel knew what treatment each participant took. This was done to make sure that the study results were not influenced in any way.

In this study, the participants were randomized in 2 groups in 2:1 ratio. This means that twice as many participants received seladelpar as those who received a placebo, as shown below.



The figure below shows how the study was done



^{*}Participants who could tolerate UDCA continued to take it during the study as part of background therapy.

After completing the treatment in this study, participants were offered to join another study (Study CB8025-317131-RE) where everyone (including those who took placebo) could receive seladelpar. Those who decided to not join the other study had a 2-week follow-up for safety assessment, after stopping the treatment.



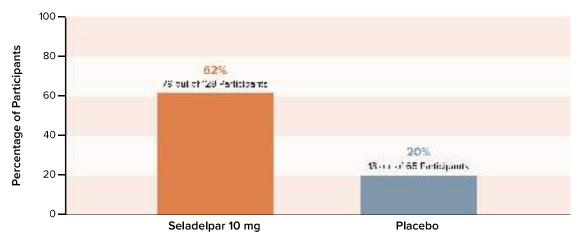
What were the results of the study?

This is a summary of the main results from this study. The individual results of each participant might be different and are not present in this summary.

How many participants showed response after 1 year of treatment, based on the levels of liver enzymes and liver substances?

Researchers checked participants' liver enzyme (ALP) and liver substance (bilirubin) levels at the start of the study and after 1 year of treatment. Participants' test results were checked to see if there were desired levels of decrease in ALP, more than or equal to a 15% decrease in ALP levels and if the bilirubin levels were normal. This indicated whether the study participants with PBC were responding well to the treatment.

The graphic below shows participants with response after 1 year of treatment.



In this study, the difference between seladelpar and placebo was significant. Higher number of participants i on seladelpar showed desired levels of decrease in ALP, more than or equal to a 15% decrease in ALP levels and normal bilirubin levels compared to placebo.

Along with the above parameter, the researchers also wanted to find out:

- How many participants had normal levels of ALP after 1 year of treatment? A total of 32 of 128 (25%) participants in seladelpar group, achieved normal levels of ALP. However, none of the participants in placebo group, could achieve the desired levels of ALP, after 1 year of treatment.
- Did participants' itching (pruritus) symptoms improve after 6 months of treatment? The researchers used a pruritus numerical rating scale (NRS) to see how well the treatment helped with itching symptom in participants with PBC. Participants used an electronic diary, to rate their symptoms daily from 0 to 10. Higher scores meant worse itching. The effect of treatment on itching is presented for 49 participants who took seladelpar and 23 participants who took placebo. These participants had NRS scores greater than or equal to 4 (moderate to severe itch) at the beginning of the study. After 6 months of treatment, the researchers compared the scores to those recorded at the study start and found that:
 - In seladelpar group, the participants showed a decrease of 3 points on average.
 - In placebo group, the participants showed a decrease of 2 points on average.

Overall, the differences between seladelpar and placebo were significant. Higher number of participants who took seladelpar showed normal levels of ALP and decrease in NRS scores, indicating better symptom management, compared to placebo.

A detailed presentation of results related to other parameters and patient-reported outcomes can be found on the websites listed at the end of this summary.

How many participants had unwanted medical events during the study?

The researchers kept track of any unwanted medical events that the participants had during the study.

An unwanted medical event is any unwanted sign or symptom that participants had during a study.



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

The table below shows participants who had any unwanted medical events during the study.

Participants with Unwanted Medical Events			
	Seladelpar 10 mg (out of 128 participants)	Placebo (out of 65 participants)	
	Number of participants (%)		
Participants with any unwanted medical events	111 (87%)	55 (85%)	
Participants with any unwanted serious medical events	9 (7%)	4 (6%)	

How many participants had laboratory test abnormalities during the study, if any?

The researchers looked at 2 types of laboratory abnormalities: hematological (related to blood) and biochemical (specific liver-related tests). They took blood samples of participants before and after taking the treatment. They checked the changes in laboratory test values to see if there were any laboratory abnormalities, meaning they were out of the laboratory reference range. They categorized abnormalities into grades: grade 1 for mild, grade 2 for moderate, grade 3 for severe, and grade 4 for potentially life-threatening.

The table below shows participants whose laboratory values shifted at least 2 grades, like going from mild to severe or a higher grade.

Perticipants with Laboratory Test Abnormalities			
	Seladelpar 10 mg (out of 128 participants)	Placebo (out of 65 participants)	
	Number of participants (%)		
Participants with blood related laboratory abnormalities	18 (14%)	8 (12%)	
Participants with specific liver-related laboratory tests abnormalities	9 (7%)	4 (6%)	

Overall, no meaningful differences were noted in percentage of participants with unwanted medical events or laboratory abnormalities between these 2 groups.



What side effects did participants have during the study?

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

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

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

Overell Side Effects			
	Seladelpar 10 mg (out of 128 participants)	Placebo (out of 65 participants)	Total (out of 193 participants)
	Number of participants (%)		(%)
How many participants had any side effects?	22 (17%)	8 (12%)	30 (16%)
How many participants stopped taking study treatment because of side effects?	2 (2%)	0	2 (1%)

None of the participants had any serious side effects or died due to any side effects during the study.

The table below shows the **top 4 most common 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 1 side effect.

The most common side effect was **headache**. This occurred more in participants taking seladelpar compared to the participants taking placebo.

The table below shows common side effects that occurred in participants during the study.

Most Common Side Effects			
	Seladelpar 10 mg (out of 128 participants)	Placebo (out of 65 participants)	Total (out of 193 participants)
Most Common Side Effects	Number of participants (%)		
Headache	4 (3%)	0	4 (2%)
Swollen belly or feeling full (Abdominal distension)	2 (2%)	1 (2%)	3 (2%)
Frequent loose watery stools (Diarrhoea)	3 (2%)	0	3 (2%)
Feeling sick to stomach (Nausea)	2 (2%)	1 (2%)	3 (2%)



? How has this study helped researchers?

The researchers learned more about the safety of seladelpar with or without UDCA and how it works in people iving with PBC who didn't get better with the usual treatment of UDCA.

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.

CymaBay has engoing studies with seladelpar which will be transitioned to Gilead Sciences.



Where can I learn more about this study?

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

www.clinicaltrials.gov



www.clinicaltrialsregister.eu



Once you are on this website, type "NCT04620733" nto the search box and click "Search"

Once you are on the website, click "Home and Search", then type "2020-004348-27" into the search box and clink "Search"

National Clinical Trials Number: NCT04620733 EU Clinical Trials Number: 2020-004348-27

For more details on the study results, click here to watch the video

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

Full Study Title: RESPONSF: A Placebo-controlled, Randomized, Phase 3 Study to Evaluate the Efficacy and Safety of Seladelpar in Patients with Primary Biliary Cholangitis (PBC) and an Inadequate Response to or an Intolerance to Ursodeoxycholic Acid (UDCA)

For more information about clinical trials, click here.

Gilead Sciences

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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.

