Clinical Study Results

This summary reports the results of only one study. Researchers must look at the results of many types of studies to understand if a study medication works, how it works, and if it is safe to prescribe to patients. The results of this study might be different than the results of other studies that the researchers review.

Sponsor:	Pfizer Inc.
Medicine(s) Studied:	Ritlecitinib (PF-06651600), brepocitinib (PF-06700841)
Protocol Number:	B7981007 (PIZZICATO)
Dates of Study:	02 February 2018 to 19 October 2023
Title of this Study:	Study to Evaluate the Efficacy and Safety of Oral PF-06651600 and PF-06700841 in Subjects with Moderate to Severe Crohn's Disease [A Phase 2a, Double-Blind, Randomized, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Oral PF-06651600 and PF-06700841 as Induction and Open Label Extension Treatment in Subjects With Moderate to Severe Crohn's Disease]
Date(s) of this Report:	07 June 2024

– Thank You –

If you participated in this study, Pfizer, the Sponsor, would like to thank you for your participation.

This summary will describe the study results. If you have any questions about the study or the results, please contact the doctor or staff at your study site.

Why was this study done?

What is Crohn's disease?

Crohn's disease is an autoimmune disease. An autoimmune disease is a condition where a patient's immune system attacks healthy parts of their body. In Crohn's disease, this causes the gut to become inflamed and damaged. People with Crohn's disease may experience diarrhea, stomach aches, blood in their stools, tiredness, and weight loss.

What is ritlecitinib and what is brepocitinib?

Ritlecitinib (ri-tul-SIT-in-ib) and brepocitinib (breh-po-SIT-in-ib) are both investigational medicines. They are being researched as possible treatments for some autoimmune conditions. An investigational medicine is one that is not approved for use outside of research studies.

Ritlecitinib and brepocitinib are each taken as a tablet, by mouth. They are called "small molecule" medicines. Small molecules can move into cells and interact with other molecules present inside a cell.

- Ritlecitinib is thought to work by blocking the activity of specific proteins in immune cells called "Janus Kinase 3" and the "TEC family kinases".
- Brepocitinib is thought to work by blocking the activity of specific proteins in immune cells called "Janus Kinase 1" and "Tyrosine Kinase 2".

These proteins act like on/off switches for the cells of the immune system. By turning off these switches, the cells of the immune system produce fewer cytokines. Cytokines are a type of protein involved in inflammation. This is expected to improve the symptoms of autoimmune diseases such as Crohn's disease.

What was the purpose of this study?

- The purpose of this study was to learn about the effects of ritlecitinib or brepocitinib on Crohn's disease by comparing them with a placebo. A placebo does not have any medicine in it, but it looks just like the study medication.
- Researchers wanted to find out if ritlecitinib or brepocitinib could be used to treat Crohn's disease.
- Researchers measured the "Simple Endoscopic Score for Crohn's Disease" for the participants. This is also called the "SES-CD." This score is used to describe how much active Crohn's disease a person has. The score is based on endoscopy results. An endoscopy is a procedure where a camera is used to look inside the gut.
- Researchers also looked at participants' laboratory test results, their "vital signs" such as blood pressure, and the electrical activity of participants' hearts. A test called a "12-lead electrocardiogram" or "12-lead ECG" was used to measure the heart's electrical activity. Researchers were looking for any abnormal results that might have had a meaningful effect on the participant.

Researchers wanted to know:

How many participants had their SES-CD score reduced by 50% or more after 12 weeks of treatment with ritlecitinib or brepocitinib compared to placebo?

How many participants experienced meaningful abnormal laboratory test results, abnormal vital signs, or abnormal results for the electrical activity of their heart during the study?

What medical problems did participants have during the study?

What happened during the study?

How was the study done?

First, a study doctor checked each participant to make sure they were able to join the study. This is known as a screening period.

There were 2 treatment phases in the study. The 1st phase lasted 12 weeks. Study participants were assigned to each group by chance alone. They were divided by chance into 2 groups (like the flip of a coin).

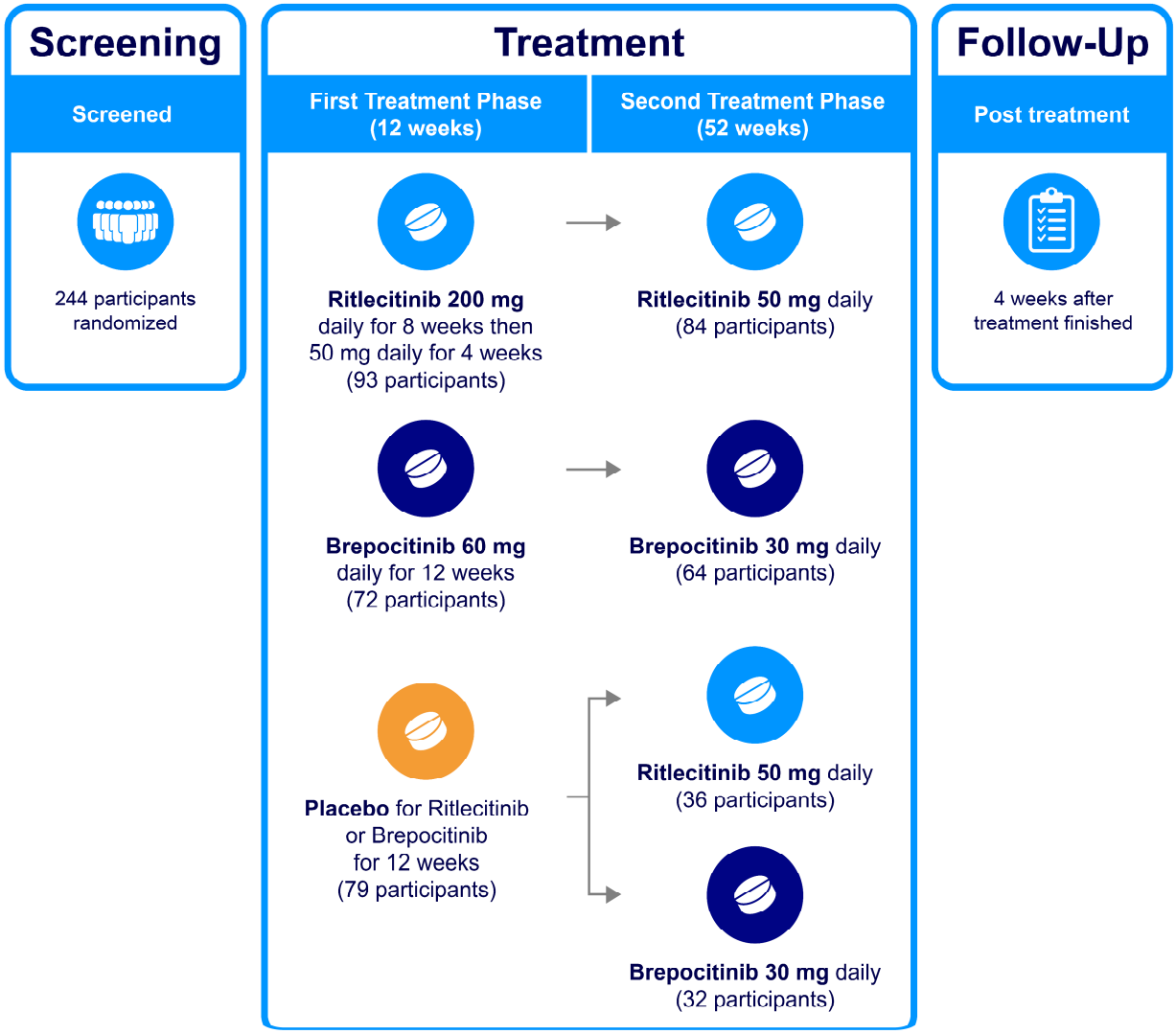
- Participants in one of these groups then had a 2 in 3 chance of being assigned to take ritlecitinib and a 1 in 3 chance of being assigned to take the placebo for ritlecitinib.
- Participants in the other group had a 2 in 3 chance of being assigned to take brepocitinib and a 1 in 3 chance of being assigned to take the placebo for brepocitinib.

- The study participants and researchers did not know who took ritlecitinib or brepocitinib and who took the placebo. This is known as a “double-blind” part of the study.
- After 27 July 2021, no new participants were assigned to take brepocitinib or the placebo for brepocitinib. This was due to a Sponsor business decision. Participants who joined the 1st phase of the study after 27 July 2021 had a 2 in 3 chance of being assigned to take ritlecitinib and a 1 in 3 chance of being assigned to take the placebo for ritlecitinib.

After the 1st phase, the 2nd treatment phase lasted 52 weeks. In the 2nd phase both the participants and the researchers knew which treatment each participant took. This is called an “open-label” part of the study. Participants were assigned to treatments based on which treatment they had received during the 1st phase.

The treatments and doses that participants took in the study are shown in Figure 1.

Figure 1: Study Plan



Researchers took samples of blood and urine from the participants during the study. Researchers checked the participants' health and asked them how they were feeling. Participants had an endoscopy at screening, at the end of the 1st phase (Week 12) and at the end of the 2nd phase (Week 64). The endoscopy results were used to find each participant's SES-CD scores.

Researchers compared the results of study participants taking ritlecitinib or brepocitinib to the results of study participants taking placebo. They looked the placebo results as one group for participants in the 1st phase.

Where did this study take place?

The Sponsor ran this study at 140 locations across 26 countries in Africa, America, Asia, Australia, Europe, the Middle East, and Russia.

When did this study take place?

It began 02 February 2018 and ended 19 October 2023.

Who participated in this study?

The study included adult participants with Crohn's disease of the last part of the small bowel, or the large bowel, or both. The participant's Crohn's disease had to have been diagnosed at least 3 months before they started the study.

- A total of 137 men participated
- A total of 107 women participated
- All participants were between the ages of 18 and 71 years.

1st Phase

Of the 244 participants who started the study, 217 participants finished the 1st phase. A total of 27 participants stopped taking study treatment in the 1st phase. The most common reasons for this were:

- A medical problem (14 participants)
- The participant left the study by their choice (4 participants)
- The study medication did not work well enough for the participant (4 participants).

2nd Phase

A total of 216 participants were treated in the 2nd phase and 120 of these participants finished the 2nd phase. A total of 96 participants stopped taking study treatment in the 2nd phase. The most common reasons for this were:

- A medical problem (39 participants)
- The participant left the study by their choice (25 participants)
- The study medication did not work well enough for the participant (24 participants).

How long did the study last?

Study participants were in the study for around 64 weeks. The entire study took around 5 years and 8 months to complete.

When the study ended in October 2023, the Sponsor began reviewing the information collected. The Sponsor then created a report of the results. This is a summary of that report.

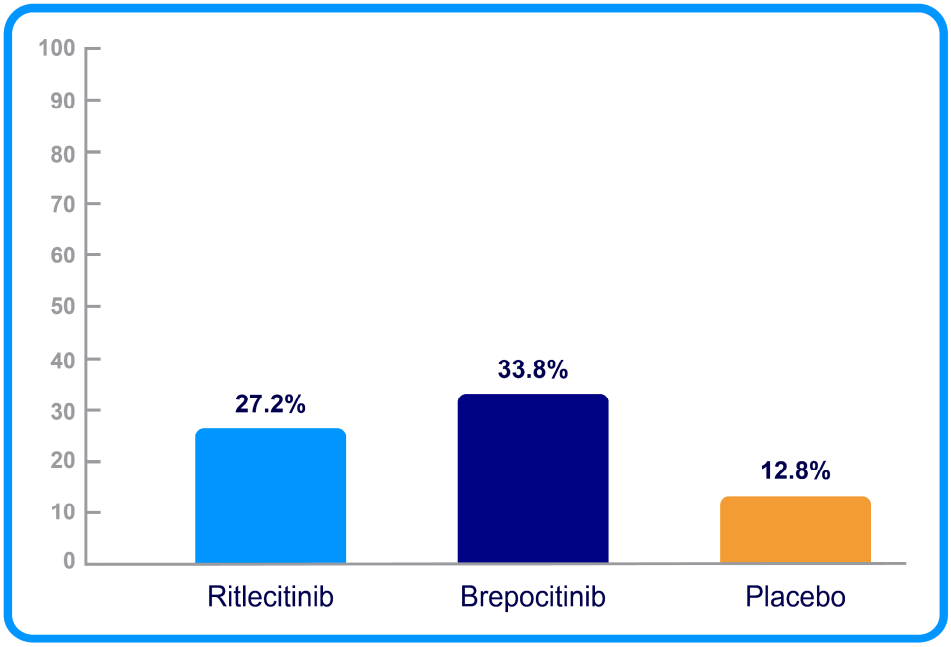
What were the results of the study?

How many participants had their SES-CD score reduced by 50% or more after 12 weeks of treatment with ritlecitinib or brepocitinib compared to placebo?

To answer this question, the researchers used the SES-CD score to assess the activity level of the participants' Crohn's disease. They compared the scores from before the participants started study treatment to when they finished Week 12. Week 12 was at the end of the 1st phase. The researchers counted the percentage of participants whose score reduced (improved) by 50% or more.

The results are shown in Figure 2 below.

Figure 2: Percentage of participants with a reduction in their SES-CD score of 50% or more after 12 weeks of treatment



The percentage of participants who had an improvement of 50% or more in their Crohn's disease activity score was 27.2% for participants taking ritlecitinib, 33.8% for participants taking brepocitinib, and 12.8% for participants taking placebo.

- A total of 25 out of 92 (27.2%) participants who took ritlecitinib had an improvement in their Crohn's disease activity score of 50% or more. This total was 24 out of 71 (33.8%) participants who took brepocitinib, and 10 out of 78 (12.8%) participants of participants who took a placebo.

How many participants experienced meaningful abnormal laboratory test results, abnormal vital signs, or abnormal results for the electrical activity of their heart during the study?

Overall, researchers found that no participants who took ritlecitinib or brepocitinib had any meaningful abnormal results.

Based on all these results, the researchers have decided that the results are not likely the result of chance. Ritlecitinib or brepocitinib may be helpful in treating Crohn's disease.

This does not mean that everyone in this study had these results. This is a summary of just some of the main results of this study. Other studies may have different results.

What medical problems did participants have during the study?

The researchers recorded any medical problems the participants had during the study. Participants could have had medical problems for reasons not related to the study (for example, caused by an underlying disease or by chance). Or, medical problems could also have been caused by a study treatment or by another medicine the participant was taking. Sometimes the cause of a medical problem is unknown. By comparing medical problems across many treatment groups in many studies, doctors try to understand what effects a study medication might have on a participant.

1st Phase

During the 1st phase of the study, 146 out of 244 (59.8%) participants had at least 1 medical problem. One participant left the study during the 1st phase because of medical problems.

The most common medical problem – a problem reported by more than 10% of participants – was a worsening of Crohn's disease symptoms. This was reported by:

- 8 out of 79 (10.1%) participants in the placebo group
- 3 out of 93 (3.2%) participants in the ritlecitinib group, and
- 2 out of 72 (2.8%) participants in the brepocitinib group.

2nd Phase

During the 2nd phase of the study, 169 out of 216 (78.2%) participants had at least 1 medical problem. One participant left the study during the 2nd phase because of medical problems. The most common medical problems – those reported by more than 10% of participants in any treatment group – are described below.

Below are instructions on how to read Table 1.

Instructions for Understanding Table 1.

- The **1st** column of Table 1 lists medical problems that were commonly reported during the study. All medical problems reported by more than 10% of participants in any treatment group are listed.
- The **2nd** column tells how many of the 36 participants who took placebo in the 1st phase and ritlecitinib in the 2nd phase reported each medical problem. Next to this number is the percentage of the 36 participants who reported the medical problem.
- The **3rd** column tells how many of the 84 participants who took ritlecitinib in the 1st phase and ritlecitinib in the 2nd phase reported each medical problem. Next to this number is the percentage of the 84 participants who reported the medical problem.
- The **4th** column tells how many of the 32 participants who took placebo in the 1st phase and brepocitinib in the 2nd phase reported each medical problem. Next to this number is the percentage of the 32 participants who reported the medical problem.

- The **5th** column tells how many of the 64 participants who took brepocitinib in the 1st phase and brepocitinib in the 2nd phase reported each medical problem. Next to this number is the percentage of the 64 participants who reported the medical problem.
- Using these instructions, you can see that 7 out of the 36 (19.4%) participants who took placebo then ritlecitinib reported worsening of Crohn's disease symptoms. A total of 12 out of the 84 (14.3%) participants who took ritlecitinib then ritlecitinib reported a worsening of Crohn's disease symptoms. A total of 4 out of 32 (12.5%) participants who took placebo then brepocitinib reported a worsening of Crohn's disease symptoms. A total of 11 out of 64 (17.2%) participants who took brepocitinib then brepocitinib reported a worsening of Crohn's disease symptoms.

Table 1. Commonly reported medical problems by study participants in the 2nd phase of the study

Medical Problem	Placebo then ritlecitinib (36 Participants)	Ritlecitinib then ritlecitinib (84 Participants)	Placebo then brepocitinib (32 Participants	Brepocitinib then brepocitinib (64 Participants)
Worsening of Crohn's disease symptoms	7 out of 36 participants (19.4%)	12 out of 84 participants (14.3%)	4 out of 32 participants (12.5%)	11 out of 64 participants (17.2%)
Abdominal pain	5 out of 36 participants (13.9%)	5 out of 84 participants (6.0%)	4 out of 32 participants (12.5%)	6 out of 64 participants (9.4%)
Positive COVID-19 test	6 out of 36 participants (16.7%)	4 out of 84 participants (4.8%)	4 out of 32 participants (12.5%)	8 out of 64 participants (12.5%)
Acne	4 out of 36 participants (11.1%)	1 out of 84 participants (1.2%)	1 out of 32 participants (3.1%)	2 out of 64 participants (3.1%)
Insomnia (difficulty sleeping)	4 out of 36 participants (11.1%)	0	1 out of 32 participants (3.1%)	0

Did study participants have any serious medical problems?

A medical problem is considered “serious” when it is life-threatening, needs hospital care, or causes lasting problems.

During the 1st phase of the study, 14 out of 244 (5.7%) participants had serious medical problems. The most common serious medical problem was a worsening of Crohn’s disease symptoms.

- A total of 6 out of 79 (7.6%) participants who took placebo had serious medical problems. None of these medical problems were believed to be related to the study treatment.
- A total of 4 out of 93 (4.3%) participants who took ritlecitinib had serious medical problems. This included 1 participant who had **fever** and 1 participant who had **worsening of Crohn’s disease symptoms** that the researchers believed were related to the study treatment.
- A total of 4 out of 72 (5.6%) participants who took brepocitinib had serious medical problems. These included 1 participant who had an **infection from a germ called “cytomegalovirus”** and 1 participant who had **gut inflammation caused by cytomegalovirus** that the researchers believed were related to the study treatment.

During the 2nd phase of the study, 37 out of 216 (17.1%) participants had serious medical problems. The most common serious medical problem was a worsening of Crohn's disease symptoms.

- A total of 10 out of 84 (11.9%) participants in the group who took ritlecitinib in the 1st phase of the study and ritlecitinib in the 2nd phase had serious medical problems. These included 1 participant who had **low levels of white blood cells called lymphocytes** and who reported **feeling sick** that the researchers believed were related to the study treatment.
- A total of 6 out of 36 (16.7%) participants who took placebo in the 1st phase of the study then ritlecitinib in the 2nd phase had serious medical problems. This included 1 participant who had **gut inflammation caused by a type of germ called "*Clostridium difficile*"** that researchers believed was related to the study treatment.
- A total of 16 out of 64 (25.0%) participants who took brepocitinib in the 1st phase of the study and brepocitinib in the 2nd phase had serious medical problems. This included 1 participant who had a **heart attack** that the researchers believed was related to the study treatment.
- A total of 5 out of 32 (15.6%) participants who took placebo in the 1st phase of the study and brepocitinib in the 2nd phase who had serious medical problems. None of these medical problems were believed to be related to the study treatment.

No participants died during the study.

Where can I learn more about this study?

If you have questions about the results of your study, please speak with the doctor or staff at your study site.

For more details on your study protocol, please visit:

www.pfizer.com/research/research_clinical_trials/trial_results	Use the protocol number B7981007

The full scientific report of this study is available online at:

www.clinicaltrials.gov	Use the study identifier **NCT03395184**
www.clinicaltrialsregister.eu	Use the study identifier 2017-003359-43

Please remember that researchers look at the results of many studies to find out which medicines can work and are safe for patients.

Again, if you participated in this study, **thank you** for volunteering. We do research to try to find the best ways to help patients, and you helped us to do that!