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: PF-06650833 (Zimlovisertib), PF-06651600 (Ritlecitinib), and Tofacitinib

Protocol Number: B7921023

Dates of Study: 29 July 2020 to 07 February 2022

Title of this Study: A Study to Assess the Efficacy and Safety of PF-06650833, PF-06651600, and Tofacitinib Alone and in Combination in Active Rheumatoid Arthritis

[A 24-Week Randomized, Double-Blind, Parallel Group, Active Comparator, Multicenter Study to Assess the Efficacy and Safety of PF-06650833, PF-06651600 (Ritlecitinib) and Tofacitinib Alone and in Combination in Participants With Moderately-Severely Active Rheumatoid Arthritis With an Inadequate Response to Methotrexate]

Date(s) of this Report: 17 March 2023

– 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 rheumatoid arthritis?

Rheumatoid arthritis, or "RA", is a disease that causes swelling, pain, and stiffness in the joints. RA is an "autoimmune disease", which means that patients with RA have an overactive immune system that attacks healthy parts of the body by mistake, such as the joints. RA can cause permanent damage to the joints if it goes unchecked.

What is methotrexate and what are DMARDs?

The standard treatment for RA is with medicines known as disease modifying anti-rheumatic drugs (DMARDs). DMARDs work to decrease pain and inflammation, reduce or prevent joint damage, and slow the progression of RA. Methotrexate is a type of DMARD and is often the first medicine given in the treatment of RA. All participants in this study had previously received methotrexate to treat their RA but their response was said to be "inadequate", meaning it was not good enough.

Researchers are looking for new RA treatments which may help to completely block joint inflammation and prevent joint damage.

What are tofacitinib, PF-06650833, and PF-06651600?

Tofacitinib (tow-fah-sit-in-ib), also known by the trade name Xeljanz®, is a medicine that has been approved and is available by prescription to treat adults with active, moderate to severe RA.

PF-06650833 (also known as zimlovisertib [zim-low-vih-ser-tib], and PF-06651600 (also known as ritlecitinib [rit-leh' sih-tih-nib], are investigational medicines that researchers think may help with the treatment of RA. Neither of these medicines were approved for general use for the treatment of RA at the time of this study.

Tofacitinib, PF-06650833, and PF-06651600 all work by reducing the activity of the immune system and decreasing inflammation. They do this by blocking certain

proteins known to be involved in controlling signals to the immune system. The specific protein(s) blocked by each of these study medicines are not all the same.

What was the purpose of this study?

The main purpose of the study was to find out if taking a combination of study treatments (either PF-06650833 + tofacitinib or PF-06650833 + PF-06651600) was more effective at relieving RA symptoms compared to taking tofacitinib alone.

Researchers wanted to know:

Did participants taking a combination of PF-06650833 + tofacitinib or PF-06650833 + PF-06651600 have more improvement in their RA disease activity after 12 weeks of treatment compared to participants taking tofacitinib alone?

What happened during the study?

How was the study done?

Participants were put into 1 of 5 treatment groups. Each participant took their study treatment, as tablets, once a day by mouth. The treatment groups were as follows:

- PF-06650833 400 milligrams (mg) + tofacitinib 11 mg in combination
- PF-06650833 400 mg + PF-06651600 100 mg in combination
- Tofacitinib 11 mg alone
- PF-06650833 400 mg alone
- PF-06651600 100 mg alone

Participants were assigned to each treatment group by chance alone. This is known as a "randomized" study. This trial was also "double-blinded". This means that participants and doctors did not know who was given each of the different study treatments. This was done to make sure that the trial results were not influenced in any way.

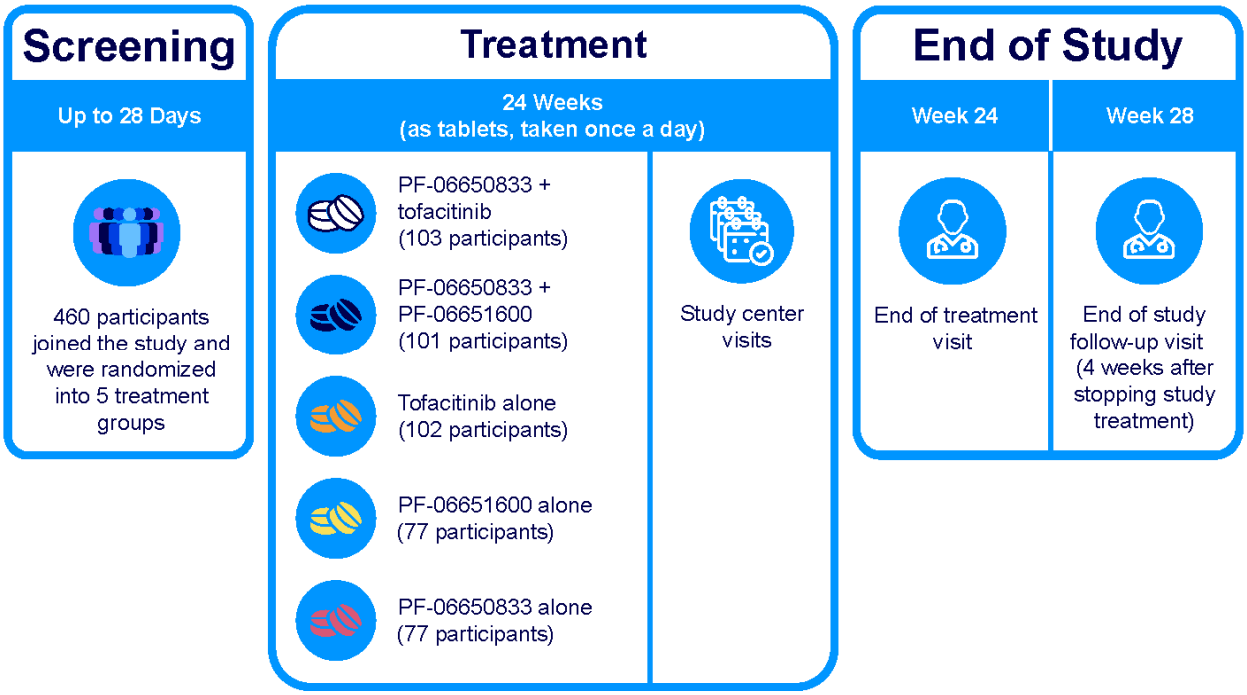
Participants received up to 24 weeks of study treatment. Participants were expected to attend 8 study center visits during the treatment phase: at Day 1, and at Weeks 2, 4, 8, 12, 16, 20, and 24. There was an additional end of study follow-up visit at Week 28 (or 4 weeks after stopping study treatment). Researchers measured the participants' RA disease activity and took samples of blood and urine from the participants at various times during the study. They also checked the participants' health and asked them how they were feeling.

Researchers measured the participants' RA disease activity using a scoring system called the "DAS28-CRP". DAS stands for "disease activity score", and the number 28 refers to the 28 joints that are examined in this assessment. CRP stands "C-reactive protein". The levels of this protein increase when there is inflammation in the body.

This report summarizes the findings for the "primary endpoint" in the study. The primary endpoint is analyzed to answer the main question in a study. The primary endpoint in this study looked at improvement in RA disease activity after participants had taken study treatment for 12 weeks (ie, at Week 12). This report also summarizes medical problems that participants had during the study. Medical problems were assessed over the full 24 weeks of treatment and during a 4-week follow-up period after stopping the study treatment.

The figure on the next page shows what happened during the entire study.

Figure 1. Study Design



Where did this study take place?

The Sponsor ran this study at 77 locations in 10 countries in Europe, North America, South America, and Asia.

When did this study take place?

It began 29 July 2020 and ended 07 February 2022.

Who participated in this study?

The study included adult participants who:

- Had a confirmed diagnosis of active, moderate to severe RA
- Had received methotrexate for treatment of their RA before joining the study
- Had been assessed by a study doctor as having an inadequate response to methotrexate treatment

Overall, 104 men and 356 women participated in the study. All participants were between the ages of 21 and 71.

Participants were to be treated for 24 weeks overall. The primary endpoint was studied after participants had taken study treatment for 12 weeks. Of the 460 participants who started the study, 408 participants (89%) completed 12 weeks of treatment, and 321 participants (70%) completed 24 weeks of treatment.

Overall, 430 participants entered and completed follow-up, and 30 participants did not complete follow-up. The most common reason for not completing follow-up was due to the participant's own choice to leave the study.

How long did the study last?

Participants were in the study for up to 32 weeks (which included the screening period, 24-week treatment period, and 4-week follow-up period). The entire study took about 1 year and 6 months to complete. This is because participants started the study at different times.

When the study ended in February 2022, the Sponsor reviewed the information collected. The Sponsor then created a report of the results. This is a summary of that report.

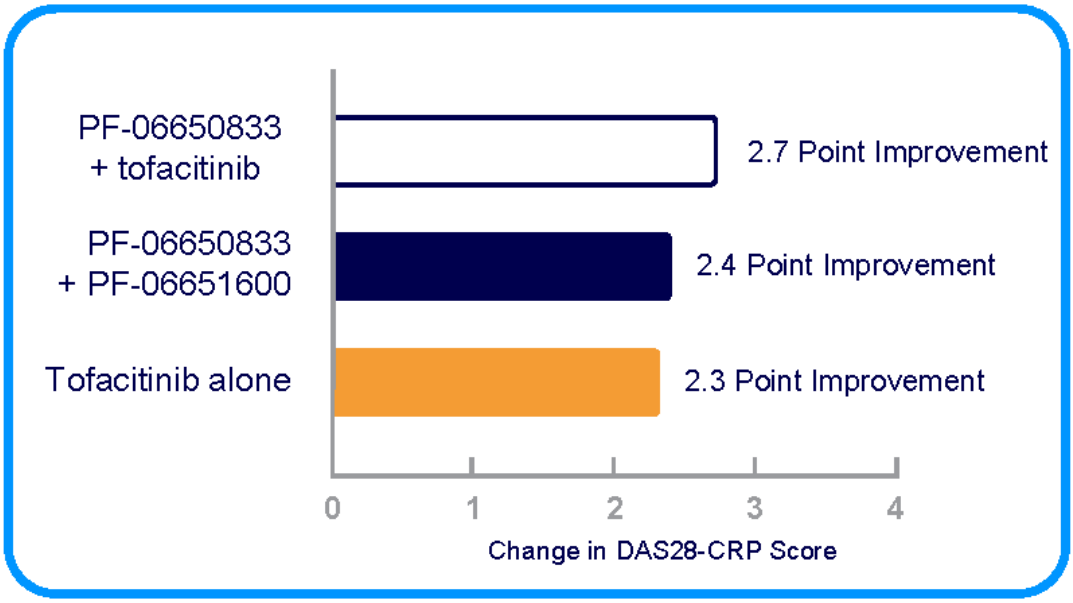
What were the results of the study?

Did participants taking PF-06650833, PF-06651600, and tofacitinib, either alone or as a combination treatment, have an improvement in their RA disease activity after 12 weeks of treatment?

To answer this question, the researchers compared each participant's DAS28-CRP score at Week 12 with their score at the start of the study. A lower DAS28-CRP score at Week 12 compared with the start of the study indicated an improvement in a participant's RA disease activity. A bigger change in DAS28-CRP score showed more improvement.

After 12 weeks of treatment, an improvement in RA disease activity was seen for all treatment groups. Figure 2 shows results for the following treatment groups: PF-06650833 + tofacitinib, PF-06650833 + PF-06651600, and tofacitinib alone.

Figure 2. Average Improvement in Rheumatoid Arthritis Disease Activity at Week 12



Did participants taking a combination of PF-06650833 + tofacitinib have more improvement in their RA disease activity compared to participants taking tofacitinib alone?

Participants taking a combination of PF-06650833 + tofacitinib had an average improvement in their RA disease activity of 2.7 points, while participants taking tofacitinib alone had an average improvement of 2.3 points.

Based on these results, the researchers have decided that the difference between the groups are not likely the result by chance. A combination of PF-06650833 + tofacitinib may be a better treatment than tofacitinib alone to help with decreasing the symptoms and severity of RA.

Did participants taking a combination of PF-06650833 + PF-06651600 have more improvement in their RA disease activity compared to participants taking tofacitinib alone?

Participants taking a combination of PF-06650833 + PF-06651600 had an average improvement of 2.4 points in their RA disease activity, while participants taking tofacitinib alone had an average improvement of 2.3 points.

Based on these results, the researchers have decided that the difference between the groups could have been due to chance. This means the study results did not suggest a combination of PF-06650833 + PF-06651600 was better than tofacitinib alone to help with decreasing the symptoms and severity of RA.

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.

Overall, 246 out of 460 participants (53%) in this study had at least 1 medical problem. A total of 22 participants (5%) stopped taking study treatment because of medical problems, and 4 additional participants (less than 1%) left the study because of medical problems.

Table 1 shows the most common medical problems in the study - those reported by at least 3% of participants in total.

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 at least 3% of participants in total are listed.
- The **2nd – 5th** columns tell how many of the participants in each treatment group reported each medical problem. Next to this number is the percentage of the participants taking the study treatment who reported the medical problem.
- Using these instructions, you can see that 4 out of the 103 participants (4%) taking PF 06650833 + tofacitinib reported a positive COVID-19 test. A total of 8 out of the 101 participants (8%) taking PF-06650833 + PF-06651600 reported a positive COVID-19 test.

Table 1. Commonly reported medical problems in the study

Medical Problem	PF-06650833 + tofacitinib (103 Participants)	PF-06650833 + PF-06651600 (101 Participants)	Tofacitinib alone (102 Participants)	PF-06651600 alone (77 Participants)	PF-06650833 alone (77 Participants)
Positive test for coronavirus disease (COVID-19)	4 out of 103 participants (4%)	8 out of 101 participants (8%)	7 out of 102 participants (7%)	1 out of 77 participants (1%)	2 out of 77 participants (3%)
Headache	3 out of 103 participants (3%)	7 out of 101 participants (7%)	4 out of 102 participants (4%)	4 out of 77 participants (5%)	2 out of 77 participants (3%)
Infection of the kidney, bladder, or urethra	7 out of 103 participants (7%)	3 out of 101 participants (3%)	5 out of 102 participants (5%)	1 out of 77 participants (1%)	1 out of 77 participants (1%)
Feeling like about to vomit (nausea)	1 out of 103 participants (1%)	3 out of 101 participants (3%)	4 out of 102 participants (4%)	5 out of 77 participants (7%)	2 out of 77 participants (3%)
Common cold	3 out of 103 participants (3%)	6 out of 101 participants (6%)	3 out of 102 participants (3%)	2 out of 77 participants (3%)	1 out of 77 participants (1%)
Joint pain	2 out of 103 participants (2%)	2 out of 101 participants (2%)	3 out of 102 participants (3%)	5 out of 77 participants (7%)	1 out of 77 participants (1%)
Rheumatoid arthritis	1 out of 103 participants (1%)	1 out of 101 participants (1%)	3 out of 102 participants (3%)	4 out of 77 participants (5%)	4 out of 77 participants (5%)

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.

In total, 10 out of 460 participants (2%) had at least 1 serious medical problem. These were reported as follows in each of the treatment groups:

- No participants (0%) in the PF-06650833 + tofacitinib group
- 1 out of 101 participants (1%) in the PF-06650833 + PF-06651600 group
- 3 out of 102 participants (3%) in the tofacitinib alone group
- 3 out of 77 participants (4%) in the PF-06651600 alone group
- 3 out of 77 participants (4%) in the PF-06650833 alone group

There were no serious medical problems that occurred in more than 1 participant. None of the serious medical problems were considered to be related to the study treatment.

There was 1 participant (in the tofacitinib alone group) who died during the study. The participant's death was due to severe COVID-19 and was not considered to be related to the study treatment.

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 **B7921023**

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

www.clinicaltrials.gov	Use the study identifier **NCT04413617**
www.clinicaltrialsregister.eu	Use the study identifier **2019-002676-14**

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!