Summary of Clinical Trial Results

A study to look at whether 2 different doses of a medicine called tocilizumab were safe and worked to treat COVID-19 pneumonia

See the end of the summary for the full title of the study.

About this summary

This is a summary of the results of a clinical trial (called a 'study' in this document) – written for:

- People who took part in the study.
- Members of the public.

This study, called MARIPOSA, started in May 2020 and ended in October 2020. This summary is based on the results known at the time it was written (July 2021).

One study can't tell us everything about the possible side effects of a medicine and whether a medicine works. It takes a lot of people in many studies to find out everything we need to know. The results from this study may be different from other studies with the same medicine.

- **This means that you should not make decisions based on this one summary. Always speak to your doctor before making any decisions about your treatment.**

Contents of the summary

Glossary

- COVID-19 = coronavirus disease 2019
- IL-6 = interleukin 6
- kg = kilogram
- mg = milligram

Thank you to the people who took part in this study

The people who took part in this study are helping researchers answer important questions about how a medicine called 'tocilizumab' works in people with moderate to severe COVID-19 pneumonia.

Key information about this study

- This study was done to look at whether a lower dose of a medicine called 'tocilizumab' was safe and worked in a similar way as a higher dose to treat people with moderate to severe COVID-19 pneumonia (an inflammation in the lungs).
- The doses of tocilizumab were based on the person's weight. 97 people in the United States were given either 4 or 8 milligrams of tocilizumab for every kilogram (equal to 2.2 pounds) of body weight (written as 4 mg/kg or 8 mg/kg).
- 49 people received 4 mg/kg tocilizumab and 48 people received 8 mg/kg tocilizumab. It was decided by chance which dose each person was given.
- The study showed that there were some small differences in how the 4 and 8 mg/kg doses affected certain proteins of the immune system. However, there were no differences for many proteins or tests investigated.
- The results from this study still do not tell us if a 4 mg/kg dose of tocilizumab should be used instead of an 8 mg/kg dose to treat people with moderate to severe COVID-19 pneumonia.
- 2 people who were given 4 mg/kg tocilizumab and 1 person who was given 8 mg/kg tocilizumab had a side effect that was thought to be related to study treatment.
- 1 person in the 8 mg/kg group had a serious side effect that was thought to be related to the study treatment. None of the people in the 4 mg/kg group had a serious side effect that was thought to be related to the study treatment.

1. General information about this study

Why was this study done?

About 20 out of 100 people who get COVID-19 (also called 'coronavirus disease 2019') will get severe swelling (inflammation) in the lungs called pneumonia. Some people with severe COVID-19 can also get a life-threatening form of inflammation in the lungs called 'acute respiratory distress syndrome'.

The body's immune system has cells and proteins that fight infections. In most people with severe COVID-19, the immune system makes too many of some proteins (this is called an 'overactive immune system'). The study medicine, tocilizumab, blocks the action of one of these proteins called interleukin 6 (also called 'IL-6'). Other studies have shown that tocilizumab is generally safe and works well in people with diseases caused by either inflammation in the body or an overactive or abnormal response by the immune system. Researchers wanted to see if tocilizumab could also work well to treat the overactive immune response some people have when they get severe COVID-19 pneumonia.

In most studies of tocilizumab in people with COVID-19 pneumonia, people were given the 8 mg/kg dose. However, some studies have used the lower 4 mg/kg dose. The exact dose of tocilizumab that should be used in people with COVID-19 pneumonia is not known.

What is the study medicine?

This study looked at a medicine called **'tocilizumab'** (known by its brand names, Actemra® or RoActemra®)

- You say this as 'toe–si–liz–oo–mab'.
- Tocilizumab works by blocking the action of a protein in the body called 'IL-6'. Too much IL-6 protein can be a part of an overactive (abnormal) response of the immune system.
- Tocilizumab is already approved to be given to adults and children with rheumatoid arthritis, some types of juvenile arthritis, giant cell arteritis, and cytokine release syndrome – an overactive immune response caused by a cancer treatment called CAR T-cell therapy.
- Researchers thought that tocilizumab could help people with severe COVID-19 pneumonia by blocking the action of IL-6.

What did researchers want to find out?

- Researchers did this study to see whether a lower dose of tocilizumab (4 mg/kg) would work the same as a higher dose (8 mg/kg) (see section 4 'What were the results of the study?').
- They also wanted to find out if the 2 different doses of tocilizumab were safe – by checking how many people had side effects (see section 5 'What were the side effects?').

The main questions that researchers wanted to answer were:

1. How quickly did the different doses of tocilizumab move through people's bodies during the study?
2. How did the different doses of tocilizumab affect the amounts of immune system proteins in the blood?

Other questions that researchers wanted to answer included:

3. What was the health condition of people at Day 28 of the study? (28 days after they received either dose of tocilizumab.)
4. How many people had left the hospital or were ready to leave by Day 28 of the study?
5. How many people had died by Day 28 of the study?
6. How many people needed a ventilator to help them breathe up to Day 28 of the study?

What kind of study was this?

The study was **'randomised'**. This means that it was decided by chance which dose of tocilizumab that people would be given – like tossing a coin.

This was a **'open-label'** study. This means that both the people taking part and the study doctors knew which of the doses people were taking.

When and where did this study take place?

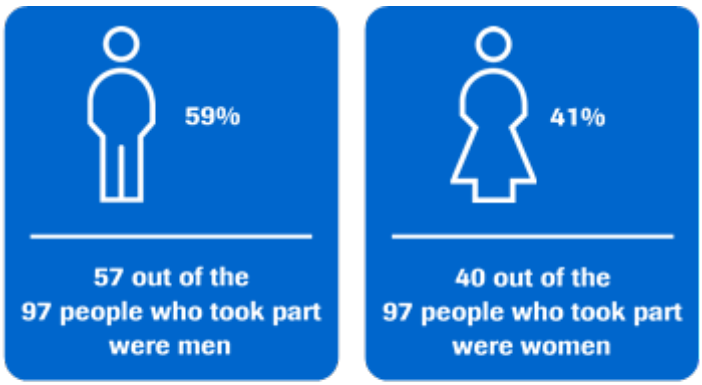
The study started in May 2020 and ended in October 2020.

The study took place at 26 study centres in the United States.

2. Who took part in this study?

In this study, 97 people with moderate to severe COVID-19 pneumonia were given a dose of either 4 mg/kg or 8 mg/kg of tocilizumab.

Here is more information about the people who took part in the study.



Age range: 25 to 91 years old

People could take part in the study if:

- They were at least 18 years old and
- They had a positive test for SARS-CoV-2 (the virus that causes COVID-19) and
- They had changes to their lungs that are usually seen in people with COVID-19 pneumonia and
- They had a blood oxygen level lower than 93% or
- They had a high level of C-reactive protein —an immune system protein that increases with inflammation —more than twice the normal amount.

People could not take part in the study if:

- They had an allergic reaction to tocilizumab or similar medication.
- They were on a machine to help them breathe – called a ventilator – for more than 24 hours or were receiving treatment to put oxygen in the blood called 'extracorporeal membrane oxygenation' or ECMO.
- They had very low blood pressure (called shock).
- They had an active infection other than COVID-19.
- They had taken a medication that prevents organ rejection or affects the immune system (including tocilizumab) in the 3 months before the study.
- They had tests showing that an organ in their body like their kidney or liver was not working normally.

3. What happened during the study?

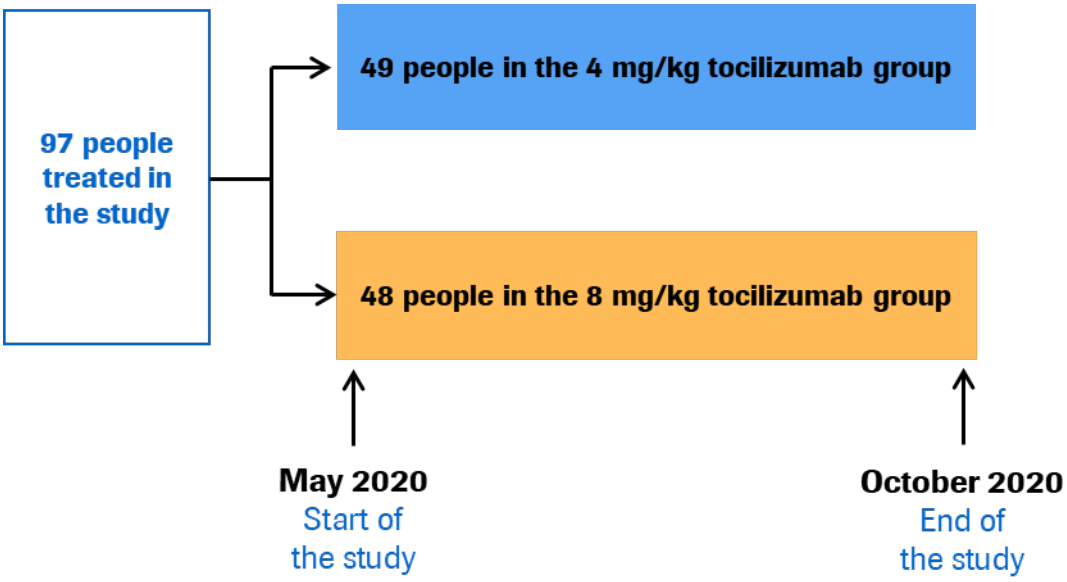
At the start of the study, 100 people had been selected to take part. All of these people were randomly assigned by a computer to be treated with a dose of either **4 mg/kg tocilizumab** or **8 mg/kg tocilizumab**.

Some of these people left the study before treatment, so only 97 people were given one of the study treatments.

People were treated with either **4 mg/kg tocilizumab** or **8 mg/kg tocilizumab** given by drip (infusion) into a vein. A second infusion could be given after 8 to 24 hours if the person had symptoms that did not improve or got worse.

All the people in this study were also given the 'standard-of-care treatment' for severe COVID-19 pneumonia (the usual treatment based on local guidelines and recommendations for doctors). This could include oxygen and medicines that reduce inflammation (steroids) or virus activity in the body (antivirals).

This picture shows what happened in the study.



- In the 4 mg/kg group, 37 people were given 1 dose of tocilizumab, and 12 people were given 2 doses.
- In the 8 mg/kg group, 39 people were given 1 dose of tocilizumab, and 9 people were given 2 doses.

4. What were the results of the study?

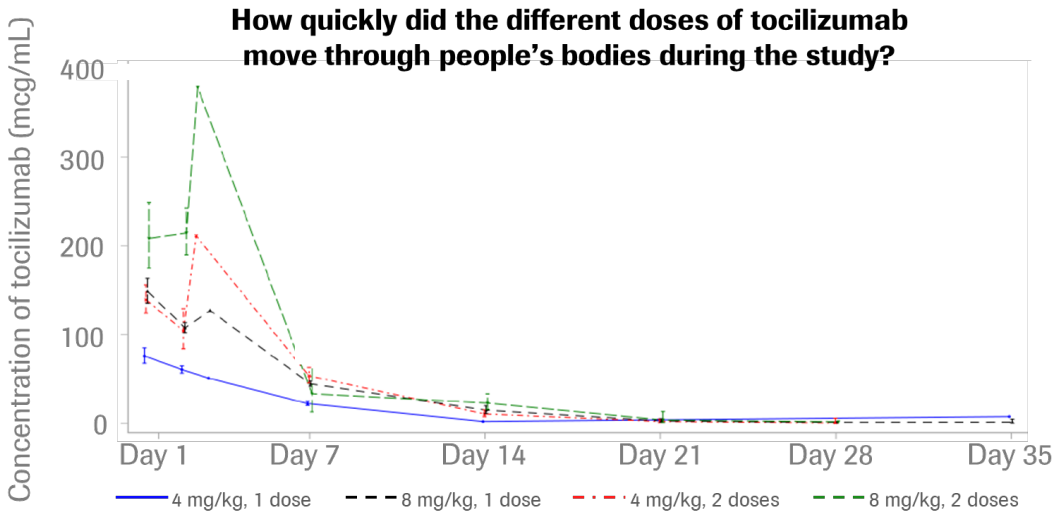
This section shows the main results from this study. You can find information about other results on the websites at the end of this summary (see section 8).

Question 1: How quickly did the different doses of tocilizumab move through people's bodies during the study?

Researchers wanted to know how quickly the study medicine moved through people's bodies in the study. Researchers tested how quickly tocilizumab moved through people's bodies by measuring how much of it was in people's blood at different times during the study.

- After each dose of tocilizumab, the amount of the drug in the blood increased and then decreased over time.
- Drug levels were higher in people who received 1 dose of 8 mg/kg compared with people who received 1 dose of 4 mg/kg.
- In people who were given 2 doses of 4 mg/kg, tocilizumab moved through the bodies in a way that was similar to people given 1 dose of 8 mg/kg.

This picture shows the amounts of tocilizumab in the blood over time.



Each color on the graph shows the average measurement of tocilizumab in the blood from all the people who were given 1 or 2 doses of either 4 mg/kg or 8 mg/kg tocilizumab.

Question 2: How did the different does of tocilizumab affect the levels of certain immune system proteins in the blood?

Researchers can also see how tocilizumab is working by looking at the levels of certain immune system proteins in the blood. In this study, the researchers looked at 4 different proteins – called soluble IL-6 receptor, IL-6, ferritin, and C-reactive protein. High levels of these proteins can be a sign of inflammation in the body. Researchers measured the levels of these 4 proteins in the blood stream at different times during the study.

There were some differences between the 4 mg/kg and 8 mg/kg groups in the levels of soluble IL-6 receptor. There were no clear differences between groups in the levels of the other 3 proteins.

Question 3: What was the health condition of people at Day 28 of the study? (28 days after they received either dose of tocilizumab)

Researchers also looked at people's health condition (based on the medical care they needed to help them breathe or help their organs to work) on Day 28 of the study.

Health condition was scored on a scale from 1 to 7, with 1 being the best health condition (the person left the hospital or was ready to leave the hospital) and 7 the worst (the person died).

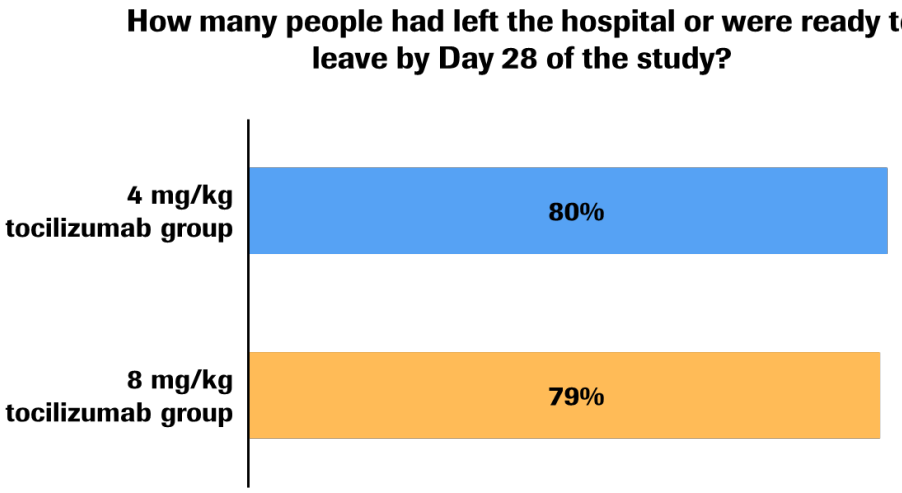
There was no clear difference in health condition between people receiving either dose of tocilizumab at Day 28.

- In the 4 mg/kg group, the median health condition score was 1 at Day 28.
- In the 8 mg/kg group, the median health condition score was 1 at Day 28.

Question 4: How many people had left the hospital or were ready to leave by Day 28 of the study?

Researchers also wanted to know how many days it took for people to leave the hospital or be ready to leave by Day 28 of the study.

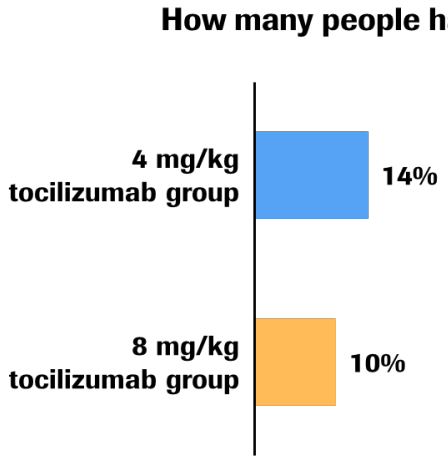
- In the 4 mg/kg group, 39 out of 49 people had left the hospital or were ready to leave by Day 28 of the study. This is 80%, or 80 out of 100 people.
- In the 8 mg/kg group, 38 out of 48 people had left the hospital or were ready to leave by Day 28 of the study. This is 79%, or 79 out of 100 people.



Question 5: How many people had died by Day 28 of the study?

Out of the 97 people who were given either 4 mg/kg or 8 mg/kg of tocilizumab, 12 people had died of any cause by Day 28 of the study.

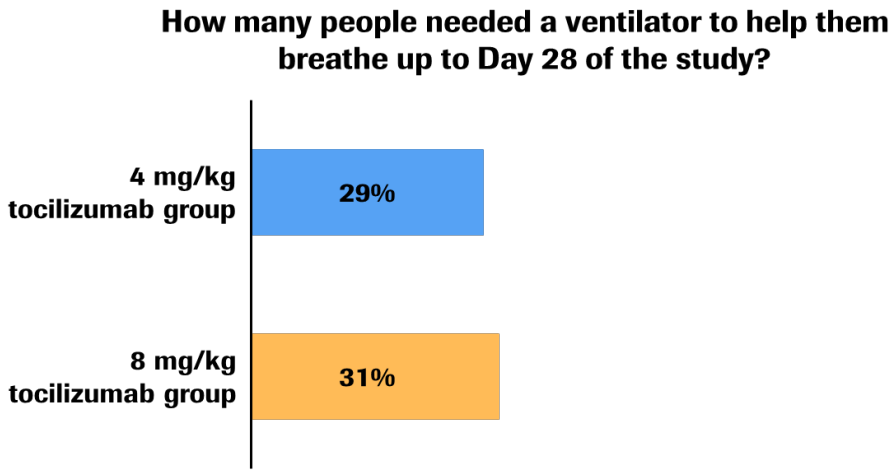
- In the 4 mg/kg group, 7 out of 49 people (14%) had died.
- In the 8 mg/kg group, 5 out of 48 people (10%) had died.
- The study researchers do not know if this is a real difference – it could have been caused by chance.



Question 6: How many people needed a ventilator to help them breathe up to Day 28 of the study?

Out of the 97 people who were given either 4 mg/kg or 8 mg/kg of tocilizumab, 29 people needed a ventilator to help them breathe up to Day 28 of the study.

- In the 4 mg/kg group, 14 out of 49 people (29%) needed a ventilator to help them breathe.
- In the 8 mg/kg group, 15 out of 48 people (31%) needed a ventilator to help them breathe.



5. What were the side effects?

Side effects are medical problems that happen during the study.

- They are described in this summary because the study doctor believed that the side effects might be related to the treatments in the study.
- Not all of the people in this study had a side effect.
- Side effects may be mild to serious and can be different from person to person.
- It is important to know that the side effects reported here are from this one study. This means that the side effects shown here may be different from those seen in other studies or those that are listed in the tocilizumab information sheet or leaflet.

Serious side effects

A side effect may be considered 'serious' if it is life-threatening, needs hospital care, or causes lasting problems.

- None of the people in the 4 mg/kg group had a serious side effect that was thought to be related to the study treatment.
- In the 8 mg/kg group, 1 out of 48 people (2%) had a serious side effect (an injury to the liver) that was thought to be related to the study treatment.

Most common side effects

A total of 3 out of 97 people (31%) had a side effect that the study doctor thought was related to the study treatment.

- In the 4 mg/kg group, 2 out of 49 people (4%) had a side effect. (1 person had a lower than normal amount of a type of white blood cell called a neutrophil, and 1 person had a higher than normal result of a test of liver function.)
- In the 8 mg/kg group, 1 out of 48 people (2%) had a side effect (an injury to the liver).

Other side effects

You can find information about other side effects (not shown in the sections above) on the websites listed at the end of this summary – see section 8.

6. How has this study helped research?

The information in this summary is from one study of 97 people with moderate to severe COVID-19 pneumonia who were treated with either 4 mg/kg or 8 mg/kg of tocilizumab. These results have helped researchers learn more about tocilizumab treatment for moderate to severe COVID-19 pneumonia.

The study showed that there were some differences in how the 4 mg/kg and 8 mg/kg doses of tocilizumab moved through people's bodies and how the different doses affected certain proteins in the body. The results from this study still do not tell us if a 4 mg/kg dose of tocilizumab should be used instead of an 8 mg/kg dose in people with moderate to severe COVID-19 pneumonia.

All of the side effects that were seen in people who were treated with tocilizumab in this study have been seen in other studies of tocilizumab or are known to be effects of COVID-19.

One study can't tell us everything about whether a medicine works and how safe it is. It takes a lot of people in many studies to find out everything we need to know. The results from this study may be different from other studies with the same medicine.

- **This means that you should not make decisions based on this one summary – always speak to your doctor before making any decisions about your treatment.**

7. Are there plans for other studies?

More studies are not currently planned. Researchers are looking at all of the results from the completed studies of tocilizumab treatment for COVID-19 pneumonia.

8. Where can I find more information?

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

- https://clinicaltrials.gov/ct2/show/NCT04363736
- https://forpatients.roche.com/en/trials/infectious-diseases/covid-19-pneumonia/a-study-to-investigate-intravenous-tocilizumab-in-parti-82314.html

Who can I contact if I have questions about this study?

If you have any more questions after reading this summary:

- Visit the ForPatients platform and fill out the contact form: https://forpatients.roche.com/en/trials/infectious-diseases/covid-19-pneumonia/a-study-to-investigate-intravenous-tocilizumab-in-parti-82314.html
- Contact your local Roche/Genentech office.

If you took part in this study and have any questions about the results:

- Speak to the study doctor or staff at the study hospital or clinic.

If you have questions about your own treatment:

- Speak to the doctor in charge of your treatment.

Who organised and paid for this study?

This study was organised and paid for by F. Hoffmann-La Roche Ltd, which has its headquarters in Basel, Switzerland.

Full title of the study and other identifying information

The full title of this study is: '**A phase II, open-label, randomized, multicenter study to investigate the pharmacodynamics, pharmacokinetics, safety, and efficacy of 8 mg/kg or 4 mg/kg intravenous tocilizumab in patients with moderate to severe COVID-19 pneumonia**.'

The study is known as 'MARIPOSA'.

- The protocol number for this study is: CA42481.
- The ClinicalTrials.gov identifier for this study is: NCT04363736.