A research study comparing the effect of a drug called rituximab with the effect of a drug called mycophenolate mofetil for the treatment of a medical condition called pemphigus vulgaris

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

Thank you!

Thank you to the people who took part in this clinical trial (called a 'study' in this document). The generous participation of these people is helping researchers answer important health questions about the treatment of pemphigus vulgaris. This study, PEMPHIX, was done to compare the effects of rituximab with the effects of mycophenolate mofetil (or 'MMF') on the symptoms of pemphigus vulgaris, to find out which drug is better.

We hope this summary helps you understand the results of this study. If you have any questions about these results, please speak with your study doctor.

About this summary

This is a summary of study results in patients with moderate to severe pemphigus vulgaris, written for:

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

Contents of the summary

The study started in May 2015 and ended in October 2019. This summary includes results of the study up to November 2018 when all patients had taken the study drugs for up to 52 weeks.

Patients were followed for up to 48 weeks after they stopped taking the study drugs. A separate summary of these results will be available sometime in 2020.

One study can't tell us everything about the risks and benefits of a medicine. It may take more people in more than one study to gather information about how well a medicine works and about its side effects. The results from this study may be different from results from other studies with the same medicine.

This means that you should not make decisions based on this one summary. Always talk to your doctor or healthcare provider before making any decisions about your treatment.

Key information about this study

- This study, named PEMPHIX, was done to compare a medicine called rituximab with another medicine called mycophenolate mofetil (or 'MMF') in people with a condition called 'pemphigus vulgaris' or 'PV'.
- In this study, people with moderate to severe PV were given either rituximab or MMF. It was decided by chance which treatment each person would receive.
- This study included 135 people in 10 countries; 67 people were given rituximab and 68 people were given MMF.
- At one centre in the United States, 10 of the 135 people in the study participated using telemedicine (the study doctor and patients used an iPhone to allow patients to participate in the study from their homes). The information from these patients contributed to the safety results but not the efficacy results.
- The study showed that after 52 weeks, 40.3% of people taking rituximab and 9.5% of people taking MMF had no symptoms of their disease and did not need to take steroids by mouth for 16 weeks or more.
- The side effects of rituximab were similar to those seen in people with other autoimmune diseases who were treated with rituximab.
- Patients were followed for up to 48 weeks after they stopped taking the study drugs. A summary of these results is expected sometime in 2020.

1. General information about this study

Why was this study done?

Pemphigus vulgaris, or 'PV'` causes painful blistering of the skin and mucous membranes lining the inside of the mouth, nose, and genitals. PV is a type of disease called an autoimmune disease. Under normal healthy conditions, the body's immune system makes proteins called 'antibodies' that help prevent or fight infection and protect the body against foreign material, such as bacteria and viruses. When a person has an autoimmune disease, the immune system mistakenly makes antibodies against parts of the person's own body. In people with PV, the immune system makes antibodies against their own skin and mucous membranes leading to blisters and sores.

People with PV are usually given medicines that decrease the activity of the immune system, such as steroids with or without mycophenolate mofetil (or 'MMF'). However, PV symptoms often come back during or after treatment with these medicines, and they can have severe side effects.

Rituximab plus steroids was shown in a previous clinical trial to be safer and work better than steroids alone in treating PV. Based on the results of that trial, rituximab was approved for the treatment of moderate to severe PV in the United States in 2018 and in Europe in 2019.

MMF has been available worldwide to treat other diseases, but it is not approved to treat PV. Steroids can have severe side effects, so doctors often give MMF to patients with PV along with steroids so patients can take lower doses of steroids. This study, PEMPHIX, was done to compare the effects, good or bad, of rituximab with the effects of MMF on symptoms of PV to find out which drug is better.

What was the study medicine?

Patients were randomly assigned to receive treatment with either rituximab intravenous infusion (given directly into the bloodstream) or MMF pills by mouth. Randomly assigned means that the patients were put into a treatment group by chance.

Rituximab works by decreasing the number of B cells in the blood and other tissues. B cells are a type of white blood cell that are part of the immune system and help the body to fight infection. In people with PV, B cells make the antibodies that cause symptoms. Rituximab may help improve the symptoms of PV by reducing the number of B cells that make these antibodies.

Rituximab (Rituxan® or MabThera®) is a medicine approved to treat:

- Pemphigus vulgaris (rituximab was not approved for PV when the PEMPHIX study was started)
- Two types of autoimmune disease of the blood vessels called granulomatosis polyangiitis and microscopic polyangiitis

- Rheumatoid arthritis, which is an autoimmune disease of the joints
- A type of blood cancer called non-Hodgkin's lymphoma
- A type of blood cancer called chronic lymphocytic leukaemia

MMF is a medicine that is approved worldwide for people who have had kidney, heart, or liver transplants to prevent the body from rejecting the transplanted organ. MMF has also been studied in people with autoimmune diseases; however, MMF is not approved for the treatment of PV. Several small clinical studies have shown that MMF may benefit patients with PV by stopping antibody production by B cells and allow patients to take lower amounts of steroids and possibly lower their risk of steroid-related side effects.

People taking part in PEMPHIX were taking steroids to treat their PV when they started the study. During the study, patients continued to take the steroids and rituximab or MMF was added. As symptoms of the disease got better, the steroid dose was gradually lowered. The goal was for the patients to stop taking steroids.

The patient and the study doctors did not know which treatment the patient received. Patients assigned to receive rituximab intravenous infusion also took a placebo pill that was made to look like MMF but did not contain any drug. Patients assigned to receive MMF also received a placebo intravenous infusion that did not contain any drug.

What did researchers want to find out?

Researchers did this study to compare rituximab with MMF to see how well the medicines worked and if rituximab is better than MMF (see section 4 'What were the results of the study?').

They also wanted to find out how safe the study medicines were by checking how many people had side effects during this study (see section 5 'What were the side effects?').

The main question that researchers wanted to answer was:

1. After 52 weeks of treatment, how many people in each treatment group were in complete remission?

   Being in complete remission meant that for 16 or more weeks in a row, the skin and mucous membranes were healed with no active disease and the patient was not taking steroids.

Other questions that researchers wanted to answer included:

2. What was the total amount of steroids that people in each treatment group took during the 52 weeks of study treatment?

3. What was the total number of disease flares in each treatment group?

   A flare was defined as having 3 or more new lesions in a month that did not heal within 1 week on their own or existing lesions that got bigger in a patient whose disease had been controlled. Disease control meant that no new lesions were appearing and existing lesions began to heal.

4. How did the study medicines affect people's health-related quality of life?

What kind of study was this?

This study was a '**Phase 3**' study. This means that rituximab had been tested in a smaller number of people with PV before this study. In this study, a larger number of people with PV received either rituximab or MMF to find out if rituximab worked better than MMF.

The study was '**randomised**'. This means that it was decided by chance which of the medicines people in the study would receive – like tossing a coin.

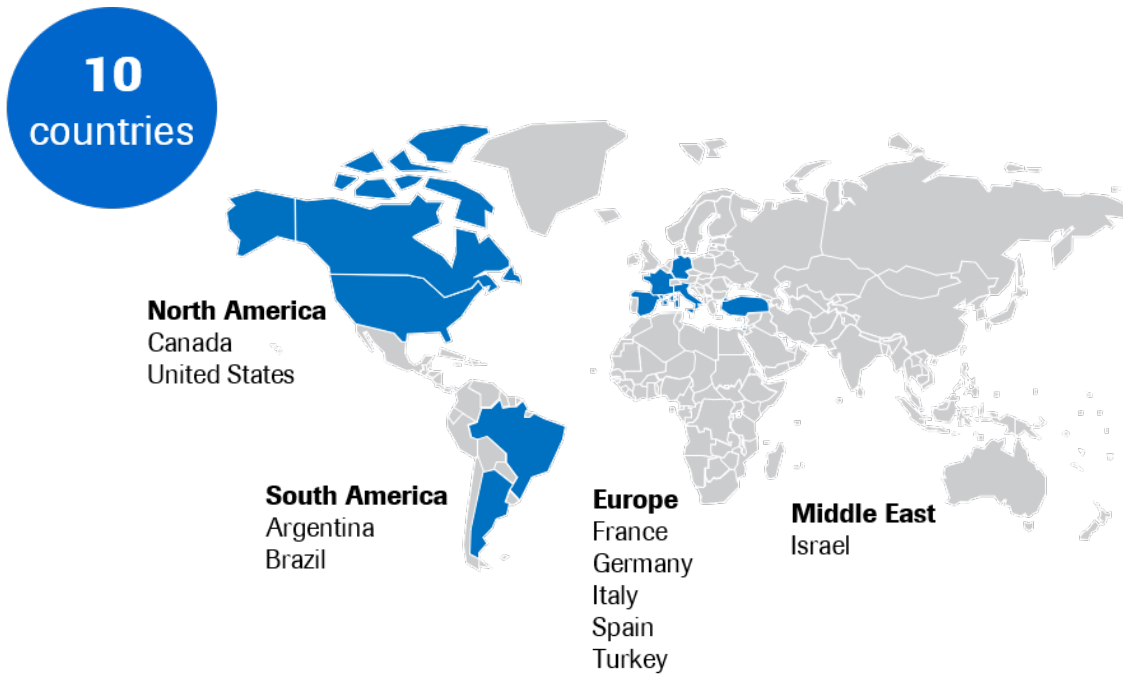
This was a '**double-blind**' study. This means that the people taking part in the study and the study doctors did not know which of the study medicines people were taking.

This was a '**double-dummy**' study, which is used to compare medicines that are different (for example, an intravenous infusion and a pill). This means that everyone in the study received one of the study medicines and a 'placebo' (or "dummy") that looked the same as a medicine but did not contain any real medicine.

When and where did the study take place?

The study started in May 2015 and ended in October 2019. This summary includes the results up to November 2018 and the complete results from the 52-week treatment period of the study.

This study took place at 49 study centres across 10 countries in Europe, the Middle East, North America, and South America. The map below shows the countries where this study took place.



2. Who took part in this study?

In this study, 135 patients with PV took part. Ten of the 135 patients at one centre in the United States participated in the study using telemedicine (the study doctor and patients used an iPhone to allow patients to participate in the study from their homes) as a way for the study doctor to communicate with and monitor the patient in order to make it easier for the patient to take part in the study.

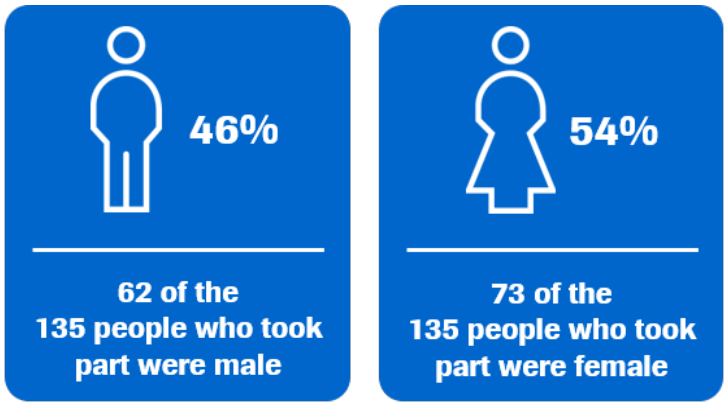
People could take part in the study if they had:

- a diagnosis of PV within the previous 24 months
- moderate to severely active PV
- been taking steroids alone and expected to benefit from adding rituximab or MMF

Patients could not take part in the study if they had:

- other types of pemphigus or autoimmune blistering disease that was not PV
- known allergic reaction to rituximab, MMF or steroids
- HIV, hepatitis B, or hepatitis C
- an active infection of any kind (except nail fungus)

Here is more information on the people who took part in the study:



Age range of patients who took part: 23 to 75 years old

3. What happened during the study?

People in the study were selected by chance (at random by a computer) to get one of the 2 treatments.

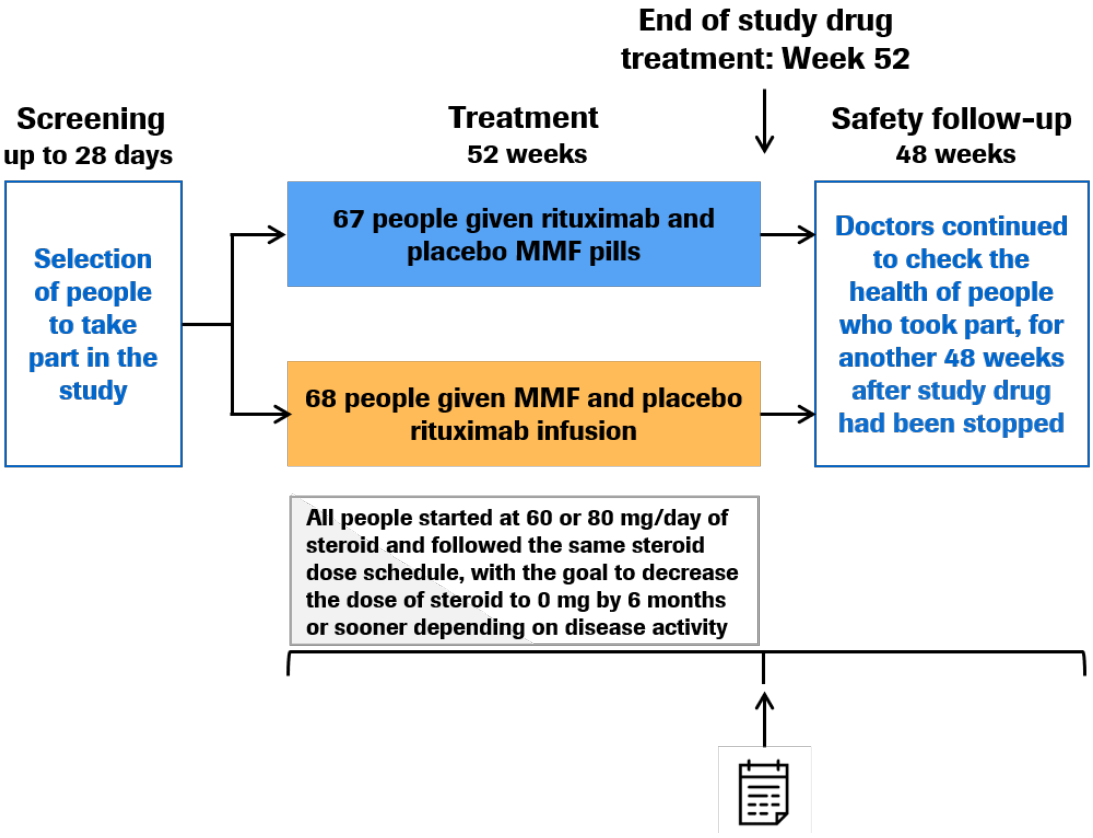
The 2 treatment groups were:

- **Rituximab** (the study medicine)—given by intravenous infusion on Days 1 and 15 and again at Weeks 24 and 26. Patients in this group also received a placebo pill made to look like MMF

- **MMF** (the comparison medicine)—pill taken by mouth twice per day. Patients in this group also received a placebo infusion that looked like rituximab

People in the study were taking **steroids** by mouth when they started the study. They continued to take the steroids and rituximab or MMF was added. As symptoms of the disease got better, the steroid dose was gradually lowered. The goal was for patients to stop taking steroids by Week 24 of the study or sooner, if appropriate.

The picture below shows what happened in the study.



The symbol on the timeline (📋) shows when the information in this summary was collected—after all patients had completed the 52-week treatment period (November 2018). Patients were also followed for up to 48 weeks after they stopped taking the study drug (safety follow-up period). The safety follow-up part of the study ended in October 2019. A separate summary of these safety follow-up findings is expected sometime in 2020.

4. What were the results of the study?

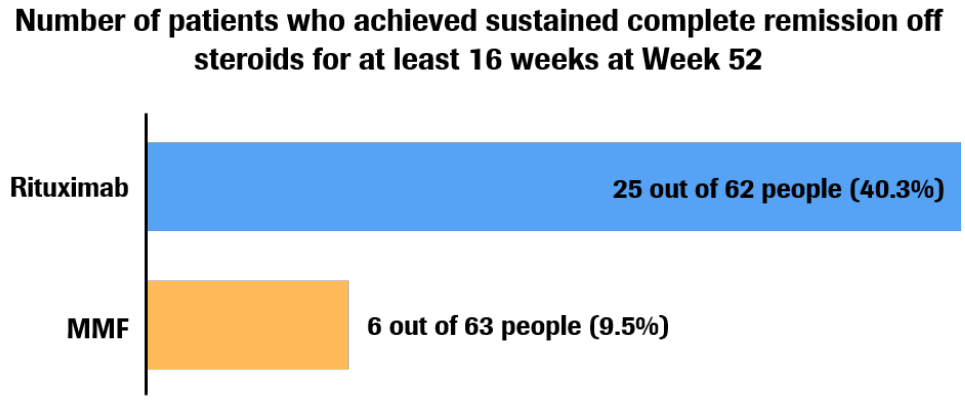
This section shows only the main results from the study during the 52-week treatment period. You can find information about all other results in the 52-week treatment period on the websites at the end of this summary (see section 8).

The 10 patients who participated using telemedicine (5 in the rituximab group and 5 in the MMF group) are not included in the results that show how well rituximab and MMF worked (called efficacy results) because doctors used photographs and video to determine how the disease was responding to treatment. All the other patients were seen in person by their study doctors. The 10 telemedicine patients, however, contributed to the side effects (safety) results (see section 5). Therefore, 125 patients' data were analysed for the efficacy results and 135 patients' data were analysed for the safety results.

Question 1: After 52 weeks of treatment, how many people in each treatment group were in complete remission?

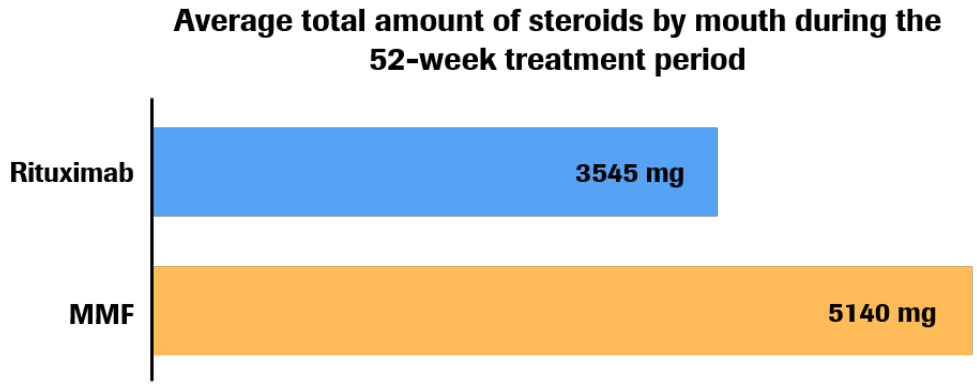
Complete remission meant that for 16 or more weeks in a row, the skin and mucous membrane were healed with no active disease while the patient was off steroids.

After 52 weeks of treatment, 40.3% of people who were given rituximab had achieved sustained complete remission off steroids for at least 16 weeks compared with 9.5% of people who were given MMF. This result was statistically significant ($P < 0.0001$), meaning that rituximab was superior to MMF.



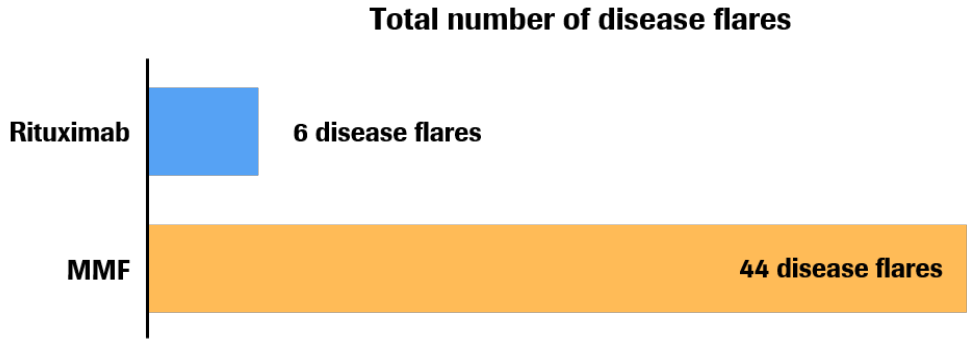
Question 2: What was the total amount of steroids that people in each treatment group took during the 52 weeks of study treatment?

People in the rituximab group took a significantly lower total amount of steroids by mouth over the 52-week treatment period than people in the MMF group. On average, people who were given rituximab took a total of 3545 mg of steroids, and people who were given MMF took a total of 5140 mg ($P = 0.0005$).



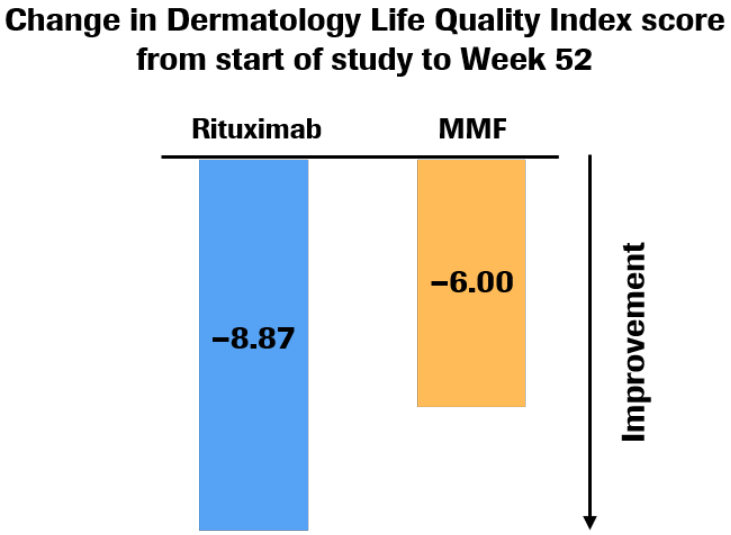
Question 3: What was the total number of disease flares in each treatment group?

People treated with rituximab had a significantly lower number of flares than people treated with MMF (6 vs 44; $P < 0.0001$).



Question 4: How did the study medicines affect people's health-related quality of life?

Researchers used a questionnaire called the Dermatology Life Quality Index to measure patients' quality of life during the study. Patients treated with rituximab had significantly greater improvements in health-related quality of life at Week 52 than patients treated with MMF (*P* = 0.0012).



5. What were the side effects?

In this study, side effects of the study medicines were looked at in all patients who received at least one dose of the study medicines, including the patients who participated using telemedicine.

Not all the patients in this study had side effects.

Side effects of rituximab

Most common side effects

Side effects of rituximab are unwanted medical events that occurred in at least 5% of patients treated with rituximab and were assessed as related to rituximab.

The following side effects in patients treated with rituximab occurred during the treatment phase (52 weeks):

Side effect	People taking rituximab (67 people total)
Reaction to the infusion	22% (15 out of 67)
Headache	15% (10 out of 67)
Infection of the nose, throat and upper airway (upper respiratory tract infection)	10% (7 out of 67)
Infection of the nose and throat — also known as a 'common cold'	9% (6 out of 67)
Oral thrush — fungal infection in the mouth or throat	9% (6 out of 67)
Joint pain	9% (6 out of 67)
Back pain	9% (6 out of 67)
An infection in the kidney, bladder, or the tubes that carry urine out of the body (urinary tract infection or 'UTI')	8% (5 out of 67)
Feeling tired	8% (5 out of 67)
Feeling dizzy	6% (4 out of 67)
Feeling weak	6% (4 out of 67)

Serious side effects

In 3 out of 15 patients who had a reaction to an infusion, the reaction was life threatening. The patients received appropriate treatment and the reaction resolved, but the patients had to stop taking rituximab.

One of the 7 patients who had an upper respiratory tract infection had to go to the hospital for treatment.

Side effects of MMF

Most common side effects

Side effects of MMF are unwanted medical events that the study doctor believes were related to MMF.

The side effects of MMF that were reported most often were common infections of the nose, throat, upper airway, urinary tract, and stomach or intestines. These infections happened in 11 out of 68 patients (16.2% of patients). The next most often reported side effects of MMF were common stomach problems such as loose stools, pain in the abdomen (between the chest and pelvic regions), nausea (urge to vomit) and

constipation. These stomach problems happened in 9 out of 68 patients (13.2% of patients).

Serious side effects

Five patients with medical events believed to be related to MMF had to go to the hospital for treatment.

Three of these 5 patients had infections: 1 patient had lung infection and flu, 1 patient had shingles, and 1 patient had worsening of his chronic lung disease where airflow from the lungs is blocked. Of the other 2 patients who were treated in a hospital, 1 had a skin ulcer and the other could not pass urine.

6. How has this study helped research?

The information presented here is from a single study of people with moderate to severe PV. These results helped researchers learn more about how effective and safe rituximab is in treating patients with moderate to severe PV compared to MMF.

Overall, this study showed that rituximab was more effective than MMF. A total of 40.3% of patients treated with rituximab had achieved sustained complete remission off steroids (skin and mucous membranes were healed and no active disease without steroids for 16 or more weeks in a row) compared to 9.5% of patients treated with MMF. Patients treated with rituximab took a lower total amount of steroid, were less likely to have a flare, and had greater improvements in quality of life than patients treated with MMF. The side effects of rituximab in patients with PV were similar to those seen in people treated with rituximab for other autoimmune diseases, such as rheumatoid arthritis, granulomatosis polyangiitis, and microscopic polyangiitis.

One study can't tell us everything about the risks and benefits of a medicine. It may take more people in more than one study to gather information about how well a medicine works and its side effects. The results from this study may be different from results 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?

An ongoing research study in France led by the French Autoimmune Bullous Diseases Study Group is looking at the effectiveness and safety of rituximab in patients with mucous membrane pemphigoid.

At the time this summary was written, Roche was not planning any more studies looking at rituximab in PV.

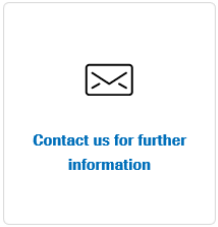
8. Where can I find more information?

You can find more information about this study on these websites:

- https://clinicaltrials.gov/ct2/show/study/NCT02383589
- https://www.clinicaltrialsregister.eu/ctr-search/search?query=2014-000382-41
- https://forpatients.roche.com/

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

If you have further questions after reading this summary:

- Visit the ForPatients website: https://forpatients.roche.com/. Click  in the bottom right corner, then click 

and fill in the contact form.

- Contact a representative at your local Roche office.

If you took part in this study and have any questions about the results or the study treatment that you received:

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

If you have questions about your own treatment for PV:

- Talk 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 whose headquarters are in Basel, Switzerland.

Full title of the study and other identifying information

The full title of this study is:

A randomised, double-blind, double-dummy, active-comparator, multicenter study to evaluate the efficacy and safety of rituximab versus MMF in patients with pemphigus vulgaris.

The study is known as 'PEMPHIX'.

The protocol number for this study is: WA29330.

The ClinicalTrials.gov identifier for this study is: NCT02383589.

The EudraCT number for this study is: 2014-000382-41.