A clinical study to look at the safety of rituximab and how it was processed through the body in children and adolescents who have granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA), diseases that cause swelling of blood vessels

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

Thank you!

Thank you for taking part in this global clinical trial (called a 'study' in this document). Your generous participation is helping researchers to answer important health questions about the study drug rituximab and GPA and MPA in children and teenagers.

We hope this summary helps you to understand the results of this study and how they will be used to improve the care of children and teenagers with GPA or MPA. If you have any questions about these results, please speak with your study doctor.

About this summary

This is a summary of the results of a clinical trial (study), written for:

- Members of the public
- Children (ages 6-12 years) and teenagers (13-17 years) who took part in the study
- Caregivers and parents of those who took part in the study

Contents of the summary

The study started in May 2013 and the last study medicine treatment was given in May 2018. This summary is based on the results known at the time it was written (August 2019).

One study can't tell us everything about the possible side effects of a medicine and the help that the medicine can give. It takes lots of people in many studies to find out everything we need to know. The results from this study in children and teenagers, may be different from results from other studies of 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 treatment for your disease.

Key information about this study

- This study was done to find out what effects, good or bad, a medicine called rituximab (the 'study medicine') has on children and teenagers with GPA or MPA. GPA and MPA are diseases that cause swelling of blood vessels in different parts of the body. Studies have already shown that the medicine works well and is safe in adults with GPA or MPA.
- In this study, children and teenagers (ages 6 to 17 years) were given the study medicine.
- This study included 25 children and teenagers in 6 countries.
- **The main finding was that rituximab could be used safely in children and teenagers with GPA or MPA, but there were some side effects that we talk about later in the summary.**

1. General information about this study

Why was this study done?

GPA and MPA cause swelling of the blood vessels, also known as 'vasculitis'. GPA and MPA are diseases called 'autoimmune diseases'. Under normal healthy conditions, the body's immune system makes proteins called 'antibodies' that attack outside invaders to help prevent or fight infection. When a person has an autoimmune disease, the immune system makes antibodies that attack the person's own body. In people with GPA or MPA, the immune system makes antibodies that attack their own blood vessels.

There are currently no medicines available that specifically treat childhood GPA or MPA and are approved for use by government health authorities. Children and teenagers with GPA or MPA are usually given medicines that decrease the activity of the immune system, such as cyclophosphamide and steroids. However, GPA and MPA symptoms often come back during or after treatment with these medicines, and they can have some bad side effects.

Studies have already shown that the study medicine, rituximab, is safe and works well in adults with GPA or MPA. However, no proper clinical studies had been done until now to look at how well rituximab works and how safe it is in children.

What was the study medicine?

Rituximab (Rituxan® or MabThera®) is a medicine already given to:

- People with a type of blood cancer called non-Hodgkin's lymphoma
- People with a type of blood cancer called chronic lymphocytic leukemia
- Adults with rheumatoid arthritis, which is an autoimmune disease of the joints
- Adults with an autoimmune disease of the skin called pemphigus vulgaris
- Adults with GPA or MPA

Rituximab works by removing a specific group of B cells. B cells are part of the immune system and help to make the antibodies that attack blood vessels and cause GPA and MPA. By removing this specific group of B cells, rituximab may help improve the bad symptoms of GPA and MPA.

All children and teenagers taking part in this study were also taking other medicines called steroids that reduce swelling and decrease the activity of the immune system. However, large amounts of steroids can cause side effects, so the dose of steroids was reduced slowly over time until a low dose was reached or until the patients were taken off steroids altogether.

What did researchers want to find out?

The main questions that researchers wanted to answer were:

1. How many children or teenagers in the study had medical problems (that may or may not have been caused by the study medicine) during the study?
2. How quickly did the study medicine move through the bodies of the children and teenagers during the study?

Other questions that researchers wanted to answer included:

3. How much and for how long did the study medicine reduce the number of B cells in the children and teenagers?
4. How well did the study medicine improve GPA or MPA symptoms?
5. How well did the study medicine improve quality of life?

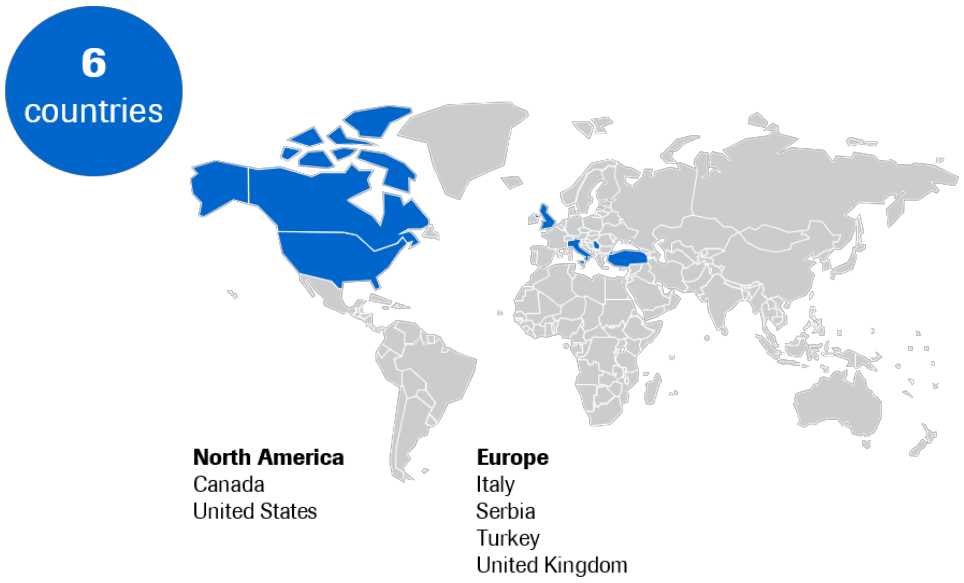
What kind of study was this?

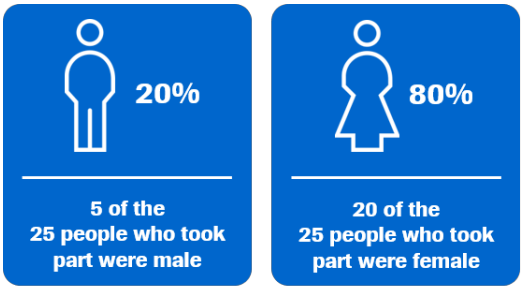
This study was a 'Phase 2a' study. This means that this was the first time this medicine was being tested in children and teenagers with GPA or MPA. The medicine had been tested before in a large number of adults with GPA and MPA and other diseases.

This was an 'open-label' 'uncontrolled' study. This means that both the study participants and the study doctors knew that rituximab was being given and that all patients received rituximab

2. Who took part in this study?

This study included 25 children or teenagers with GPA or MPA from 11 study centres in 6 countries in Europe and North America. Here is more information about the people who took part in the study.





Age range: 6 to 17 years old

People could take part in the study if they had:

- Newly diagnosed or relapsing GPA or MPA
- GPA or MPA that was severe or potentially organ- or life-threatening

Note

Patients were not allowed to take part in the study if they:

- *Needed a machine to help with breathing*
- *Needed a treatment called plasmapheresis to filter the blood to remove harmful antibodies*
- *Needed a treatment called dialysis that works like the kidneys do to remove harmful waste from the body*
- *Had any other serious health problem*

3. What happened during the study?

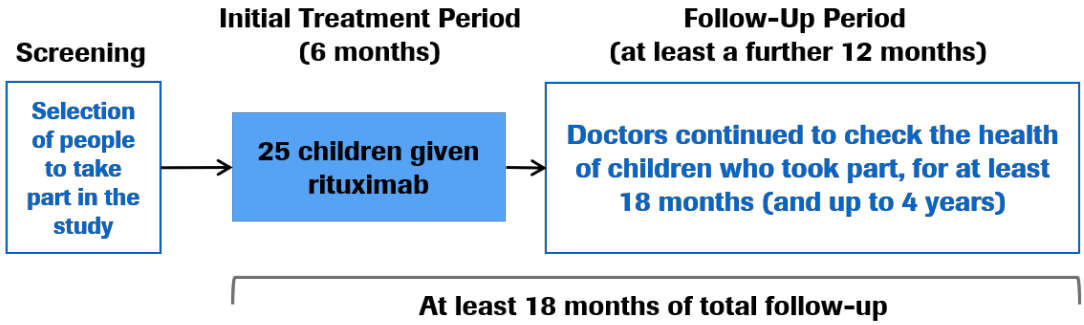
During the study, all 25 children and teenagers were given:

- **Rituximab** (the study medicine)—given by drip into a vein (infusion) once per week for 4 weeks.
- **Steroids** (other medicine used to treat GPA/MPA)—taken by mouth. The amount of this medicine was decreased over the first 6 months of the study.

The study was divided into 2 phases:

- **The initial treatment phase:** Children and teenagers in the study were given rituximab once a week for the first 4 weeks of the study and then were examined by a doctor at 1, 2, 4 and 6 months after their first treatment. During this phase, the amount of steroids was gradually reduced.
- **Follow-up phase:** Six months after starting rituximab, the children and teenagers went back to the study centre for more visits for at least another 12 months. During this time, the children and teenagers were given treatment for their GPA or MPA based on their doctor's decision (this could include rituximab or other medicines).
    - Patients received between 4 and 28 infusions of rituximab and most patients were followed in the study for between 18 months and 3 years.

The picture below' shows what happened in the study.



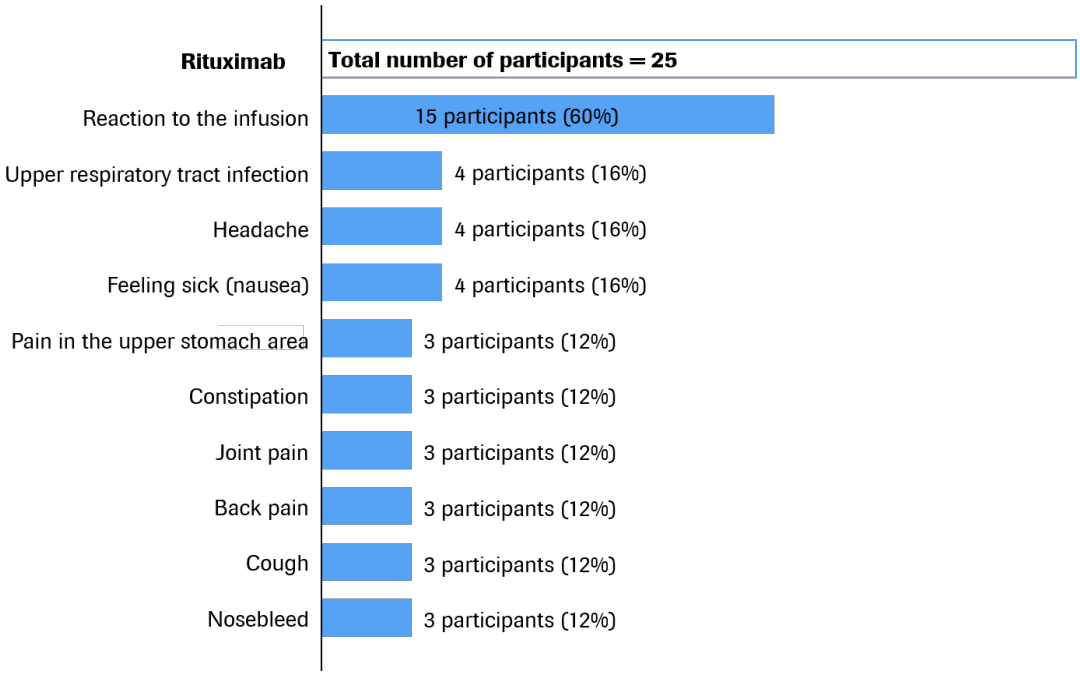
4. What were the results of the study?

Question 1: How many children or teenagers in the study had medical problems (that may or may not have been caused by their treatment) during the study?

Here, we talk about all medical problems that the children and teenagers experienced in the study whether or not they were related to the study medicine. Side effects are medical problems believed to be caused by the study medicine. We talk about side effects in Section 5 (What were the side effects of the study medicine?).

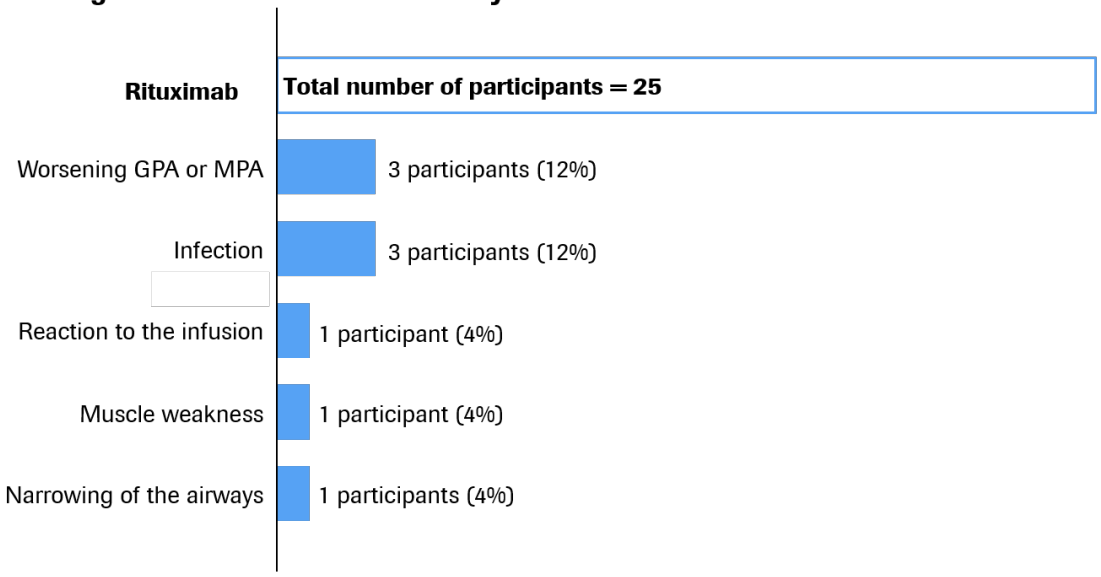
All children and teenagers in this study who were given rituximab had at least one medical problem during the initial treatment phase (first 6 months) of the study. This picture shows the most common medical problems that happened during the initial treatment phase (first 6 months) of the study.

What were the most common medical problems during the first 6 months of the study?



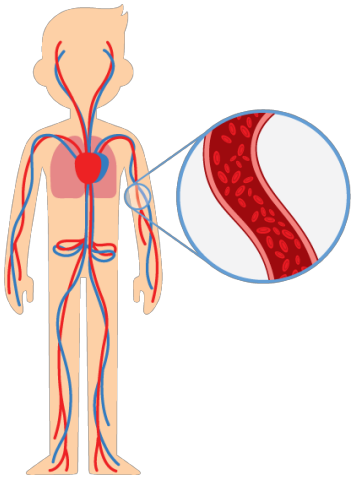
“Serious medical problems” were medical problems that required the patient to go to hospital and/or stay in hospital for urgent treatment. They may or may not have been related to the study medicine. Serious medical problems happened in 7 of the 25 children and teenagers (28%) during the initial treatment phase (first 6 months) of the study. No children or teenagers died in this study. The picture below shows the serious medical problems that happened during the initial treatment phase (first 6 months) of the study.

How many children or teenagers had each of these serious medical problems during the first 6 months of the study?



Question 2: How quickly did the study medicine move through the bodies of the children and teenagers during the study?

Another piece of information that researchers collected was how quickly the study medicine moved through the children's and teenagers' bodies. Researchers tested this by measuring how much rituximab was in the children's and teenagers' blood at different times throughout the study.

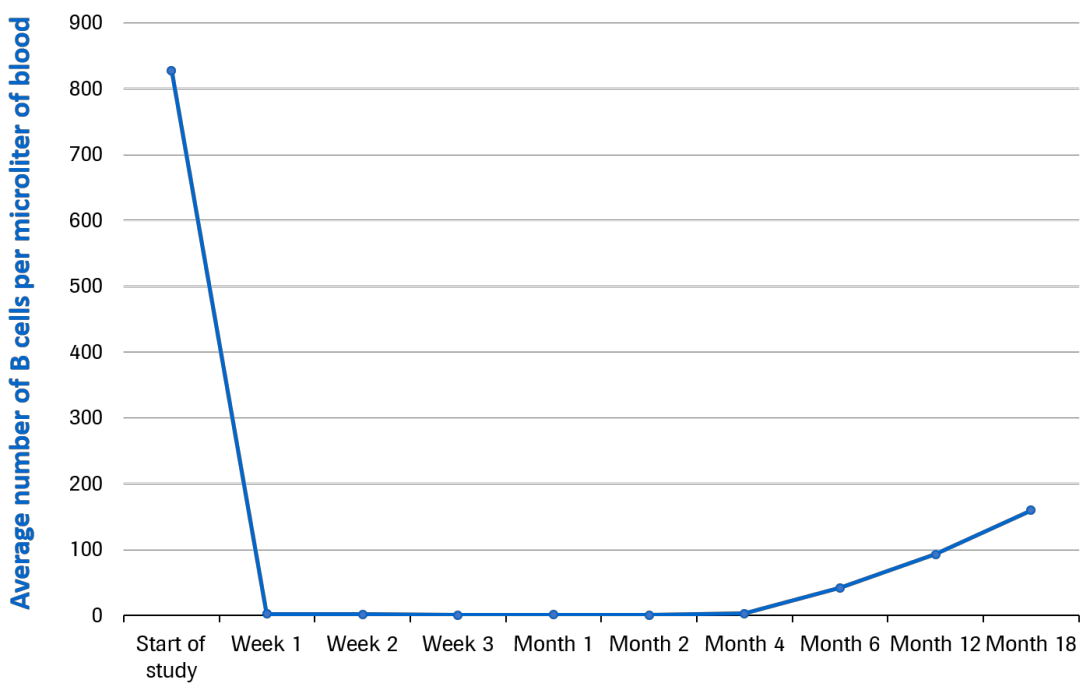


- Rituximab moved more slowly through the bodies of smaller sized children and teenagers than larger sized children and teenagers. In general, it moved more slowly through the bodies of all the children and teenagers in this study than adults who took rituximab in a previous study.
- The total amount of rituximab they were given (4 infusions of 375 mg per m^2) increased with the body size of the child/teenager. This made sure that all of the children and teenagers had the right amount of rituximab in their bodies even though the drug moved more slowly through the bodies of smaller sized children and teenagers. **Tests showed that all of the children and teenagers had similar total amounts of the drug in their blood.**

Question 3: How much did the study medicine reduce B cells in the children and teenagers?

Rituximab works by removing a specific type of B cells. Researchers measured how many of these B cells the children and teenagers had at different times during the study. They did this to see if the study medicine was doing what it is supposed to do in the body.

- The specific type of B cells that rituximab removes were almost completely gone in the children and teenagers in this study, often within 1 week after they started rituximab treatment.
- The number of B cells remained low for 6 months, then the number of B cells began to slowly increase. The blue line in this picture shows the average number of B cells over time.



Question 4: How well did the study medicine improve GPA and MPA symptoms in children and teenagers?

- Researchers looked at how many children and teenagers had no active symptoms of their GPA or MPA after receiving rituximab infusions and reducing their steroid dose to 10mg/day or less by Month 6, Month 12, or Month 18. The number of children or teenagers who had no symptoms of GPA or MPA after starting rituximab treatment was:
  - **By 6 months:** 14 out of the 25 children and teenagers (56%)
  - **By 12 months:** 23 out of the 25 children and teenagers (92%)
  - **By 18 months:** all of the 25 children and teenagers (100%)

- The children and teenagers in the study had no symptoms of their GPA or MPA following rituximab treatment (and without receiving additional steroid treatment) for an average of about 1.4 years.

Question 5: How well did the study medicine improve the children's and teenagers' quality of life?

Children and teenagers in this study were given a survey called the Children's Health Assessment Questionnaire that asked questions about how much pain they had and the amount of disability they had (measured by their ability to do daily tasks, their need to use special aids, and their need for help from others).

- **Disability:** The children and teenagers in this study reported that their disability got better within 1 month after starting rituximab treatment. This improvement stayed at the same level for the following 17 months.
- **Pain:** The children and teenagers in this study also reported that their pain got better within 1 month after starting rituximab treatment. This reduction in pain stayed at the same level for the following 17 months

5. What were the side effects of the study medicine?

In Section 4, we talked about all medical problems that happened during the study that may or may not have been caused by rituximab. In this section, we talk about side effects (also known as 'adverse reactions'), which are medical problems that happened during the study and that the study doctor believed were related to rituximab.

Most common side effects

During the entire study (initial treatment and follow up phases), 15 out of the 25 children and teenagers (60%) had a side effect believed to be related to rituximab treatment. This table shows the 5 most common side effects believed to be related to rituximab treatment.

Most common side effects reported in this study	**Children or teenagers taking rituximab** (25 people total)
Reaction to the infusion	28% (7 out of 25)
Infections	24% (6 out of 25)
Immune system disorder	12% (3 out of 25)
Upset stomach	8% (2 out of 25)
Decrease in immune cells in the blood	8% (2 out of 25)

Serious side effects

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

- During the entire study, there was one serious side effect (the flu) believed to be related to rituximab treatment.
- No children or teenagers died during the study.

6. What do these results mean for doctors and patients?

The information presented here is from one study of 25 children and teenagers with a type of vasculitis called GPA or MPA. These results helped researchers learn more about rituximab treatment for children and teenagers with GPA or MPA.

There were only 25 children and teenagers in this study, so it's hard to know whether the results will be the same in all children and teenagers. Also, all of the children and teenagers in the study received rituximab, so there was no way to compare the results to children and teenagers who did not receive rituximab.

Overall, this study showed that rituximab was safe to use in children and teenagers with GPA or MPA. The side effects were similar to those seen in previous studies of rituximab in adults with GPA and MPA and also in people with other diseases. Rituximab either reduced or stopped the symptoms of GPA and MPA.

7. Are there plans for other studies?

At the time the summary was written, no more studies looking at rituximab in adults, children, or teenagers were planned.

Study doctors are continuing to check some children and teenagers from this study with follow-up visits.

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/study/NCT01750697
- https://www.clinicaltrialsregister.eu/ctr-search/trial/2012-002062-13/results
- https://forpatients.roche.com/

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

If you have any more questions:

- Visit the ForPatients website and fill out the contact form: https://forpatients.roche.com/
- Contact a representative at your local Roche office.

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

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

If you have questions about your own treatment:

- 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 main office is in Basel, Switzerland.

Full title of the study and other identifying information

Full Title of the Study: A phase IIa, international, multicenter, open-label, uncontrolled study to evaluate the safety and pharmacokinetics of 4 x 375 mg/m^2 intravenous rituximab in pediatric patients with severe granulomatosis with polyangiitis (Wegner's) or microscopic polyangiitis

The study is known as 'PePRS' or Study WA25615.

National Clinical Trial #: NCT01750697

EudraCT #: 2012-002062-13

Protocol #: WA25615