A study to look at how well vaccines work in people living with multiple sclerosis treated with ocrelizumab

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:

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

This summary is based on information known at the time of writing (May 2020).

The study started in October 2015 and is expected to end in December 2022. This summary includes the results up until February 2017, when Part 1 of the study, i.e. the testing of the vaccine response, ended. At the time of writing this summary, Part 2 (also known as the 'optional ocrelizumab extension') of this study, in which all the people in the study receive ocrelizumab and long-term safety information on ocrelizumab is collected, is ongoing. This summary presents the complete results from Part 1 of the study.

No single study can tell us everything about the risks and benefits of a medicine. It takes lots 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

Thank you to the people who took part in this study

The people who took part have helped researchers to answer important questions about a disease called 'multiple sclerosis' or 'MS', and the study medicine. In MS, the immune system goes wrong and attacks the protective layer around the nerve called the myelin sheath. If the protective layer around the nerve breaks down, the way the nerve sends signals is disturbed.

Key information about this study

- This study was done to look at how well vaccines work in people living with multiple sclerosis (MS) treated with ocrelizumab
- In this study, people living with MS were put into one of two groups. In the first group, they received the study medication, ocrelizumab (a drug approved for treating MS). In the second group (control group), people either continued taking 'interferon beta' (another drug approved for treating MS) if they were taking it before the study started, or took no drug to treat their MS. The group that people in the study were assigned to was decided by chance
- Everyone was then given different types of vaccines, which are medicines that help the body to protect itself from an infection through bacteria or viruses in the future. The study included vaccines that help people fight off infections from bacteria that cause tetanus (and other illnesses) and some of the viruses that cause flu (see below)
- This study included 102 people in two countries (USA and Canada)
- In Part 1 of the study (completed), the results show that vaccines still work in people living with MS taking ocrelizumab, but not as well as in people living with MS who are not taking ocrelizumab
- There were no serious side effects experienced by the people who took part in Part 1 of the study
- At the time of writing this summary, Part 2 of the study (in which all people in the study receive ocrelizumab) is still ongoing. The aim is to collect long-term safety information on ocrelizumab

1. General information about this study

Why was this study done?

Injections of medicines that help to protect us from infections through bacteria and viruses (vaccines) are important to keep people healthy.

Vaccines work by allowing the immune system (the body's defence system) to recognise bacteria and viruses that can cause an infection before the body experiences them for real by making the body produce antibodies (proteins that help fight infections). This means that the body's immune system can react faster if it recognises bacteria or viruses for the first time.

Vaccines are very important for people living with MS because:

- Infections can make MS worse
- Some medicines used to treat MS can weaken the immune system and make people more likely to catch an infection.

MS is a disease that affects the way the brain sends signals to nerves in the body. In MS, the immune system goes wrong and attacks the protective layer around the nerve called the myelin sheath. If the protective layer around the nerve breaks down, the way the nerve sends signals is disturbed. Some medicines for MS make people more likely to catch an infection because they impact the cells in the immune system that are involved in causing the nerve damage but are also involved in how your body fights infections.

This study was done to see if people living with MS who are taking a treatment for MS called ocrelizumab have the same reaction to vaccines as people living with MS who were taking a different medicine for MS called interferon beta, or were taking no medicine for MS.

What are the study medicines?

'Ocrelizumab' (Ocrevus) is an approved medicine given to people living with MS.

- You say this as 'oh-kre-liz-ooh-mab'.
- Ocrelizumab is an antibody that attaches to a specific type of cell (B cells) in your immune system that have a role in damaging the nerve's protective layer. Ocrelizumab targets and removes some specific B cell types which stops your immune system from attacking the myelin around the nerve cells, which then reduces the chance of having a relapse and slows the progression of the disease.
- Because ocrelizumab only removes a specific type of B cells from the body, it allows your immune system to continue to recognise and defend itself against bacteria and viruses that it has seen before (this is the immune system's 'memory'). If you stop taking ocrelizumab then all types of B cells will grow back (this process is called 'repletion').

In this study, researchers looked at how people living with MS responded to vaccines after taking ocrelizumab and compared these results to how the 'control group' responded to the same vaccines.

People in the "control group" took no medicines for MS or carried on taking another medicine for MS called interferon beta if they were already taking it when they joined the study. Interferon beta was chosen because researchers do not think that it affects how the immune system reacts to a vaccine. Therefore, people living with MS who took no medicine or took interferon beta can be thought of as being similar in this study in how their immune system would react to a vaccine.

What vaccines were used in this study?

Vaccines are medicines that help the body to protect itself from an infection through bacteria or viruses in the future. This study used non-live vaccines, meaning that the vaccines used did not contain living bacteria and viruses that could cause a real infection. The vaccines used in this study were:

- **Tetanus vaccine**: stops you getting tetanus (also known as lockjaw), a rare disease caused by bacteria getting into a wound
- **Pneumococcal vaccine**: protects against an infection with pneumococcal bacteria that can cause many infections in humans, including pneumonia which causes a swelling (inflammation) in the tissue of one or both lungs and commonly causes breathing difficulties and chest pain. Two different pneumococcal vaccines were used in this study – they provide protection against 13 or 23 different types of pneumococcal bacteria
  (13-PCV or 23-PCV). Because the 13-PCV vaccine protects you against 12 of the same types of bacteria that 23-PCV does, the 13-PCV vaccine can increase, or 'boost', the response to the same bacteria in 23-PPV if you have been given 23-PPV first
- **Flu vaccine**: protects against the common types of virus that cause flu (influenza)
- **Keyhole limpet haemocyanin (KLH):** is a protein from the keyhole limpet (a type of mollusc) that is completely foreign to the human body and is used to see how the immune system reacts to something it has not seen before.

The reason why different vaccines were tested is because not all vaccines work in the same way and it was important to check how the body of people living with MS responds to different types of vaccines. Responses to vaccines are measured by looking at the level of antibodies (proteins made in the body that help to fight infections) in the blood.

What did researchers want to find out?

- Researchers did this study to look at how well vaccines work in people living with MS who are taking ocrelizumab. Responses to the vaccines were compared between people living with MS treated with ocrelizumab, and a control group of people living with MS who were not receiving an MS medication or were treated with a medication called interferon beta (see section 4 "What were the results of the study?").

The main question that researchers wanted to answer was:

1. Does the tetanus vaccine work in people living with MS who are treated with ocrelizumab?

Other questions that researchers wanted to answer included:

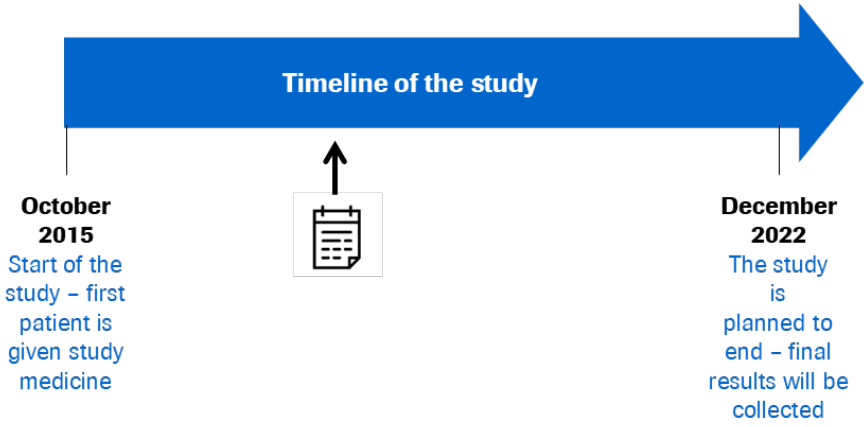
2. Does the pneumococcal vaccine work in people living with MS who are treated with ocrelizumab?
3. Does the body of people living with MS treated with ocrelizumab react to the foreign KLH protein?
4. Does the flu vaccine work in people living with MS treated with ocrelizumab?

What kind of study was this?

- "Open label" study: both the people taking part in the study and the study doctors knew which of the study medicines people were taking.
- "Randomised" study: the study groups in which people in the study would take part (ocrelizumab or control group) were decided by chance – like tossing a coin.

When and where did the study take place?

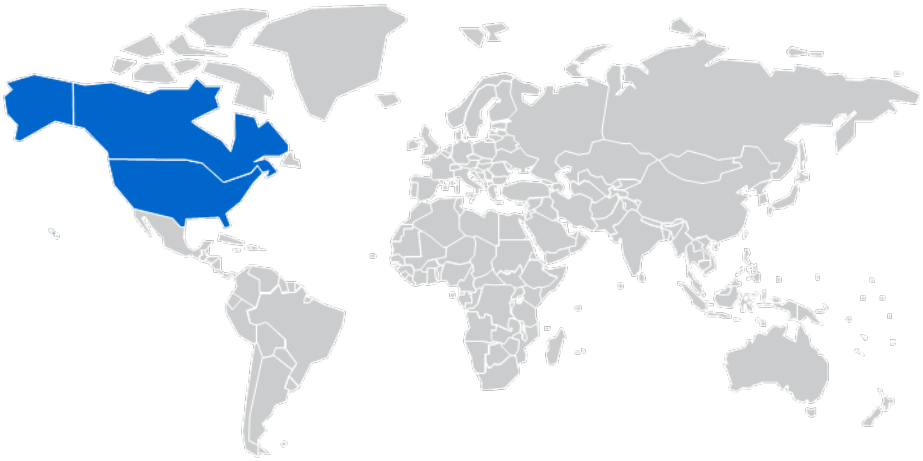
The study started in October 2015 and will end in December 2022. This summary includes the results from Part 1 of the study that was completed in February 2017 (in which the response to vaccines was looked at). At the time of writing this summary, the second part of the study is still ongoing.



Because Part 2 of the study is still ongoing, the symbol on the timeline ( ) shows when the information presented in this summary (Part 1) was collected.

After February 2017, people taking part in the study could choose to stay in the study for Part 2 where all people in the study received ocrelizumab. That means that people in the ocrelizumab group carried on taking ocrelizumab and people in the control group began receiving ocrelizumab.

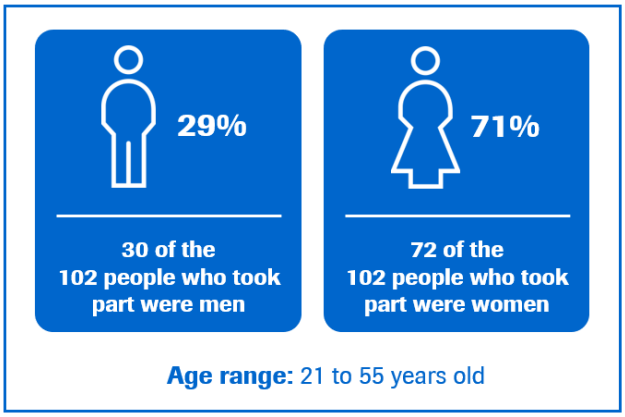
The study took place at 21 study centres in Canada and the USA.



2. Who took part in this study?

In this study, 102 adult people living with MS took part.

These people were between 21 and 55 years old. There were more females than males in this study because more females than males are affected by MS. More information on the people who took part is given below.



People could take part in the study if they had:

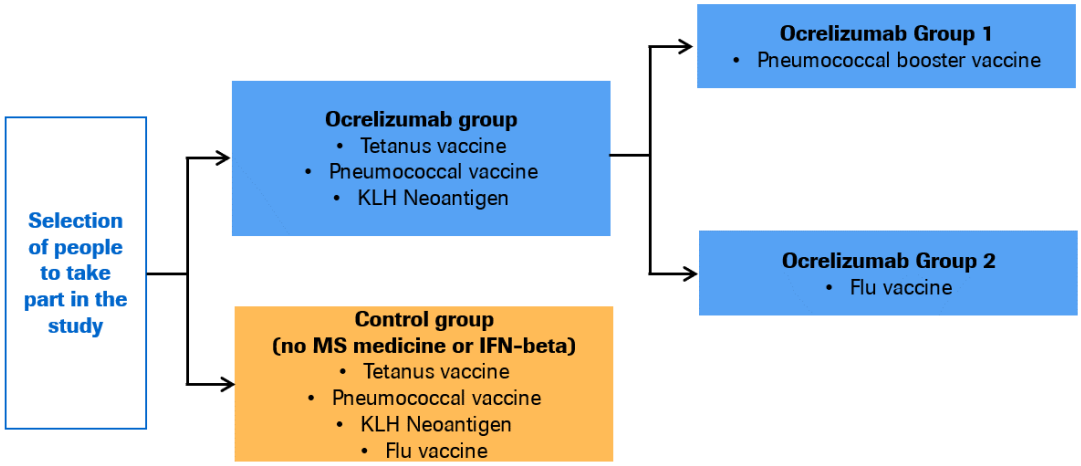
- Relapsing forms of MS
    - Relapsing forms of MS have a pattern of new symptoms occurring or old symptoms becoming worse (relapses) followed by a period where those symptoms get better (remission)
- A score between 0 and 5.5 on the Expanded Disability Status Scale (EDSS). This scale measures physical disability in MS on a scale of 0 to 10
    - A higher score means a higher level of disability. For example, an EDSS score of 0.0 means that MS is not affecting the person and a score of 5.5 means that the person can walk 100 meters without a walking aid
    - All people living with MS taking part in the study had a score that means they did not have any big difficulties taking part in the study
- Been given at tetanus vaccine at least once previously but more than 2 years before the start of the study.

People could not take part in the study if they:

- Were pregnant
- Had been treated before with ocrelizumab, or other medicines that work like ocrelizumab or some other medicine that affects the immune system
- Had been given a pneumococcal vaccine less than 5 years before the start of the study
- Had ever been given KLH or the seasonal flu vaccine for the years 2015/2016 or 2016/2017
- Had a weak immune system.

3. What happened during the study?

During Part 1 of the study, people were selected by random chance using a computer to be in one of the two groups.



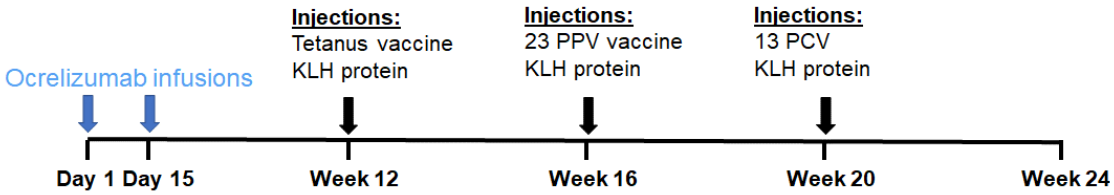
The treatment groups were:

- **Ocrelizumab** (the study medicine) – one full standard dose, given as two separate half-dose infusions into a vein, separated by 2 weeks.

The ocrelizumab group was further split into two smaller groups or 'subgroups'. This was done to allow the testing of how the body of people living with MS who were given ocrelizumab responds to an additional pneumococcal vaccination called 13-PCV in ocrelizumab subgroup 1 and the flu vaccine in ocrelizumab subgroup 2. People in both ocrelizumab subgroups were given the tetanus, pneumococcal vaccine (23-PPV) and KLH. More details of when vaccinations were given to both ocrelizumab subgroups 1 and 2 are below.

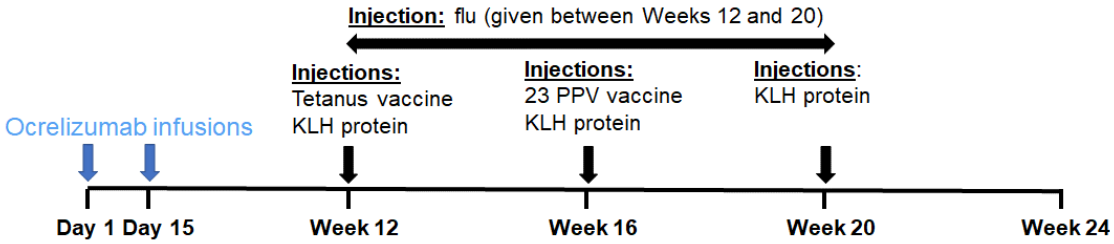
- **Ocrelizumab subgroup 1:**
  - 12 weeks after starting ocrelizumab, people were given one tetanus vaccine as an injection into a muscle
  - 4 weeks later they were given one pneumococcal vaccine (23-PPV) as an injection into a muscle
  - 4 weeks after being given the 23-PPV pneumococcal vaccine, people were given the additional pneumococcal vaccine (13-PCV), called a booster vaccination
  - The KLH protein was given at three different times (12, 16 and 20 weeks after starting ocrelizumab), as an injection just under the skin.

Order of infusions and injections in people in the ocrelizumab subgroup 1



- **Ocrelizumab subgroup 2:**
  - 12 weeks after starting ocrelizumab, people were given one tetanus vaccine as an injection into a muscle
  - 4 weeks later they were given one pneumococcal vaccine (23-PPV) as an injection into a muscle
  - People were given the flu vaccine as an injection into a muscle 12–20 weeks after starting ocrelizumab
  - KLH was given at three different times (12, 16 and 20 weeks after starting ocrelizumab), as an injection just under the skin.

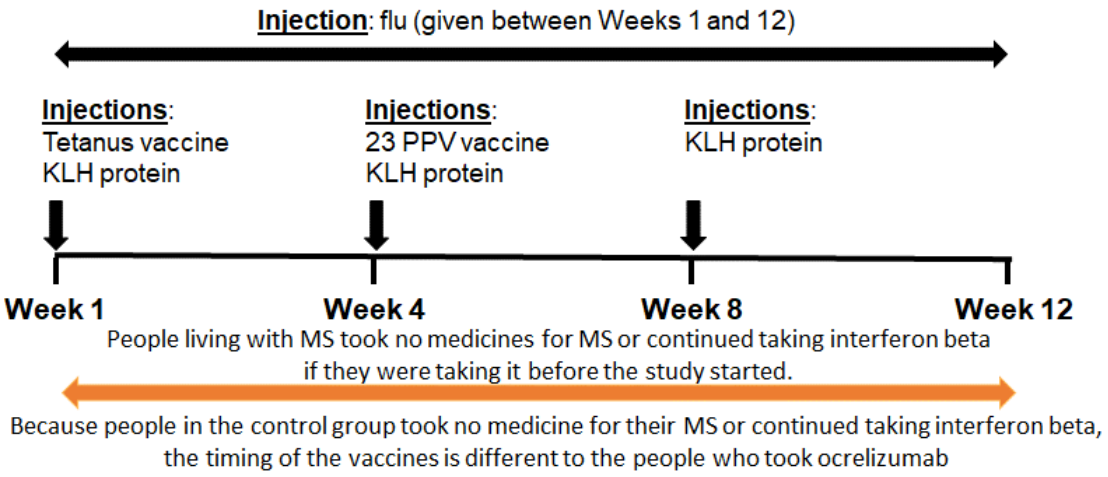
Order of infusions and injections in people in the ocrelizumab subgroup 2



The second overall treatment group was the control group where people living with MS took no medicines for MS or continued taking interferon beta if they were taking it before the study started.

- **Control** (no MS medicine or interferon beta):
  - At the start of the study, people in the control group were given one tetanus vaccine as an injection into a muscle, and 4 weeks later they were given one pneumococcal vaccine (23-PPV) as an injection into a muscle
  - People were given the flu vaccine between the start of the study and 12 weeks after the start of the study
  - KLH was given at three different times (at the start, 4, and 8 weeks after starting ocrelizumab), as an injection just under the skin.

Order of injections in people in the control group



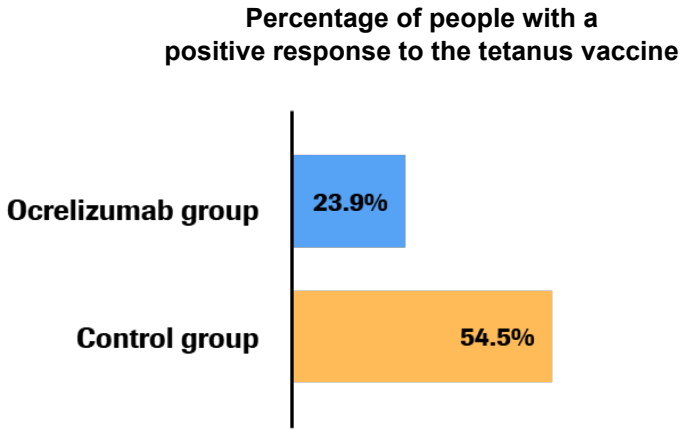
Because people in the control group took no medicine for their MS or continued taking interferon beta, the timing of the vaccines is different to the people who took ocrelizumab

4. What were the results of the study at this point?

Question 1: Does the tetanus vaccine work in people living with MS who are treated with ocrelizumab?

Researchers looked at whether the tetanus vaccine worked as well in people living with MS who take ocrelizumab, compared to those who don't take ocrelizumab. This was done by looking for an at least 4 times increase in the amount of a certain type of antibody (called IgG) in the blood that help fights tetanus. This was tested 8 weeks after the vaccine was given and compared to the antibody levels before it was given.

- In the ocrelizumab group, 23.9% of people had an at least 4 times higher amount of antibodies against tetanus in their blood after the vaccination than before the vaccination (positive response).
- In the control group, 54.5% of people had an at least 4 times higher amount of antibodies in the blood after the vaccination than before the vaccination.
- In both treatment groups, only three people (all in the ocrelizumab group) did not have a high enough level of antibodies to protect them against an infection from tetanus before receiving the vaccine in the study. All three people had high enough antibody levels to protect them against a tetanus infection 8 weeks after they received the tetanus vaccine in the study.

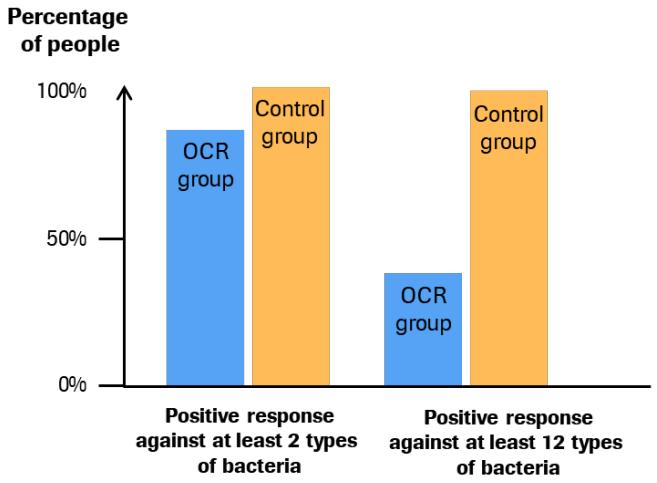


Question 2: Does the pneumococcal vaccine work in people living with MS who are treated with ocrelizumab?

Another piece of information that researchers collected was whether pneumococcal vaccines worked as well in people living with MS who take ocrelizumab, compared to people living with MS who don't take ocrelizumab. This was done by looking at how many people had at least 2 times increases in the number of antibodies 4 weeks after the 23-PPV (also known as Pneumovax) vaccination compared to before the vaccination (for all people in both ocrelizumab subgroups and the control group). In the ocrelizumab subgroup 1, the researchers also looked at if a different type of pneumococcal vaccine (Prevnar or 13-PCV) could boost (meaning increase) the response to the 23-PPV if given 4 weeks after 23-PPV. This was compared against the response to 23-PPV alone in the ocrelizumab subgroup 2. Unlike for the tetanus vaccination, researchers have not defined a level of antibodies that is considered 'protective' for pneumococcal vaccines. Four weeks after receiving the vaccine:

- 86.6% of people in both ocrelizumab groups overall had at least 2 times increases in the amount of antibodies against at least two types of pneumococcal bacteria in 23-PPV, compared to 100% of people in the control group
- 37.3% of people in both ocrelizumab groups overall had at least 2 times increases in the amount of antibodies against at least 12 types of bacteria in 23-PPV, compared to 97.1% of people in the control group.

Percentage of people who had a positive response against different types of pneumococcal bacteria in 23-PPV

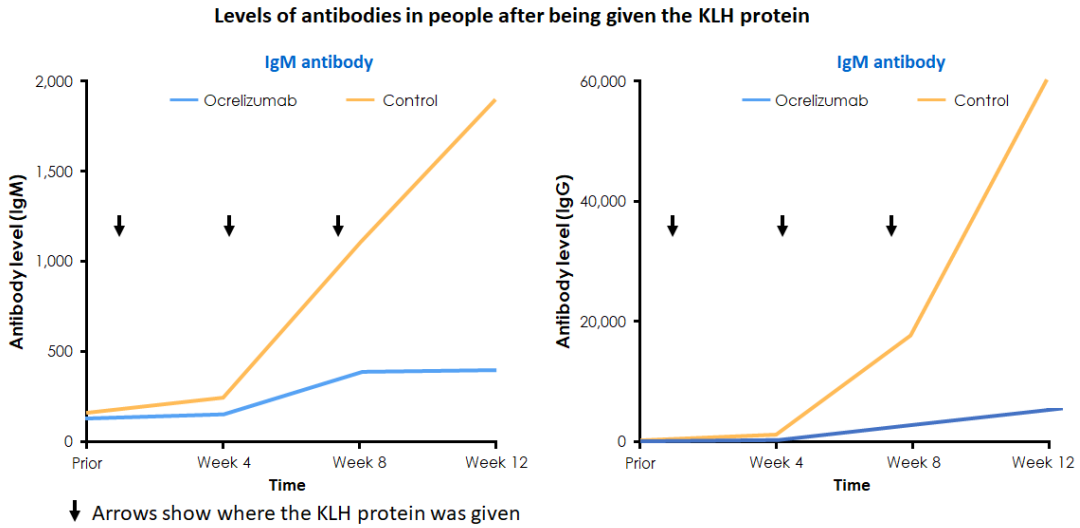


No increase in response was detected in people living with MS in ocrelizumab subgroup 1 who had the additional vaccine (13-PCV), compared to those in ocrelizumab subgroup 2 who received the 23-PPV vaccine only.

Question 3: Does the body react to keyhole limpet haemocyanin in people living with MS treated with ocrelizumab?

Researchers also looked at whether people living with MS treated with ocrelizumab reacted to the KLH protein in the same way as people living with MS who were not treated with ocrelizumab. They did this by looking at the amount of certain types of antibodies against KLH (called IgG and IgM) that were in people's blood 12 weeks after they were given their first of the three KLH injections.

- People who were taking ocrelizumab had an increase in the amount of both types of antibodies, but not as much as the control group. People in the control group had 5 times more IgM antibodies and 11 times more IgG antibodies against KLH than those in the ocrelizumab group.

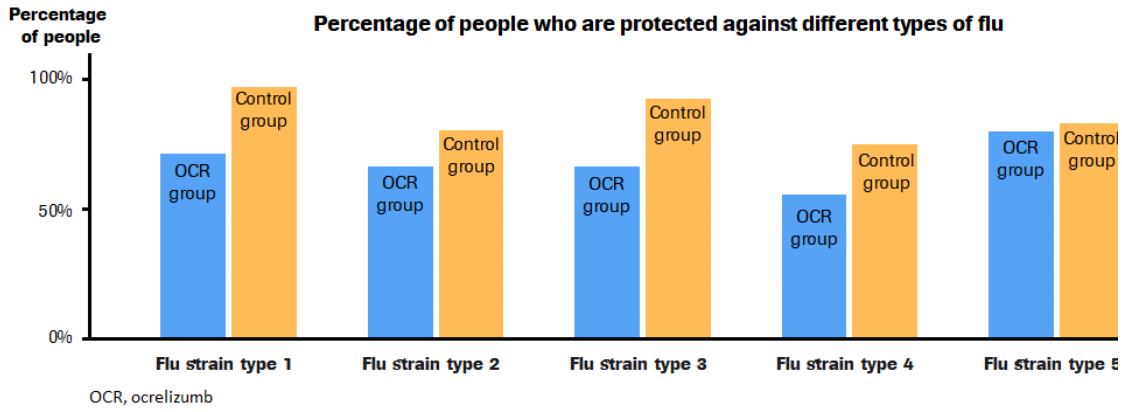


Question 4: Does the flu vaccine work in people living with MS treated with ocrelizumab?

Researchers also looked at whether the seasonal flu vaccine worked as well in people living with MS treated with ocrelizumab compared with people living with MS who are not treated with ocrelizumab.

They did this by looking at how many people in each group were protected against five different types of flu virus 4 weeks after having been given the vaccine. People were considered to be protected against flu if they increased the amount of antibodies against flu to above a certain level considered to be 'protective'.

- The percentage of people who were protected against individual flu virus types (strains) were between 3–26% lower in people in the ocrelizumab group than in the control group, depending on the type of flu virus.



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

5. What were the side effects?

Side effects (also known as 'adverse reactions') are unwanted medical problems (such as a headache) that happen during the study.

- They are described in this summary because the study doctors believe the side effects were related to the treatments in the study.
- Not all the people living with MS in this study had all of the side effects.

Serious and common side effects are listed in the following sections.

Serious side effects

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

During the first part of the study, no one taking ocrelizumab:

- Had a serious side effect
- Had to stop taking their medication because of side effects.

No one in the study died.

Most common side effects

During the first part of this study, 32 people in the ocrelizumab group (47.1%) had at least one side effect that was caused by ocrelizumab.

The most common side effect was an infusion-related reaction (IRR). This occurred when a person had an allergic reaction that the study doctors thought was caused by the infusion of the study medicine, ocrelizumab. In total, 29 people in the ocrelizumab group (42.6%) had an IRR.

There were nine other ocrelizumab-related side effects reported, each by one person only. These are shown in the table below.

Side effect reported	**People in the ocrelizumab group** (68 people in total)
An infection that affects the kidney, bladder or the tubes in which people pass water from the body (urinary tract infection or 'UTI')	1.5% (1 out of 68)
An infection that affects the nose, throat and lungs (upper respiratory tract infection or 'URTI')	1.5% (1 out of 68)
Swelling in the passages of the nose and throat – commonly known as a 'cold'	1.5% (1 out of 68)
Swollen and blocked sinuses – commonly known as 'sinusitis'	1.5% (1 out of 68)
Feeling sick (nausea)	1.5% (1 out of 68)
Diarrhoea	1.5% (1 out of 68)
Feeling tired	1.5% (1 out of 68)
Headache	1.5% (1 out of 68)
Diseases that cause scarring of the lungs (Interstitial Lung Disease)	1.5% (1 out of 68)

Overall, 32 out of 68 people in the ocrelizumab group (47.1%) had at least one infection during the first part of the study. Most of the infections (93.8%) were mild to moderate. Two people in the ocrelizumab group had severe infections; one had a viral infection and one had swollen and blocked sinuses – commonly known as 'sinusitis'. The study doctors could not tell if the infections were caused by ocrelizumab (unlike the side effects listed above like IRRs and those in the table).

The people who were in the control group did not have ocrelizumab infusions during this part of the study, so they did not have any side effects that were caused by ocrelizumab.

Overall, 5 out of 34 people in the control group (14.7%) had at least one infection during the study. Most of these were mild to moderate. There was one person with a severe infection (mumps).

Other side effects

You can find information about other side effects of ocrelizumab (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 presented here is from a single study of 102 people living with MS. These results helped researchers learn more about giving vaccines to people living with MS who are taking ocrelizumab. In addition, the side effect profile of this study is the same as previously seen in other ocrelizumab studies and adds more data to the overall safety information on ocrelizumab as a medicine for people living with MS.

Limitations of the study:

- People who were given the flu vaccine were not all given the same flu vaccine. The study researchers used different vaccines (for the years 2015/2016 and 2016/2017) that included any of three, four or five of the types of flu they wanted to study to make it easier to get people to take part in the study. Although this made it easier to let people take part in the study, it made understanding the results harder
- Many people in the ocrelizumab subgroup 2 who were given the flu vaccine were already protected against the specific flu virus before the flu vaccine was given in this study (likely from previous vaccinations containing the same type of virus, or from having the flu caused by that virus in the past)
- Only antibody levels were measured – how the body responded to the vaccines/KHL by increasing levels of other cells in the immune system was not tested.

This study has shown that people living with MS who take ocrelizumab respond to the vaccines studied by producing antibodies. However, the responses to different vaccines in people who took ocrelizumab were not as strong as those in people in the study who did not take ocrelizumab (control group).

It is recommended that people living with MS should be up to date with vaccinations before taking ocrelizumab. People who take ocrelizumab should be given the non-live yearly flu vaccine (as in this study) and other non-live vaccines should be considered. Some vaccines contain live or live-attenuated viruses, where a weakened form of the bacteria or virus is used to provide protection, but the safety of this type of vaccine in people who take ocrelizumab has not been looked at. It is not recommended to use live or live-attenuated vaccines in people who take ocrelizumab.

No single study can tell us everything about the risks and benefits of a medicine. It takes lots 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?

The second part of this study is still ongoing. Other studies looking at the long-term safety and effectiveness of ocrelizumab are taking place.

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/results/NCT02545868
- https://www.clinicaltrialsregister.eu/ctr-search/trial/2015-001357-32/results
- https://forpatients.roche.com/en/trials/neurodegenerative-disorder/multiple-sclerosis/a-study-to-evaluate-the-effects-of-ocrelizumab-on-immun-95763.html

If you would like to find out more about the results of this study, the full title of the relevant scientific paper is: "Effect of ocrelizumab on vaccine responses in patients with multiple sclerosis: The VELOCE study". The authors of the scientific paper are: Amit Bar-Or, Jonathan C. Calkwood, Cathy Chognot, Joanna Evershed, Edward J. Fox and others. The paper is published in the journal 'Neurology', volume number 95 (14), on pages e1999-e2008 https://doi.org/10.1212/WNL.0000000000010380.

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

If you have any further questions after reading this summary:

- Visit the ForPatients platform and fill out the contact form – https://forpatients.roche.com/en/trials/neurodegenerative-disorder/multiple-sclerosis/a-study-to-evaluate-the-effects-of-ocrelizumab-on-immun-95763.html
- Contact a representative at your local Roche office.

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

- Speak with 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 who have their headquarters in Basel, Switzerland.

Full title of the study and other identifying information

The full title of this study is: "A Study to Evaluate the Effects of Ocrelizumab on Immune Responses in Participants with Relapsing Forms of Multiple Sclerosis".

The study is known as 'VELOCE'.

- The protocol number for this study is: BN29739.
- The ClinicalTrials.gov identifier for this study is: NCT02545868.
- The EudraCT number for this study is: 2015-001357-32.