

Clinical Trial Results – Layperson Summary

A study to assess how safe* shorter infusion times of ocrelizumab are in people with multiple sclerosis, compared to the normal infusion time

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 (September-2020). More information may now be known.

The study started in November 2018 and is planned to end May 2021. This summary includes the results up until December 2019. At the time of writing this summary, the study is still happening – this summary presents the complete results from one part 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.

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Thank you to the people who took part in this study

The people taking part are helping researchers to answer important questions about a disease that affects the way the brain signals to nerves in the body – called ‘multiple sclerosis’ or ‘MS’ – and the study medicine.

*i.e. to understand whether any undesirable reactions (or side effects) occur, not necessarily caused by the study drug.

Key information about this study

- This study is being done to see if it is safe to give the study medicine (called ‘ocrelizumab’) by a drip into the vein over a shorter time than it is currently given.
- In this study, people are being given ocrelizumab by a drip for either 2 hours or 3.5 hours – it was decided by chance how long each person would be given the study medicine for.
- This study includes 745 people in 22 countries.
- So far, the study has shown that ocrelizumab may be given to people over a shorter time of 2 hours, without worsening the side effects.
- Around 1.1% of people (4 out of 371 people) taking ocrelizumab over the normal time had serious side effects, compared to around 1.3% of people (5 out of 374 people) taking ocrelizumab over the shorter time.
- At the time of writing this summary, the study is still happening. It is planned to end in May 2021.

1. General information about this study

Why is this study being done?

Ocrelizumab is a medicine that is approved for people with MS.

Ocrelizumab is currently given to people by a drip (infusion) into a vein. The first dose is given as two separate infusions 2 weeks apart, each lasting at least 2.5 hours. All doses after this are given to people every 6 months as one infusion lasting at least 3.5 hours.

In general, but especially due to the COVID-19 pandemic, there is a lot of pressure on people with MS and hospital staff. By shortening the infusion time of ocrelizumab, people with MS can spend less time at the hospital, and the amount of work required for the hospital staff can be reduced.

What is the study medicine?

‘Ocrelizumab’ (Ocrevus®) is an approved medicine given to people with MS.

- You say this as ‘oh – kre – liz – ooh – mab’.
- Ocrelizumab is a protein that attaches to specific types of cells (B cells) in your immune system that have a role in damaging the nerve’s protective layer. Ocrelizumab targets and removes some types of B cell which stop your immune system from attacking the nerve cells’ protective layer. This reduces the chance of having a relapse and slows the progression of the disease.
 - A relapse lasts for at least 24 hours and is when new symptoms occur, or old symptoms become worse, not accompanied by a fever.

In this study, people are being given ocrelizumab for either 3.5 hours (a normal infusion time) or for 2 hours (a shorter infusion time).

- Researchers are comparing normal infusion times of ocrelizumab to shorter infusion times of ocrelizumab, so they can show which side effects are actually caused by the infusion time.

What do researchers want to find out?

- Researchers are doing this study to compare the side effects of normal ocrelizumab infusion times with the side effects of shorter ocrelizumab infusion times (see section 4 – ‘What are the results of the study?’).

The main question that researchers wanted to answer was:

1. How many people had an unwanted reaction to the infusion of ocrelizumab (an infusion-related reaction), while they were taking it or in the 24 hours after?

Other questions that researchers wanted to answer included:

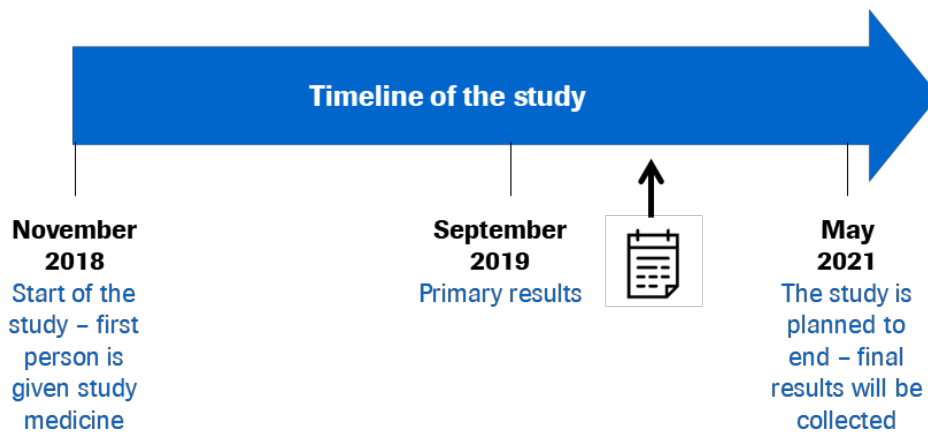
2. How bad were the infusion-related reactions?
3. What are the symptoms of the infusion-related reactions so far and when did they happen?
4. How were the symptoms of the infusion-related reactions treated?
5. What were the outcomes of the infusion-related reactions?
6. What was the overall safety of shorter ocrelizumab infusions?

What kind of study is this?

- ‘Randomized’ study: It was decided by chance which of the 2 groups people in the study would be put in (normal infusion time of 3.5 hours or shorter infusion time of 2 hours) – like tossing a coin.
- ‘Double-blind’ study: This means that neither the people taking part in the study nor the study doctors or nurses taking care of the patients during the infusions know which of the infusion times people are getting.
 - ‘Blinding’ of a study is done so that any effect seen from the medicine is not due to something people expected to happen – if they had known which medicine they were taking.

When and where is the study taking place?

The study started in November 2018 and is planned to end in May 2021. This summary includes the results up until December 2019. At the time of writing this summary, the study is still happening – this summary presents the complete results from one part of the study.



This study is still happening, so the symbol on the timeline (📅) shows when the information shown in this summary was collected – after ~2 years (December 2019).

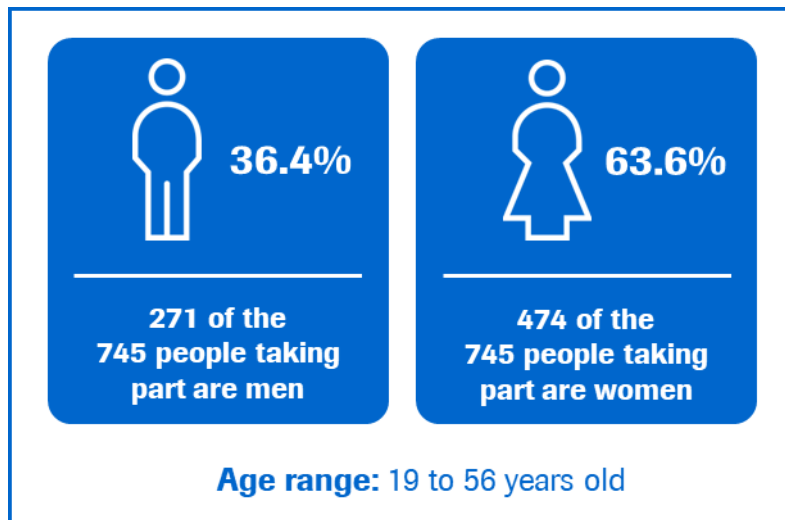
The study is taking place at 96 study centers – across 22 countries around the world. The countries are:

- Argentina
- Australia
- Belgium
- Bulgaria
- Canada
- Croatia
- France
- Germany
- Italy
- Lebanon
- Mexico
- Netherlands
- Poland
- Portugal
- Romania
- Slovakia
- Slovenia
- Spain
- Switzerland
- Turkey
- UK
- USA

2. Who is taking part in this study?

In this study, 745 people with MS are taking part.

People taking part in the study were between 19 and 56 years of age when the study started. 271 of the 745 people (36.4%) are male and 474 of the 745 people (63.6%) are female.



People could take part in the main study if they:

- Were aged 18–55 years
- Had relapsing-remitting forms of MS
 - Relapsing forms of MS have a pattern of new symptoms occurring or old symptoms becoming worse (relapses) followed by a period in which those symptoms get better (remission).
- Had MS for no longer than 3 years before the start of the study
- Had a relapse or had signs of disease activity measured by an MRI scan, within the last year
- Had a score between 0.0 and 3.5 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 3.5 means that the person has moderate disability in one part of their normal functions (e.g. eyes, balance, bladder/bowel, memory) and more than minimal disability in several others, but no problems with walking.
 - All people in the study started with an EDSS score that meant they would not have any big difficulties taking part.

People could not take part in the main study if they:

- Had another disease of the brain or spinal cord
- Were pregnant or breastfeeding
- Could not have an MRI scan.

People could not be included in this specific substudy if they had a previous serious infusion-related reaction with ocrelizumab.

- An infusion-related reaction is considered ‘serious’ if it:
 - Causes death
 - Is life-threatening
 - Is seen as medically significant by the doctor
 - Needs hospital care
 - Leads to disability or causes lasting problems
 - Causes birth defects.

3. What is happening during the study?

During the study, people were selected by chance to be put in one of the 2 infusion time arms. Which of the 2 infusion times people got was selected at random – by an independent computerized system.

The treatment groups are:

- **Normal-infusion group** (existing infusion duration) – given to people through a drip (infusion) into a vein, over about 3.5 hours every 24 weeks.
- **Shorter-infusion group** (new infusion duration) – given to people through a drip (infusion) into a vein, over about 2 hours every 24 weeks.

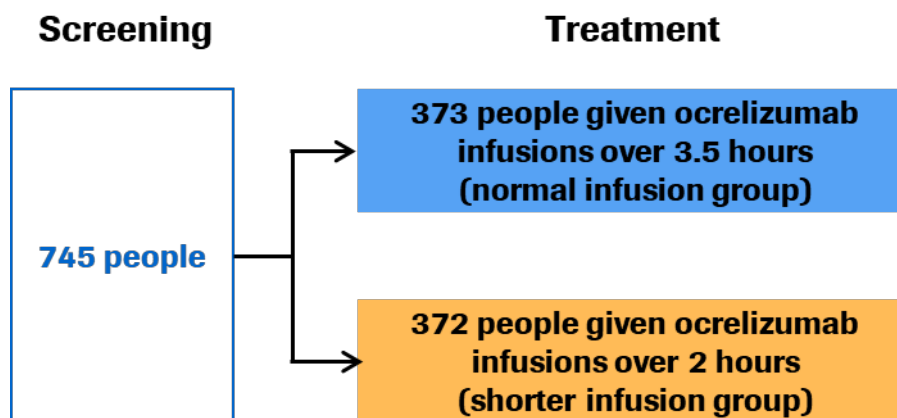
To mask the duration of the infusion, the shorter-infusion group received another infusion of saline for 1.5 hours. The infusion bags and pump were hidden in a cover bag to blind the infusions and not influence the outcome.

After the end of the infusion the patient stayed in observation at the site for another hour. 24 hours after the end of the infusion, the site contacted the patient by phone to collect the adverse events which might have been happening during these periods.

For all people in the study, the first dose of ocrelizumab was given as two separate infusions, 14 days apart.

Both groups are given an antihistamine 60 minutes before the ocrelizumab infusion and a corticosteroid administered intravenously 30 minutes before the ocrelizumab infusion. These are medicines which help to reduce the risk of potential infusion-related reactions.

This study is still ongoing, so some people are still being treated in the blinded arms with the study medicine. When the study finishes, the people who took part will be asked to go back to their study center to continue their treatment in the main study, which looks at the effectiveness and side effects of ocrelizumab for their MS. Look below to see more information about what has happened in the study so far – and what the next steps are.



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

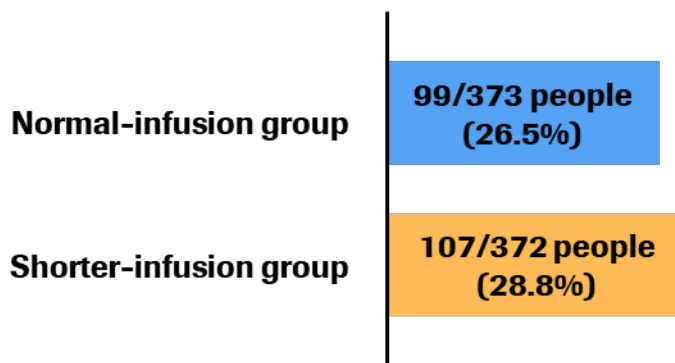
Question 1: How many people had an unwanted reaction to the first blind infusion of ocrelizumab (an infusion-related reaction), while they were taking it or in the 24 hours after?

Researchers looked at the number of people who had an unwanted reaction to having ocrelizumab by drip while they were taking it or in the 24 hours after.

This was measured when people had the first full ocrelizumab infusion after they had been put into the normal- or shorter-infusion group (the first blind infusion).

In people who were given ocrelizumab over the normal infusion time of 3.5 hours, 99 out of 373 people had an infusion-related reaction (26.5% of people). This compares with 107/372 people who were given ocrelizumab during the shorter infusion time of 2 hours (28.8% of people).

How many people had an infusion-related reaction after the first Randomized Dose



Question 2: How bad were the infusion-related reactions?

Another piece of information that researchers collected was how severe the infusion-related reactions were.

These are graded on a scale from 1 to 5:

1. Mild
2. Moderate
3. Severe
4. Life-threatening
5. Fatal (causes death).

NB: the severity of an infusion-related reaction is not the same as the seriousness of an infusion-related reaction. For example, a rash could be severe but is not likely to be a serious side effect (see section 5). Likewise, a severe headache is not necessarily a serious side effect.

- Nearly all of the infusion-related reactions reported were mild (Grade 1, e.g. dizziness, nausea) or moderate (Grade 2, e.g. headache).
- In the whole study, there were 4 severe (Grade 3) infusion-related reactions so far:
 - 1 in the normal-infusion group at the second blinded dose (throat inflammation)
 - 3 in the shorter-infusion group at the first blinded dose (one throat pain, one feeling tired and one headache).
- Nobody in the study had a life-threatening (Grade 4) infusion-related reaction.
- Nobody in the study died from an infusion-related reaction.
- Nobody stopped taking part in the study due to infusion-related reactions.

Question 3: What were the symptoms of the infusion-related reactions so far and when did they happen?

Researchers also looked at what symptoms people had when they had a bad reaction to the first full ocrelizumab infusion after being put into the normal- or shorter-infusion group.

They also looked at when these reactions happened.

- While the infusion was happening, 44/373 people (11.8%) in the normal-infusion group and 65/372 people (17.5%) in the shorter-infusion group had infusion-related reactions.
 - The most common symptoms during the infusion, which happened in $\geq 5\%$ of people in each group, were sore throat, problems with swallowing, and itchy ears.
- In the 24 hours after the infusion, 66/373 people (17.7%) in the normal-infusion group and 53/372 people (14.2%) in the shorter-infusion group had infusion-related reactions.
 - The most common symptoms in the 24 hours after the infusion were feeling tired, headache, and feeling sick (nausea).

Question 4: How were the symptoms of the infusion-related reactions treated?

Researchers also looked at how the people who had a bad reaction to the first full ocrelizumab infusion were treated.

- 42 out of the 99 people in the normal-infusion group who had an infusion-related reaction were given medicine to treat symptoms of the reaction.
- 45 out of 107 people in the shorter-infusion group who had an infusion-related reaction were given medicine to treat symptoms of the reaction.
- The most common medicines given to people in both groups were:
 - Antihistamines – drugs given to relieve symptoms of allergies
 - Antiemetics – drugs given to stop people feeling sick or being sick
 - Pain killers.
- In total, 22 out of the 373 people (5.9%) in the normal-infusion group had infusion-related reactions that meant the infusion had to be slowed down or stopped for a little bit.
- 39 out of 372 people (10.5%) in the shorter-infusion group had infusion-related reactions that meant the infusion had to be slowed down or stopped for a little bit.
- Examples of reactions which led to the infusion being slowed down or stopped for a little bit included sore throat, itchy ears, tiredness and headaches.
- The slowing down or temporary stopping of the infusion did not increase the overall duration of the infusion (3.5 hours for normal infusion and 2 hours for the shorter infusion).

Question 5: What were the outcomes of the infusion-related reactions?

Researchers also looked at what happened to the people who had a bad reaction to the first full ocrelizumab infusion after being put into the normal or shorter-infusion group.

- Everyone in the normal-infusion group who had an infusion-related reaction recovered completely, with no lasting damage.
- In the shorter-infusion group, 106 out of the 107 people with an infusion-related reaction recovered completely, with no lasting damage.
 - One person in the shorter-infusion group was still recovering from moderate back pain, tiredness and sickness.
- Nobody in the study had to stop taking ocrelizumab because of infusion-related relations.

Question 6: How safe were the shorter ocrelizumab infusions?

Researchers also looked at how safe the shorter ocrelizumab infusions were compared to the normal infusion time.

- Overall, the normal and shorter infusions were similarly safe.
- The side effects that people in the shorter-infusion group had were similar to the known side effects of ocrelizumab.

More details on the side effects are in section 5 of this summary – ‘What were the side effects?’.

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 doctor believes the side effects were related to the treatment in the study.
- Not all of the people 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:

- Causes death
- Is life-threatening
- Is seen as medically significant by the doctor
- Needs hospital care
- Leads to disability or causes lasting problems
- Causes birth defects.

During this study, 9 out of 745 people (1.2%) had at least one serious side effect. Around 1.1% of people having the normal infusion time of 3.5 hours had a serious side effect, compared to around 1.3% of people having the shorter infusion time of 2 hours.

The serious side effects which people had during this study are shown in the following table.

Serious side effects reported in this study	People having the normal infusion time (371 people total)	People having the shorter infusion time (374 people total)
Typhoid fever	Less than 1% (1 out of 371)	0
Fibula (calf bone) fracture	Less than 1% (1 out of 371)	0
Non-cancerous lump in breast	Less than 1% (1 out of 371)	0
Depression	Less than 1% (2 out of 371)	0
Appendicitis (painful swelling of the appendix)	0	Less than 1% (1 out of 374)
An infection that affects the kidney, bladder or the tubes in which people pass water from the body (urinary tract infection or 'UTI')	0	Less than 1% (1 out of 374)
Swelling of the face, torso, or limbs (edema)	0	Less than 1% (1 out of 374)
Low level of white blood cells	0	Less than 1% (1 out of 374)
Low blood pressure	0	Less than 1% (1 out of 374)

Nobody in the study has died due to side effects that may have been related to the study medicine.

During the study, some people decided to stop taking their medicine because of side effects.

- 1 out of 371 people (0.3%) having the normal infusion time of 3.5 hours stopped taking their medicine.
- Nobody having the shorter infusion time of 2 hours stopped taking their medicine.
- There was one patient who stopped the study due to depressive syndrome (related to the MS disease).

Most common side effects

During this study so far, 423 out of 745 people (56.8%) had a side effect that was not considered serious. Around 58.8% of people having the normal infusion time had a side effect that was not considered serious, compared to around 54.8% of people having the shorter infusion time.

The most common side effects are shown in the following tables – these are the 3 most common side effects across both treatment groups. These occurred in >5% of people overall.

Most common side effects reported in this study	People having the normal infusion time (371 people total)	People having the shorter infusion time (374 people total)
Infusion-related reactions	31% (115 out of 371)	34% (127 out of 374)
Swelling in the passages of the nose and throat – commonly known as a ‘cold’	5.9% (22 out of 371)	5.6% (21 out of 374)
Headache	6.7% (25 out of 371)	3.2% (12 out of 364)

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 presented here is from a single study of 745 people with relapsing-remitting multiple sclerosis. These results are helping researchers learn more about how safe it is to give ocrelizumab over a shorter time of 2 hours, instead of the normal time of 3.5 hours.

Results so far from the study show that the number of people who have infusion-related reactions is similar between normal and shorter ocrelizumab infusions. The majority of infusion-related reactions in the shorter-infusion group were mild to moderate, which shows that shorter ocrelizumab infusions are well tolerated. A shorter infusion time reduces the burden on the patient and site staff. Less time spent at the infusion site is particularly important during the COVID-19 pandemic.

This summary was written in September 2020, when the study was still ongoing. The safety of shorter ocrelizumab infusions will continue to be monitored closely in this 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.

7. Are there plans for other studies?

Other studies looking at the safety of shorter ocrelizumab infusions are taking place.

This study is ongoing (study doctors are still collecting information).

8. Where can I find more information?

The ENSEMBLE PLUS study is a substudy of the main ENSEMBLE study.

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

- <https://clinicaltrials.gov/ct2/show/results/NCT03085810>
- <https://www.clinicaltrialsregister.eu/ctr-search/trial/2016-002937-31/results>
- <https://forpatients.roche.com/en/trials/neurodegenerative-disorder/multiple-sclerosis/study-to-evaluate-the-effectiveness-and-safety-of-ocrelizumab-in.html>

If you would like to find out more about the results of this study, the full title of the relevant scientific paper is: “Shorter infusion time of ocrelizumab: Results from the randomized, double-blind ENSEMBLE PLUS substudy in patients with relapsing-remitting multiple sclerosis”. The authors of the scientific paper are: H-P Hartung, T Berger, RA Bermel, B Brochet, WM Carroll and others. The paper is published in the journal ‘Multiple Sclerosis and Related Disorders’, volume number 46 (doi: 10.1016/j.msard.2020.102492).

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/study-to-evaluate-the-effectiveness-and-safety-of-ocrelizumab-in.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 organized and paid for this study?

This study was organized 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 substudy to evaluate the safety of a shorter infusion of ocrelizumab in patients with early stage relapsing remitting multiple sclerosis”.

The study is known as ‘ENSEMBLE PLUS’.

- The protocol number for this study is: MA30143.
- The ClinicalTrials.gov identifier for this study is: NCT03085810.
- The EudraCT number for this study is: 2016-002937-31.