For an audio version of this summary, click on the links: Part 1 Part 2 Part 3 Part 4

Summary of Clinical Trial Results

A study to compare different doses and timings of a study medicine called faricimab with a monthly dose of ranibizumab, in people living with damage to the back of the eye, called wet age-related macular degeneration, caused by the growth of abnormal blood vessels

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:

- The general public, and
- People who took part in the study.

This summary is based on information known at the time of writing (December 2020 to March 2021). More information may now be known.

The study started in August 2015 and finished in September 2017. This summary was written after the study had ended.

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 about a study drug. 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

1. What were the results of the study?
2. General information about this study
3. Who took part in this study?
4. What happened during the study?
5. What were the side effects?
6. How has this study helped research?
7. Are there plans for other studies?
8. Where can I find more information?

Glossary

Wet AMD = age-related damage to the back of the eye (retina) caused by the growth of abnormal blood vessels

Thank you to the people who took part in this study

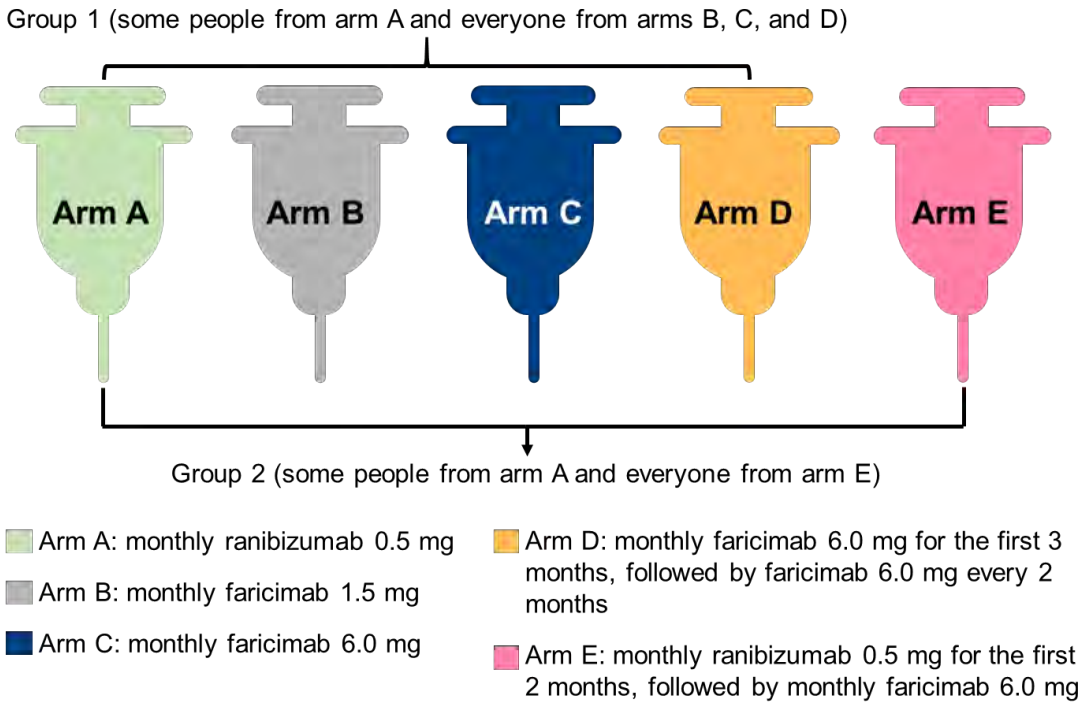
The people who took part have helped researchers to answer important questions about damage to the back of the eye caused by the growth of abnormal blood vessels and the study medicine, faricimab.

Key information about this study

- This study compared a new study medicine called faricimab with an existing medicine called ranibizumab, in people living with damage to the back of the eye caused by the growth of abnormal blood vessels. This condition is called neovascular or wet age-related macular degeneration (wet AMD for short).
- People received different doses of faricimab at different intervals. Other people received a set dose of ranibizumab each month.
- People were divided into 5 treatment groups called arms. It was decided by random chance—by a computer—which treatment each person was given (Figure 1).
  - People in arm A received monthly ranibizumab (0.5 milligrams, or mg for short).
  - People in arm B received monthly faricimab at a low dose (1.5 mg).
  - People in arm C received monthly faricimab at a high dose (6.0 mg).
  - People in arm D received monthly faricimab at a high dose (6.0 mg) for the first 3 months, then high-dose (6.0 mg) faricimab every 2 months.
  - People in arm E received monthly ranibizumab for the first 2 months, then monthly faricimab at a high dose (6.0 mg).
- People were divided into 2 groups to assess whether faricimab was safe, and whether it worked.
  - Group 1 included people in arms A–D, apart from some people in arm A who did not respond well to treatment by month 3.
  - Group 2 included people who received ranibizumab for at least part of the study. These were the people from arm A who did not respond well to treatment by month 3 of the study, and the people in arm E.
- This study included 244 people in the United States.
- The main result of the study was peoples' scores on an eye test. The researchers compared their scores at the end of the study (week 36 or month 9) with their scores at the start of the study for people in group 1, or at week 12 (month 3) of the study for people in group 2. The test used an eye chart with rows of letters that get smaller from top to bottom.

- In group 1, people who received monthly low-dose faricimab could see an average of about 11 more letters on the eye chart at month 3 than at the start of the study. People who received monthly high-dose faricimab and people who received monthly high-dose faricimab for the first 3 months followed by every 2 months could see an average of about 6 more letters. People who received monthly ranibizumab could see an average of about 9 more letters.
- In group 2, people who received monthly ranibizumab for the first 2 months followed by monthly high-dose faricimab could see on average, about 1 more letter on the chart. People who received monthly ranibizumab could see an average of about 2 more letters.
- Faricimab was well tolerated at the different doses and dose timings used. The researchers did not see any new or unexpected side effects in the study.

Figure 1: Doses and dose timings used in the study



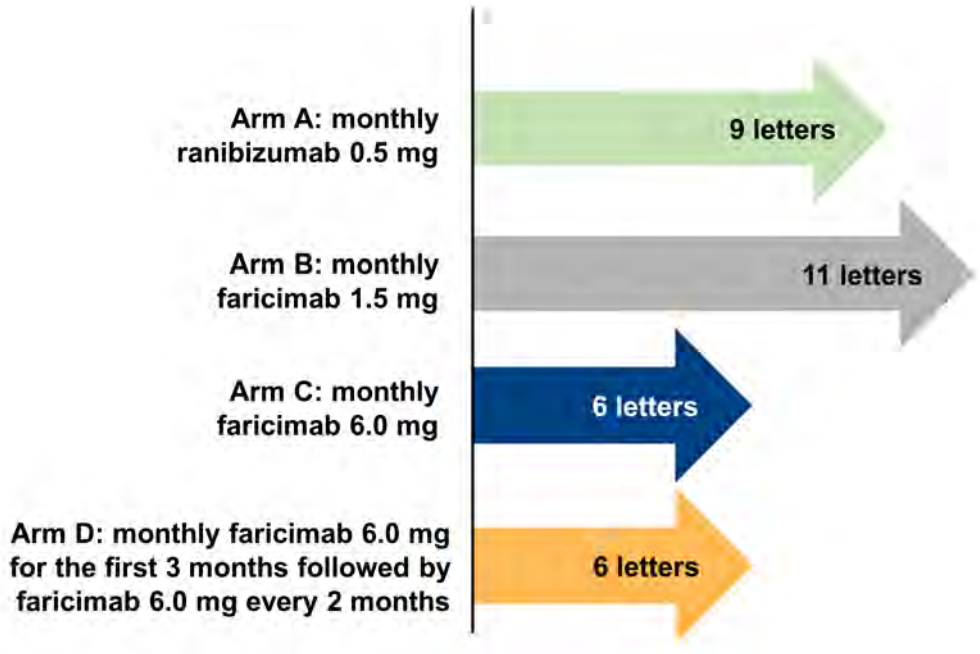
1. What were the results of the study?

Question 1: How did faricimab at different doses and dose timings compare with monthly ranibizumab in treating people living with wet AMD?

At the start of the study, before receiving treatment, the people in the different treatment arms all had similar clearness of their eyesight (known as visual acuity) in the eye that was to be treated and also had similar amounts of swelling at the back of the eye.

In group 1, people in arm A could see an average of about 9 more letters on the eye chart at month 9 compared with the start of the study. People in arm B could see an average of about 11 more letters. This means that people in arms A and B could read up to 2 more lines on the eye chart. People in arm C and arm D could see about 6 more letters, or read 1 more line on the eye chart. Figure 2 illustrates these changes.

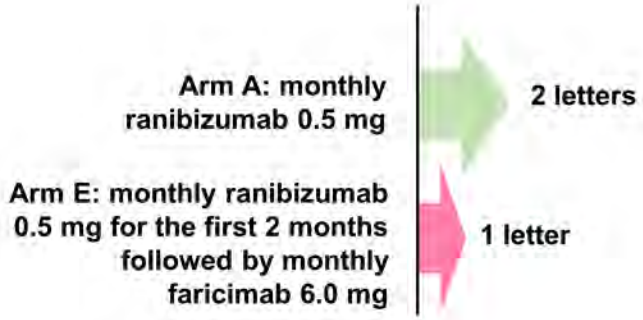
Figure 2: How many more letters were people in group 1 able to see on an eye chart?



Please refer to Figure 1 for information on the treatment received in arms A to E.

In group 2, people in arm A could see an average of about 2 more letters on the eye chart at month 9 compared with the start of the study. People in arm E could see an average of about 1 more letter, as shown in Figure 3.

Figure 3: How many more letters were people in group 2 able to see on an eye chart?

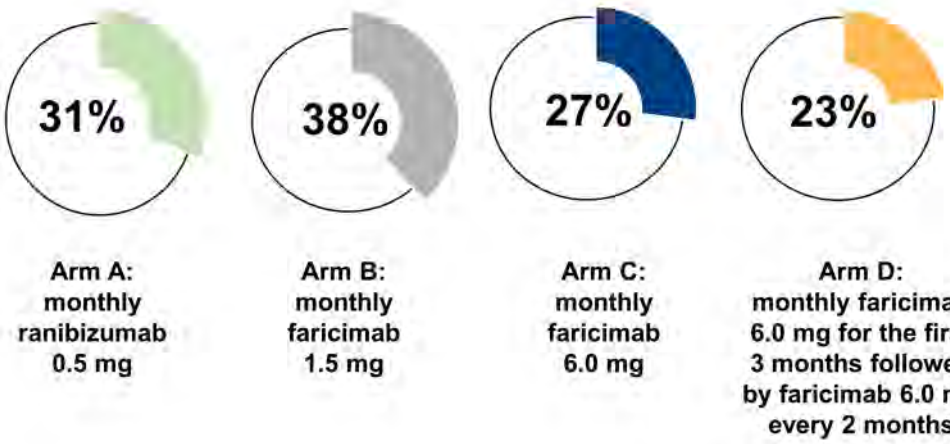


Please refer to Figure 1 for information on the treatment received in arms A to E.

Question 2: How many people living with wet AMD improved their sight with different doses and dose timings of faricimab compared with monthly ranibizumab?

In group 1, nearly one-third (31%) of the people in arm A improved their sight during the study. This means that they could see 15 more letters on the eye chart compared with the start of the study, which is equivalent to gaining 3 lines on the eye chart. Around 4 in 10 (38%) people in arm B, around 3 in 10 (27%) of people in arm C, and around 2 in 10 (23%) of people in arm D improved their sight. The proportions of people who improved their sight are illustrated in Figure 4.

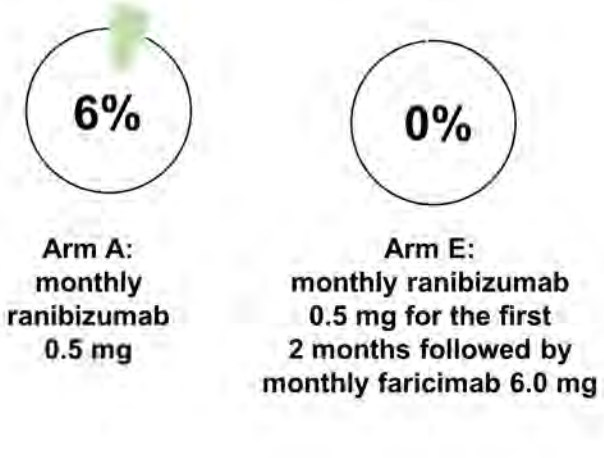
Figure 4: The proportion of people in group 1 who improved their sight



Please refer to Figure 1 for information on the treatment received in arms A to E.

In group 2, 6 in 100 (6%) of the people in arm A and nobody in arm E improved their sight during the study, as illustrated in Figure 5.

Figure 5: The proportion of people in group 2 who improved their sight



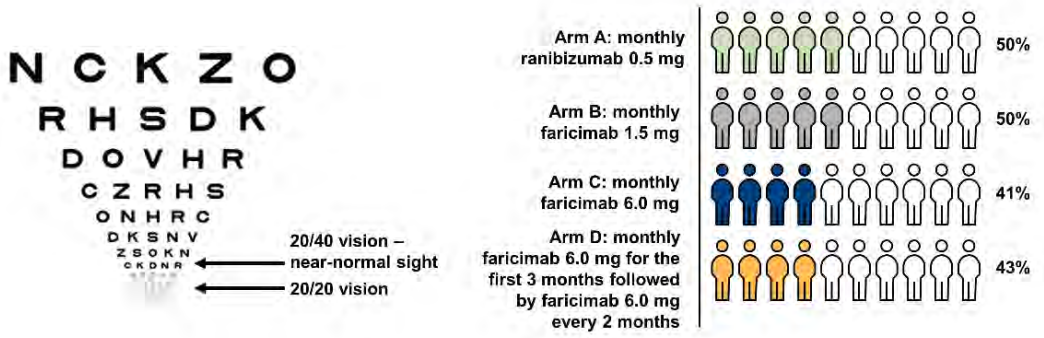
Please refer to Figure 1 for information on the treatment received in arms A to E.

Question 3: Did faricimab at different doses and following different dose timings impact the proportion of persons living with wet AMD with near-normal or severely low sight at the end of the study?

In group 1, half (50%) of the people in arm A and arm B had near-normal sight at the end of the study (month 9). This means that the clearness of their eyesight (known as visual acuity) was 20/40 or better. They could see at 20 feet what someone with normal vision can see at 40 feet away. This is an important milestone, because in many countries, 20/40 is the minimum level of visual acuity required for people to be permitted to drive. Around 4 in 10 people in arm C (41%) and arm D (43%) also had near-normal sight.

The image below shows the line of letters a person with near-normal vision might be able to read on an eye chart (not true size in this summary). On the right of the image, the proportion of people in each arm who had near-normal vision is illustrated by the number of filled in shapes in Figure 6.

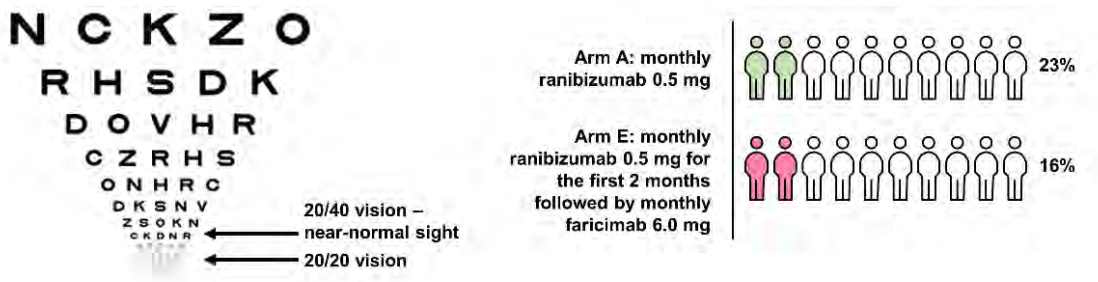
Figure 6: The proportion of people in group 1 who had near-normal sight at the end of the study



Please refer to Figure 1 for information on the treatment received in arms A to E.

In group 2, around one-quarter (23%) of the people in arm A and nearly 2 in 10 (16%) people in arm E had near-normal sight at the end of the study. This is illustrated in Figure 7.

Figure 7: The proportion of people in group 2 who had near-normal sight at the end of the study

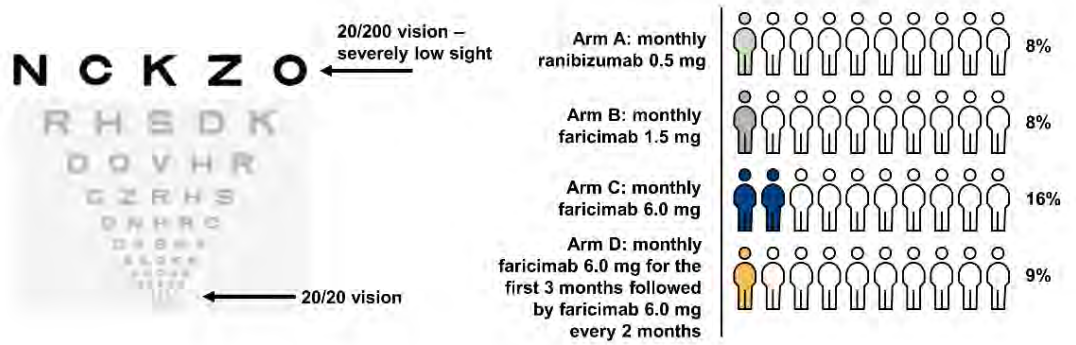


Please refer to Figure 1 for information on the treatment received in arms A to E.

In group 1, around 1 in 10 (8%) of people in arm A and arm B had severely low sight at the end of the study (month 9). This means that their visual acuity was 20/200 or worse. They could see at 20 feet what someone with normal vision can see at 200 feet away. Nearly 2 in 10 (16%) of people in arm C and 1 in 10 (9%) of people in arm D also had severely low sight.

Figure 8 shows the line of letters a person with severely low sight might be able to read on an eye chart (not true size in this summary). On the right of the image, the proportion of people in each arm who had severely low sight is illustrated by the number of filled in shapes in this image.

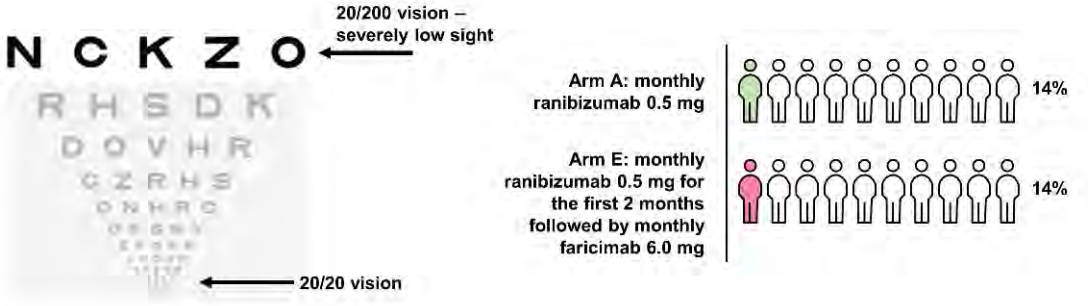
Figure 8: The proportion of people in group 1 who had severely low sight at the end of the study



Please refer to Figure 1 for information on the treatment received in arms A to E.

In group 2, around 1 in 10 (14%) people in arm A and arm E had severely low sight at the end of the study, as illustrated in Figure 9.

Figure 9: The proportion of people in group 2 who had severely low sight at the end of the study



Please refer to Figure 1 for information on the treatment received in arms A to E.

Question 4: Did faricimab at different doses and following different dose timings reduce swelling at the back of the eye in people living with wet AMD?

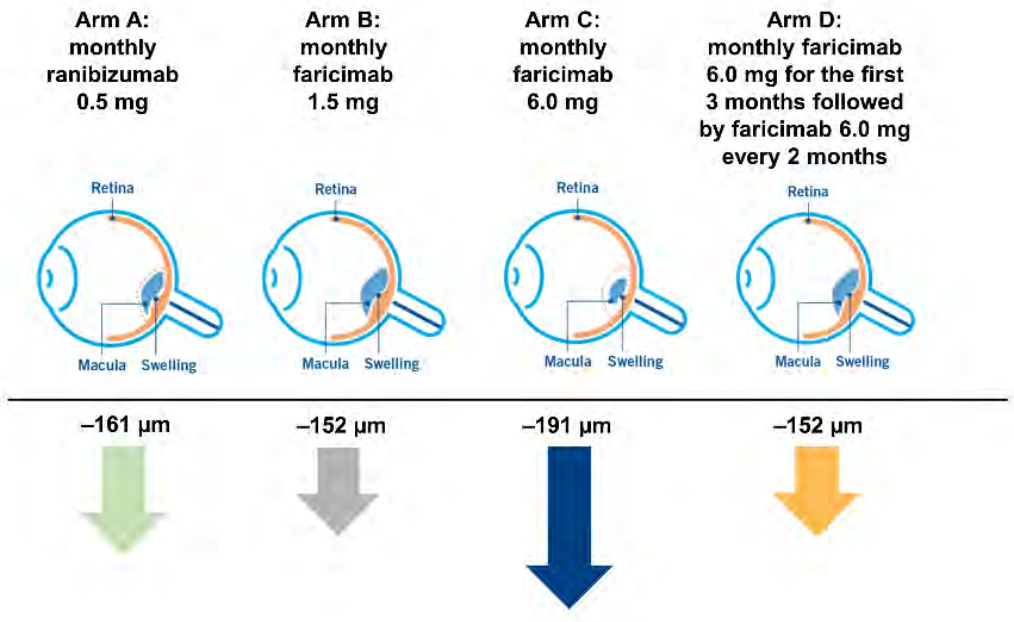
Swelling at the back of the eye (the retina) is also known as retinal swelling. In people living with wet AMD, this is caused by fluid leaking from abnormal blood vessels. In this study, the researchers measured the swelling (thickness) of the retina in micrometers (one-millionth of a meter, or µm for short). They looked at whether the swelling decreased by the end of the study (month 9).

In group 1, retinal swelling decreased on average by:

- 161 µm for people in arm A
- 152 µm for people in arm B
- 191 µm for people in arm C
- 152 µm for people in arm D.

The decrease in retinal; swelling is illustrated by the eye images below, each one showing a reduction in swelling at the back of the eye. The arrow bars in Figure 10 show the amount of reduction in swelling for arms A to D.

Figure 10: Decrease in retinal swelling during the study for people in group 1



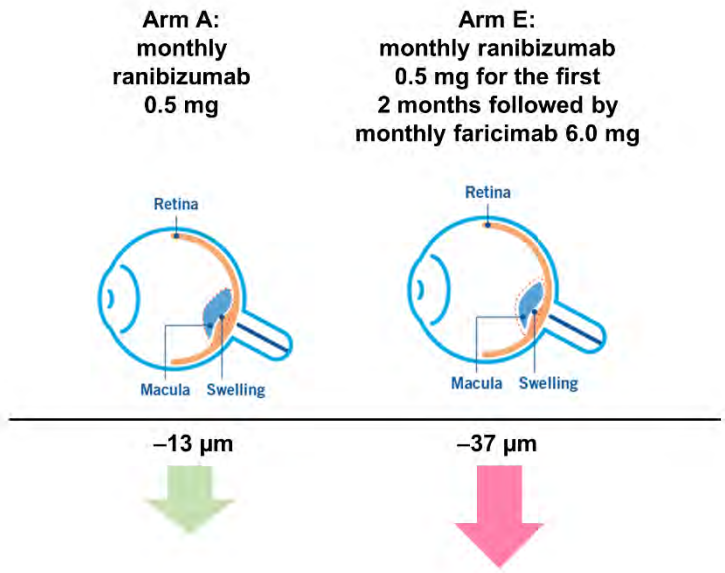
Please refer to Figure 1 for information on the treatment received in arms A to E.

In group 2, retinal swelling decreased on average by:

- 13 µm for people in arm A
- 37 µm for people in arm E.

This is illustrated in Figure 11. The eye images illustrate the reduction in retinal swelling in arm A and arm E. The arrow bars below show the amount of swelling reduction in arm A and arm E.

Figure 11: Decrease in retinal swelling during the study for people in group 2



Please refer to Figure 1 for information on the treatment received in arms A to E.

Question 5: Did faricimab at different doses and following different dose timings reduce the amount of damage and area of blood vessel leakage at the back of eye for people living with wet AMD?

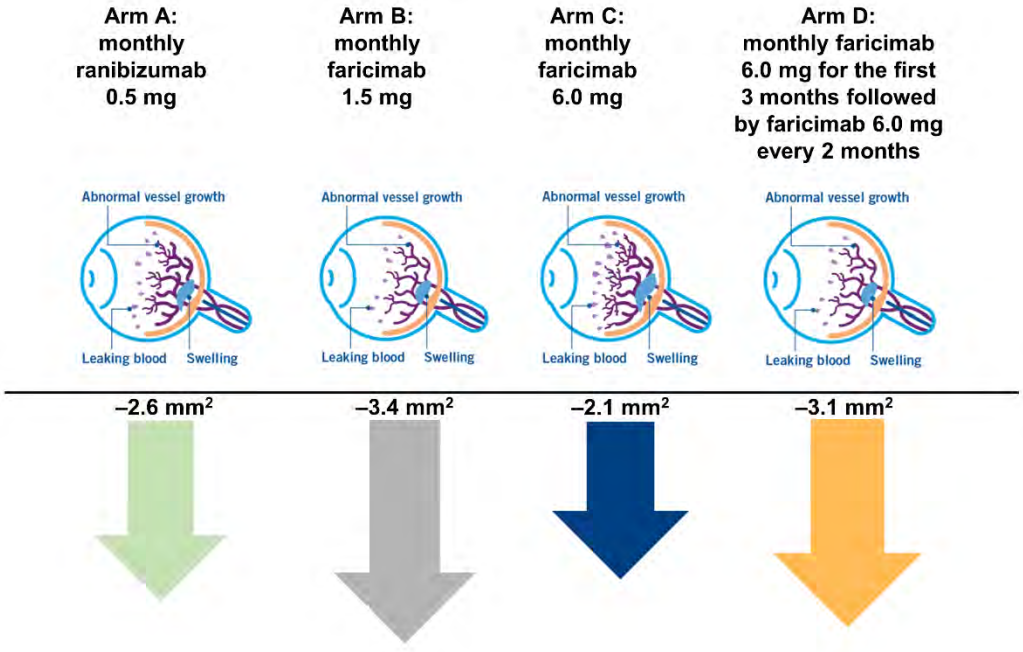
The researchers looked at the total area at the back of the eye affected by wet AMD, and the total area of blood vessel leakage. They looked at whether these decreased by the end of the study (month 9).

In group 1, the total area at the back of the eye affected by wet AMD decreased on average by:

- 2.6 millimeters squared (or mm^2 for short) for people in arm A
- 3.4 mm^2 for people in arm B
- 2.1 mm^2 for people in arm C
- 3.1 mm^2 for people in arm D.

The reduction in the area at the back of the eye affected by wet AMD in the different treatment arms is illustrated in the following graphic image (Figure 12). The eye images illustrate the reduction in swelling, abnormal blood vessel growth and leakage, and the arrows show the average reduction in the treatment arms in area affected by wet AMD.

Figure 12: Decrease in the area at the back of the eye affected by wet AMD for people in group 1



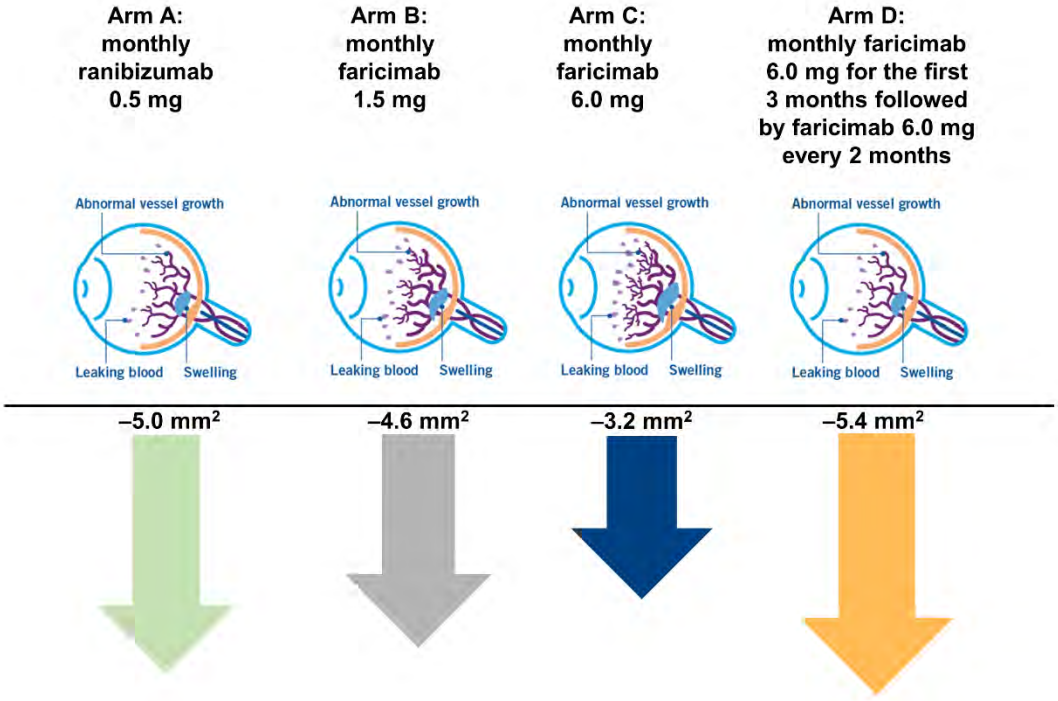
Please refer to Figure 1 for information on the treatment received in arms A to E.

The area of blood vessel leakage at the back of the eye decreased on average by:

- 5.0 mm^2 for people in arm A
- 4.6 mm^2 for people in arm B
- 3.2 mm^2 for people in arm C
- 5.4 mm^2 for people in arm D.

The reduction in blood vessel leakage in the different treatment arms is illustrated in the following graphic image (Figure 13). The eye images illustrate the reduction in blood vessel leakage, and the arrows show the average reduction leakage in the treatment arms.

Figure 13: Decrease in the area of blood vessel leakage at the back of the eye for people in group 1

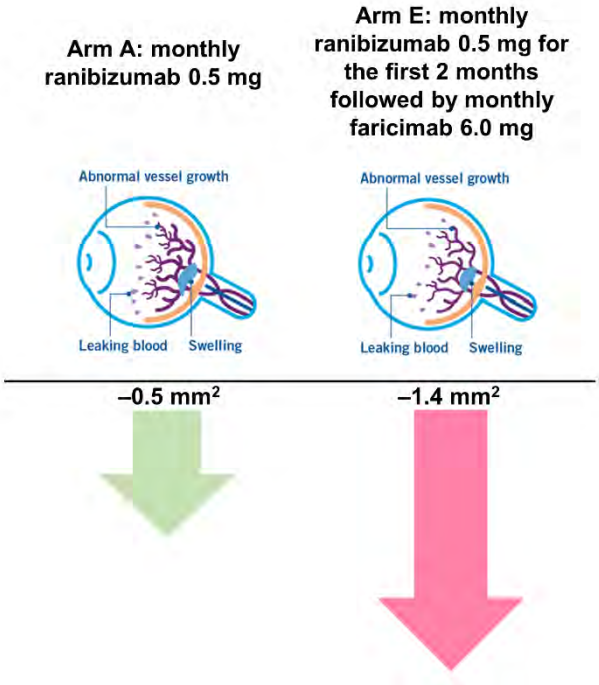


Please refer to Figure 1 for information on the treatment received in arms A to E.

In group 2 (Figure 14), the total area at the back of the eye affected by wet AMD decreased on average by:

- 0.5 mm^2 for people in arm A
- 1.4 mm^2 for people in arm E.

Figure 14: Decrease in the area at the back of the eye affected by wet AMD for people in group 2

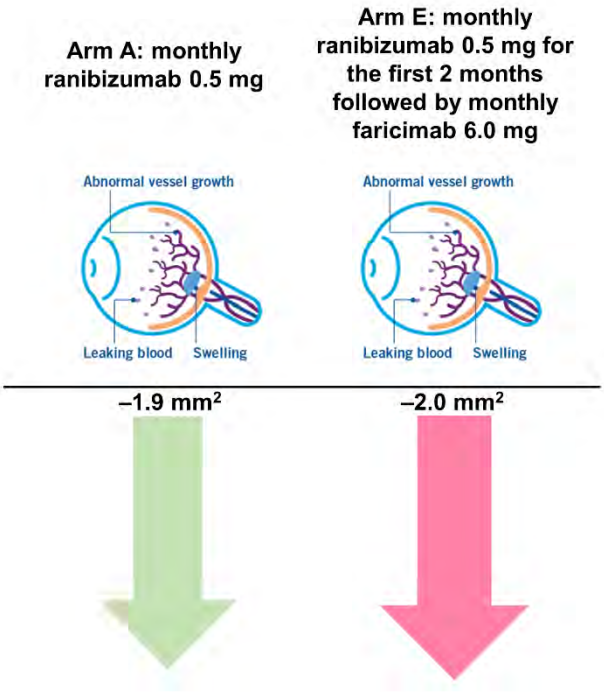


Please refer to Figure 1 for information on the treatment received in arms A to E.

The area of blood vessel leakage at the back of the eye, shown in Figure 15, decreased on average by:

- 1.9 mm^2 for people in arm A
- 2.0 mm^2 for people in arm E.

Figure 15: Decrease in the area of blood vessel leakage at the back of the eye for people in group 2



Please refer to Figure 1 for information on the treatment received in arms A to E.

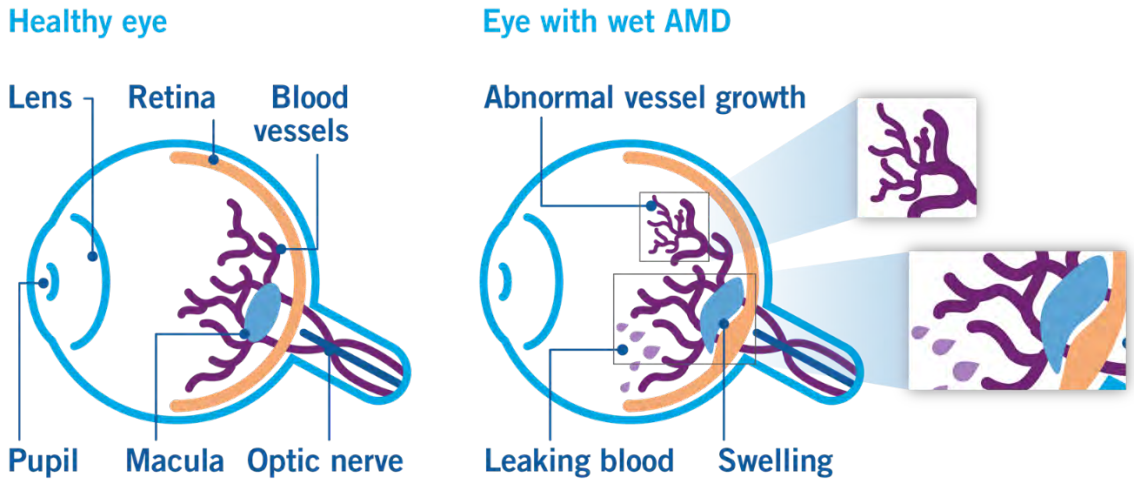
2. General information about this study

Why was this study done?

Age-related macular degeneration (or AMD for short) is a common cause of sight loss among people who are 50 years of age or older. In one type of this condition, called neovascular or wet AMD, abnormal vessels grow at the back of the eye (the retina) and leak fluid. This causes swelling in the central part of the retina called the macula, which is responsible for clear vision, and causes loss of vision.

Figure 16 below shows a healthy eye and an eye with wet AMD. The smaller square images show a close-up of the extra blood vessels and leaking blood.

Figure 16



Please refer to Figure 1 for information on the treatment received in Arms A to E.

The most common treatments for wet AMD are medicines such as ranibizumab and aflibercept, which are injected into the eye. These medicines block a substance that causes growth of abnormal blood vessels that leak fluid. This substance is called vascular endothelial growth factor (or VEGF for short).

Other treatments, which are rarely used, include eye injections of medicines called steroids to reduce swelling, and laser treatments to destroy the abnormal blood vessels.

Existing anti-VEGF treatments have improved eyesight for people living with wet AMD, but there is room for further improvement. New treatments may also reduce how often people need to get eye injections, as well as target different factors that cause wet AMD.

What were the study medicines?

Ranibizumab (Lucentis®) is an existing treatment for wet AMD. People receive ranibizumab as an injection into the eye, once a month.

- You say this as “rah-nih-bizz-yoo-mab.”
- Ranibizumab blocks **one** factor that causes leakage of fluid and growth of abnormal blood vessels in the eyes of people living with wet AMD.
- Ranibizumab is a medicine that is officially approved for use.

Faricimab is the medicine that was being studied here. People receive faricimab as an injection into the eye.

- You say this as “far-ih-see-mab.”
- Faricimab works in a different way than ranibizumab. It blocks **two** different factors in eyes of people living with wet AMD. One factor causes leakage of fluid and growth of abnormal blood vessels. The other factor weakens blood vessels so they are more likely to leak.
- This may mean that people could have more improvement in their eyesight and go longer before they need another treatment.
- Faricimab is a new medicine that is still being studied. It has not yet been approved by health authorities for use as a medical treatment.

What did researchers want to find out?

- Researchers did this study to compare faricimab given at different doses and times between doses, with ranibizumab given every month. They wanted to see how well faricimab worked at these doses and dose timings (see section 1 “What were the results of the study?”).
- They also wanted to find out how safe faricimab was when given using these different doses and dose timings by checking how many people had side effects when taking faricimab or ranibizumab during this study (see section 5 “What were the side effects?”).

The main question that researchers wanted to answer was:

1. How did faricimab at different doses and following different dose timings compare with monthly ranibizumab in treating persons living with wet AMD?

Other questions that researchers wanted to answer included:

2. Did faricimab at different doses and dose timings impact the proportion of persons living with wet AMD who improved their sight compared with monthly ranibizumab?
3. Did faricimab at different doses and dose timings impact the proportion of persons living with wet AMD with near-normal or severely low sight at the end of the study?
4. Did faricimab at different doses and dose timings reduce retinal swelling in the eyes of persons living with wet AMD?
5. Did faricimab at different doses and dose timings reduce disease-affected area and area of blood vessel leakage in the eyes of persons living with wet AMD?

What kind of study was this?

This study was a phase 2 study. This means that faricimab had been tested in a number of people living with wet AMD before this study in other clinical trials to select suitable doses of faricimab and test their efficacy. In this study, people received:

- Ranibizumab every month
- Faricimab every month at a low dose (1.5 mg)
- Faricimab every month at a high dose (6.0 mg)
- Faricimab at a high dose (6.0 mg) every month for the first 3 months followed by faricimab at a high dose (6.0 mg) every 2 months

- Ranibizumab every month for the first 2 months followed by faricimab every month at a high dose (6.0 mg).

Ranibizumab was always given at a set 0.5-mg dose. The researchers wanted to find out whether these different doses and dose timings of faricimab worked as well as monthly ranibizumab.

The study was randomized. This means that it was decided by random chance, using a computer, which of the medicines and dose timings people in the study would be assigned to—like tossing a coin.

The study was double masked. This means that neither the people taking part in the study nor the study doctors who assessed the outcomes knew whether people were taking faricimab or ranibizumab and did not know which of the different doses and dose timings people were using.

Masking 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, dose, or dose timing they were receiving.

When and where did the study take place?

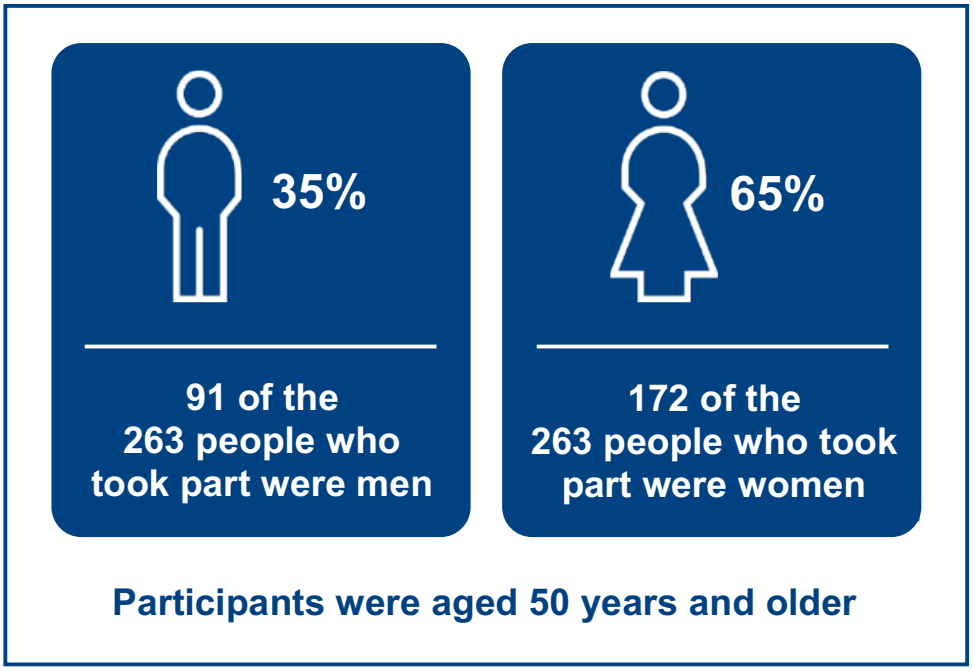
The study started in August 2015 and finished in September 2017. This summary was written after the study had ended.

The study took place at 58 study centers in the United States.

3. Who took part in this study?

263 adults (50 years and older) with wet AMD took part in the study. 244 people completed all visits up to month 9 (Figure 17).

Figure 17



People could take part in the study if they:

- Had active growth of abnormal blood vessels in the macula due to AMD
- Could read between 73 and 24 letters on an eye chart. This means that participants, at best, had vision of 20/40, so that they had poorer than average eyesight and required glasses because of their AMD, or, at worst, had severely low sight. No more than 40% of the people had 20/40 vision at the start of the study.

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

- Abnormal blood vessel growth in the macula due to causes other than AMD
- Bleeding behind the retina or scarring within the eye
- Breakdown of more than half of the affected area within the eye and/or breakdown involving the central part of the macula
- Cataract surgery (to replace the lens of the eye if it has become cloudy) within 3 months of the start of the study or had ever had any other surgery involving the eye
- A major illness or surgery within 1 month before the start of the study
- High blood pressure that was not effectively treated
- Previously taken VEGF-blocking medicines, such as ranibizumab or aflibercept, or had other treatment for wet AMD
- Any other eye condition that might make treatment less likely to work or might make injection into the eye less safe.

4. What happened during the study?

During the study, people were divided into treatment groups by random chance to get 1 of 5 treatments. The treatments were selected at random by a computer.

The treatment groups (known as arms) were:

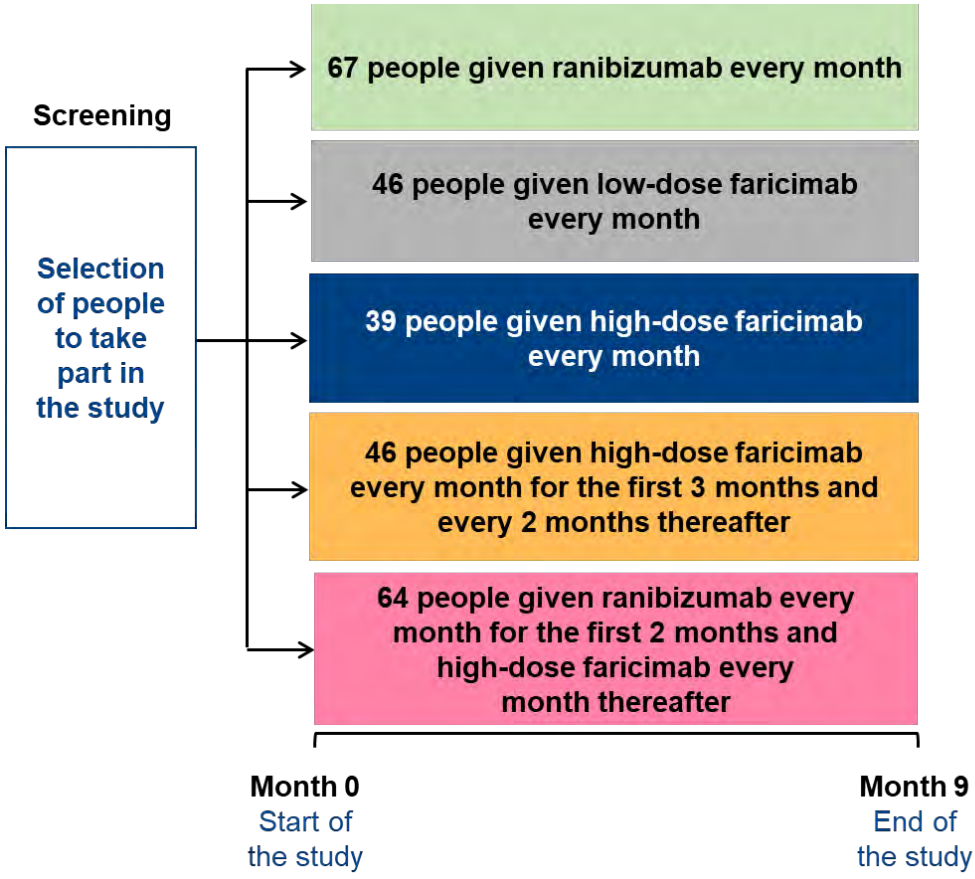
- **Monthly ranibizumab (arm A):** ranibizumab 0.5 mg injected into the eye once every month
- **Monthly faricimab at a low dose (arm B):** faricimab 1.5 mg injected into the eye once every month
- **Monthly faricimab at a high dose (arm C):** faricimab 6.0 mg injected into the eye once every month
- **Faricimab at a high dose given monthly for the first 3 months followed by once every 2 months (arm D):** faricimab 6.0 mg injected into the eye once every month for the first 3 months of the study, followed by faricimab 6.0 mg once every 2 months
- **Monthly ranibizumab for the first 2 months followed by monthly faricimab at a high dose (arm E):** ranibizumab 0.5 mg injected into the eye once every month for the first 2 months of the study, followed by faricimab 6.0 mg once every month.

In total, people in all 5 arms received treatment for 9 months (Figure 18).

People were divided into 2 groups to look at whether faricimab was safe, and whether it worked. Group 1 included people in arms A–D, apart from some people in arm A who did not respond well to treatment by month 3. Group 2 included people who received ranibizumab for at least part of the study. These were the people from arm A who did not respond well to treatment by month 3 of the study, and the people in arm E.

People took eye tests at different time points in the study. The main finding of the study (see section 1 “What were the results of the study?”) was based on the results of eye tests done at month 9 (the end of the study). These were compared with eye tests done at the start of the study for people in group 1, or eye tests done at month 3 for people in group 2.

Figure 18



5. What were the side effects?

Side effects (also known as adverse reactions or adverse events) are unwanted medical problems (for example, a headache,) that happen during the study and were reported as caused by the treatment administered by the researchers. This section describes the side effects that occurred in the eye during the study.

- Side effects believed to be caused by study procedures, as well as those related to the progression of the disease being studied, are described.
- Not all of the people in this study had all of the side effects.

Of the 262 people who received at least 1 dose of study drug, around 8 in 10 (214 or 82%) experienced at least 1 side effect during the study.

Five people experienced 6 serious side effects in the eye. This included a single retinal bleeding event that was reported to be caused by study treatment. In addition, 2 people experienced

infection of the tissues or fluids inside the eyeball (endophthalmitis). The researchers agreed that this was caused by the injection procedure. 11 people experienced side effects that led to them stopping treatment.

Overall, the researchers concluded that the safety of faricimab was similar to that of ranibizumab.

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.

A single retinal bleeding event was reported as related to study treatment.

Most common side effects

The most common side effects people had in the eye that had the injection are shown in the following table. These are the 7 most common side effects across all treatment arms:

Most common side effects	Arm A	Arm B	Arm C	Arm D	Arm E
	67 people total	**46** people total	**39** people total	**46** people total	**64** people total
Bleeding in the white of the eye	**13** people 19%	**4** people 9%	**6** people 15%	**6** people 13%	**6** people 9%
Eye pain	**2** people 3%	**4** people 9%	**2** people 5%	**5** people 11%	**3** people 5%
Vitreous detachment (separation of the jelly-like substance in the eye from the retina)	**2** people 3%	**5** people 11%	**3** people 8%	**3** people 7%	**3** people 5%
Vitreous floaters (clumps in the jelly-like substance in the eye)	**2** people 3%	**3** people 7%	**4** people 10%	**2** people 4%	**0** people 0%
Eye irritation	**0** people 0%	**1** person 2 %	**4** people 10%	**4** people 9%	**1** person 2%
Blurred vision	**2** people 3%	**1** person 2%	**3** people 8%	**2** people 4%	**2** people 3%
Hypertension	**2** people 3%	**1** person 2%	**1** person 3%	**3** people 7%	**3** people 5%

Please refer to Figure 1 for information on the treatment received in arms A to E.

There were no new or unexpected safety concerns with faricimab in this study.

6. How has this study helped research?

The information presented here is from a single study of 244 people living with wet AMD. These results helped researchers learn more about wet AMD and faricimab.

In this study, people receiving faricimab at different doses and dose timings showed improvement in their vision similar to people taking monthly ranibizumab, as measured by eye tests. This means that faricimab, as used in the study, is similar to the currently licensed medicine ranibizumab in the treatment of wet AMD. There were no new or unexpected side effects for faricimab compared with ranibizumab.

No single study can tell us everything about the harms and effectiveness 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?

This study has now closed, but two further clinical trials (called TENAYA and LUCERNE) are currently underway and will further investigate the long-term effects and safety of faricimab in much larger groups of persons living with wet AMD.

8. Where can I find more information?

You can find more information about this study at the website listed below:

- https://clinicaltrials.gov/ct2/show/NCT02484690

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

If you have any further questions after reading this summary:

- 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 Proof-of-Concept Study of Faricimab (RO6867461) in Participants With Choroidal Neovascularization (CNV) Secondary to Age-Related Macular Degeneration (AMD) (AVENUE).”

The study is known as AVENUE.

- The protocol number for this study is: BP29647.
- The ClinicalTrials.gov identifier for this study is: NCT02484690
- The study was recently published in a medical journal: Sahni J, et al. *JAMA Ophthalmology*. July 2020.
- The journal publication of the study “Safety and Efficacy of Different Doses and Regimens of Faricimab vs Ranibizumab in Neovascular Age-Related Macular Degeneration. The AVENUE Phase 2 Randomized Clinical Trial” is available here: https://pubmed.ncbi.nlm.nih.gov/32729888/