

Clinical Trial Results – Layperson Summary

A study to compare different doses of a study medicine called faricimab with an existing medicine called ranibizumab – in people with damage to the back of the eye caused by diabetes (diabetic macular edema)

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 the official publication of study results (October 2019). More information may now be known.

The study started in April 2016 and finished in December 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. 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.

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 diabetes and the study medicine faricimab.

Key information about this study

- This study was done to compare a new study medicine (called ‘faricimab’) with an existing medicine (called ‘ranibizumab’) in people with diabetes and damage to the back of the eye caused by high blood sugar levels. This condition is called diabetic macular edema (DME for short).
- In this study, people received either a high or low dose of faricimab or ranibizumab – it was decided by random chance which treatment each person was given.
- This study included 226 people in the United States.
- The main finding was in people who had not been treated for DME before. They took an eye test using an eye chart with rows of letters that get smaller from top to bottom. People who received high-dose faricimab were able to see about 14 more letters on this eye chart than at the start of the study. People who received ranibizumab were able to see about 10 more letters on this eye chart.
- Faricimab was well tolerated and showed no new or unexpected side effects.

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1. What were the results of the study?

Question 1: Did faricimab improve eyesight in people who had not received treatment for DME before?

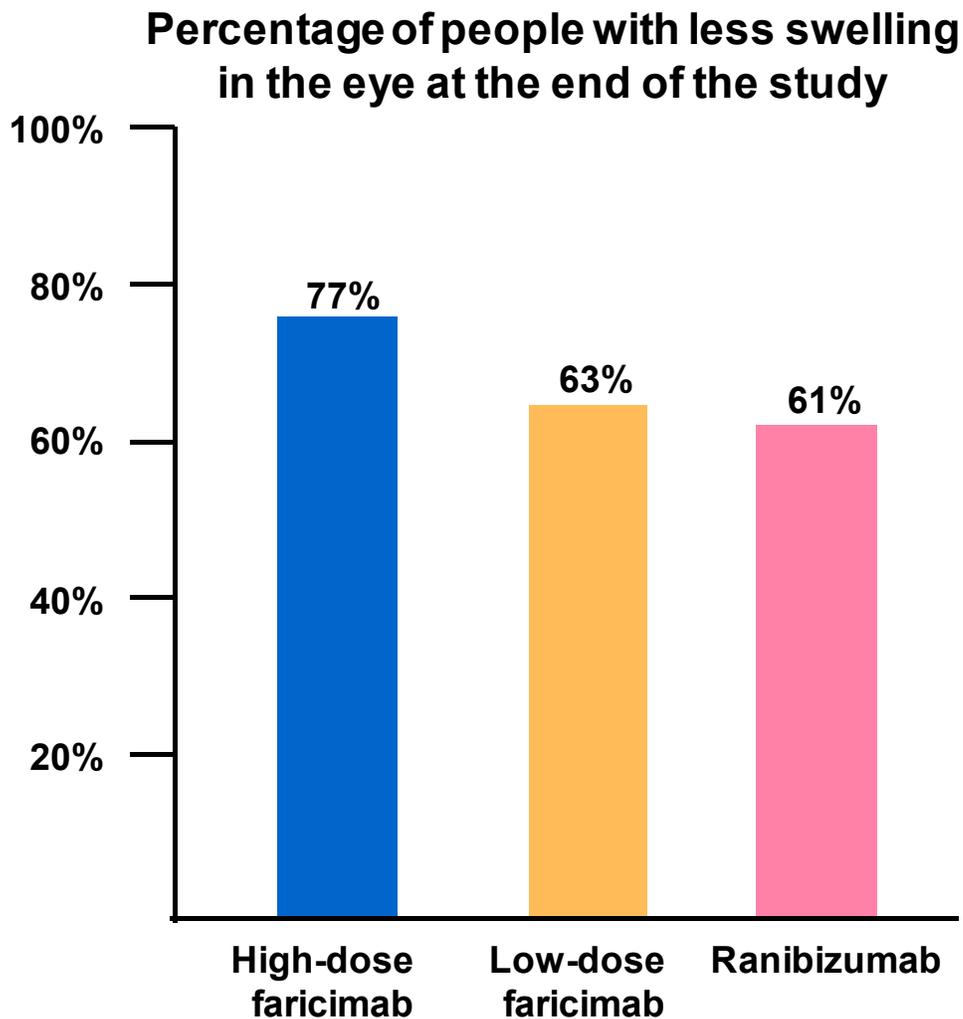
Patients who received high-dose faricimab were able to see about 14 more letters on an eye chart compared with when they started the study. People who received ranibizumab were able to see about 10 more letters.

How many more letters were people able to see on an eye chart?



Question 2: Did faricimab improve the swelling and leakiness of blood vessels in the eye?

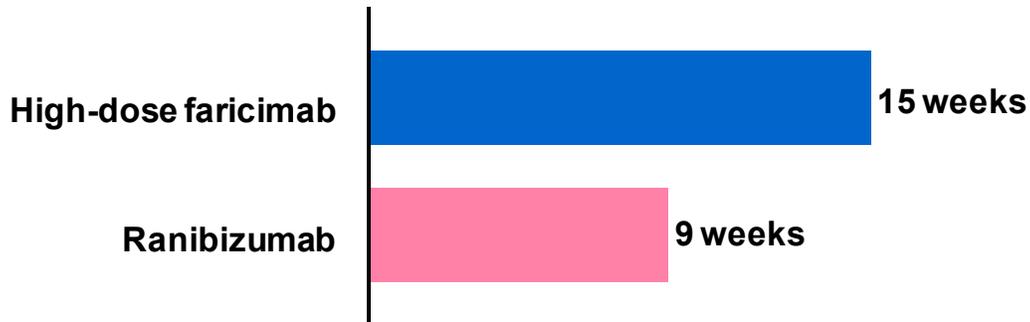
Among patients who received high-dose faricimab, 77% had less swelling in the eye at the end of the study, compared with 61% of those who received ranibizumab.



Question 3: Were people who received faricimab able to go longer before they needed another treatment?

After the last study treatment, half of the people who received high-dose faricimab did not require another treatment until 15 weeks when DME symptoms came back, compared with 9 weeks for those who received ranibizumab.

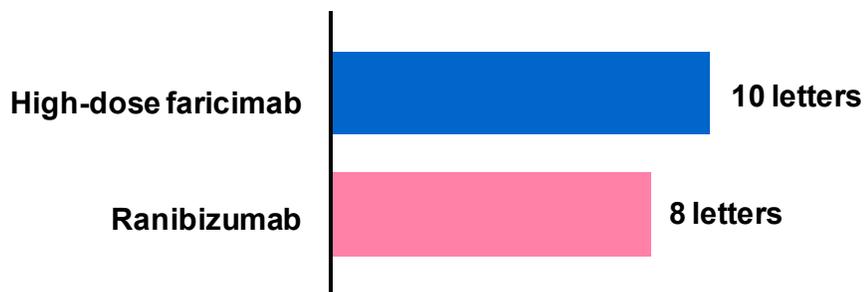
How long before people needed another treatment?



Question 4: Did faricimab improve eyesight in people who had received previous treatments for DME?

Patients who received high-dose faricimab were able to see about 10 more letters on an eye chart than when the study first started. This compares with about 8 more letters for people who received ranibizumab.

How many more letters were people able to see on an eye chart?

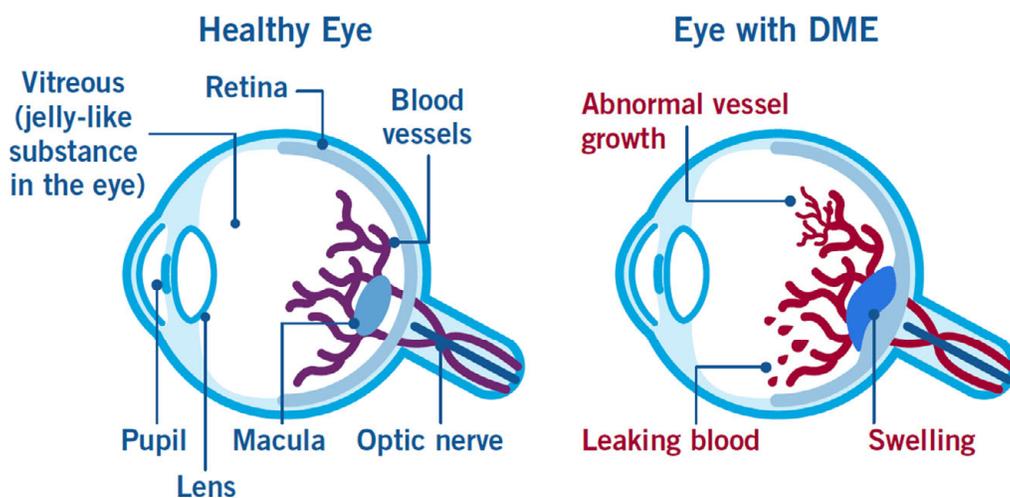


This section only shows the key results from the study. You can find information about all other results on the websites at the end of this summary (see section 8).

2. General information about this study

Why was this study done?

Many people with diabetes develop eye complications. The retina is the part of the back of the eye that sends images to the brain. The macula is an area in the center of the retina that gives you sharp, clear vision. Diabetic macular edema (DME for short) is a condition where the macula swells with fluid leaked from damaged blood vessels. DME is a major cause of severe vision loss. Currently, DME can be treated with medicines such as ranibizumab and aflibercept that are injected into the eye. These medicines block a factor that causes leakage of fluid and growth of abnormal blood vessels (vascular endothelial growth factor [VEGF] – further details in section 8). Other treatments include eye injections of medicines called steroids to reduce swelling, and laser treatments to stop blood vessels from leaking.



The existing medicine (called ranibizumab or aflibercept) has improved eyesight for people with diabetes, 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 DME than the existing treatments target.

What were the study medicines?

'Ranibizumab' (Lucentis®) is an existing medicine given to people with DME. It is 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 with diabetes.
- Ranibizumab is a medicine that is officially approved for use.

'Faricimab' is the medicine that was being studied here – it works in a different way to ranibizumab.

- You say this as 'far-ih-see-mab'.
- Faricimab blocks **two** different factors in eyes of people with diabetes. 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 may have more improvement in their eyesight and go longer before they need another treatment.
- Faricimab was tested at different doses.
- Faricimab is a new medicine being studied and 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 the study medicine (faricimab) with an existing medicine (ranibizumab) – to see how well faricimab worked (see section 4 "What were the results of the study?").
- They also wanted to find out how safe faricimab was – 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. Did faricimab improve eyesight in people who had not received treatment for DME before?

Other questions that researchers wanted to answer included:

2. Did faricimab improve the swelling and leakiness of blood vessels in the eye?
3. Were people who received faricimab able to go longer before they needed another treatment?
4. Did faricimab improve eyesight in people who had received other treatments for DME before the study?

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 with eye disease before this study, to select the ideal dose of faricimab to be further tested for effectiveness. In this study, people with DME were given either faricimab or ranibizumab – this was to find out about the safety of faricimab and if faricimab worked to improve eyesight in people who had not been treated before.

The study was ‘randomized’. This means that it was decided by random chance which of the medicines people in the study would have – like tossing a coin.

The study was ‘double-masked’. This means that neither the people taking part in the study or the study doctors knew if people were taking the new medicine (faricimab) or the existing medicine (ranibizumab).

‘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 they were taking.

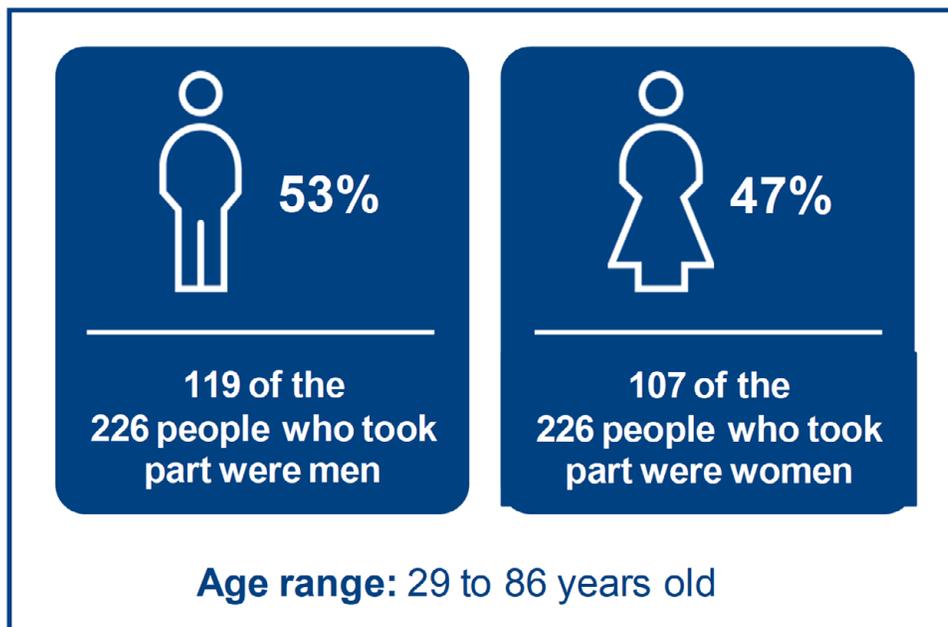
When and where did the study take place?

The study started in April 2016 and finished in December 2017. This summary was written after the study had ended.

The study took place at 59 study centers in the United States.

3. Who took part in this study?

In this study, 226 adults with DME took part.



People could take part in the study if they had:

- DME (see explanation in section 2) that involved the center of the retina at the back of the eye
- Swelling at the back of the eye (the researchers measured this as a thickness at or above 325 micrometers)
- 20/40 to 20/320 vision. A person with 20/40 vision needs to be at 20 feet to see what a person with good vision can see at 40 feet. On the other hand, 20/320 is very poor vision – someone with this vision can see at 20 feet what a person with good vision can see at 320 feet

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

- Severe damage to the back of the eye caused by diabetes (called 'high-risk proliferative diabetic retinopathy') where abnormal blood vessels can bleed into the eye and damage vision
- Laser therapy to treat damage in the retina
- Treatment with ranibizumab within 3 months of the start of the study

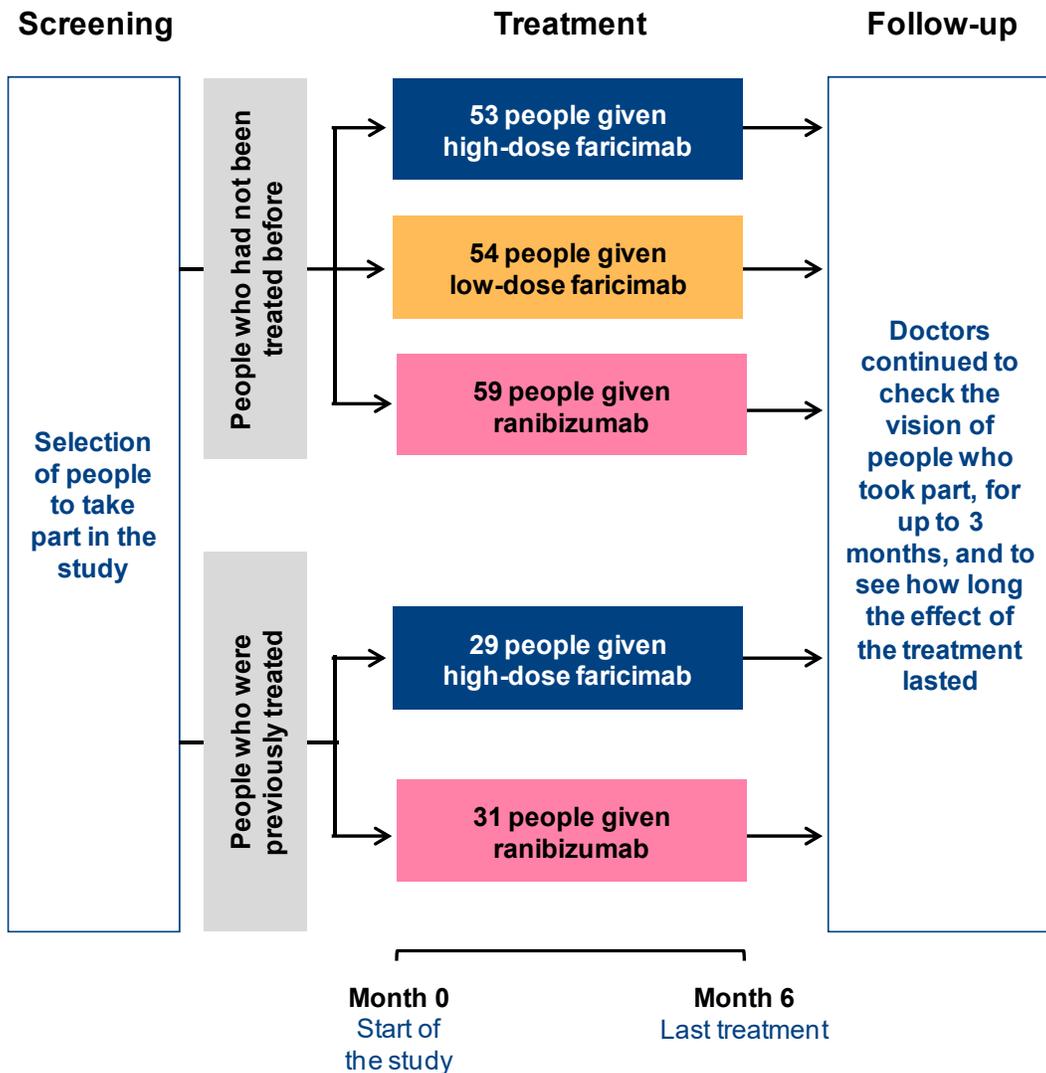
4. What happened during the study?

During the study, people who had not been treated with medicines (such as ranibizumab or aflibercept) before the study were divided into groups by random chance to get one of 3 treatments. People who had received treatment before with existing or similar medicine were selected by chance to get one of 2 treatments (high-dose faricimab or ranibizumab). The treatments were selected at random – by a computer.

The treatment groups were:

- **High-dose faricimab** (the study medicine) – 6 milligrams (6 mg) faricimab injected into the eye once every month.
- **Low-dose faricimab** (the study medicine) – 1.5 milligrams (1.5 mg) faricimab injected into the eye once every month.
- **Ranibizumab** (the existing medicine) – 0.3 milligrams (0.3 mg) injected into the eye once every month.

People in the study received the treatments for 6 months. When the study finished, the people who took part were checked at their study clinic regularly for the next 3 months – to see how their vision was and how long the effect of the treatment lasted. Look below to see more information about what happened in the study.



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 and were reported as related to 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 related to 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.

Most non-serious side effects in the eye were considered unrelated to the study medicine.

Four non-serious side effects that were considered related to the study medicine occurred in 3 patients:

- Lens disorder (mild)
- Separation of the jelly-like substance (vitreous) at the back of the eye from the retina (mild)
- Spots in vision (floaters) and cataract (moderate)

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 this study, 1 patient receiving faricimab and 1 patient receiving ranibizumab had a serious side effect each. Neither of these side effects was considered to be related to faricimab by the study doctor. Both of these side effects were however considered as sight-threatening side effects.

- The patient receiving faricimab had blood leak into the fluid that fills the eye (called 'vitreous hemorrhage') on the first day after treatment.
 - This was thought to be due to the injection. The patient was better at the end of the study.
- The patient receiving ranibizumab had severe damage to the back of the eye as a complication of preexisting diabetes.

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

- In the low-dose faricimab group, treatment was stopped in a patient who had an infection (gangrene) as a complication of diabetes.
- In the ranibizumab group, treatment was stopped to do eye surgery in a patient who had complications in the eye due to diabetes

Most common side effects

The most common side effects that occurred in the eye that had the injection are shown in the following table – these are the 5 most common side effects across all treatment groups.

Most common side effects reported in this study	People taking high-dose faricimab (80 people total)	People taking low-dose faricimab (55 people total)	People taking ranibizumab (89 people total)
Bleeding in the white of the eye	10% (8 out of 80 people)	4% (2 out of 55 people)	6% (5 out of 89 people)
Eye pain	3% (2 out of 80 people)	5% (3 out of 55 people)	2% (2 out of 89 people)
Hard deposits in the back of the eye (retina)	3% (2 out of 80 people)	5% (3 out of 55 people)	1% (1 out of 89 people)
Separation of the jelly-like substance (vitreous) at the back of the eye from the retina	1% (1 out of 80 people)	5% (3 out of 55 people)	2% (2 out of 89 people)
Spots in vision (floaters)	3% (2 out of 80 people)	4% (2 out of 55 people)	2% (2 out of 89 people)

Other side effects

You can find information about other side effects (not shown in the sections above) on the websites or scientific publication 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 226 people with DME. These results helped researchers learn more about DME and faricimab.

Faricimab (the study medicine) improved eyesight more than ranibizumab (the existing medicine), and people treated with faricimab were able to go longer before they needed another treatment. The researchers did not see any new or unexpected side effects.

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 and effects of faricimab are taking place. Two of these studies are looking at the use of faricimab in a larger group of people (1,800 adults) with DME worldwide and over a longer period of time (2 years). Two other studies are also looking at the use of faricimab in 1,280 patients with neovascular age-related macular degeneration (nAMD), another eye condition that may cause blindness due to growth of abnormal blood vessels.

This study finished in December 2017. This summary was written after the study had ended.

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/NCT02699450>
- <https://forpatients.roche.com/en/trials/eye-disorder/dme/a-study-of-ro6867461-in-participants-with-center-involving-diabe.html>

If you would like to find out more about the results of this study, the full title of the relevant scientific paper is: “Simultaneous Inhibition of Angiopoietin-2 and Vascular Endothelial Growth Factor-A with Faricimab in Diabetic Macular Edema: BOULEVARD Phase 2 Randomized Trial.” The authors of the scientific paper are: J. Sahni, S.S. Patel, P.U. Dugel, A.M. Khanani, C.D. Jhaveri and others. The paper is published in the journal ‘Ophthalmology’, volume number 126, on pages 1155-1170.

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/eye-disorder/dme/a-study-of-ro6867461-in-participants-with-center-involving-diabe.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 Multiple-Center, Multiple-Dose, Randomized, Active Comparator-Controlled, Double-Masked, Parallel Group, 36-Week Study to Investigate the Safety, Tolerability, Pharmacokinetics, and Efficacy of RO6867461 Administered Intravitreally in Patients With Diabetic Macular Edema.”

The study is known as ‘BOULEVARD’.

- The protocol number for this study is: BP30099.
- The ClinicalTrials.gov identifier for this study is: NCT02699450.
- The study was recently published in a medical journal: Sahni J, et al. *Ophthalmology*. 2019 Aug;126(8):1155-1170.
- The full-text of the publication is available here:
<https://www.ncbi.nlm.nih.gov/pubmed/30905643>
- You can find out more about VEGF and how anti-VEGF medicines work at <https://www.aao.org/eye-health/drugs/anti-vegf-treatments>