NOVARTIS

Clinical Trial Results Summary

A clinical trial to compare the effects and safety of brolucizumab with aflibercept in treating participants with loss of vision due to Diabetic Macular Edema (DME)

Protocol number: CRTH258B2302

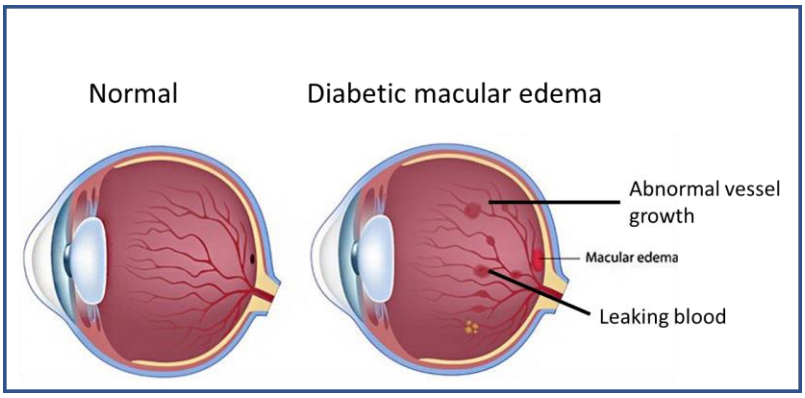
Thank You!

Novartis sponsored this trial and believes it is important to share what was learned from the results of this trial with the participants and the public. Thank you for taking part in this trial for the drug brolucizumab, also known as RTH258. You helped researchers learn more about how brolucizumab works in people with Diabetic Macular Edema.

This summary only shows the results of a single clinical trial. Other clinical trials may have different findings. Researchers and health authorities, such as the Food and Drug Administration (FDA) in the United States, and the European Drugs Agency (EMA) in Europe look at the results of many clinical trials to understand which drugs work and if they are safe. Websites listed at the end of the summary may have more information about this trial. If you have any questions about these trial results, please talk to the doctor or staff at your trial site.

Why was the research needed?

Researchers were looking for a better way to treat Diabetic Macular Edema (DME). DME is the most common cause of vision loss in people with diabetes. In DME, there is swelling (edema) in the macula which causes fluid to leak from the damaged blood vessels of the retina. 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 us sharp, clear vision. Over time, DME can cause vision to become blurred. Eventually, these changes can become permanent.



Source: EveryDayHealth.com

Drug	***Pronounced as***
Brolucizumab	*BRO-lu-SIZ-oo-mab*
Aflibercept	*a-FLI-ber-sept*

Currently, DME can be treated with drugs such as ranibizumab or aflibercept. These drugs block a protein called vascular endothelial growth factor (VEGF) that causes abnormal growth and leakage of blood vessels at the back of the eye. Other treatments include drugs called steroids that reduce swelling, and laser treatments to stop blood vessels from leaking.

The main question the researchers wanted to answer in this trial was:

Did vision test scores show similar improvement for participants on brolucizumab compared to those on aflibercept after 52 weeks of treatment?

The other questions researchers wanted to explore in this trial were:

- Did vision test scores show similar improvement for participants on brolucizumab compared to those on aflibercept during and up to the end of the trial (Week 100)?
- Did participants on brolucizumab show a similar reduction in the thickness (swelling) of the central part of the retina compared to participants on aflibercept at the end of the trial (Week 100)?

Trial drugs

The drugs given in this trial were:

Brolucizumab is a drug that is not yet approved for the treatment of DME. It has been approved for the treatment of a similar condition known as wet age-related macular degeneration. It is given as an injection into the eye.

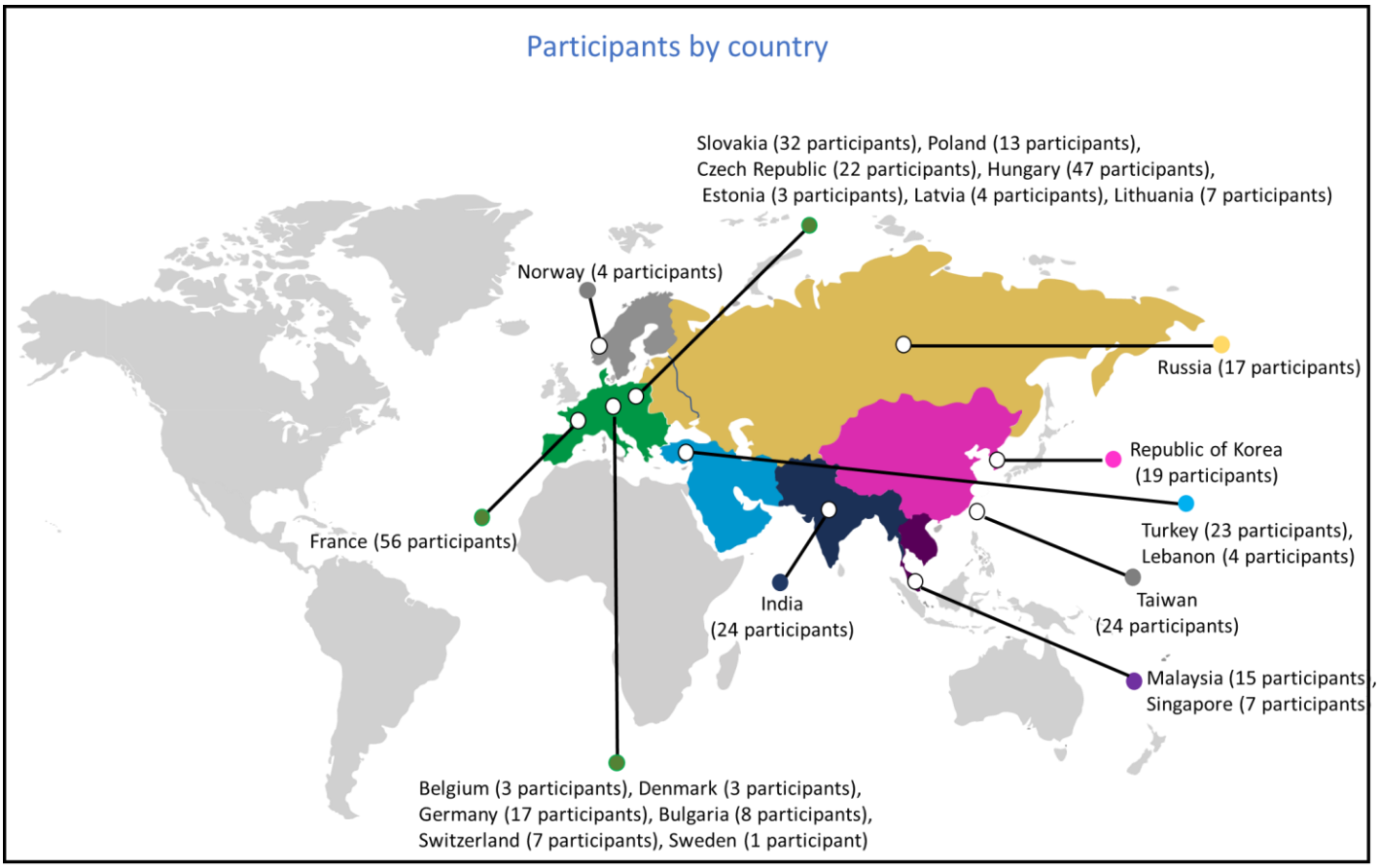
Aflibercept is a drug approved for the treatment of DME. It is given as an injection into the eye.

Who was in this trial?

The participants could take part in this trial if they:

- were aged 18 years or older,
- had type-1 or type-2 diabetes,
- had DME, and could read at least 23 letters to 78 letters in a vision test, and
- did not have any other eye diseases.

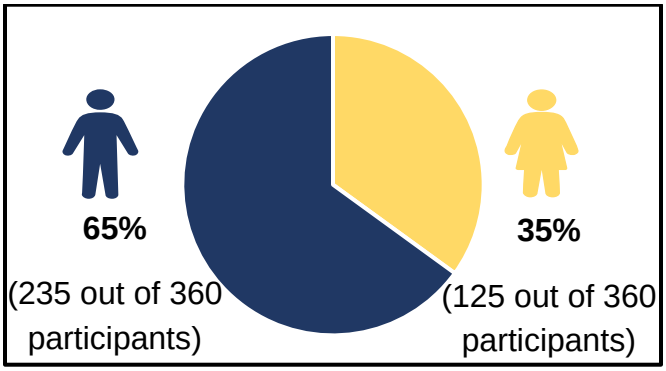
A total of 360 participants from 23 countries participated in this trial.



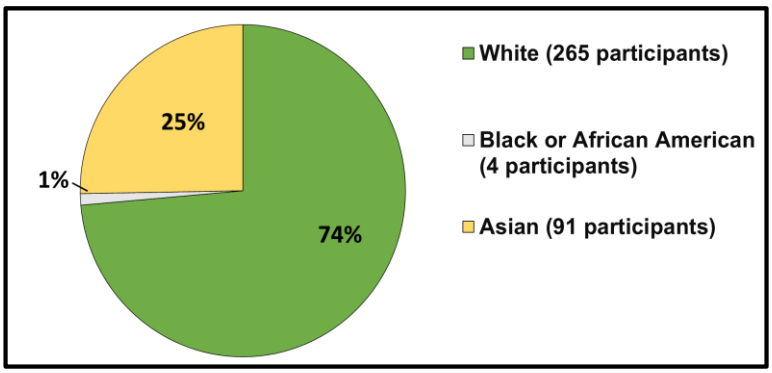
Participants' age ranged from 24 to 86 years. The average age of participants was 62 years.

The majority of participants were men and white, as shown below:

Participants by Gender



Participants by Race



How was this trial done?

Before Treatment (2 weeks)

The trial doctors checked if participants could take part in this trial. None of the participants, trial doctors, or trial staff knew which treatment participants were going to receive.

During Treatment (96 weeks)

Participants were randomly assigned to 1 of 2 treatment groups to receive either:

Brolucizumab 6 mg (milligram) injection once every 6 weeks until Week 24, and then once every 12 or 8 weeks (depending on the severity of their disease) until Week 96 (last dose).

At Week 72, participants also had the option to extend the treatment interval from every 8 weeks to every 12 weeks, or from every 12 weeks to every 16 weeks, OR

Aflibercept 2 mg injection every 4 weeks until Week 16, and then once every 8 weeks until Week 96 (last dose).

Brolucizumab 6 mg	**Aflibercept** 2 mg
179 participants	181 participants

The drug was injected directly into the selected study eye. For all participants, there was a 1 in 2 chance of receiving either of these study drugs. Participants did a vision test at every visit to the site. Researchers monitored the participants' health throughout the trial.

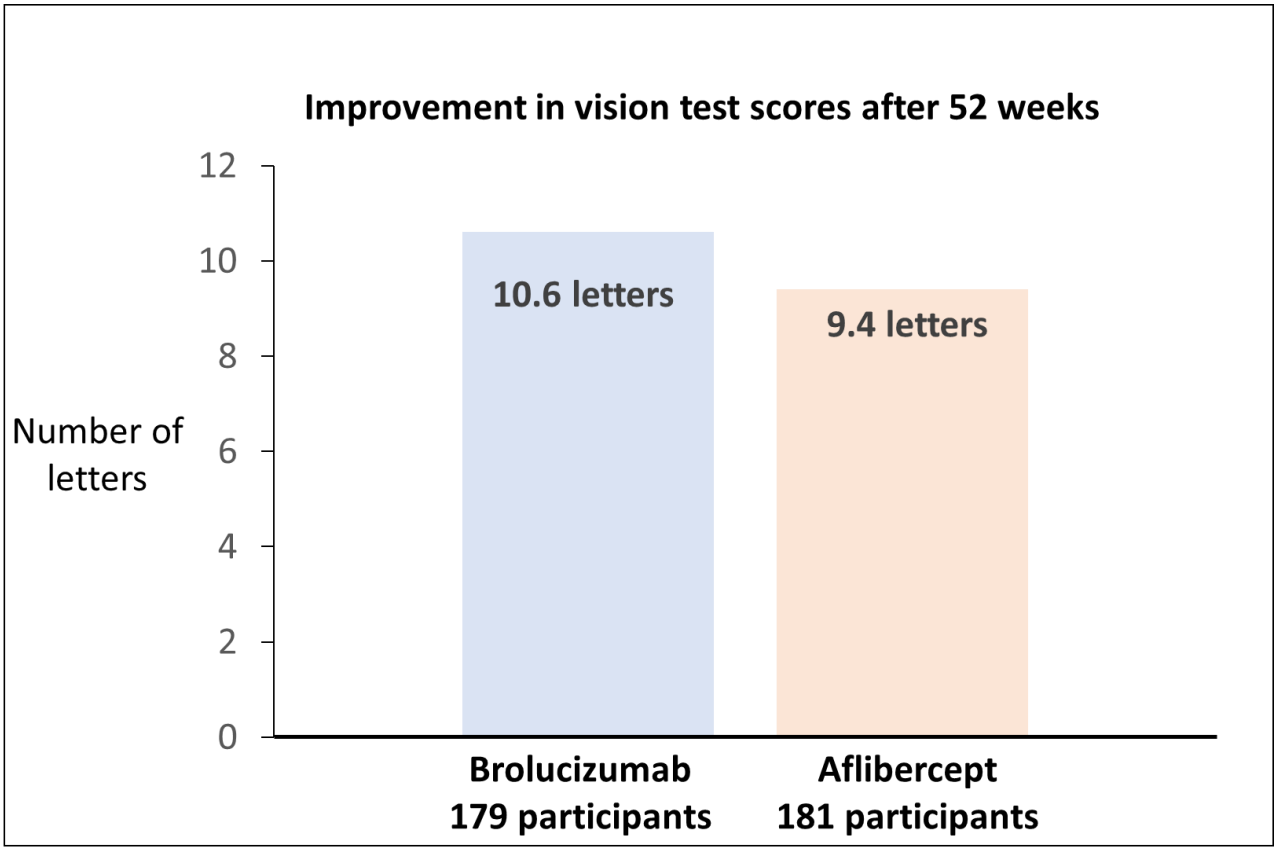
After Treatment (4 weeks)

Participants had their end of trial visit 4 weeks after their last treatment dose. Researchers completed this trial as planned.

What were the key results of this trial?

Did vision test scores show similar improvement for participants on brolucizumab compared to those on aflibercept after 52 weeks of treatment?

Following 52 weeks of treatment, the average vision test score improved by +10.6 letters for participants on brolucizumab and by +9.4 letters for participants on aflibercept. This means the participants on brolucizumab were able to read +1.2 letters more than participants on aflibercept. This showed that the improvement of vision in participants who took brolucizumab was similar to participants who took aflibercept.



What were the other results of this trial?

Did vision test scores show similar improvement for participants on brolucizumab compared to those on aflibercept during and up to the end of the trial (Week 100)?

The average vision test scores were numerically higher at each visit in participants on brolucizumab compared to participants on aflibercept during and up to the end of the trial.

Did participants on brolucizumab show a similar reduction in the thickness (swelling) of the central part of the retina compared to participants on aflibercept at the end of the trial (Week 100)?

At the end of the trial (Week 100), on average, participants in the brolucizumab arm showed a numerically better reduction in the thickness (swelling) of the central part of the retina compared to participants in the aflibercept arm.

What medical problems did the participants have during the trial?

Medical problems that happen in clinical trials are called “adverse events”.

A lot of research is needed to know whether a drug causes an adverse event. During a trial, all adverse events are recorded, whether or not they are thought to be caused by the trial drug. When new drugs are being studied, researchers keep track of all adverse events participants have.

This section is a summary of the adverse events that happened during this trial. The websites listed at the end of this summary may have more information about all the adverse events that happened in this trial.

An adverse event is an unwanted sign, symptom, or disease that participants have during a trial.

An adverse event is considered “serious” when it is life-threatening, causes lasting problems, or the participant needs hospital care. These problems may or may not be caused by the trial drug.

How many participants had adverse events?

In this trial, researchers wanted to distinguish between the ocular adverse events (adverse events of the eye) and non-ocular adverse events. The number of participants with ocular or non-ocular adverse events are presented in the table below.

Number of Participants (%) With Ocular Adverse Events

Category	Brolucizumab 6mg (Out of 179 Participants)	Aflibercept 2mg (Out of 181 Participants)
At least 1 ocular adverse event	73 (41%)	74 (41%)
At least 1 serious ocular adverse event	5 (3%)	3 (2%)
Stopped drug due to ocular adverse event	5 (3 %)	4 (2%)

Number of Participants (%) With Non-Ocular Adverse Events

Category	Brolucizumab 6mg (Out of 179 Participants)	Aflibercept 2mg (Out of 181 Participants)
At least 1 non-ocular adverse event	136 (76%)	141 (78%)
At least 1 serious non-ocular adverse event	48 (27%)	58 (32%)
Stopped drug due to non-ocular adverse event	10 (6%)	4 (2%)

What were the most common non-serious adverse events?

Non-serious ocular adverse events

The most common non-serious ocular adverse events that happened in at least 5% of participants in any group are presented below.

Number of Participants (%) With Most Common Non-Serious Ocular Adverse Events

	Brolucizumab (Out of 179 participants)	**Aflibercept** (Out of 181 participants)
Blood spots on white part of the eye - treated eye (Conjunctival hemorrhage - study eye)	9 (5%)	6 (3%)
Blood spots on white part of the eye - untreated eye (Conjunctival hemorrhage - fellow eye)	1 (<1%)	9 (5%)
Clouding of the eye - treated eye (Cataract- study eye)	12 (7%)	19 (11%)
Clouding of the eye - untreated eye (Cataract - fellow eye)	11 (6%)	16 (9%)
Dry eye - treated eye (Dry eye - study eye)	9 (5%)	9 (5%)
Dry eye - untreated eye (Dry eye - fellow eye)	9 (5%)	7 (4%)
Worsening of Diabetic retinal edema - untreated eye (Diabetic retinal edema - fellow eye)	18 (10%)	16 (9%)

Non-serious non-ocular adverse events

The most common non-serious non-ocular adverse events that happened in at least 5% of participants in any group are presented below.

Number of Participants (%) With Most Common Non-Serious Non-Ocular Adverse Events

	Brolucizumab (Out of 179 participants)	**Aflibercept** (Out of 181 participants)
Common cold (Nasopharyngitis)	16 (9%)	17 (9%)
Cough (Cough)	5 (3%)	10 (6%)
High blood pressure (Hypertension)	15 (8%)	17 (9%)
Increase in level of protein in the urine (Proteinuria)	6 (3%)	13 (7%)

What were the most common serious adverse events?

Ocular serious adverse events

Less than 1% of participants in any group had ocular serious adverse events, therefore data is not reported in this summary.

Non-ocular serious adverse events

The most common non-ocular serious adverse events that happened in at least 2% of participants in any group are shown below.

Number of Participants (%) With Most Common Non-Ocular Serious Adverse Events

	Brolucizumab (Out of 179 participants)	**Aflibercept** (Out of 181 participants)
COVID-19 infection (COVID-19)	4 (2%)	3 (2%)
Death of body tissue due to a lack of blood flow (Gangrene)	3 (2%)	2 (1%)
Heart attack (Myocardial infarction)	0	3 (2%)
Gradual loss of kidney function over time (Chronic kidney disease)	0	3 (2%)
Lung infection (Pneumonia)	4 (2%)	3 (2%)
Worsening of heart failure (Cardiac failure)	2 (1%)	4 (2%)

A total of 22 participants died during the study. This included 13 participants in the brolucizumab group and 9 participants in the aflibercept group.

How many participants stopped trial drug due to adverse events?

Ocular adverse events

During the trial, 3 out of 179 (2%) participants stopped brolucizumab early. Among these, 2 participants stopped brolucizumab due to **inflammation in the eye wall** (uveitis) and 1 participant stopped brolucizumab due to **blockage of blood vessel carrying oxygen to the retina** (retinal artery occlusion).

4 out of 181 (2%) participants stopped aflibercept early due to **inflammation in the eye wall** (uveitis), **blockage of blood vessel carrying oxygen to the retina** (retinal artery occlusion), **feels like something is rubbing against your eyes when you blink** (foreign body sensation in eyes) and **infection inside the eye** (endophthalmitis).

Non-ocular adverse events

During the trial, 7 out of 179 (4%) participants stopped brolucizumab early and 4 out of 181 (2%) participants stopped aflibercept early due to a non-ocular adverse event.

How was this trial useful?

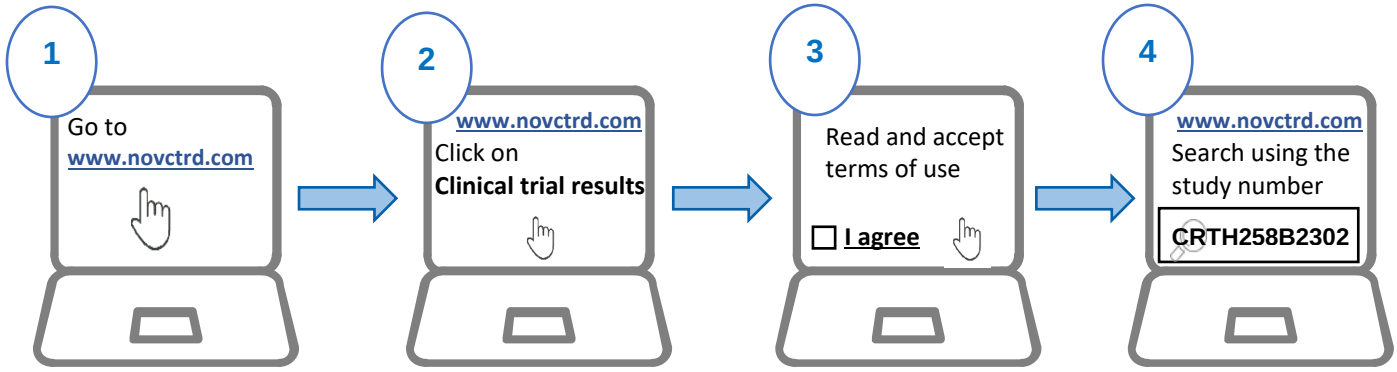
Researchers learned about the effects and safety of brolucizumab in participants with DME. The data collected at the end of this trial supported the administration of brolucizumab as an effective and safe treatment for DME patients.

Results from this trial may be used in other clinical trials for people with DME. If you have any questions about these trial results, please talk to the doctor or staff at your trial site.

Where can I learn more about this trial?

More information about the results and adverse events in this trial can be found in the scientific summary of the results available on the Novartis Clinical Trial Results website (www.novctrd.com).

Please follow the below steps:



You can find more information about this trial on the following websites:

- www.clinicaltrials.gov Use the NCT identifier NCT03481660 in the search field.
- https://www.clinicaltrialsregister.eu/ctr-search/search Use the EudraCT identifier 2017-003960-11 in the search field.

Full clinical trial title: A two-year, two-arm, randomized, double masked, multicenter, phase III study assessing the efficacy and safety of brolucizumab versus aflibercept in adult patients with visual impairment due to diabetic macular edema (KITE)

Trial Dates: The trial started in July 2018 and ended in June 2021.

Thank you

Thank you for taking part in this trial. As a clinical trial participant, you belong to a large community of people around the world. You helped researchers answer important health questions and test new medical treatments.

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Novartis is a global healthcare company based in Switzerland that provides solutions to address the evolving needs of patients worldwide.

1-888-669-6682 (US); +41-61-324-1111 (EU); www.novartisclinicaltrials.com