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: CRTH258B2305

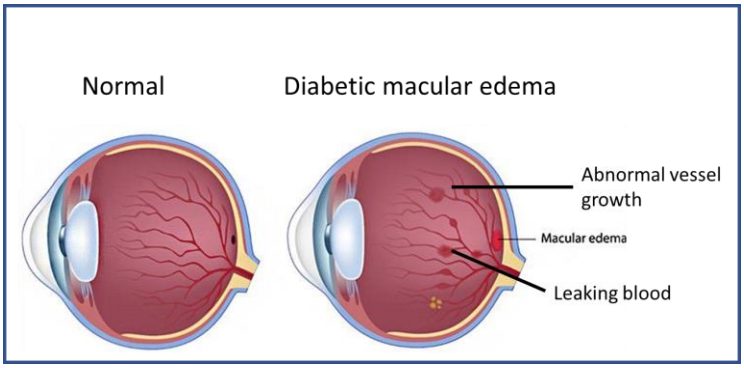
Thank You!

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 Medicines 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 in the macula with fluid leaked from the damaged blood vessels of the retina. The macula is an area in the center of the retina that gives us sharp, clear vision. The retina is a thin layer of tissue at the back of the eye that sends images to the brain. Over time, DME can cause vision to become blurred. Eventually, these changes 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 medicines such as aflibercept or ranibizumab. These medicines 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 medicines 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 improve by a similar number in participants on brolucizumab compared to those on aflibercept by Week 52?

Trial drugs

During the trial, participants received either one of these 2 drugs:

Brolucizumab is a drug approved in some countries 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 in some countries 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:

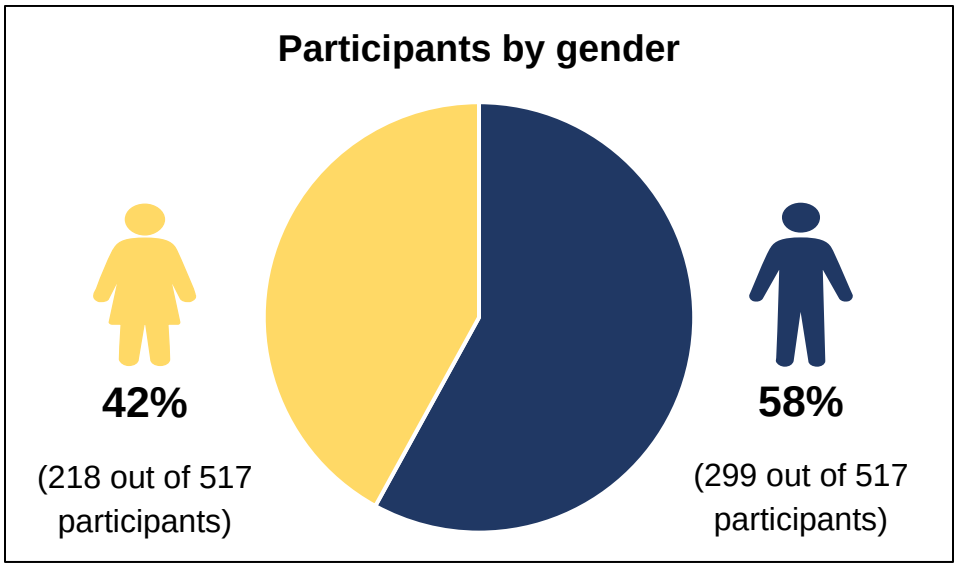
- were aged 18 years or older,
- had type-1 or type-2 diabetes,
- had DME and could read from at least 23 letters to 73 letters in a vision test, and
- did not have any other eye problems.

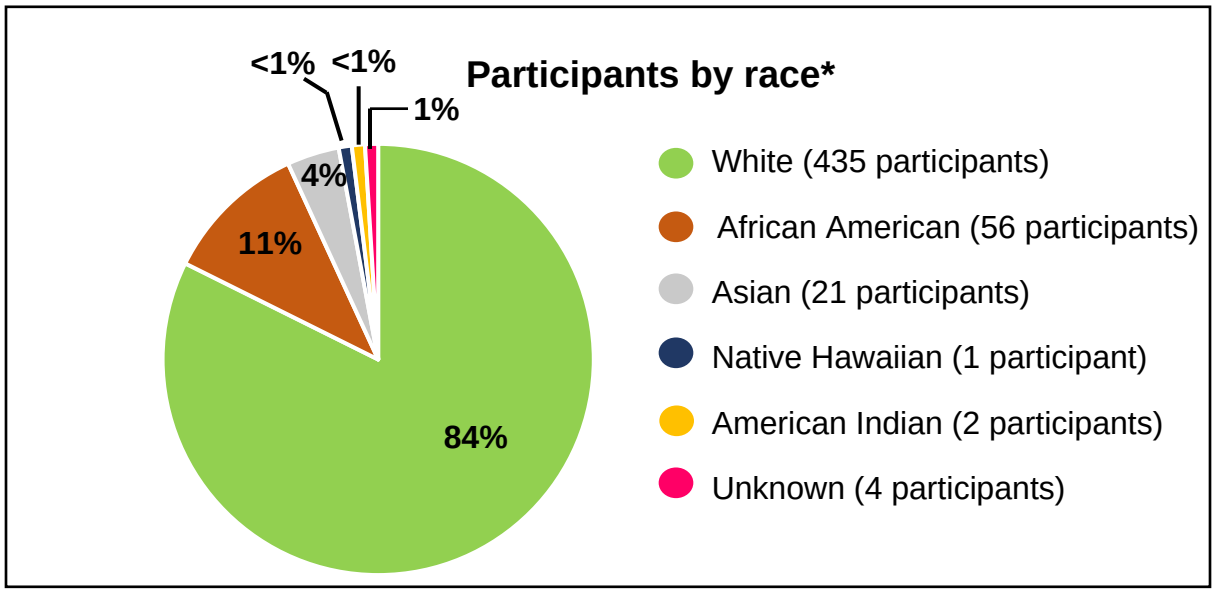
A total of 517 participants from 4 countries participated in this trial.

Country	Number of participants
Hungary	51 (10%)
Israel	27 (5%)
Slovakia	47 (9%)
United States	392 (76%)

Participants' age ranged from 26 to 89 years. The average age of participants was 61 years.

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





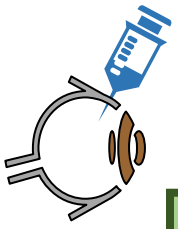
*The numbers are greater than 517 because a participant could select multiple races.

How was this trial done?

Before Treatment (2 weeks)

The researchers assessed participants to ensure they could take part in the trial. This study was a double-blind study. This means that none of the participants, trial doctors, or trial staff knew what treatment participants were going to receive.

During Treatment (48 weeks)



Participants were randomly assigned to 1 of the 2 treatment groups in a 2:1 ratio. This means participants had 2 chances of receiving brolucizumab for every chance of receiving aflibercept.

Brolucizumab 6 milligrams (mg)	**Aflibercept** 2 mg
346 participants	171 participants

Participants received brolucizumab or aflibercept as an injection into the eye, once every 4 weeks up to Week 48, for a total of 12 injections. Researchers monitored the participants' health throughout the trial.

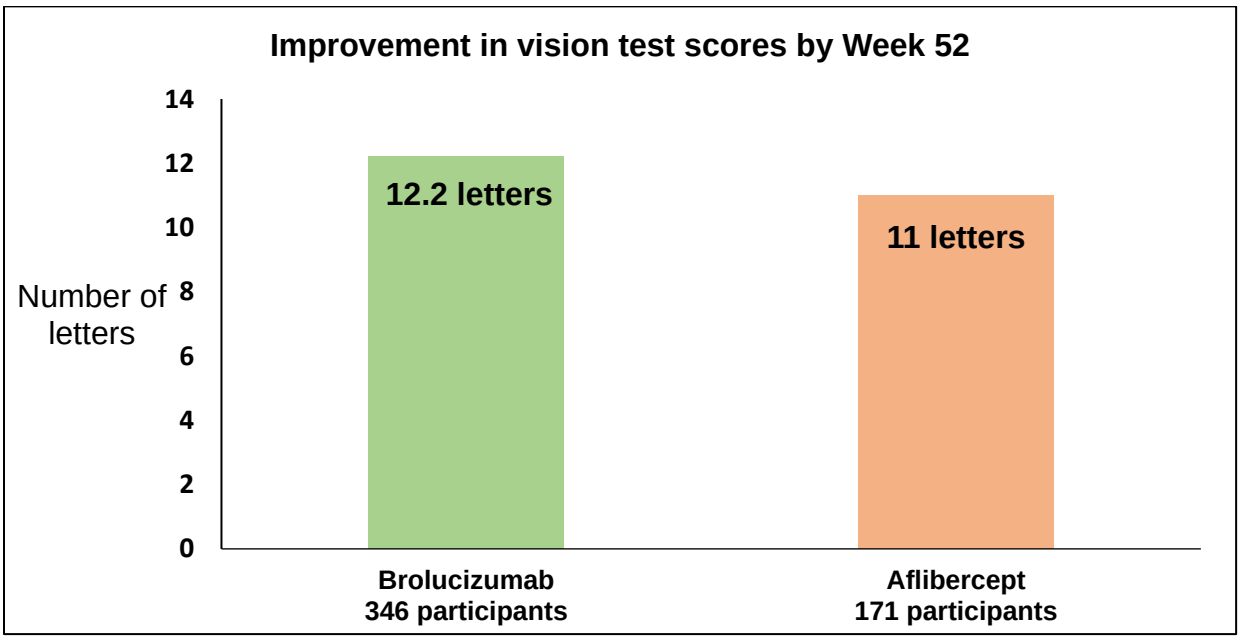
After Treatment (4 weeks)

After Week 48, participants were monitored for 4 weeks (Week 52). Researchers completed this trial as planned.

What were the key results of this trial?

Did vision test scores improve by a similar number in participants on brolucizumab compared to those on aflibercept by Week 52?

By Week 52, the average vision test score improved by 12.2 letters for participants who received brolucizumab. For participants who received aflibercept, the vision test score improved by 11 letters. Therefore, the improvement in vision test scores was similar in participants who took brolucizumab compared to participants who took aflibercept.



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 adverse events is presented in the table below.

Number of Participants (%) With Ocular Adverse Events

Category	**Brolucizumab** (Out of 346 participants)	**Aflibercept** (Out of 171 participants)
At least 1 ocular adverse event	105 (30%)	59 (35%)
At least 1 serious ocular adverse event	3 (1%)	0
Stopped drug due to ocular adverse event	7 (2%)	3 (2%)

The number of participants with non-ocular adverse events is presented in the table below.

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

Category	Brolucizumab (Out of 346 participants)	Aflibercept (Out of 171 participants)
At least 1 non-ocular adverse event	209 (60%)	96 (56%)
At least 1 serious non-ocular adverse event	69 (20%)	36 (21%)
Stopped drug due to non-ocular adverse event	10 (3%)	5 (3%)

What were the most common non-serious adverse events?

Ocular non-serious adverse events

Less than 5% of participants in any group had ocular non-serious adverse events, therefore data is not reported in this summary.

Non-ocular non-serious 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 346 participants)	Aflibercept (Out of 171 participants)
COVID-19 infection (COVID-19)	11 (3%)	11 (6%)
Cough (Cough)	3 (1%)	9 (5%)
High blood pressure (Hypertension)	18 (5%)	13 (8%)

What were the most common serious adverse events?

Ocular serious adverse events

Less than 1% of participants in any group 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 346 participants)	**Aflibercept** (Out of 171 participants)
Stroke (Cerebrovascular accident)	6 (2%)	6 (4%)
COVID-19 infection (COVID-19)	8 (2%)	1 (1%)

A total of 12 participants died during the study. This included 7 participants in the brolucizumab group and 5 participants in the aflibercept group.

How many participants stopped trial drug due to adverse events?

7 out of 346 participants (2%) in the brolucizumab group and 3 out of 171 participants (2%) in the aflibercept group stopped trial drug early due to ocular adverse events.

10 out of 346 participants (3%) in the brolucizumab group and 5 out of 171 participants (3%) in the aflibercept group stopped trial drug early due to non-ocular adverse events.

How was this trial useful?

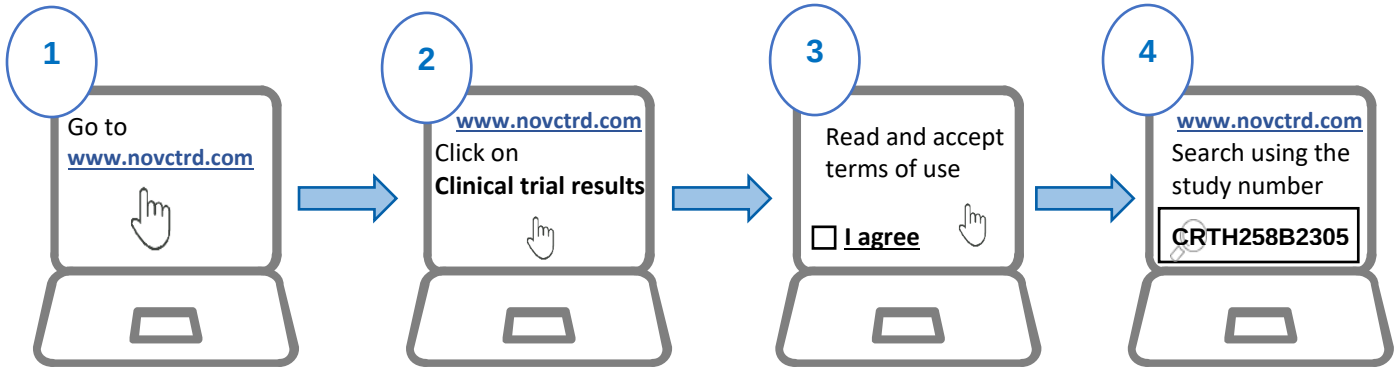
Researchers learned about the effects and safety of brolucizumab in participants with DME. The data collected during this study supported the administration of brolucizumab as an effective and safe treatment for DME patients.

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 NCT03917472 in the search field.
- https://www.clinicaltrialsregister.eu/ctr-search/search Use the EudraCT identifier 2019-001004-37 in the search field.

Full clinical trial title: A 12-Month, 2-Arm, Randomized, Double-Masked, Multicenter Phase III Study Assessing the Efficacy and Safety of Brolucizumab every 4 weeks versus Aflibercept every 4 weeks in Adult Patients with Visual Impairment due to Diabetic Macular Edema (KINGFISHER)

Trial Dates: The trial started in July 2019 and ended in March 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.

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