NOVARTIS

Clinical Trial Results Summary

A clinical trial to compare the effects and safety of brolucizumab with aflibercept in people with vision difficulties caused by Macular Edema due to Central Retinal Vein Occlusion

Protocol number: CRTH258C2302

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 macular edema due to central retinal vein occlusion.

This summary only shows the results of a single clinical trial. Other clinical trials may have different findings.

? **If you have any questions about the trial results, please talk to the doctor or staff at your trial site.**

How long was this trial?

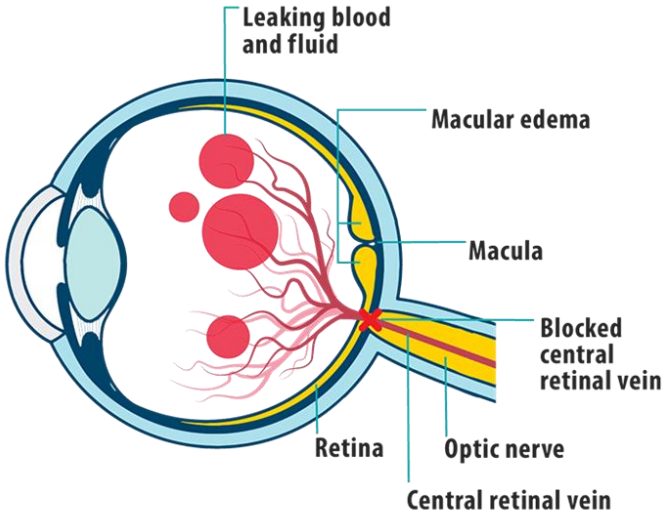
This trial started in July 2019 and ended in July 2021. The entire duration, from enrolling the first participant to the last participant completing the trial was around 2 years. An individual participant could have been in this trial for up to 18 months.

The researchers reviewed safety data from a previous trial (CRTH258AUS04) with the same drugs and found an increased frequency of medical problems* with brolucizumab, also known as RTH258. Researchers also found a similar frequency of medical problems during this trial, so they ended this trial early due to safety concerns. When the trial ended, researchers created a report of the trial results. This summary is based on that report.

**Medical problems that happen in clinical trials are called "adverse events". An adverse event is an unwanted sign, symptom, or disease that participants have during a trial.*

Why was the research needed?

Researchers were looking for a better way to treat macular edema due to central retinal vein occlusion (CRVO). CRVO is an eye disorder that affects the main vein in the retina. The retina is a thin layer of tissue at the back of the eye that sends images to the brain. CRVO is mostly seen in people with lifestyle-related diseases, such as high blood pressure. Development of macular edema is the main cause of vision difficulties in people with CRVO. In macular edema, there is swelling in the macula with fluid leaking 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.



Source: preventblindness.org

Currently, macular edema due to CRVO can be treated with medicines such as aflibercept or ranibizumab. Aflibercept is approved for the treatment of macular edema due to CRVO. 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 treatment includes laser treatment, which stops the blood vessels from leaking.

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

Brolucizumab, RTH258 is the trial drug and is an approved treatment for wet age-related macular degeneration and diabetic macular edema. In this trial, researchers wanted to compare the effects of brolucizumab, RTH258 with aflibercept to find out if these 2 medicines provided similar relief in people with macular edema due to CRVO.

Who was in this trial?

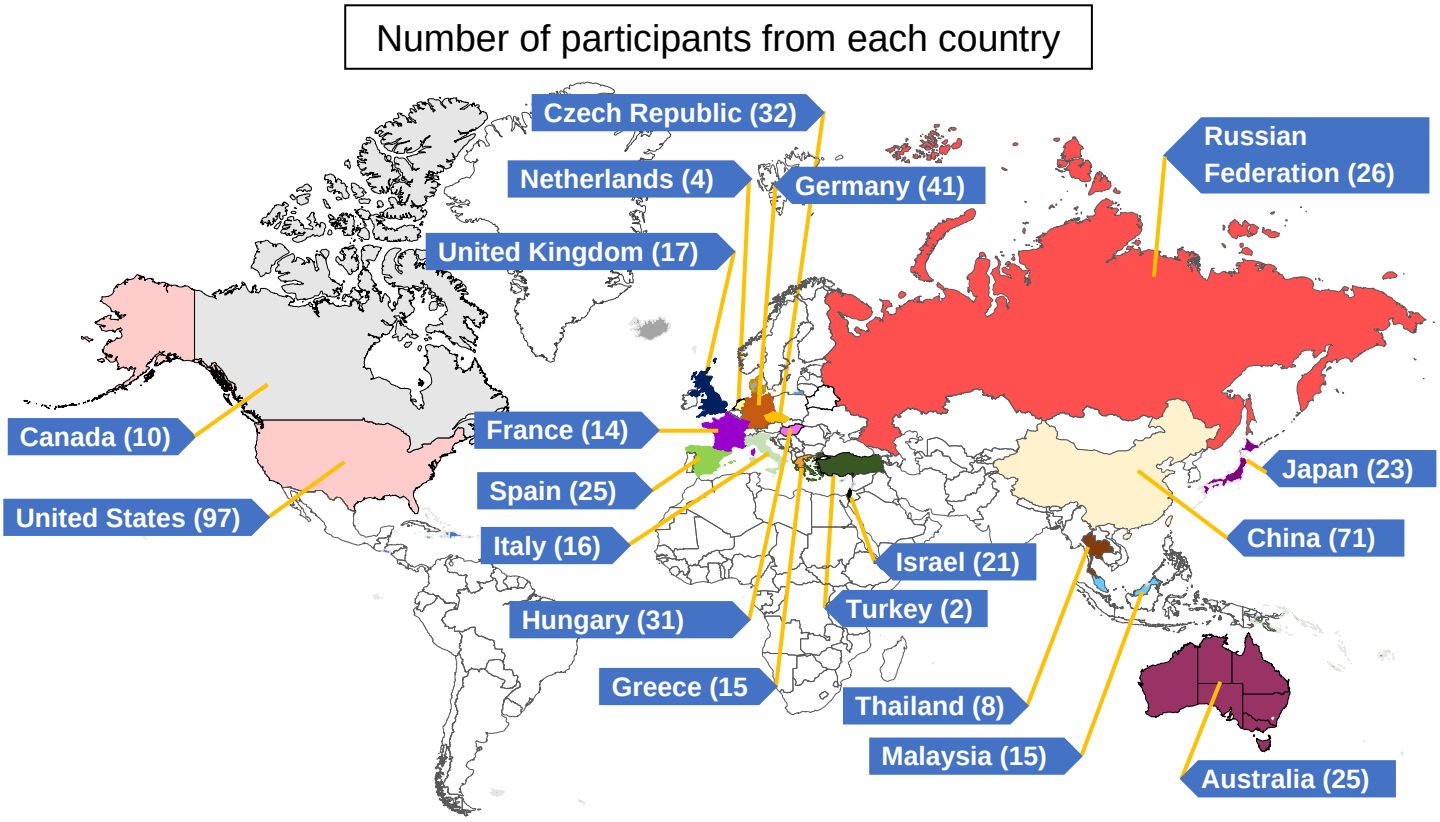
The participants could take part in this trial if they:

- were aged 18 years or older,
- had vision difficulties caused by macular edema due to CRVO for not more than 6 months before participating in the trial,
- could read between 23 to 78 letters in a vision test, and
- did not have any other eye diseases.

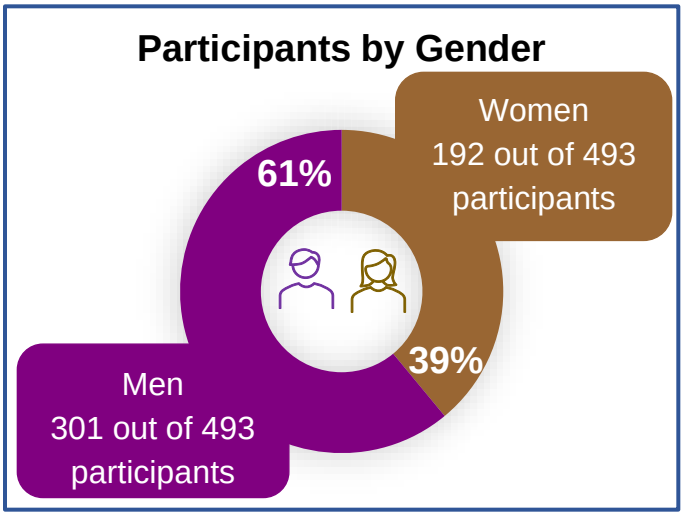
A total of 635 participants from 19 countries participated in this trial.

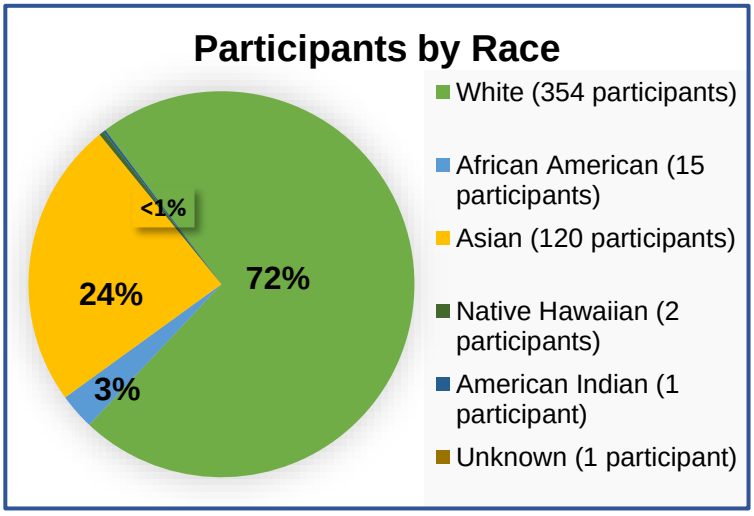
Out of those, 493 participants were randomly assigned to treatment groups using a computer system and all participants received treatment. This process is called

randomization. It means that each participant could be assigned to any group, and it helps to make sure the groups are distributed fairly.



Participants' age ranged from 22 to 92 years. The average age of participants was 64 years. Just over half of the participants were men (61%) and the majority of the participants were white (72%).





What treatments did the participants take?

Treatment drug		Comparator drug	
	Brolucizumab, 6 milligrams (mg) injection was given into the participants' eye 6 times every 4 weeks for up to 20 weeks, followed by 48 weeks of **individualized flexible treatment*** from Week 24 onwards.		**Aflibercept,** 2 mg injection was given into the participants' eye 6 times every 4 weeks for up to 20 weeks, followed by 48 weeks of **individualized flexible treatment*** from Week 24 onwards.

**Individualized flexible treatment* meant that after up to 20 weeks of treatment:*

- *if the participant's disease did not stabilize, they continued to receive either brolucizumab or aflibercept injections every 4 weeks.*
- *if the participant's disease had become stable, treatment with either brolucizumab or aflibercept was discontinued.*

What happened during this trial?

Before treatment

The trial doctors checked if participants could take part in this trial.
None of the participants, trial doctors, or trial staff knew what treatment the participants were receiving.

Up to 4 weeks before treatment

During treatment

Eligible participants were randomly assigned to 1 of the 2 treatment groups in a 1:1 ratio. This means participants had an equal chance to receive either brolucizumab or aflibercept:

- **Brolucizumab: 247** participants were planned to receive brolucizumab 6 mg as injection into one eye, 6 times every 4 weeks, for up to 20 weeks, followed by 48 weeks of individualized flexible treatment from Week 24 to Week 72.
- **Aflibercept: 246** participants were planned to receive aflibercept 2 mg as injection into one eye, 6 times every 4 weeks, for up to 20 weeks, followed by 48 weeks of individualized flexible treatment from Week 24 to Week 72.

For individualized flexible treatment definition, please refer to page 2, section "What treatments did the participants take?"

Up to 72 weeks

After treatment

After Week 72, researchers monitored participants' health.

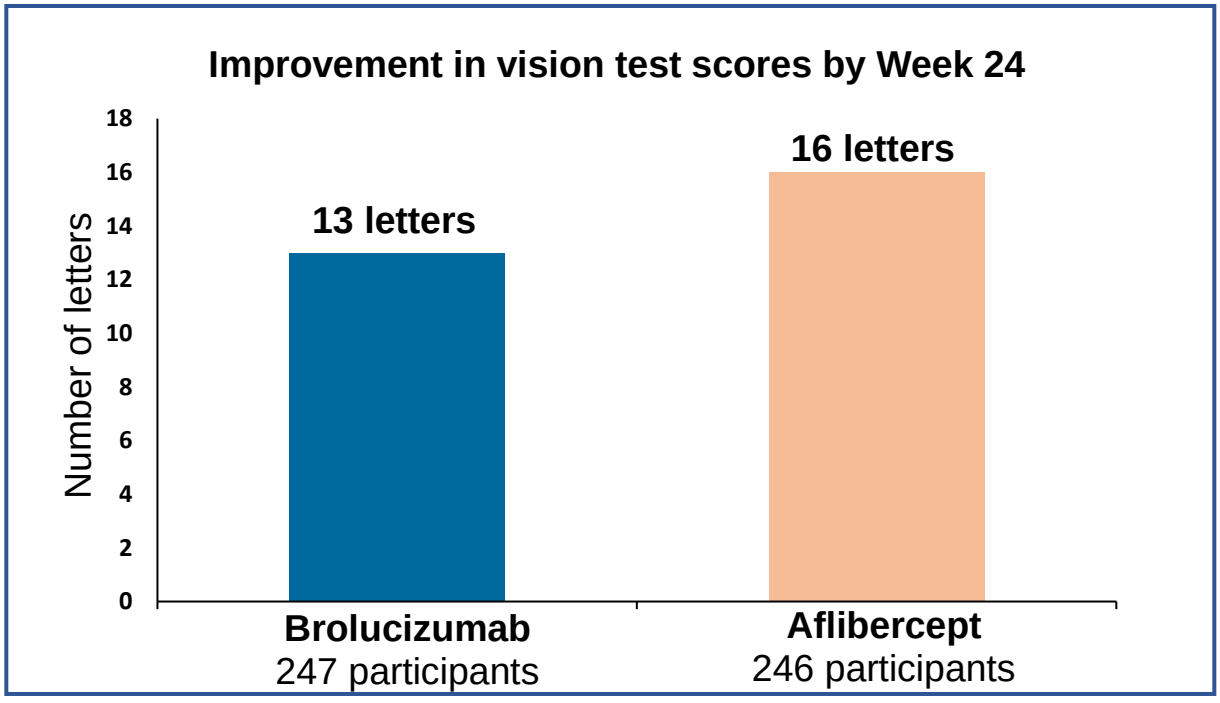
Up to 4 weeks after their last dose

What were the main results of this trial?

Did vision test scores show similar improvement for participants on brolucizumab compared to those on aflibercept after 24 weeks of treatment?

To answer this question, researchers measured the participants' vision after treatment in their treated eye. They calculated the number of letters that participants were able to read before and after treatment to see if they could read more letters by Week 24. Researchers conducted an eye exam called best corrected visual acuity (BCVA). BCVA is defined as the best possible vision an eye can see with corrective lenses.

By Week 24, the average vision test score improved by 13 letters for participants who received brolucizumab. For participants who received aflibercept, the vision test score improved by 16 letters. Therefore, the improvement in vision test scores was less in participants who received brolucizumab compared to the participants who received 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 (adverse events not related to eye).

The number of participants with ocular adverse events is presented in the table below:

Number of Participants (%) With Ocular Adverse Events				
	Brolucizumab (Out of 247 participants)		Aflibercept (Out of 246 participants)	
Category	**Treated Eye**	**Untreated Eye**	**Treated Eye**	**Untreated Eye**
At least 1 ocular adverse event	111 (45%)	43 (17%)	89 (36%)	36 (15%)

Number of Participants (%) With Ocular Adverse Events				
	Brolucizumab (Out of 247 participants)		Aflibercept (Out of 246 participants)	
Category	**Treated Eye**	**Untreated Eye**	**Treated Eye**	**Untreated Eye**
At least 1 ocular serious adverse event	8 (3%)	1 (<1%)	2 (1%)	1 (<1%)
Stopped drug due to ocular adverse event	10 (4%)	-	4 (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 247 participants)**	**Aflibercept (Out of 246 participants)**
At least 1 non-ocular adverse event	119 (48%)	117 (48%)
At least 1 non-ocular serious adverse event	29 (12%)	17 (7%)
Stopped drug due to non-ocular adverse event	5 (2%)	2 (1%)
Death	2 (1%)	1 (<1%)

What were the most common serious adverse events?

Ocular serious adverse events

The most common ocular serious adverse events in the treated eye (at least 2 participants) and the untreated eye (at least 1 participant) in any group are presented on the next page:

Number of Participants (%) With Most Common Ocular Serious Adverse Events				
	Brolucizumab (Out of 247 participants)		Aflibercept (Out of 246 participants)	
	Treated Eye	Untreated Eye	Treated Eye	Untreated Eye
Clouding of the eye (Cataract)	0	0	1 (<1%)	1 (<1%)
Formation of a thin layer of tissue on the surface of the retina (Epiretinal membrane)	0	1 (<1%)	0	0
Lack of oxygen to the back of the eye (Retinal artery occlusion)	2 (1%)	0	0	0
Swelling of the retinal blood vessel (Retinal vasculitis)	2 (1%)	0	0	0

Non-ocular serious adverse events

The most common non-ocular serious adverse event that happened in at least 2 participants in any group are presented in the table below:

Number of Participants (%) With Most Common Non-Ocular Serious Adverse Events		
	Brolucizumab (Out of 247 participants)	**Aflibercept (Out of 246 participants)**
Abnormal "ballooning" in blood vessels (Aneurysm)	2 (1%)	0
COVID-19 infection (COVID-19)	4 (2%)	2 (1%)
Lung infection due to COVID-19 infection (COVID-19 pneumonia)	2 (1%)	0

What were the most common non-serious adverse events?

Ocular non-serious adverse events

The most common ocular non-serious adverse events in the treated eye (at least 5%, 5 out of 100 participants) and the untreated eye (at least 2%, 2 out of 100 participants) in any group are presented on the next page:

Number of Participants (%) With Most Common Ocular Non-Serious Adverse Events				
	Brolucizumab (Out of 247 participants)		Aflibercept (Out of 246 participants)	
	Treated Eye	Untreated Eye	Treated Eye	Untreated Eye
Blood spots on white part of the eye (Conjunctival hemorrhage)	16 (6%)	0	11 (4%)	0
Damage to a nerve at the back of the eye (Glaucoma)	5 (2%)	5 (2%)	5 (2%)	5 (2%)
Decrease in clarity of vision (Visual acuity reduced)	22 (9%)	0	9 (4%)	0
Dry eye	6 (2%)	5 (2%)	6 (2%)	5 (2%)
Increase in eye fluid pressure (Intraocular pressure increased)	10 (4%)	0	13 (5%)	0
Worsening of macular edema (Macular edema)	18 (7%)	0	11 (4%)	0

Non-ocular non-serious adverse events

The most common non-ocular non-serious adverse events that happened in at least 3% participants (3 out of 100) in any group are presented in the table below:

Number of Participants (%) With Most Common Non-Ocular Non-Serious Adverse Events		
	Brolucizumab (Out of 247 participants)	**Aflibercept (Out of 246 participants)**
Common cold (Nasopharyngitis)	8 (3%)	6 (2%)
Headache	3 (1%)	8 (3%)
High blood pressure (Hypertension)	19 (8%)	10 (4%)
Joint pain (Arthralgia)	9 (4%)	7 (3%)

How many participants stopped trial drug due to adverse events?

Ocular adverse events

During the trial, 10 out of 247 (4%) participants in the brolucizumab group and 4 out of 246 (2%) participants in the aflibercept group stopped trial drugs due to ocular adverse events in the treated eye. The most common adverse events that led to stopping the trial drugs were **swelling of the retinal blood vessel** (retinal vasculitis), **inflammation of the colored part of the eye** (iridocyclitis), and **inflammation of the middle layer of the eye, uvea** (uveitis).

Non-ocular adverse events

During the trial, 5 out of 247 (2%) participants stopped brolucizumab early due to **diseases of the heart** (hypertensive heart disease), **sudden loss of hearing** (sudden hearing loss), **lung infection due to COVID-19** (COVID-19 pneumonia), **a type of cancer of the white blood cells** (Waldenstrom's macroglobulinemia), and **bleeding within the brain** (cerebral hemorrhage).

2 out of 246 (1%) participants stopped aflibercept early due to **COVID-19 infection** (COVID-19) and **certain type of cancer of the disease-fighting system** (diffuse large B-cell lymphoma).

How was this trial useful?

The trial helped researchers to learn about the effects and safety of brolucizumab in participants with macular edema due to CRVO.

The results of this trial showed that improvement of vision in participants who received brolucizumab was less compared to participants who received aflibercept.

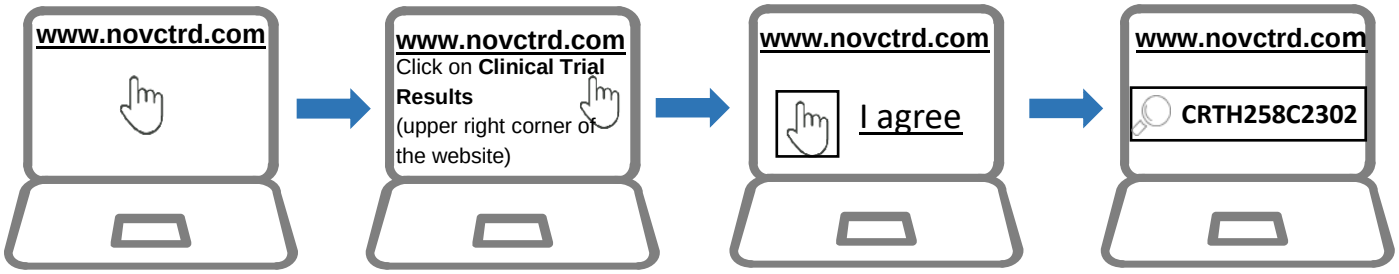
This trial ended early because the researchers found an increased frequency of medical problems with brolucizumab, RTH258 in another trial (CRTH258AUS04) which was confirmed in this trial.

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 NCT03810313 in the search field.
- https://www.clinicaltrialsregister.eu/ctr-search/search Use the EudraCT identifier 2018-001788-21 in the search field.

Full clinical trial title: An eighteen-month, 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 macular edema secondary to central retinal vein occlusion (RAVEN)

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.

NOVARTIS

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

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