Clinical Trial Results Summary

A clinical trial to learn more about the safety and effects of a new formulation of brolucizumab as an extension trial in participants with loss of central vision due to aging

Protocol number: CRTH258A2301E1

Thank You!

Novartis, the sponsor of this clinical trial, would like to thank you for taking part in this extension trial for the drug RTH258, also known as brolucizumab. You helped researchers learn more about how the new formulation of brolucizumab compares with the formulation used in the core trial when given to people who lose their central vision due to aging.

As a clinical trial participant, you belong to a large community of people around the world. Your invaluable contribution to medicine and healthcare is greatly appreciated.

Important note: This trial used a new formulation of brolucizumab. Before entering this trial, the same participants completed an earlier trial for the original formulation of brolucizumab. This summary compares the results of this second trial with the results of the same participants during the last 6 months of the first trial. If you have any questions about these trial results, please talk to the doctor or staff at your trial site.

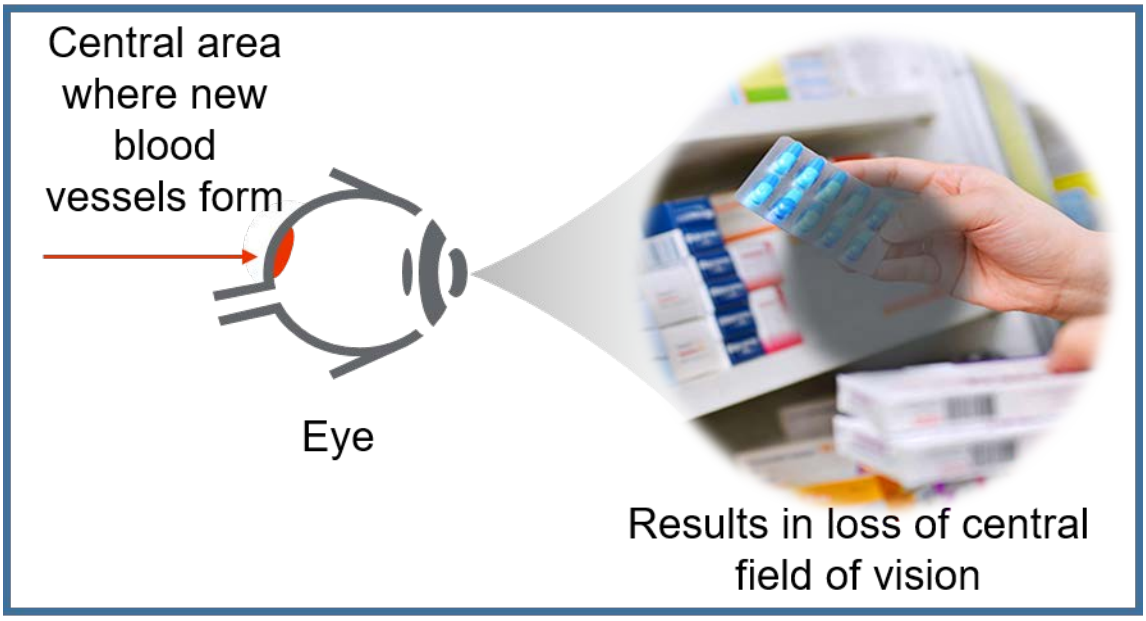
How long was this trial?

This trial was an extension trial done after the core trial was completed. This extension trial started in January 2018 and ended in September 2018. An individual participant could be in this extension trial for up to 6 months.

The researchers completed this trial as planned. When the trial ended, the researchers compared the results with information collected in the last 6 months of the core trial and created a report. This summary is based on that report.

Why was the research needed?

Researchers were looking for a better way to treat an eye disorder called neovascular age-related macular degeneration. Usually, this disorder causes loss of eyesight in the central field of vision as a person grows older. Eyesight is lost because of new blood vessels forming inside the eye, as shown below. The new blood vessels that form are very delicate and leak blood and fluid into the eye. This causes swelling and slowly leads to eyesight loss.



Brolucizumab was one of the investigational treatments given in the core trial to participants with central vision loss due to aging. After the core trial had started, some changes were made to the brolucizumab solution to make it easier to make in large amounts. To confirm that the change in formulation did not affect how brolucizumab works, participants from trial sites in the United States of America (USA) who completed the core trial were enrolled in this extension trial.

Participants who received brolucizumab (3 mg or 6 mg) in the core trial were given the new formulation of brolucizumab (6 mg) in the extension trial. Participants who received aflibercept (2 mg) in the core trial continued to receive aflibercept (2 mg). This was done so participants would not know which treatment they received in the core trial. No additional data analyses were done for participants who received aflibercept.

Trial drugs

The drugs given in this trial were:

- **Brolucizumab (RTH258):** an investigational treatment that is being studied for the treatment of central vision loss due to aging. In this extension trial, a new formulation of brolucizumab (6 mg) was studied.
- **Aflibercept:** a drug that is approved for treating central vision loss due to aging. Participants in the core trial who were given aflibercept continued to receive aflibercept during the extension trial so participants would not know which treatment they received in the core trial.

Trial purpose

This trial was done to learn more about the safety and effects of the new formulation of brolucizumab. The main question the researchers wanted to answer in this trial was:

- Did the new formulation of brolucizumab cause any medical problems in the eyes or other medical problems? How did these compare to the medical problems in the eyes and other medical problems seen by the same participants in the last 6 months of the core trial?

Another question the researchers wanted to answer in this trial was:

- Was there a change in participants' vision throughout the extension trial compared to their vision at the start of the extension trial?

Who was in this trial?

Participants could take part in this trial if they:

- completed the core trial for the original formulation before entering this trial and lived in the USA
- had not received any other treatment for the same disorder after completing the core trial
- had not had a stroke or heart attack within 3 months of first trial visit for the extension trial.

A total of 150 participants at 68 centers in the USA participated in this trial.

The average age of the participants was 80 years. Participants' age ranged from 52 to 98 years. About 61% of trial participants, or 91 out of 150, were female.

What kind of trial was this?

This was a double-blind trial. This means that none of the participants, the trial doctor, or trial staff knew what treatment the participants were receiving. Some trials are done

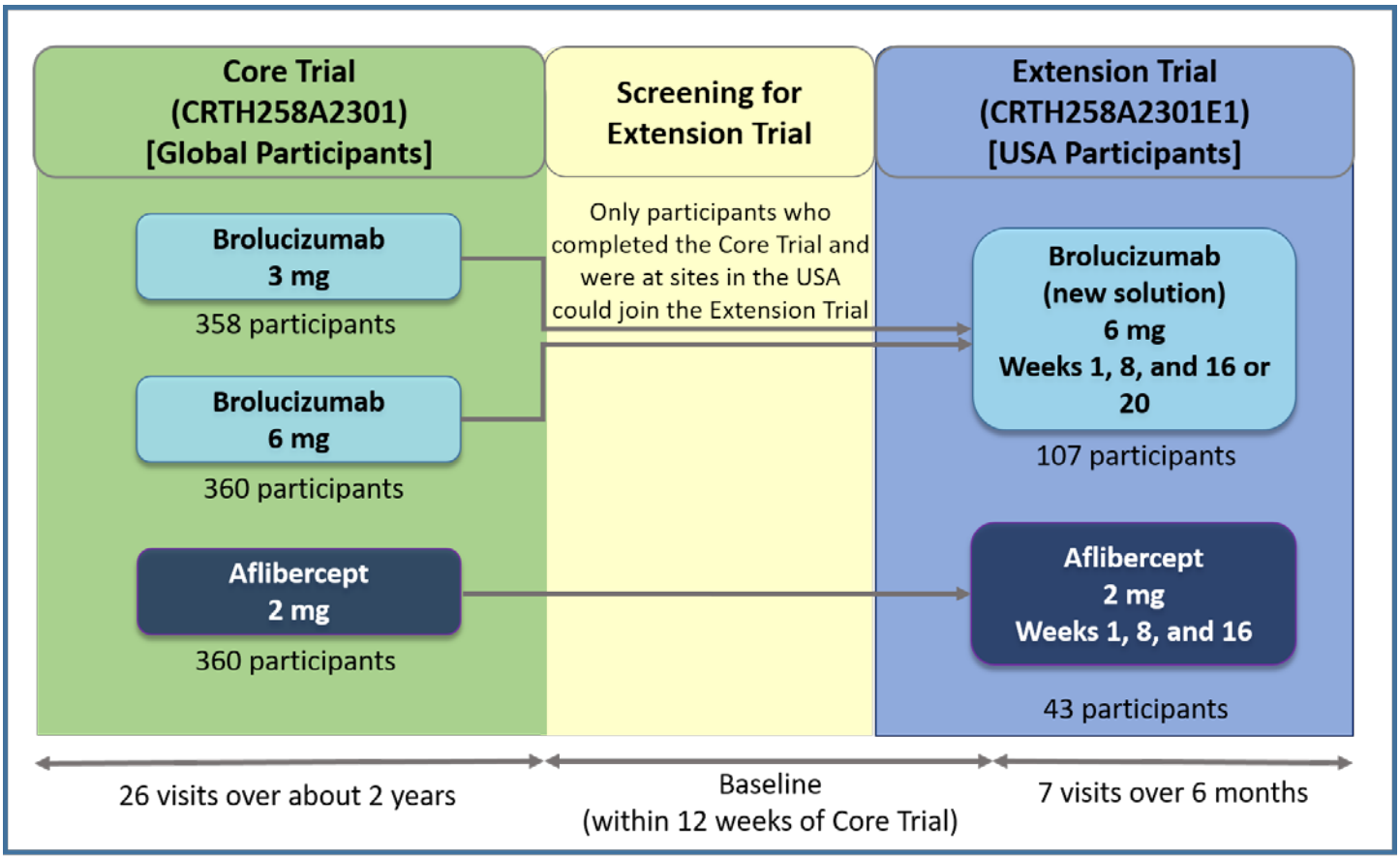
this way because knowing what treatment each participant is getting can affect the results of the trial. Doing a trial this way helps to make sure that the results are looked at with fairness towards all treatments.

What happened during this trial?

The participants entered the extension trial either immediately after the core trial or within 12 weeks after the core trial ended.

Participants who were given brolucizumab (3 mg or 6 mg) in the core trial received the new formulation of brolucizumab (6 mg) in the extension trial. Participants who were given aflibercept (2 mg) in the core trial continued to receive aflibercept (2 mg) in the extension trial.

The investigational treatments were given as an injection in the same eye that was treated in the core trial. The participants received 3 injections at the time points shown in the trial diagram below. During every visit in the treatment period, an eye exam was also done.



What were the key results of this trial?

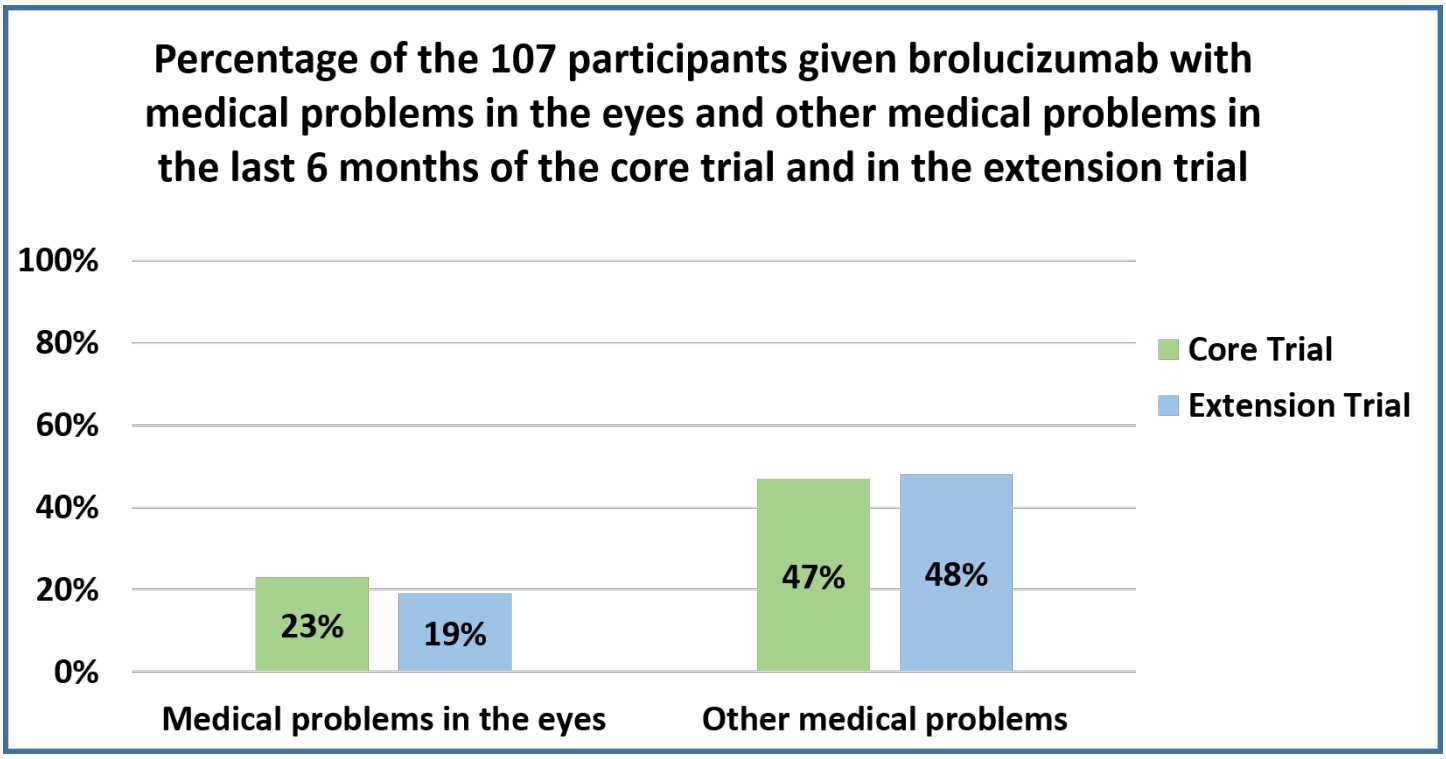
This is a summary of the average results for all participants in the brolucizumab treatment group. It does not show the results of each individual participant. Results of individual participants could be different from the results of the total group of participants. A detailed presentation of the results can be found on the websites listed at the end of this summary.

Did the new formulation of brolucizumab cause any medical problems in the eyes or other medical problems? How did these compare to the medical problems in the eyes and other medical problems seen by the same participants in the last 6 months of the core trial?

In the last 6 months of the core trial, 23% (25 out of 107) of participants given brolucizumab (3 mg and 6 mg) who continued on to the extension trial reported medical problems in the eyes. In the extension trial, 19% (20 out of 107) of participants given the new formulation of brolucizumab (6 mg) reported medical problems in the eyes. No individual participant in the extension trial had the same medical problems as he or she had during the last 6 months of the core trial.

In the last 6 months of the core trial, 47% (50 out of 107) of participants given brolucizumab (3 mg and 6 mg) who continued on to the extension trial reported other medical problems. In the extension trial, 48% (51 out of 107) of participants given the new formulation of brolucizumab (6 mg) reported other medical problems.

More information about the most common medical problems reported by participants is given below, in the “Medical Problems” section of this summary.



What were the other results of this trial?

Was there a change in participants' vision throughout the extension trial compared to their vision at the start of the extension trial?

The participants' vision was measured by noting the number of letters they were able to read during an eye exam. Overall, no major differences were seen in the participants' vision at any extension trial visit compared with the start of the extension trial. This means that the effect of brolucizumab was maintained during the extension trial.

What medical problems did the participants have during the trial?

Medical problems that happen in clinical trials are called "adverse events". An adverse event is an unwanted sign or symptom that participants have during a trial. An adverse event is considered "serious" when it is life-threatening, causes lasting problems, or if

the participant needs hospital care. These problems may or may not be caused by the trial drug.

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 the participants report.

This section is a summary of the adverse events that happened during this extension trial. Although no other results were analyzed for the aflibercept group in the extension trial, adverse events reported by participants who received aflibercept were recorded. The websites listed at the end of this summary have more information about the adverse events that happened in this trial.

How many participants had adverse events?

The safety results were recorded for the participants given brolucizumab during the last 6 months of the core trial who continued on to the extension trial. In this trial, adverse events were recorded for 107 participants who were given brolucizumab and 43 participants who were given aflibercept.

Percentage (Number) of Participants With Adverse Events

	Brolucizumab Overall Extension (up to 6 months)	Brolucizumab Overall (last 6 months of the core trial)	Aflibercept Extension (up to 6 months)
Non-serious adverse events that happened in more than 5% of participants	11% (12)	13% (14)	30% (13)
At least 1 serious adverse event	7% (7)	7% (7)	23% (10)
Stopped drug due to adverse event	Less than 1% (1)	0	0
Death	Less than 1% (1)	0	0

What were the most common non-serious adverse events?

The most common non-serious adverse events that happened in at least 5% (5 out of 100) of the 107 brolucizumab participants and 43 aflibercept participants are presented below.

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

	Brolucizumab Overall Extension (up to 6 months)	Brolucizumab Overall (last 6 months of the core trial)	Aflibercept Extension (up to 6 months)
Common cold	5% (5)	4% (4)	7% (3)
Urinary tract infection	4% (4)	6% (6)	14% (6)

Percentage (Number) of Participants With Most Common Non-Serious Adverse Events			
	Brolucizumab Overall Extension (up to 6 months)	Brolucizumab Overall (last 6 months of the core trial)	Aflibercept Extension (up to 6 months)
Age-related eye disorder of the eye other than the study eye	2% (2)	2% (2)	7% (3)
Blurred vision of eye other than the study eye	1% (1)	1% (1)	7% (3)
Blood in the urine	0	1% (1)	7% (3)

What were the serious adverse events?

7% (7 out of 107) of the participants given brolucizumab and 23% (10 out of 43) of the participants given aflibercept had serious adverse events.

Percentage (Number) of Participants With Serious Adverse Events			
	Brolucizumab Overall Extension (up to 6 months)	Brolucizumab Overall (last 6 months of the core trial)	Aflibercept Extension (up to 6 months)
Abnormally large red blood cells	0	0	2% (1)
Advanced cancer of the prostate	0	0	2% (1)
Accidental overdose	0	1% (1)	0
Bleeding in the skull	1% (1)	0	0
Blockage of veins carrying blood away from the back of the eye – study eye	1% (1)	0	0
Brain damage	0	0	2% (1)
Break in the kneecap	0	0	2% (1)
Break in the thighbone	1% (1)	1% (1)	0
Disease of the lymph nodes	0	0	2% (1)

Percentage (Number) of Participants With Serious Adverse Events			
	Brolucizumab Overall Extension (up to 6 months)	Brolucizumab Overall (last 6 months of the core trial)	Aflibercept Extension (up to 6 months)
Life-threatening response of the body to an infection	0	0	2% (1)
Fainting	0	0	7% (3)
Fever	0	0	2% (1)
Flesh-eating disease	0	0	2% (1)
Flu	0	1% (1)	0
Fracture in the front of the hip bone	0	1% (1)	0
Heart failure	1% (1)	0	0
High blood pressure	1% (1)	0	0
Infection of the bone	0	0	2% (1)
Inflammation in the gallbladder	1% (1)	0	0
Lack of oxygen to the back of the eye – study eye	1% (1)	0	0
Lack of proper nutrition not related to study treatment or treatment procedure	0	0	2% (1)
Left part of the heart not working properly	0	0	2% (1)
Lung disease that blocks airflow from the lungs	0	1% (1)	0
Lung infection	1% (1)	0	2% (1)
Multiple organ failure	1% (1)	0	0
Not enough oxygen in the lungs	1% (1)	0	0
Prostate cancer	0	1% (1)	0
Stones in the bile duct, which carries bile from the gallbladder to the intestine	1% (1)	0	0
Stones in the gallbladder	0	0	2% (1)
Urinary tract infection	0	1% (1)	0

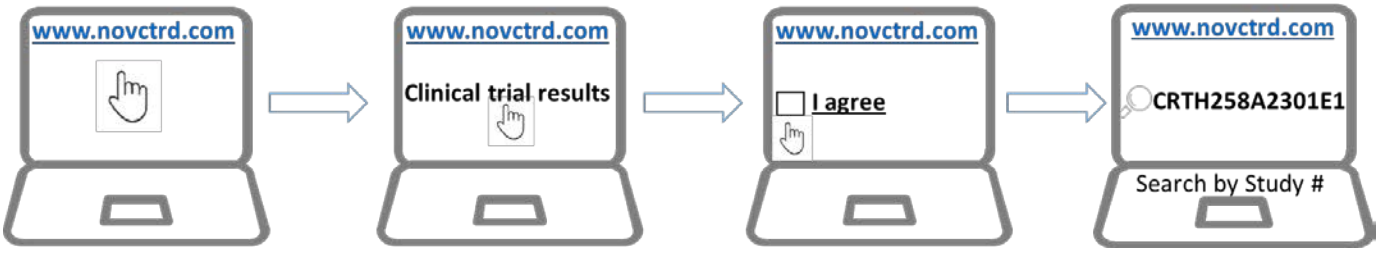
Percentage (Number) of Participants With Serious Adverse Events			
	Brolucizumab Overall Extension (up to 6 months)	Brolucizumab Overall (last 6 months of the core trial)	Aflibercept Extension (up to 6 months)
Water in the lungs	0	0	2% (1)

How was this trial useful?

This trial helped researchers learn about the safety and effects of the new formulation of brolucizumab. Participants who were given brolucizumab in the core trial and participants who were given the new formulation of brolucizumab in the extension trial had the same kind of results. No individual participant in the extension trial had the same medical problems as he or she had during the last 6 months of the core trial. Please remember, this summary only shows the results of this extension trial and reports them with the results reported for the same brolucizumab-treated participants during the last 6 months of the core 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).



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

- www.clinicaltrials.gov. Use the NCT identifiers NCT02307682 for the core trial and NCT03386474 for the extension trial in the search field.

Full clinical trial title: A 24-week, double-masked, multicenter, two-arm extension study to collect safety and efficacy data on brolucizumab 6 mg drug product intended for commercialization in subjects with neovascular age-related macular degeneration who have completed the CRTH258A2301 study

Thank you

Thank you for taking part in this trial. As a clinical trial participant, you belong to a large community of participants 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.

1-888-669-6682 (US); +41-61-324-1111 (EU);

www.novartisclinicaltrials.com