NOVARTIS

Clinical Trial Results Summary

A clinical trial to compare the effects and safety of brolucizumab with aflibercept in treating people with wet age-related macular degeneration with persistent fluid in the eye

Protocol number: CRTH258AUS04

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. Thanks to the participants for taking part in this trial for the drug brolucizumab, also known as RTH258. They helped researchers learn more about how brolucizumab works in people with wet age-related macular degeneration with persistent fluid in the eye.

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?

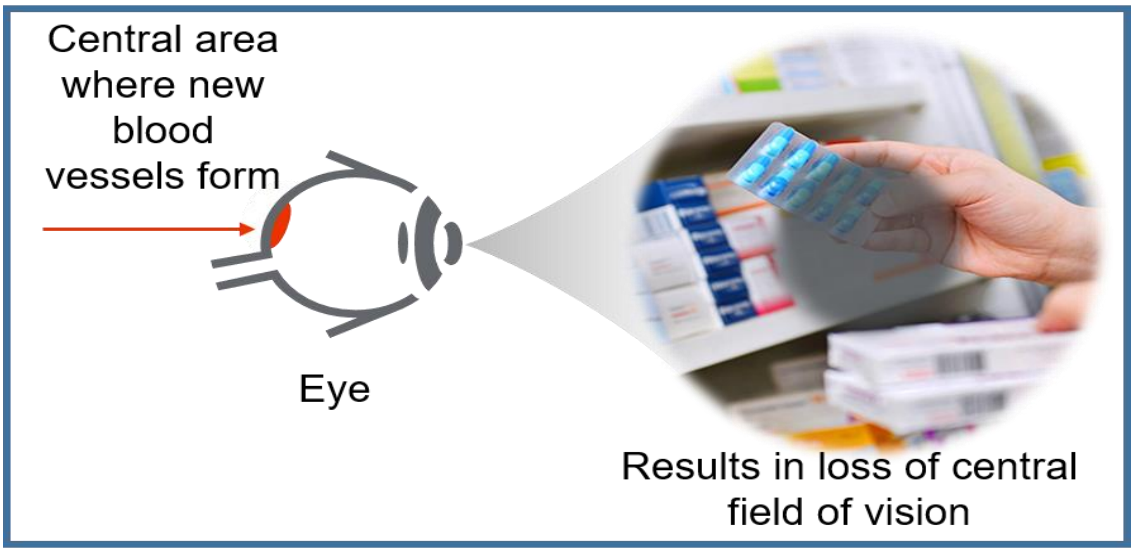
This trial started in October 2018 and ended July 2021. The entire duration, from enrolling the first participant to the last participant completing the trial was about 2 years and 8 months. An individual participant could have been in this trial for an average of 2 years.

The sponsor ended this trial early as the risks of using brolucizumab as used in this trial outweighed its benefits. In this trial, brolucizumab was given in a continuous manner every 4 weeks in participants with wet age-related macular degeneration with persistent fluid in the eye.

When the trial ended, researchers created a report of the trial results. 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 (or wet) age-related macular degeneration with persistent fluid in the eye. The participants included in the trial had a lot of adverse events *(medical problems that happen in clinical trials are called "adverse events")*. These adverse events may have been because of the drug used or because of participant's age and other diseases or disorders coexisting with their aggressive form of age related macular degeneration with persistent fluid in the eye. 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 in the next page. The new blood vessels formed are very delicate and leak blood and fluid into the eye. This causes swelling and slowly leads to eyesight loss.



Brolucizumab is the investigational treatment in this trial. Brolucizumab is an approved treatment in the United States (US) for wet age-related macular degeneration at a dose of 6 milligrams (mg) injection every 4 weeks for the first 3 months and then 6 mg injection every 8 to 12 weeks.

In this trial, researchers wanted to compare the effects and safety of brolucizumab to aflibercept in participants with wet age-related macular degeneration with persistent fluid in the eye. The trial aimed to study a different dosing frequency of brolucizumab (every 4 weeks) instead of the current approved dosing frequency (every 8 to 12 weeks).

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?**

Brolucizumab and aflibercept are medicines that block the activity of a protein called vascular endothelial growth factor. This protein helps in forming new blood vessels inside the eye. Brolucizumab and aflibercept help to stop formation of new blood vessels in the eye.

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

Who was in this trial?

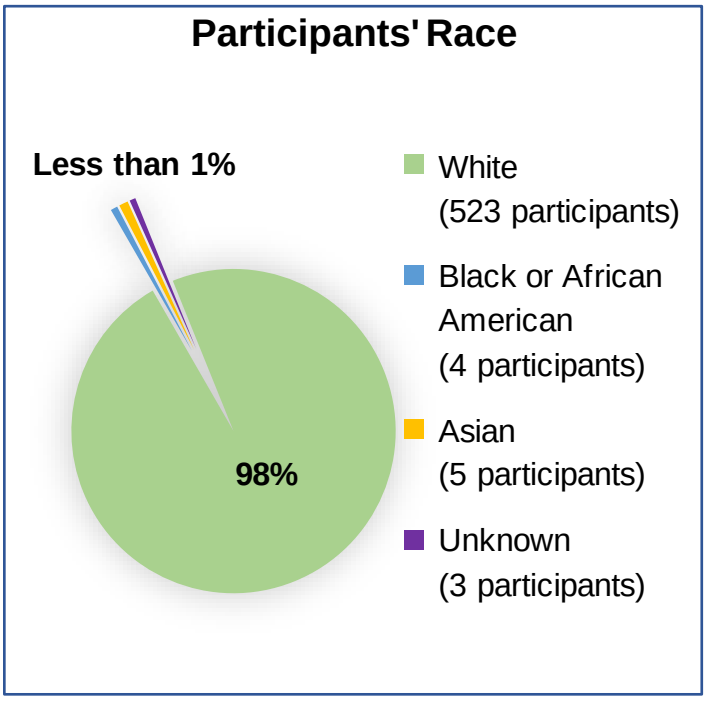
The participants could take part in this trial if they:

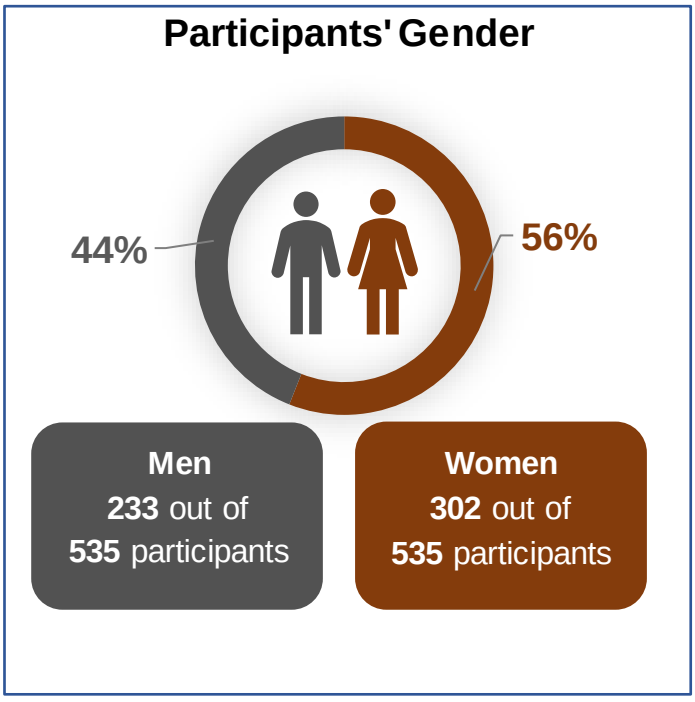
- were men or women aged 50 years or older,
- had wet age-related macular degeneration with persistent fluid in the eye, and
- had positive previous response to treatment with injections to stop formation of new blood vessels in the eye.

A total of 535 participants from the US participated in this trial.

All the 535 participants were randomly assigned to treatment groups using a computer system and all the 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 54 to 98 years. The average age of participants was 76 years. The majority of participants were women (56%), and the majority of the participants were white (98%).





What treatments did the participants take?

Treatment drug		Comparator drug	
	**Brolucizumab** was given at a dose of 6 mg injection into the eye every 4 weeks.		**Aflibercept** was given at a dose of 2 mg injection into the eye every 4 weeks.

What happened during this trial?

Before treatment

The trial doctors checked if participants could take part in this trial.

This was a double masked trial. This means that none of the participants, trial doctors, or trial staff knew what treatment participants were going to receive.

Up to 2 weeks before treatment

During treatment

Eligible participants were randomly assigned to receive either brolucizumab or aflibercept in a 2:1 ratio. This means participants had 2 chances of receiving brolucizumab for every chance of receiving aflibercept.

- **Brolucizumab**: 356 participants received 6 mg injection into the treated eye, every 4 weeks.
- **Aflibercept**: 179 participants received 2 mg injection into the treated eye, every 4 weeks.

Researchers monitored the health of the participants throughout the trial.

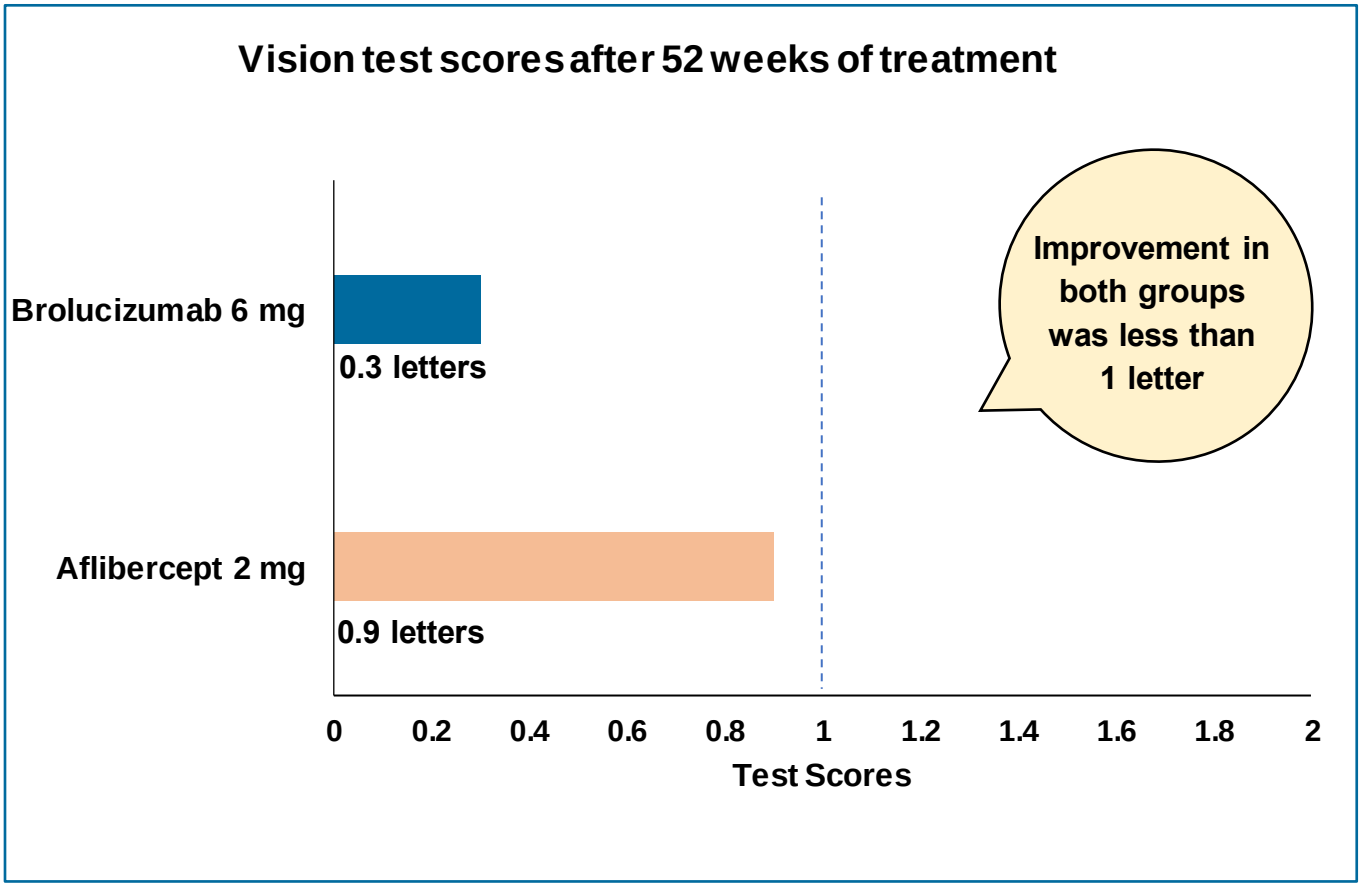
Up to 104 weeks of treatment

What was the main result of this trial?

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

To answer this question, researchers measured participants' vision by noting the number of letters they were able to read during an eye exam.

After 52 weeks of treatment, the average vision test score improved by 0.3 letters for participants on brolucizumab and by 0.9 letters for participants on aflibercept. The improvement of vision was similar and less than 1 letter in both brolucizumab and aflibercept groups in this trial.



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 website 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).

Number of Participants (%) With Ocular Adverse Events		
Category	**Brolucizumab 6 mg (Out of 356 participants)**	**Aflibercept 2 mg (Out of 179 participants)**
At least 1 ocular adverse event	203 (57%)	87 (49%)
At least 1 serious ocular adverse event in the treated eye	12 (3%)	2 (1%)

Number of Participants (%) With Ocular Adverse Events		
Category	**Brolucizumab 6 mg (Out of 356 participants)**	**Aflibercept 2 mg (Out of 179 participants)**
At least 1 serious ocular adverse event in the untreated eye	2 (less than 1%)	1 (less than 1%)
Stopped drug due to ocular adverse event in the treated eye	25 (7%)	6 (3%)
Stopped drug due to ocular adverse event in the untreated eye	0	0

Number of Participants (%) With Non-Ocular Adverse Events		
Category	**Brolucizumab 6 mg (Out of 356 participants)**	**Aflibercept 2 mg (Out of 179 participants)**
At least 1 non-ocular adverse event	274 (77%)	136 (76%)
At least 1 serious non-ocular adverse event	63 (18%)	43 (24%)
Stopped drug due to non-ocular adverse event	1 (less than 1%)	1 (less than 1%)

A total of 14 (3%) participants died during this trial. This included 10 out of 356 (3%) participants in the brolucizumab group and 4 out of 179 (2%) participants in the aflibercept group.

What were the most common serious adverse events?

Ocular serious adverse events in the treated eye

The most common serious adverse events in the treated eye that happened in at least 2 participants in any group are shown below:

Number of Participants (%) With Most Common Ocular Serious Adverse Events in the Treated Eye		
	Brolucizumab (Out of 356 participants)	**Aflibercept (Out of 179 participants)**
Inflammation of the middle layer of the eye (uvea) (Uveitis)	4 (1%)	0
Lack of oxygen to the back of the eye (Retinal artery occlusion)	2 (less than 1%)	0

Ocular serious adverse events in the untreated eye

All serious adverse events in the untreated eye that happened in any group are shown below:

Number of Participants (%) With Most Common Ocular Serious Adverse Events in the Untreated Eye		
	Brolucizumab (Out of 356 participants)	**Aflibercept (Out of 179 participants)**
Clouding of the eye (Cataract)	0	1 (less than 1%)
Tumor in the middle vascular coat of the eye called choroid (Choroid neoplasm)	1 (less than 1%)	0

Number of Participants (%) With Most Common Ocular Serious Adverse Events in the Untreated Eye		
	Brolucizumab (Out of 356 participants)	**Aflibercept (Out of 179 participants)**
Worsening of wet age-related macular degeneration (Neovascular age-related macular degeneration)	1 (less than 1%)	0

Non-ocular serious adverse events

The most common serious non-ocular adverse events that happened in at least 1% (1 out of 100) of participants in any group are shown below:

Number of Participants (%) With Most Common Non-Ocular Serious Adverse Events		
	Brolucizumab (Out of 356 participants)	**Aflibercept (Out of 179 participants)**
Cancer of prostate gland (located between the bladder and the penis) (Prostate cancer)	1 (less than 1%)	2 (1%)
Fainting (Syncope)	2 (less than 1%)	2 (1%)
Fracture in hip (Hip fracture)	0	2 (1%)
Inflammation of the bronchial tubes, which carry air to and from the lungs (Bronchitis)	0	2 (1%)

Number of Participants (%) With Most Common Non-Ocular Serious Adverse Events		
	Brolucizumab (Out of 356 participants)	**Aflibercept (Out of 179 participants)**
Irregular heartbeat (Atrial fibrillation)	1 (less than 1%)	3 (2%)
Lung infection (Pneumonia)	5 (1%)	1 (less than 1%)
Mild stroke (Transient ischemic attack)	0	2 (1%)

What were the most common non-serious adverse events?

Ocular non-serious adverse events in the treated eye

The most common non-serious ocular adverse events in the treated eye that happened in at least 5% (5 out of 100) of participants in any group are shown below:

Number of Participants (%) With Most Common Ocular Non-Serious Adverse Events in the Treated Eye		
	Brolucizumab (Out of 356 participants)	**Aflibercept (Out of 179 participants)**
Blood spots on white part of the eye (Conjunctival hemorrhage)	32 (9%)	14 (8%)
Clouding of the eye (Cataract)	23 (6%)	4 (2%)

Number of Participants (%) With Most Common Ocular Non-Serious Adverse Events in the Treated Eye		
	Brolucizumab (Out of 356 participants)	**Aflibercept (Out of 179 participants)**
Dark small shadowy shapes that obstruct the vision (Vitreous floaters)	21 (6%)	10 (6%)
Decrease in clarity of vision (Visual acuity reduced)	22 (6%)	6 (3%)
Dry eye	19 (5%)	4 (2%)
Increase in eye fluid pressure (Intraocular pressure increased)	19 (5%)	7 (4%)
Pulling away of gel-like fluid (vitreous) from retina (back of the eye) (Vitreous detachment)	18 (5%)	5 (3%)

Ocular non-serious adverse events in the untreated eye

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

Number of Participants (%) With Most Common Ocular Non-Serious Adverse Events in the Untreated Eye		
	Brolucizumab (Out of 356 participants)	**Aflibercept (Out of 179 participants)**
Bleeding in the back of the eye (retina) (Retinal hemorrhage)	9 (3%)	6 (3%)
Blood spots on white part of the eye (Conjunctival hemorrhage)	6 (2%)	7 (4%)
Clouding of the eye (Cataract)	13 (4%)	3 (2%)
Worsening of wet age-related macular degeneration (Neovascular age-related macular degeneration)	19 (5%)	13 (7%)

Non-ocular non-serious adverse events

The most common non-serious non-ocular adverse events that happened in at least 5% (5 out of 100) of participants in any group are shown below:

Number of Participants (%) With Most Common Non-Ocular Non-Serious Adverse Events		
	Brolucizumab (Out of 356 participants)	**Aflibercept (Out of 179 participants)**
Common cold (Nasopharyngitis)	12 (3%)	10 (6%)
Fall	23 (6%)	6 (3%)
High blood pressure (Hypertension)	28 (8%)	23 (13%)
Infection in any part of the urinary tract (Urinary tract infection)	36 (10%)	16 (9%)
Irregular heartbeat (Atrial fibrillation)	9 (3%)	10 (6%)
Swelling inside the nose (Sinusitis)	11 (3%)	11 (6%)

How many participants stopped trial drug due to adverse events?

25 out of 356 (7%) participants in the brolucizumab group and 6 out of 179 (3%) participants in the aflibercept group stopped trial drug due to ocular adverse events in the treated eye.

The most common adverse events that led to stopping the trial treatment were:

- **inflammation of the middle layer of the eye** (uveitis),
- **inflammation of the colored part of the eye** (iridocyclitis),
- **inflammation of the choroid (thin pigmented vascular coat of the eye) and retina of the eye** (chorioretinitis), and
- **inflammation of gel-like part (vitreous cavity) of the eye** (vitritis).

None of the participants stopped trial treatment due to ocular adverse events in the untreated eye.

1 participant in each group stopped trial treatment due to non-ocular adverse events. In the brolucizumab group, the participant stopped trial treatment early due to **liver cancer** (hepatic cancer) and in the aflibercept group, the participant stopped trial treatment early due to **a type of lung cancer** (non-small cell lung cancer).

How was this trial useful?

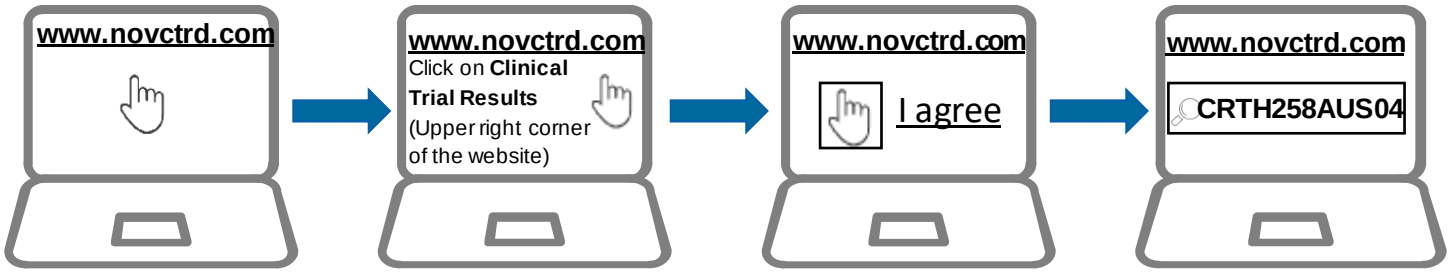
The trial helped researchers to understand the effects and safety of brolucizumab compared to aflibercept in participants with wet age-related macular degeneration with persistent fluid in the eye. Results from this trial showed that the efficacy of brolucizumab is similar compared to aflibercept, however, the treatment frequency studied in this trial showed more eye related adverse events in the treated eye with brolucizumab compared to aflibercept.

The trial ended early as the risks of using brolucizumab as used in this trial outweighed its benefits. In this trial, brolucizumab was given in a continuous manner every 4 weeks in participants with wet age-related macular degeneration with persistent fluid in the eye.

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 website:

- www.clinicaltrials.gov Use the NCT identifier NCT03710564 in the search field.

Full clinical trial title: A multicenter, randomized, double-masked Phase 3a study to assess safety and efficacy of brolucizumab 6 mg q4 weeks compared to aflibercept 2 mg q4 weeks in patients with neovascular age-related macular degeneration (nAMD) with persistent retinal fluid (MERLIN)

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.

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