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Clinical Trial Results Summary

A clinical trial to learn about the effect and safety of QVM149 compared to salmeterol/fluticasone + tiotropium for the treatment of people with uncontrolled asthma

Protocol number: CQVM149B2306

Thank You!

Novartis, the sponsor of this clinical trial, would like to thank you for taking part in this trial for the drug QVM149. You helped researchers learn more about how QVM149 affects quality of life for people with moderate to severe asthma whose symptoms are not completely controlled by the medicine they are already taking.

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.

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. It takes many people in multiple clinical trials around the world to advance medical science and healthcare. If you have any questions about these trial results, please talk to the doctor or staff at your trial site.

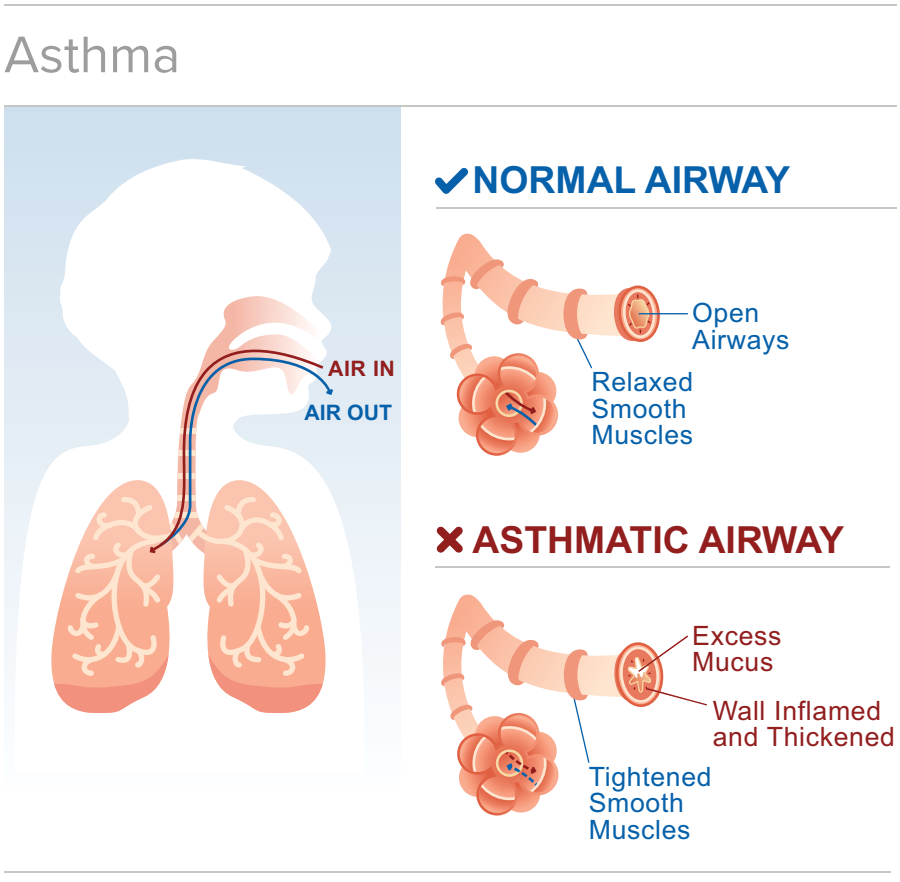
How long was this trial?

This trial was designed so that a participant could take part for about 7 months. The trial started in February 2018 and ended in July 2019.

The researchers completed this trial as planned. When the trial ended, the researchers collected information on the trial treatments (QVM149 and salmeterol/fluticasone + tiotropium) and created a report of the trial results. This summary is based on that report.

Why was the research needed?

Asthma is a condition that narrows the airways that carry oxygen into the lungs, making it hard to breathe. Researchers were looking for a better treatment to improve the quality of life for patients with moderate to severe asthma which is not completely improved by their current inhaled treatments.



This condition causes some of the following symptoms at varying times:

- inflammation (swelling) in the lungs
- tightness in the chest
- wheezing
- coughing

Although there is no known cure for asthma, there are treatments available that can help manage the symptoms.

QVM149 is an investigational drug that combines two long acting bronchodilators (a beta agonist [LABA] and a muscarinic receptor antagonist [LAMA]) to help relax the airways of the lungs, and an anti-inflammatory (inhaled corticosteroid [ICS]) to reduce inflammation. As a result, this combination improves asthma symptoms.

In this trial, researchers included participants who had already taken other inhaled asthma medicine, but still had symptoms that were not improving. Researchers wanted to find out if giving QVM149 to participants would improve their quality of life at least as much compared to a standard inhalation treatment that is widely used.

Researchers checked the quality of life of participants with a questionnaire that measures changes in impairments on daily life that are often experienced by people with asthma.

Trial drugs

The drugs given in this trial were:

- **QVM149,** an investigational drug made of a combination of indacaterol acetate, glycopyrronium bromide, and mometasone that was being studied for the treatment of uncontrolled moderate to severe asthma in medium and high doses. QVM149 was taken once daily via inhaler.
- **Salmeterol/fluticasone + tiotropium,** a loose or fixed standard treatment drug combination for the treatment of moderate to severe uncontrolled asthma. Salmeterol/fluticasone was taken twice daily via inhaler + tiotropium once daily via inhaler.

All participants were on asthma inhalation treatment with an ICS and a LABA prior to the treatment period of the study but still had uncontrolled asthma.

Participants were given inhalers of salbutamol, also known as albuterol, to use as needed when their asthma symptoms got worse. This medicine is known as “rescue” medicine.

Trial purpose

In this trial, researchers compared the results of all participants after 24 weeks of treatment with either QVM149 or the standard treatment salmeterol/fluticasone + tiotropium.

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

- Did the quality of life of participants taking QVM149 improve at least as much compared with participants taking salmeterol/fluticasone + tiotropium, as measured after 24 weeks of treatment?

The other question researchers wanted to answer in this trial was:

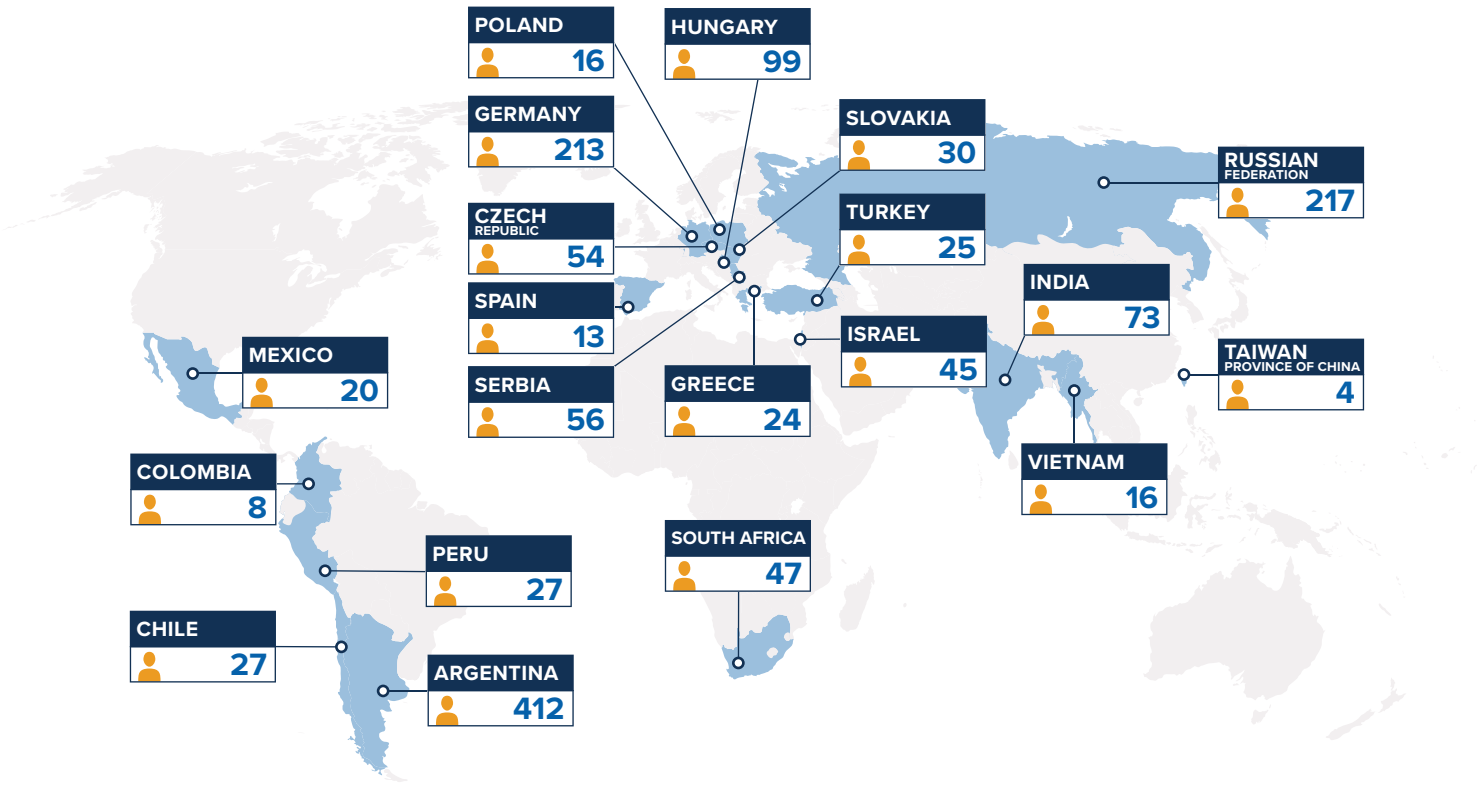
- How much more air could participants breathe out in one second at the end of 24 weeks of treatment compared with the start of the trial?

Who was in this trial?

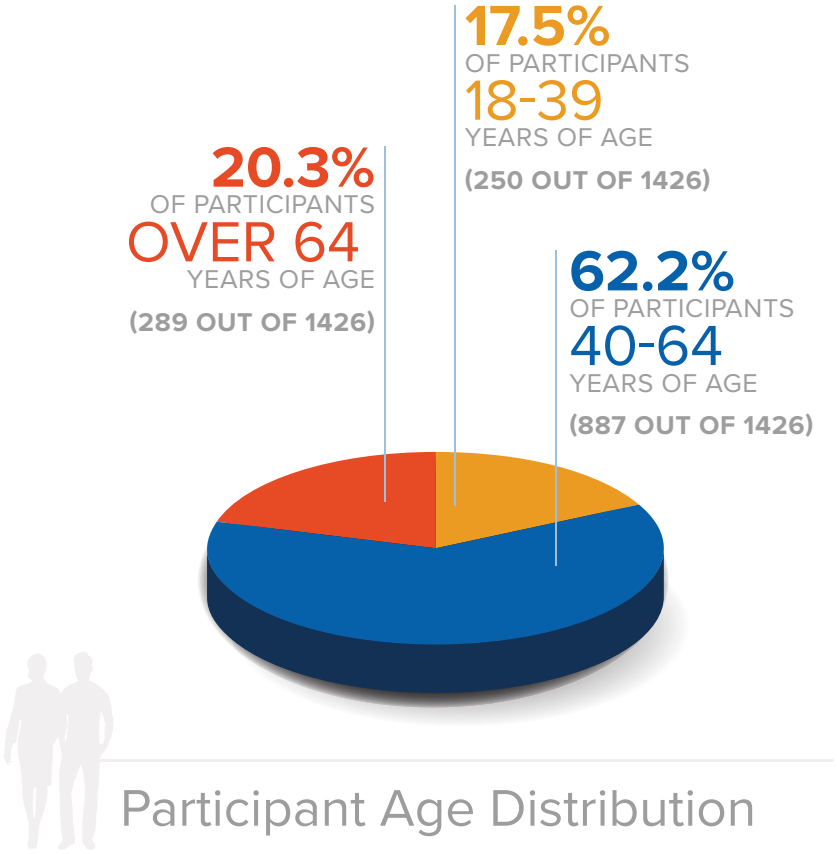
The participants could take part in this trial if they:

- were 18 years of age or older and had uncontrolled moderate to severe asthma for at least 6 months before they entered the trial;
- were experiencing uncontrolled moderate to severe asthma symptoms despite previous treatment with asthma medication;
- had a history of at least 1 asthma attack which required medical care or hospitalization and corticosteroid treatment in the 12 months prior to first trial visit;
- did not have any heart problems or other serious medical conditions.

A total of 1426 participants from 20 countries participated in this trial.



The average age of participants in this trial was 52.5 years. About 63.3% of the trial participants, or 902 out of 1426, were female. About 83.0% of participants (1184 out of 1426) were White, 7.2% of participants (103 out of 1426) were Asian, 1.1% of participants (16 out of 1426) were American Indian or Alaska Native, 1.0% of participants (14 out of 1426) were Black or African American, and 7.6% of participants (109 out of 1426) were other ethnicities. Participants' age ranged from 18 years to 82 years.



Participant Age Distribution

What kind of trial was this?

This trial had both open-label and partially-blinded periods. The run-in period was “open-label”, which meant that the participants, trial doctors, and trial staff knew what treatment participants were receiving. The treatment period was “partially-blinded”, which meant that the participants knew if they were given QVM149 or salmeterol/fluticasone + tiotropium, however participants did not know which dose of QVM149 treatment was given, and the trial doctors did not know which treatments were given to participants.

What happened during this trial?

Participants went through a 1-week screening period to confirm that they could take part in the trial. Participants who qualified then entered the 2-week run-in period, wherein they were given open-label salmeterol/fluticasone. During these two periods, participants recorded their symptoms and all asthma medicines they were taking in their electronic diaries.

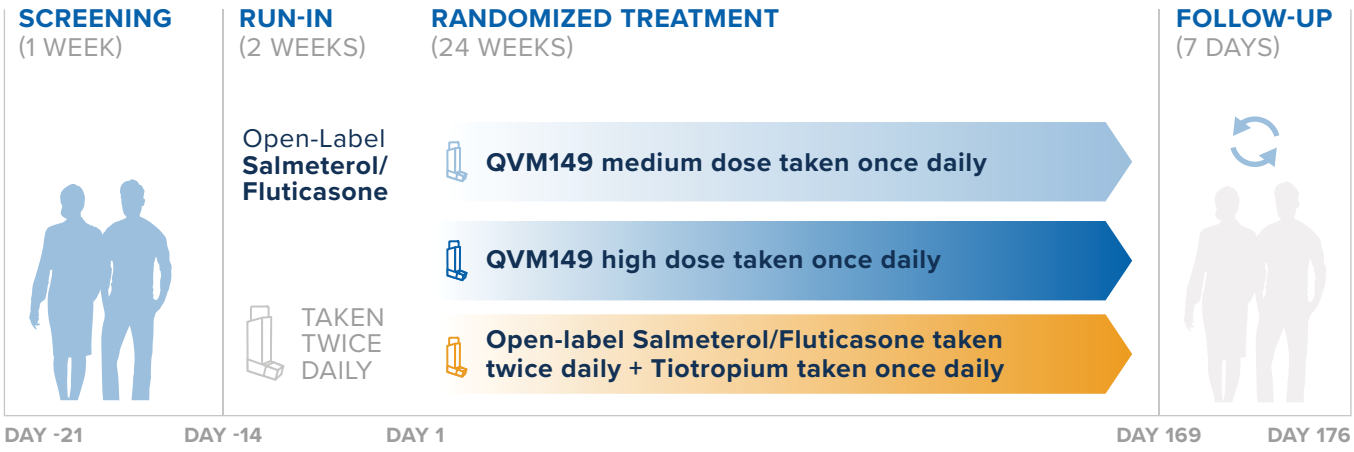
Researchers measured participants’ quality of life throughout the trial with the Asthma Quality of Life Questionnaire (AQLQ). This questionnaire was given to participants to measure impairments in participants’ daily lives as a result of asthma, such as negative impacts on physical activity and emotion. Researchers also measured participants’ lung function throughout the trial with a lung function test. The lung function test measured how much air participants could forcefully breathe out of their lungs in one second. This helped researchers learn about how severe the participants’ asthma was.
The results recorded at the start of the trial were later used as the baseline to which researchers compared after-treatment results.

After the placebo run-in period, participants were randomly (by chance) put into 3 groups. This process is called randomization. The participants were to receive either:

- **QVM149** taken via inhaler once a day, at a medium dose (150/50/80) micrograms [µg])
- **QVM149** taken via inhaler once a day, at a high dose (150/50/160 µg)
- **Standard treatment Salmeterol/Fluticasone** taken via inhaler twice a day (50/500 µg) + **Tiotropium** taken via inhaler once a day (5 µg)

If needed, participants could also use rescue medicine for worsening asthma symptoms during the trial.

Trial Design



During the 24-week treatment period, participants visited their clinic every 8 weeks. Researchers compared the change in quality of life and lung function at the start of the trial and at the end of Week 24 to see the effect of treatment.

Researchers also tracked the participants' health throughout the trial. Participants were contacted by telephone 7 days after their last dose of treatment for a follow-up.

What were the key results of this trial?

This is a summary of the average results for all participants in different treatment groups. 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 quality of life of participants taking QVM149 improve at least as much compared with participants taking salmeterol/fluticasone + tiotropium, as measured after 24 weeks of treatment?

Quality of life information came from the Asthma Quality of Life Questionnaire (AQLQ) that participants completed during the study. For the high dose, QVM149 was found to show greater improvement of quality of life after 24 weeks when compared to salmeterol/fluticasone + tiotropium. For the medium dose, QVM149 was found to show similar improvement of quality of life after 24 weeks when compared to salmeterol/fluticasone + tiotropium.

What were the other results of this trial?

Researchers also wanted to know the answer to the following question after 24 weeks of treatment.

How much more air could participants breathe out in one second at the end of 24 weeks of treatment compared with the start of the trial?

For the high dose, QVM149 was found to show a greater increase in the amount of air breathed out in one second after 24 weeks when compared to the standard treatment salmeterol/fluticasone + tiotropium. The medium dose of QVM149 showed similar effects on the change in the amount of air breathed out in one second after 24 weeks when compared to the standard treatment salmeterol/fluticasone + tiotropium.

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 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, 252 out of 474 participants (53.2%) in the QVM149 medium dose group, 249 out of 476 participants (52.3%) in the QVM149 high dose group, and 245 out of 475 participants (51.6%) in the salmeterol/fluticasone + tiotropium group reported at least 1 adverse event. One participant in the salmeterol/fluticasone + tiotropium group died during the treatment period as a result of a stroke, which was not considered related to their treatment.

Number of Participants (%) With Adverse Events

	QVM149 Medium Dose (Out of 474 participants)	QVM149 High Dose (Out of 476 participants)	Salmeterol/ Fluticasone + Tiotropium (Out of 475 participants)
At least 1 adverse event	252 (53.2%)	249 (52.3%)	245 (51.6%)
At least 1 serious adverse event	14 (3.0%)	18 (3.8%)	19 (4.0%)
Stopped drug due to adverse event	5 (1.1%)	3 (Less than 1%)	3 (Less than 1%)

What was the most common non-serious adverse event?

Asthma attack was the most common non-serious adverse event that happened in at least 10 out of 100 (10%) of the participants in the QVM149 medium dose group, QVM149 high dose group, or the standard treatment salmeterol/fluticasone + tiotropium group.

For a full list of the non-serious adverse events that occurred in this trial, please visit the websites listed at the end of this summary.

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

	QVM149 Medium Dose (Out of 474 participants)	QVM149 High Dose (Out of 476 participants)	Salmeterol/ Fluticasone + Tiotropium (Out of 475 participants)
Asthma attack	125 (26.4%)	114 (23.9%)	125 (26.3%)

What was the most common serious adverse event?

The most common serious adverse events were pneumonia and asthma attack.

For a full list of the serious adverse events that occurred in this trial, please visit the websites listed at the end of this summary.

Number of Participants (%) With Most Common Serious Adverse Event

	QVM149 Medium Dose (Out of 474 participants)	QVM149 High Dose (Out of 476 participants)	Salmeterol/ Fluticasone + Tiotropium (Out of 475 participants)
Pneumonia	0 (0%)	5 (1.1%)	0 (0%)
Asthma attack	4 (Less than 1%)	3 (Less than 1%)	2 (Less than 1%)

How many participants stopped trial drug due to adverse events?

During the trial, 1.1% (5 out of 474) of participants in the QVM149 medium dose group and less than 1% (3 out of 476) of participants in the QVM high dose group stopped QVM149 early due to adverse events such as dry mouth, high fever, laryngitis, throat discomfort, itching, headache, burning, and hoarseness. Itching and hoarseness were reported by one participant in the QVM149 medium dose group. Headache and burning were reported by one participant in the QVM149 high dose group.

Less than 1% (3 out of 475) of participants stopped salmeterol/fluticasone + tiotropium early because of adverse events such as atopic dermatitis, stroke, and irritation of the throat.

How was this trial useful?

This trial helped researchers learn about how the medium and high doses of QVM149 given once a day affects quality of life and lung function of people with moderate to severe asthma that is not completely controlled by currently available treatments.

QVM149 high dose showed greater benefit when compared to standard treatment salmeterol/fluticasone + tiotropium. QVM149 medium dose showed similar benefits when compared to standard treatment salmeterol/fluticasone + tiotropium. Both the QVM149 and salmeterol/fluticasone + tiotropium groups also reported similar adverse events.

This clinical trial was used to support approval for the QVM149 high dose in the European Union, Canada, and Japan. Please remember, this summary only shows the results of a single clinical trial. Researchers and health authorities look at the results of many clinical trials to understand which drugs work, and if they are safe. It takes many people in multiple clinical trials around the world to advance medical science and healthcare. 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 websites:

- www.clinicaltrials.gov Use the NCT identifier NCT03158311 in the search field.
- https://www.clinicaltrialsregister.eu/ctr-search/search Use the EudraCT identifier 2017-000136-34 in the search field.

Full clinical trial title: A multicenter, partially-blinded, randomized, 24-week, parallel-group, non-inferiority, open-label active controlled study to compare the efficacy and safety of QVM149 with a free triple combination of salmeterol/fluticasone + tiotropium in patients with uncontrolled asthma

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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