Plain Language Summary of Publication

Ravulizumab for adults with generalized myasthenia gravis: a plain language summary of three studies

Journal of Comparative Effectiveness Research

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Summary

What is this summary about?

Generalized myasthenia gravis (often shortened to gMG) is a rare health condition that causes muscular weakness. This summary gives an overview of three published articles that report the results of research studies of a medicine called ravulizumab, a treatment approved for adults with gMG. These studies are:

- The CHAMPION MG study.
- The CHAMPION MG extension study.
- A study of how the body processes and responds to ravulizumab (known as pharmacokinetics and pharmacodynamics).

These studies looked at how effective and safe ravulizumab is for people with gMG.

How to say (double click on the sound icon to play the sound)

Generalized myasthenia gravis: JEN-ruhl- ized MAI-uhs-thee-nee-uh GRAA-vuhs
Ravulizumab: RAV-yoo-LIH-zoo-mab
Monoclonal antibody: MAH-noh-KLOH-nul AN-tee-BAH-dee
Placebo: pluh-SEE-boh
Acetylcholine: Uh-she-tuhl-KOW-leen
Steroids: STEH-roydz
Corticosteroids: kor-tuh-kow-STEH-roydz

What were the results?

Overall, participants with gMG who received ravulizumab showed a significant and rapid improvement in their muscle strength and ability to do daily activities. These improvements were sustained for up to 60 weeks of treatment. Ravulizumab was well-tolerated overall, and no-one in the study had a meningococcal infection (a type of bacterial infection preventable with vaccination). Results from the pharmacokinetic and pharmacodynamic study support the use of ravulizumab every 8 weeks to maintain improvements in gMG.

What do the results of the study mean?

Ravulizumab can be considered as a treatment option for adults with gMG who are appropriately protected against meningococcal infection before starting treatment. The drug, administered every 8 weeks, improves muscle strength and daily performance. These positive effects have been observed to persist over a long period of time.

Where can I find the original articles on which this summary is based?

You can read the original articles for free at the following links:

- The CHAMPION MG study in the journal *NEJM Evidence*, "Terminal complement inhibitor ravulizumab in generalized myasthenia gravis." – https://evidence.nejm.org/doi/full/10.1056/EVIDoa2100066

Becaris PUBLISHING

- The CHAMPION MG extension study in the journal *Journal of Neurology*, "Long-term efficacy and safety of ravulizumab in adults with anti-acetylcholine receptor antibody-positive generalized myasthenia gravis: results from the phase 3 CHAMPION MG open-label extension." – https://link.springer.com/article/10.1007/s00415-023-11699-x

- Pharmacokinetics and pharmacodynamics of ravulizumab in the *Journal of Neurology*, "Ravulizumab pharmacokinetics and pharmacodynamics in patients with generalized myasthenia gravis." – https://link.springer.com/article/10.1007/s00415-023-11617-1

Who is this article for?

This article may be helpful for:

- People diagnosed with generalized myasthenia gravis (also referred to as gMG), as active participants in their care, and their caregivers.

- Patient associations or other groups which support people with gMG and their caregivers.

- Healthcare providers such as physicians and nurses who provide care for people with gMG.

- Healthcare providers or policymakers who draft gMG management recommendations.

What is myasthenia gravis?

- MG is a rare condition, affecting approximately 15-20 people per 100,000 worldwide. In the United States, it is estimated that between 36,000 and 60,000 people are living with this condition.

- This condition affects muscles under conscious control (known as voluntary muscles).

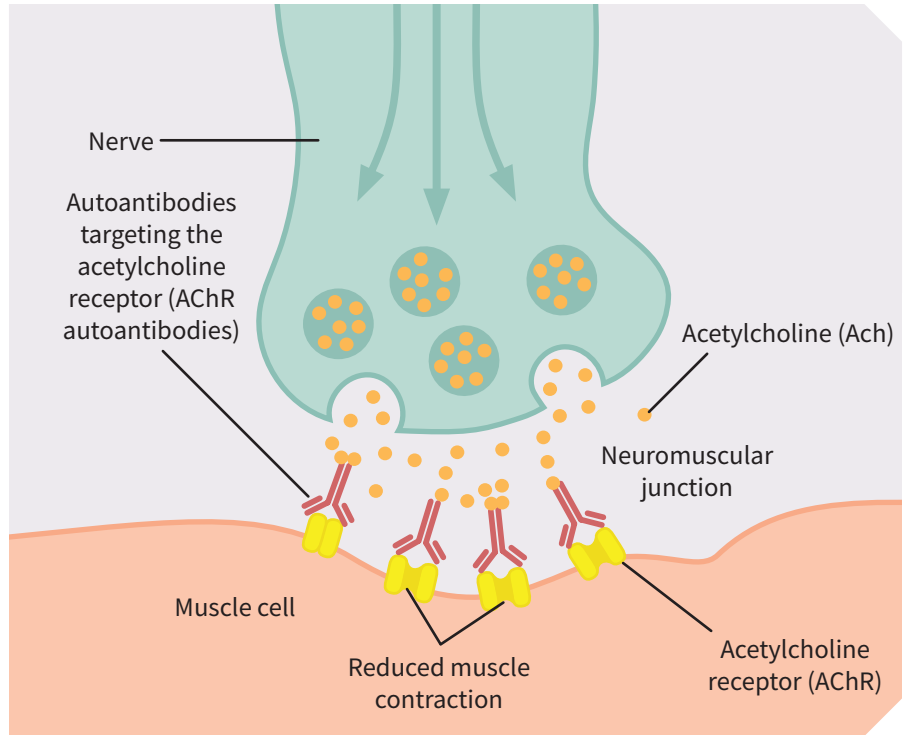
- Weakness of the muscles that control the eyes and eyelids is often an early sign of MG, causing symptoms such as eyelid droop and double vision. This is called ocular MG, which affects approximately 10-15% of people. However, most people (around 80-90%) go on to develop symptoms affecting other muscle groups, including jaw muscles, arm and leg muscles, and muscles that help with swallowing and breathing. This is called gMG.

- In addition to muscle weakness, people with gMG may experience a wide range of other symptoms, such as extreme fatigue, difficulty speaking (dysarthria), changes in facial expressions, and even trouble breathing in severe cases.

- Although it can occur at any age, MG more commonly affects young women (aged 20-30) and men aged 50 and above.

- The root cause of this condition is an issue with the immune system (the body's natural defense system), which usually produces antibodies (a type of protein) to fight infections. In some conditions (known as autoimmune conditions) the immune system produces antibodies that attack the body's' own tissues (called autoantibodies). In MG, autoantibodies attack the connections between nerves and muscles (known as neuromuscular junctions), leading to muscle weakness.

- For most people with gMG (approximately 85%), the immune system produces autoantibodies that block a substance called acetylcholine from properly interacting with acetylcholine receptors (AChRs for short) on the muscles. Acetylcholine is a chemical messenger released by nerves that helps the muscles receive the signal to contract (a process which changes the length of muscle tissue). When the autoantibodies attack acetylcholine receptors (areas of tissue that respond to certain substances, in this case to acetylcholine), it makes it difficult for the muscles to get this signal, leading to muscle weakness and fatigue. This type of MG is known as AChR autoantibody-positive MG.

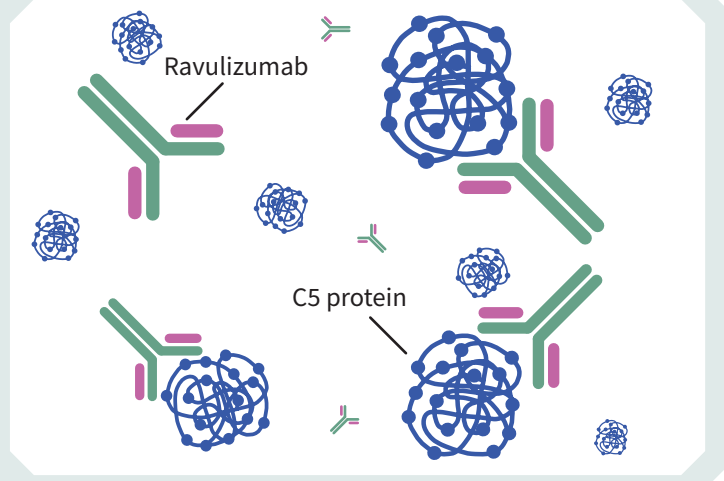


- Although MG cannot be cured, its symptoms can be effectively managed for many people through medical care. An important goal of treatment is to increase muscle strength, improving people's ability to function and their quality of life, while acknowledging that individual goals may vary.
- Some treatments for MG aim to control symptoms by reducing the ability of autoantibodies to attack the connection between nerves and muscles.
  - Older treatments, such as steroids (also known as corticosteroids), work by suppressing the immune system in general. This means the immune system is less active and less likely to attack the AChR More recently, treatments have been developed to target specific parts of the immune system.

What is ravulizumab, and how does it work?

Ravulizumab is a type of treatment called a monoclonal antibody. This is a type of protein that can bind to specific targets in the body that cause health conditions.

The target of ravulizumab is the C5 protein, an immune system protein. When ravulizumab inhibits C5, the immune system cannot cause damage to the neuromuscular junctions.



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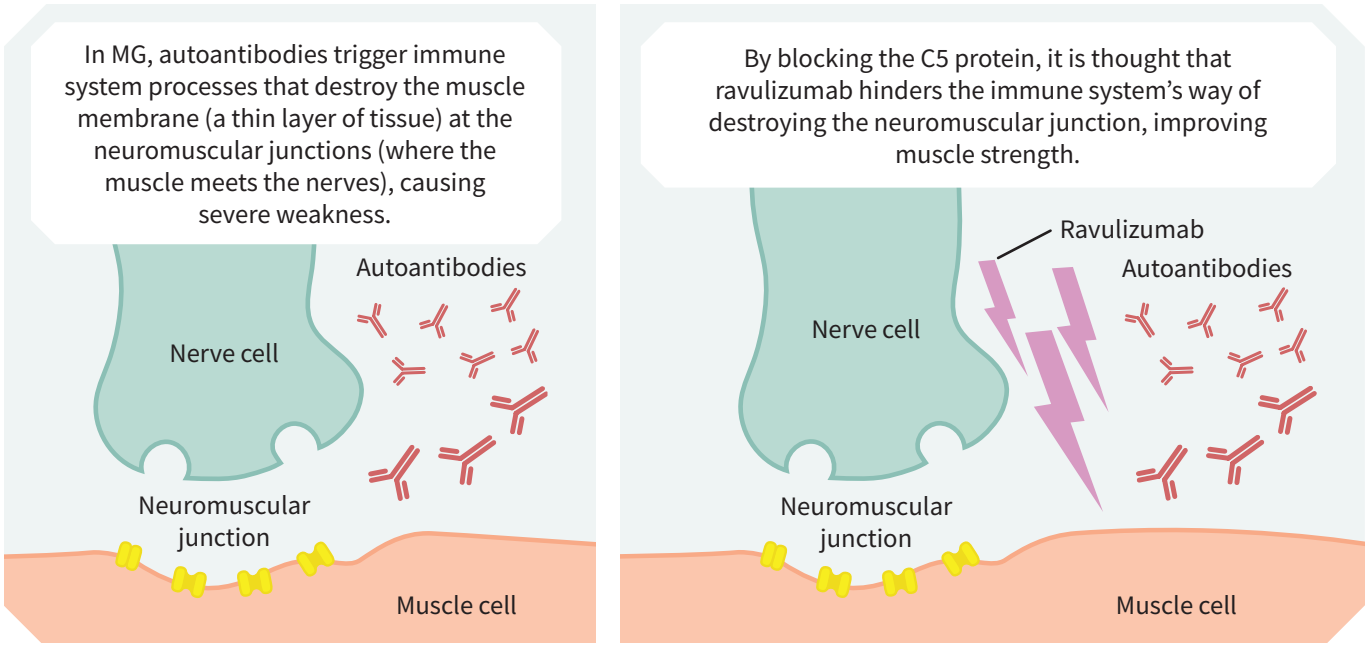


- Ravulizumab is given through an infusion into a vein (known as an intravenous infusion) using a drip. The first dose, called a loading dose, is larger to quickly reach the right level of the drug in the blood. For adults, this is followed by smaller maintenance doses every 8 weeks. For children, maintenance doses are given every 4-8 weeks, depending on their weight.

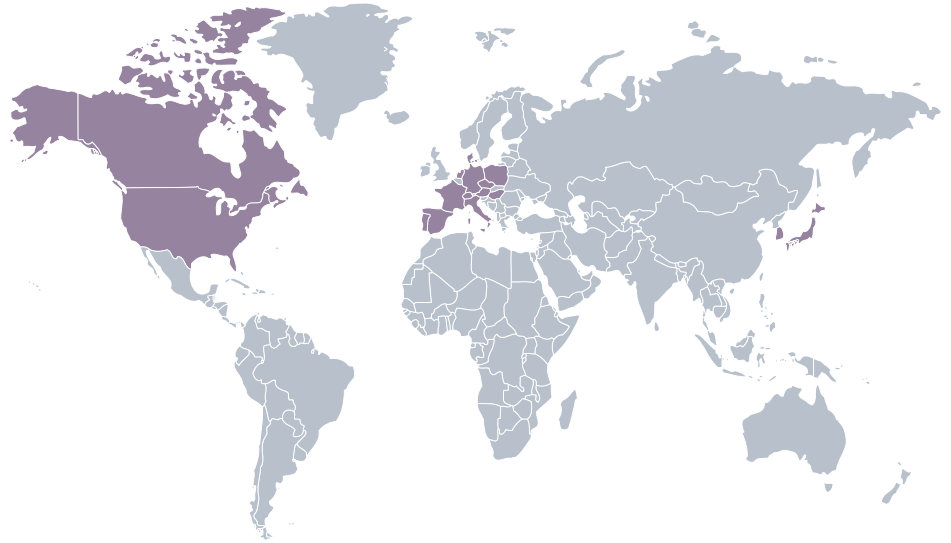
What did the CHAMPION MG study and its extension study look at?

The CHAMPION MG study and the CHAMPION MG extension study looked at the impact of ravulizumab on muscle strength, daily activity performance, and quality of life in adults with gMG.

How were the studies done?

In the CHAMPION MG study, the researchers looked at how effective and safe ravulizumab was compared to a placebo (a treatment that looks the same and is taken in the same way as the study drug but does not contain any active ingredient).

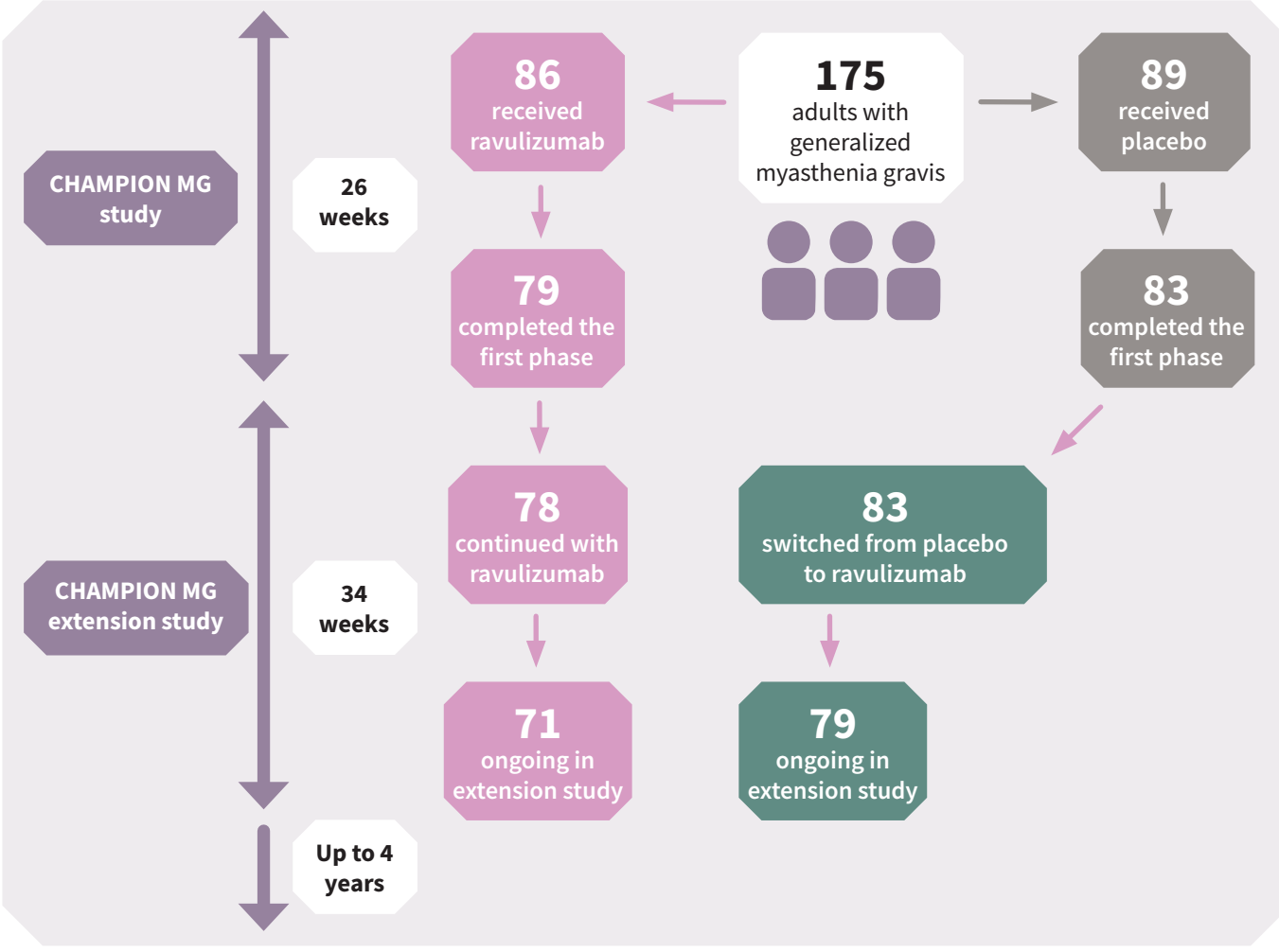
- The study lasted 26 weeks (6.5 months) and took place in multiple countries.



- Participants were enrolled into the study between March 2019 and November 2020.
- 175 adults with gMG received either ravulizumab or a placebo. This was done at random i.e. by chance (like tossing a coin)
- This study was double-blinded, meaning that neither the investigators nor the participants knew who received ravulizumab and who received a placebo. A placebo is used in clinical trials to compare the real drug's effects with something inactive, ensuring that any effects are truly due to the drug and not other factors.

In the CHAMPION MG extension study, the researchers are looking at how effective and safe ravulizumab is over a longer period of time.

- Once the 26 weeks of the CHAMPION MG study were completed, people who initially received ravulizumab continued with the same treatment. People who initially received placebo then switched to ravulizumab.
- In the extension study, both the investigators and the participants knew what treatment the participants were receiving. This is known as an open-label study.
- This summary shows results from 60 weeks (just over 1 year) after the CHAMPION MG study started. This means that people in the study who started on ravulizumab had received 60 weeks of treatment, and people who started on placebo had received 34 weeks of ravulizumab after switching.
- The research will carry on for up to 4 years.



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Who took part in the study?

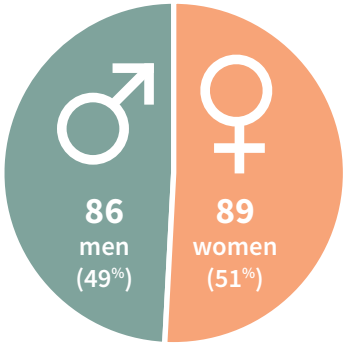
Who could participate (inclusion criteria)

- Adults 18 years or older with gMG with AChR autoantibodies.
- People who had been living with gMG for at least six months before joining the study.
- Those with mild to moderate symptoms that were affecting their daily life.
- All participants had to be vaccinated against meningococcal infections within three years before starting ravulizumab. Meningococcal infections are bacterial infections that can be associated with treatments weakening the immune system, such as ravulizumab.

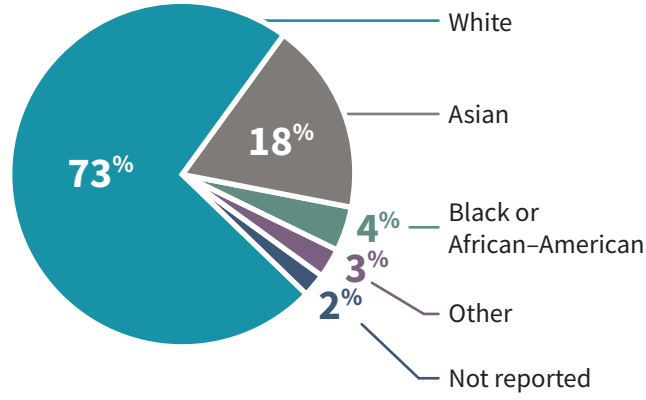
Who couldn't participate (exclusion criteria)

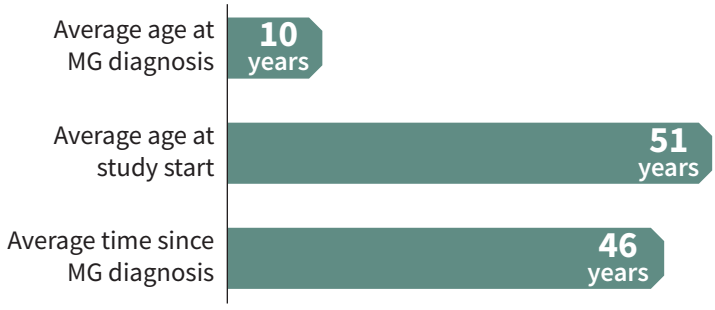
- People with a recent history of thymus gland cancer or other serious thymus-related conditions unless they were fully cured. The thymus is a small gland in the chest that helps the immune system, especially during childhood, by teaching the body to recognize and fight infections. In MG, the thymus is often abnormal and may contribute to the disease by triggering the production of harmful antibodies
- Anyone who recently received treatments like intravenous immunoglobulin (a mixture of antibodies given through a vein to help or calm the immune system), procedures to clean the blood (plasma exchange), or rituximab (a potent treatment that suppresses the immune system).
- People with a history of meningococcal infection.

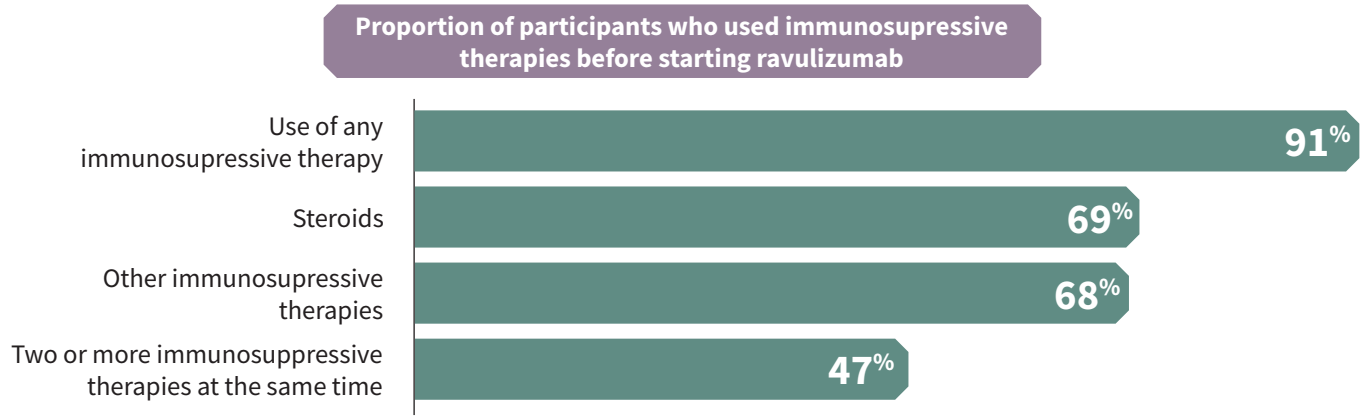
Proportion of men and women



Race







How did the researchers measure whether ravulizumab was effective?

The researchers used questionnaires to assess how severe peoples' MG symptoms were.

Test	Test description	What the test measures	Timing of assessments	Who answered
The Myasthenia Gravis-Activities of Daily Living (MG-ADL) scale	This assesses the impact of MG on a person's daily functions, such as talking, chewing, getting up from a chair, or brushing teeth. Higher scores indicate greater severity of symptoms.	**Activities of daily living** 	**These assessments were done:** • At the screening visit (the first visit to check if participants qualified for the study). • At the start of the study. • At weeks 1, 2, 4, 10, 12, 18, and 26 during the CHAMPION MG study. • At weeks 28, 30, 36, 38, 44, 52, and 60 during the CHAMPION MG extension study.	Filled out by the participant
The Quantitative Myasthenia Gravis (QMG) score	This assessment is completed by clinicians and gives a score to symptoms and weakness in different muscle groups. Higher scores indicate greater disease severity.	**Muscle weakness** 		Filled out by the doctor
The revised 15-item Myasthenia Gravis Quality of Life (MG-QOL15r) questionnaire	This allows clinicians to assess the impact of MG on a person's quality of life, including physical, social, and psychological components. Higher scores represent lower quality of life.	**Quality of life** 	**These assessments were done:** • At baseline. • At weeks 4, 12, 18, and 26 during the CHAMPION MG study. • At weeks 30, 38, 44, 52, and 60 during the CHAMPION MG extension study.	Filled out by the participant
The Neurological Quality of Life (Neuro-QoL) Fatigue subscale	This is a survey that assesses fatigue levels. Higher scores indicate higher levels of fatigue and greater impact on daily activities due to MG.	**Fatigue** 		Filled out by the participant

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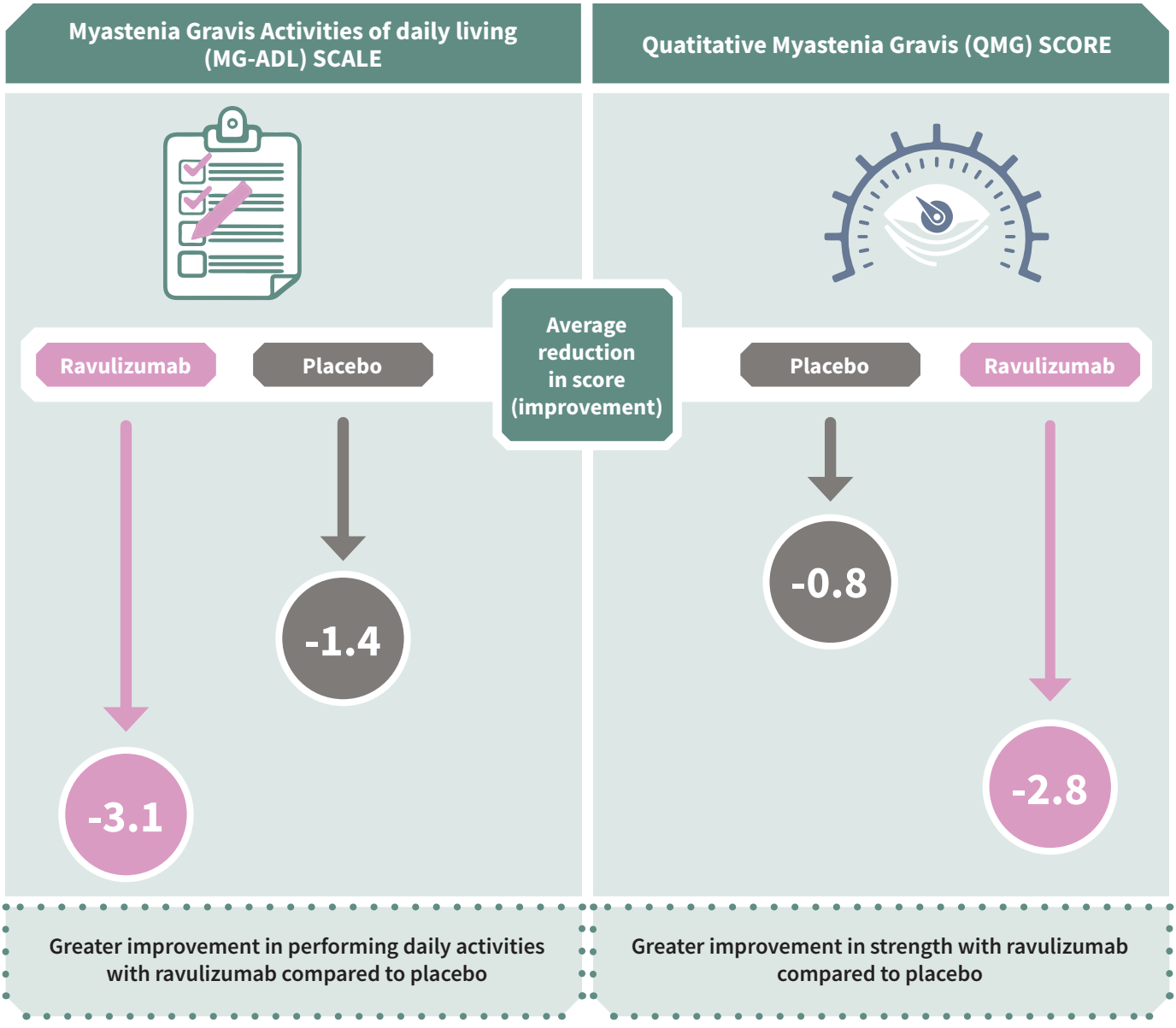
What did researchers find out in the CHAMPION MG study?

After 26 weeks, people who received ravulizumab showed greater improvement in their ability to perform daily activities and in their muscle strength compared to people who received a placebo. These results were based on the MG-ADL scale and the QMG score.



The proportion of people who experienced adverse events was similar between the ravulizumab and placebo groups, with no notable differences in the types of adverse events.

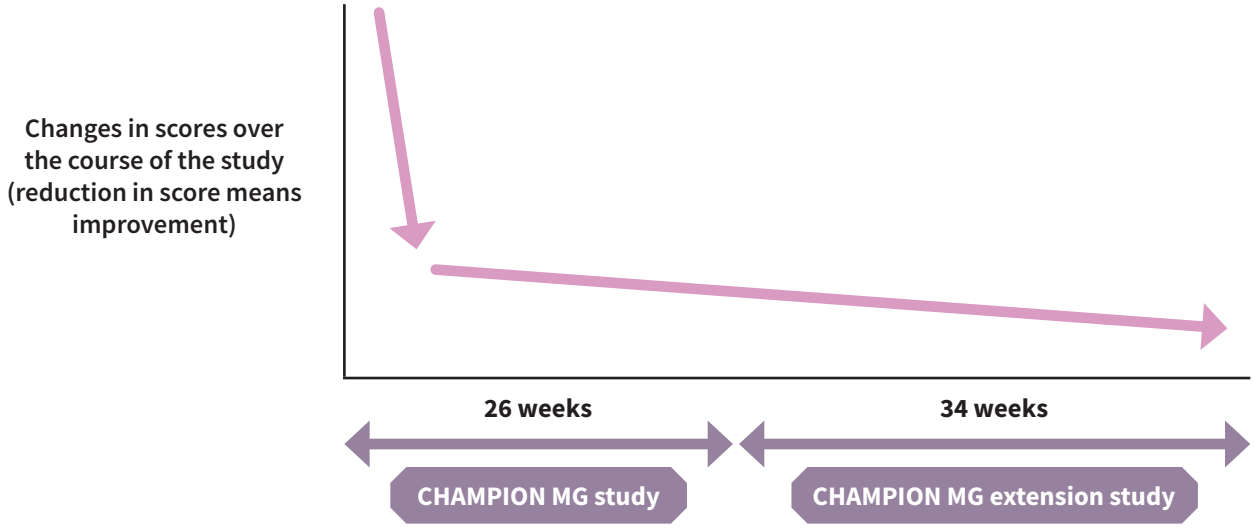
- An adverse event is any negative medical incident that occurs after taking a medication, even if it may not be directly caused by the medication.

The most frequent adverse event was headache, experienced by 16 people (19%) in the ravulizumab group and 23 people (26%) in the placebo group.

What have researchers found out so far in the CHAMPION MG extension study?

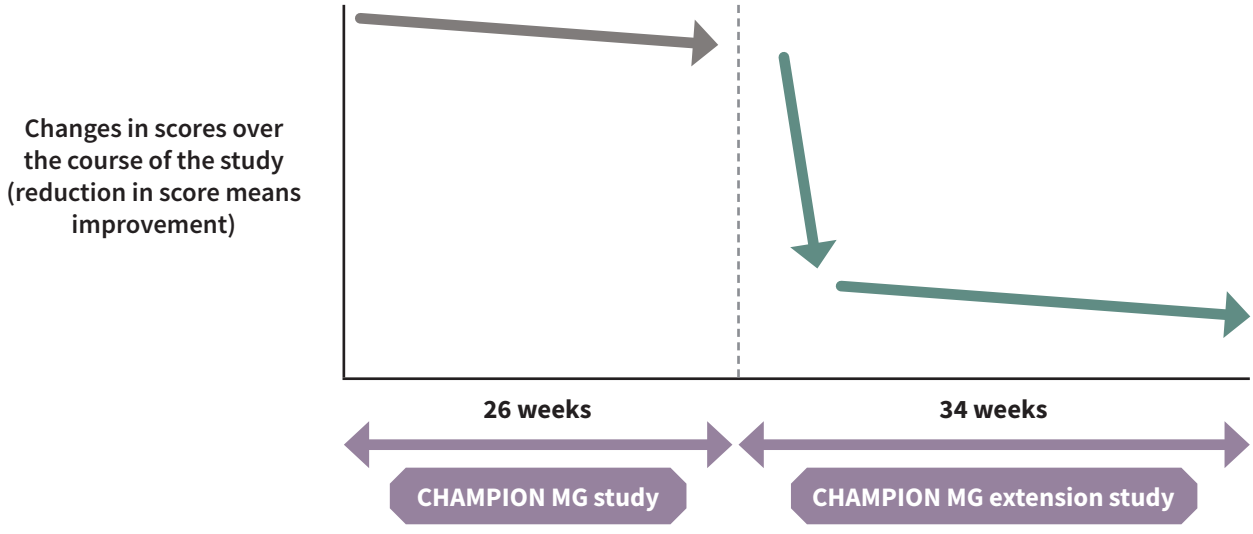
People who continued receiving ravulizumab

Participants treated with ravulizumab experience rapid improvement of all scores from the beginning, which was maintained over time in the study.



People who switched from placebo to ravulizumab

In participants initially on placebo, significant improvement in scores occurred after switching to ravulizumab.



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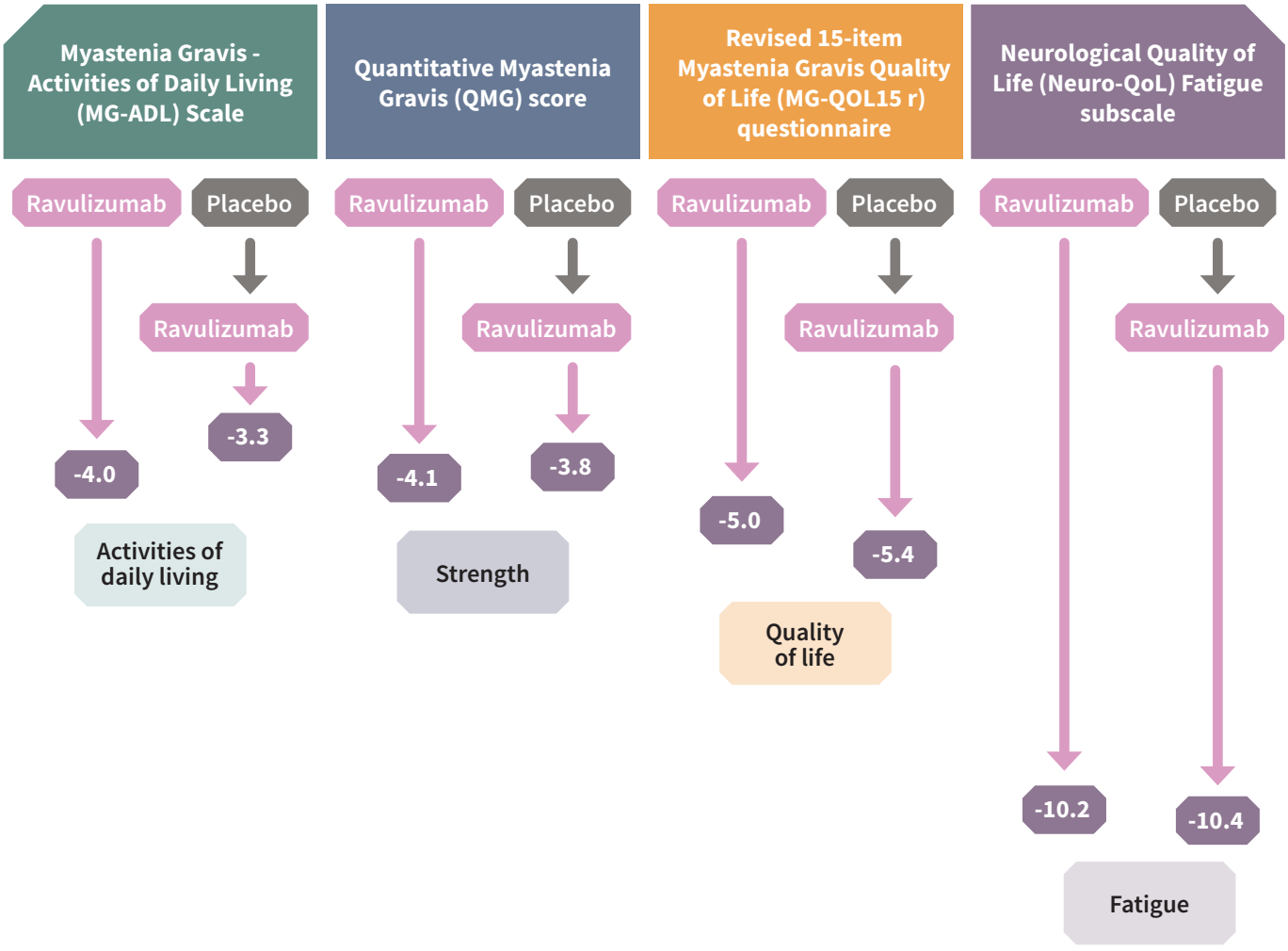

Pink bars represent the decrease in scores seen with ravulizumab, which indicates an improvement in what is being measured

Brown bars represent the decrease in scores seen with placebo, which indicates an improvement in what is being measured

- Ravulizumab was generally well tolerated.
- No additional adverse events were found beyond those reported in the CHAMPION MG study.
- The most common adverse events were headaches and diarrhea (loose or watery poo).
- Most adverse events (89%) were mild in severity.
  - Adverse events are typically classified by severity, from Grade 1 (mild) to Grade 5 (death). 'Mild' events are manageable without significant intervention, while 'severe' events may require hospitalization or cause major disruptions to daily life.
- No cases of meningococcal infections, which are severe infections of the lining of the brain and spinal cord, were reported.

Main adverse events		
	169 people who received ravulizumab during the CHAMPION MG study and the CHAMPION MG extension study	89 people who received placebo during the CHAMPION MG study
Headache	16.6%	25.8%
Diarrhea (loose or watery poo)	13.6%	12.4%
Nausea (feeling sick)	9.5%	10.1%
Fatigue (extreme tiredness)	9.5%	6.7%
Back pain	9.5%	5.6%
Arthralgia (joint pain)	8.9%	7.9%
Nasopharyngitis (inflammation of the inside of the nose and throat)	8.9%	5.6%
Urinary infection	8.9%	4.5%
Dizziness	8.3%	3.4%
COVID-19	5.3%	3.4%
Abdominal pain (stomach pain)	5.3%	0.0%
Upper respiratory tract infection (infection of the breathing system, e.g., sinuses, throat and airways)	5.3%	2.2%
Fever	3.6%	5.6%
Reaction to infusion	0.6%	5.6%

How does the body processes and respond to ravulizumab?

- The researchers analyzed samples from 86 people who took part in the CHAMPION MG study to gain a better understanding of how ravulizumab interacts with the body and what its effects are. This is known as pharmacokinetics (how a medication is absorbed, distributed, broken down and eliminated from the body) and pharmacodynamics (how a medication affects the body).
- People receive ravulizumab by infusion into a vein via a drip (intravenous infusion). Ravulizumab treatment requires an initial high dose followed by a series of lower maintenance doses every 8 weeks (2 months).

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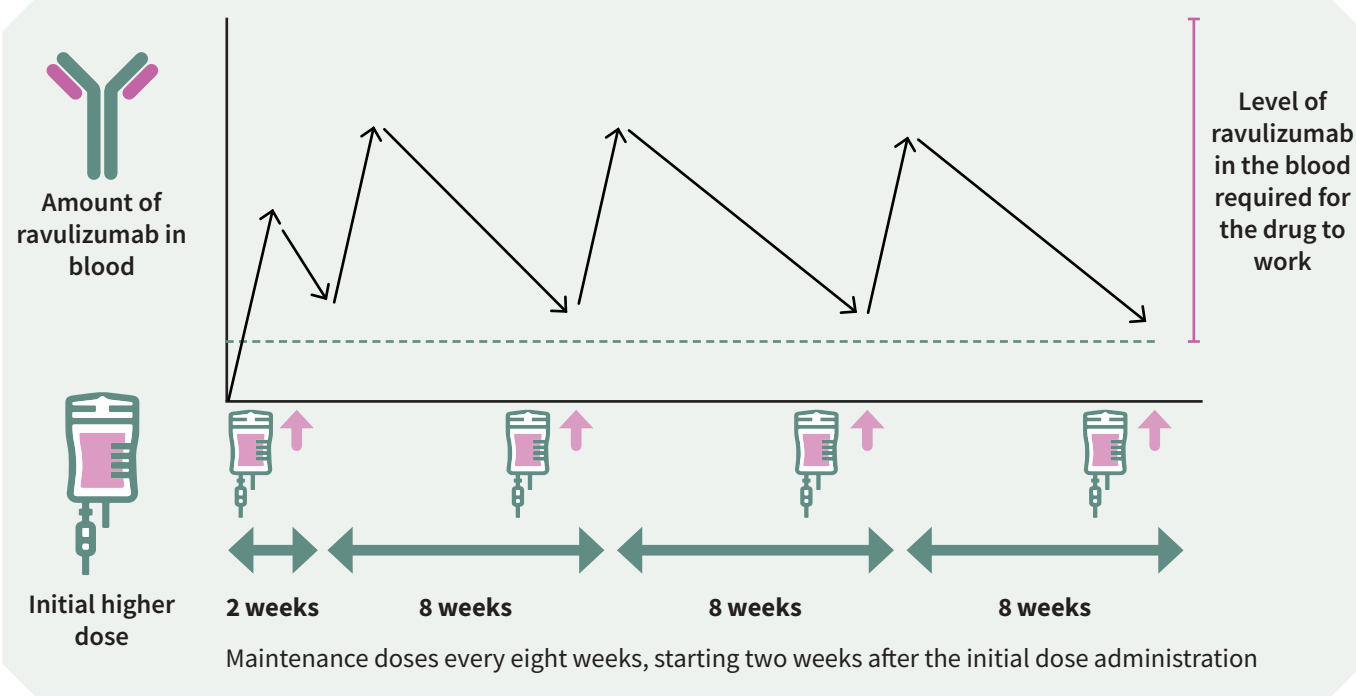
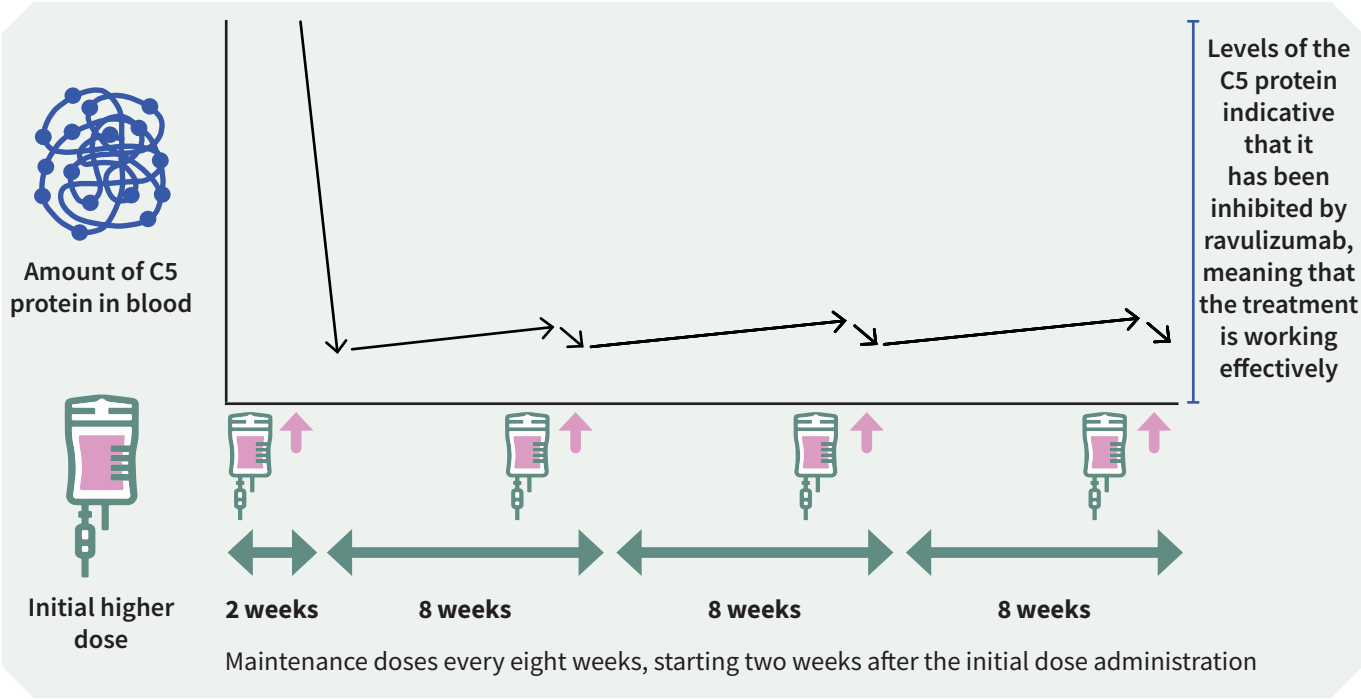
- The researchers found that when the first dose of ravulizumab was given, the required level of the drug in the bloodstream was reached within 30 minutes after finishing the infusion.
- This required level of ravulizumab in the blood was then consistently maintained by dosing every 8 weeks throughout the entire 26-week treatment period.



- The researchers also looked at peoples' levels of C5 protein, the target of ravulizumab. They found that the C5 protein was immediately and completely inhibited after the first infusion of ravulizumab. This inhibition was sustained throughout the 26-week treatment period.



What do the results of this study mean?

- The results of the CHAMPION MG study and extension study showed that ravulizumab, administered every 8 weeks, is a potential treatment option for adults with MG and AChR autoantibodies.
- The results of the ongoing CHAMPION MG extension study show that people receiving ravulizumab can maintain improvements in their symptoms for up to 60 weeks of treatment. In addition, people who switched from placebo to ravulizumab experienced rapid and sustained improvements similar to those seen in people who received ravulizumab from the start of the study.
- Ravulizumab is well-tolerated in the long term.

Where can readers find more information on these studies?

This summary is based on three published articles and readers can find more information about these publications below.

CHAMPION MG study

- The original article is called: Terminal complement inhibitor ravulizumab in generalized myasthenia gravis.
- The full citation of this article is: Vu T, Meisel A, Mantegazza R, Annane D, Katsuno M, Aguzzi R *et al.* Terminal Complement Inhibitor Ravulizumab in Generalized Myasthenia Gravis. *NEJM Evid.* 1(5): 2100066 (2022).
- You can read the article for free at: https://evidence.nejm.org/doi/full/10.1056/EVIDoa2100066

CHAMPION MG extension study

- The original article is called: Long-term efficacy and safety of ravulizumab in adults with anti-acetylcholine receptor antibody-positive generalized myasthenia gravis: results from the phase 3 CHAMPION MG open-label extension.
- The full citation of this article is: Meisel A, Annane D, Vu T, Mantegazza R, Katsuno M, Aguzzi R, *et al.* Long-term efficacy and safety of ravulizumab in adults with anti-acetylcholine receptor antibody-positive generalized myasthenia gravis: results from the phase 3 CHAMPION MG open-label extension. *J. Neurol.* 270(8):3862–3875 (2023).
- You can read the article for free at: https://link.springer.com/article/10.1007/s00415-023-11699-x

Study into how the body processes and responds to ravulizumab (known as pharmacokinetics and pharmacodynamics)

- The original article is called: Ravulizumab pharmacokinetics and pharmacodynamics in patients with generalized myasthenia gravis.
- The full citation of this article is: Vu T, Ortiz S, Katsuno M, Annane D, Mantegazza R, Beasley KN, *et al.* LRavulizumab pharmacokinetics and pharmacodynamics in patients with generalized myasthenia gravis. *J. Neurol.* 270(6):3129–3137 (2023).
- You can read the article for free at: https://link.springer.com/article/10.1007/s00415-023-11617-1

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Where can readers find more information about aHUS?

For more information about aHUS, readers can check the following websites:

- https://myasthenia.org/
- https://www.ninds.nih.gov/Disorders/All-Disorders/Myasthenia-Gravis-Information-Page
- https://medlineplus.gov/myastheniagravis.html
- https://www.mayoclinic.org/diseases-conditions/myasthenia-gravis/symptoms-causes/syc-20352036
- https://my.clevelandclinic.org/health/diseases/17252-myasthenia-gravis-mg

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Competing interests disclosure

The authors have no competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Writing disclosure

Dr Pablo Rivas helped the authors write this PLSP on behalf of Content Ed Net.