Plain Language Summary of Publication

Long-term effectiveness and safety of ravulizumab in paroxysmal nocturnal hemoglobinuria: a plain language summary

Celso Arrais[1], Natalia Carnelutto[2] and Jheremy Reyes[3]
[1]Universidade Federal de São Paulo, São Paulo, Brazil. Hospital Nove de Julho, Rede DASA, São Paulo, Brazil; [2]Hematology Department, Hospital de Clinicas José de San Martín, Buenos Aires, Argentina; [3]Hematology Department, Los Cobos Medical Center, Bogota, Colombia

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Summary

What is this summary about?
Paroxysmal nocturnal hemoglobinuria (PNH) is a rare disease where red blood cells break apart because they lack certain protective proteins. This makes them easy targets for the immune system, which can also affect other blood cells. PNH can lead to blood clots and serious organ damage.

Ravulizumab and eculizumab block C5, part of the immune system that destroys blood cells in PNH. Ravulizumab is given every 8 weeks, reducing treatment burden compared to eculizumab's 2-week schedule.

Ravulizumab was studied in two 26-week trials (301 and 302) for PNH. One compared it to eculizumab in participants new to treatment, and the other looked at switching from eculizumab. Both medicines were equally effective and well-tolerated.

This summary covers the extension period – an extra phase after the main study – of studies 301 and 302, to see if ravulizumab stayed safe and effective over up to 2 years. Participants on ravulizumab continued treatment, while those on eculizumab switched to ravulizumab. It also includes an additional analysis from studies 301 and 302 on breakthrough intravascular hemolysis (BTH), where red blood cells can break apart during treatment due to insufficient medication or health issues such as infections.

What were the results?
A total of 434 people continued taking ravulizumab during the extension period. For up to 2 years, 90–95% of participants maintained a low level of LDH, a blood marker of red blood cell breakdown, indicating that PNH was under control. Most participants did not need blood transfusions. The improvement in participants' quality of life lasted over the 2 years. Ravulizumab was well tolerated.

In studies 301 and 302, ravulizumab had a lower risk of BTH compared to eculizumab.

What do the results of the studies mean?
This study shows that ravulizumab remains safe and effective for long-term PNH treatment.

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

Aplastic anemia: ay-PLAS-tik uh-NEE-mee-uh
Allogenic: al-uh-JEN-ik
Dysphagia: dis-FAY-jee-uh
Eculizumab: ek-yoo-LIH-zoo-mab
Hemoglobin: HEE-muh-gloh-bin
Hemorrhage: HEM-uh-rij
Intravascular hemolysis: In-truh-VAS-kyoo-lur hee-MOL-uh-sis
Lactate dehydrogenase: LAK-tayt dee-HY-druh-juh-nays
Monoclonal antibody: MAH-noh-KLOH-nul AN-tee-BAH-dee
Meningococcal infections: meh-NIN-goh-KAH-kul in-FEK-shunz
Paroxysmal nocturnal hemoglobinuria: PAYR-ok-SIZ-mul nok-TER-nul HEE-moh-GLOH-bih-NOO-ree-uh
***PIGA* gene:** PY-guh jeen
Platelets: PLAYT-lets
Ravulizumab: RAV-yoo-LIZ-yoo-mab
Thrombosis: throm-BOH-sis

Becaris PUBLISHING

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

The original article discussing the extension period of 301 and 302 studies was published in *European Journal of Haematology* and is called "Long-term safety and efficacy of ravulizumab in patients with paroxysmal nocturnal hemoglobinuria: 2-year results from two pivotal phase 3 studies". You may access and read the article for free at this link: https://onlinelibrary.wiley.com/doi/10.1111/ejh.13783

The additional analysis from studies 301 and 302 on unforeseen events of the destruction of red blood cells despite ongoing treatment (breakthrough intravascular hemolysis) was published in the journal *Haematologica*. The article is called "Characterization of breakthrough hemolysis events observed in the phase 3 randomized studies of ravulizumab versus eculizumab in adults with paroxysmal nocturnal hemoglobinuria" and you can read the article for free at this link: https://haematologica.org/article/view/9614

Who is this article for?

This article may be helpful for:

- People who have **paroxysmal nocturnal hemoglobinuria** (also called PNH) or who know someone with this disease.
- Patient associations or other organizations helping people with PNH.
- Healthcare providers (mainly physicians and nurses) who treat people with PNH.
- Healthcare **policymakers** involved in developing or updating PNH management guidelines or recommendations, including organizations such as medical societies, healthcare institutions, and relevant governmental or policy bodies.

Paroxysmal nocturnal hemoglobinuria (PNH): A rare blood disease where blood cells break easily because they lack a protective protein.

Policymakers: People or groups who make important decisions, rules, or laws for organizations, communities, or governments. In health care, they help decide how health services are provided and funded.

What is PNH?

- PNH is a rare, acquired disorder, meaning it is not inherited but develops during a person's lifetime. It is unrelated to lifestyle factors such as smoking, diet, or exercise. Anyone can develop PNH, regardless of how healthy or unhealthy their habits are.
- This condition affects all types of blood cells, including **red blood cells**, **white blood cells**, and **platelets**.
- The condition originates in the bone marrow, the spongy tissue within bones responsible for producing blood cells.

Red blood cells: Blood cells that carry oxygen throughout the body.

White blood cells: Blood cells that help fight infections.

Platelets: Small blood cells that help form clots to stop bleeding

What does the term 'paroxysmal nocturnal hemoglobinuria' mean?

The term "paroxysmal nocturnal hemoglobinuria" is derived from three words:

P	N	H
Paroxysmal	**Nocturnal**	**Hemoglobinuria**
which means 'sudden and irregular'	which means 'at night'	which means 'hemoglobin in urine'. Hemoglobinuria makes urine (wee) look dark.

Therefore, 'paroxysmal nocturnal hemoglobinuria' refers to sudden, irregular episodes of passing dark-coloured urine, especially at night or in the early morning, and is how the disease is usually noticed initially.

However, this term was described a long time ago, and now it should be noted that:

1. The condition is not strictly paroxysmal; it is characterized by **chronic hemolysis** (long-term hemolysis) punctuated by **acute** (sudden) worsening.
2. The condition is not solely nocturnal as patients may experience intermittent hemolysis episodes at any time of the day.

The condition does not always involve hemoglobinuria; approximately 55% of patients do not present with hemoglobinuria.

Who gets PNH?

- PNH more commonly diagnosed in young adults, but the reason for this is not known.
- It affects men and women equally.
- In people with PNH, a mutation (alteration) has occurred in a **gene** called ***PIGA***, which is essential for attaching a protective shield to the surface of blood cells.
  - This shield helps defend blood cells from attacks by the body's **immune system**, particularly from the **complement system**, a group of **proteins** that target germs and damaged cells.

Chronic: A health problem or symptom that lasts a long time, often for months or years. Chronic conditions usually develop slowly and can last for the rest of a person's life. This is the opposite of "acute".

Hemolysis: The process of red blood cells breaking apart.

Acute: A health problem or symptom that starts quickly and lasts a short time. It often comes on suddenly and can be severe, but it does not last long.

Gene: Contains DNA, which is the "instruction manual" for living organisms to develop, survive and reproduce. Genes are passed down from biological parents to their children (i.e., they are hereditary).

***PIGA* gene:** A gene that, when mutated (altered), causes PNH by preventing the formation of a protective shield on blood cells.

Immune system: The body's natural defense system. It produces antibodies, which are a type of protein that help the body to fight against infections and germs.

Complement system: A group of proteins in the immune system that helps fight infections but can harm blood cells in PNH. In healthy people, the complement system does not damage blood cells because special surface proteins protect them. In PNH, blood cells lack this protection, so the complement system can attack and destroy them.

Proteins: A substance found in every cell of the body that is made up of building blocks called amino acids. Proteins help build, repair, and maintain the body's tissues, like muscles, skin, and organs. They also play important roles in carrying oxygen, fighting infections, and making sure the body works properly.

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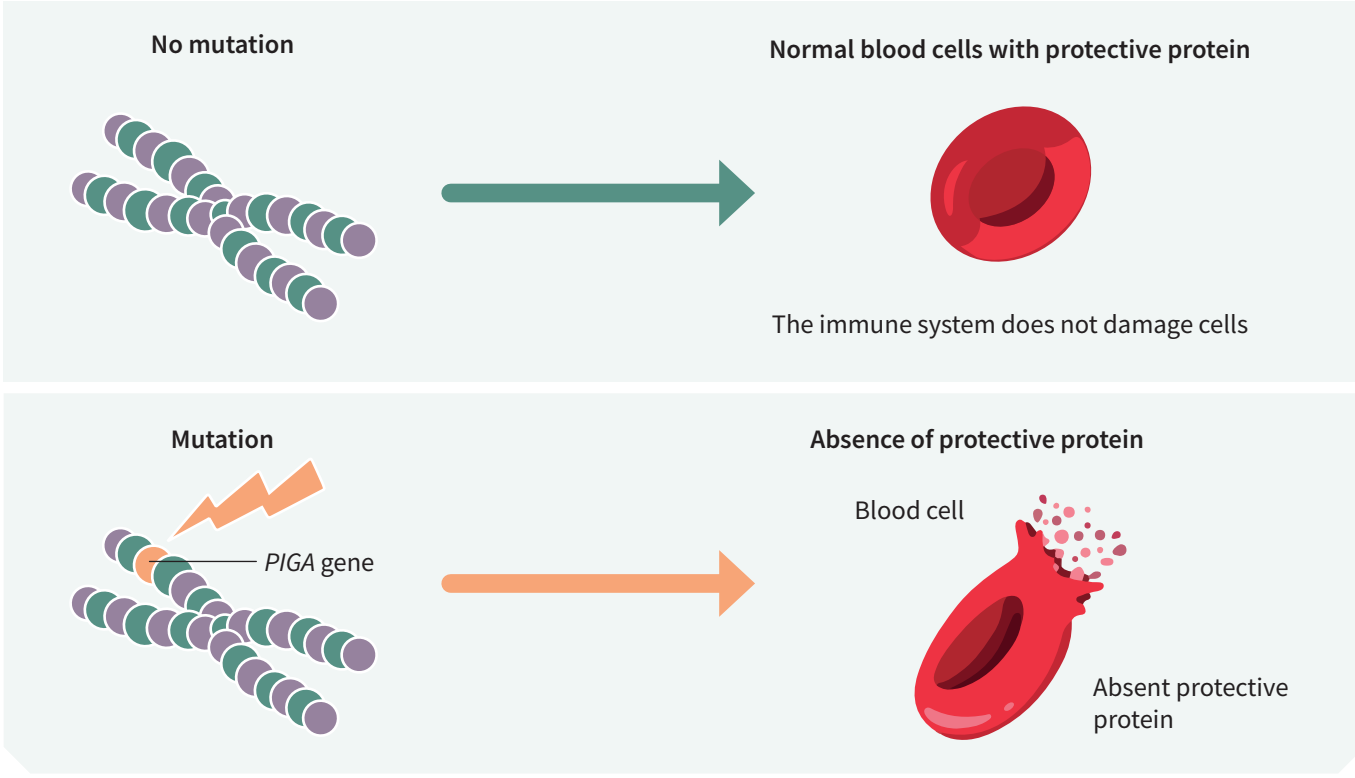
How a change in the *PIGA* gene causes PNH



- When the *PIGA* gene is mutated, blood cells lose the protective proteins that normally shield them from the complement system. Without this protection, the complement system mistakenly recognizes these cells as damaged or abnormal and attacks and destroys otherwise healthy blood cells, leading to many of the symptoms seen in PNH:
  - Red blood cells: Without their protective shield, they are quickly destroyed by the complement system in the bloodstream, a process called **intravascular hemolysis**. This leads to an environment prone to blood clotting, and **anemia**, which can cause symptoms like fatigue (extreme tiredness or lack of energy), weakness, and pale skin.
  - Platelets: Without their shield, platelets are more likely to clot. This can lead to an increased risk of blood clots (**thrombosis**) and, in some cases, dysfunction or excessive use of platelets, which may cause bleeding episodes. Additionally, defective platelets and vessel blockages send signals to the immune system, triggering inflammation that may affect other organs, such as the kidneys or lungs, and worsen symptoms like fatigue.
  - White blood cells: The lack of a protective shield can disrupt their function, although the impact on white blood cells is less visible than on red blood cells. This is because, unlike red blood cells, changes in white blood cells don't typically result in obvious symptoms detectable in blood tests or by patients. However, these changes may result in chronic inflammation and a reduced ability to fight infections. Additionally, the activation of both white blood cells and platelets by the complement system contributes to an increased risk of blood clots.

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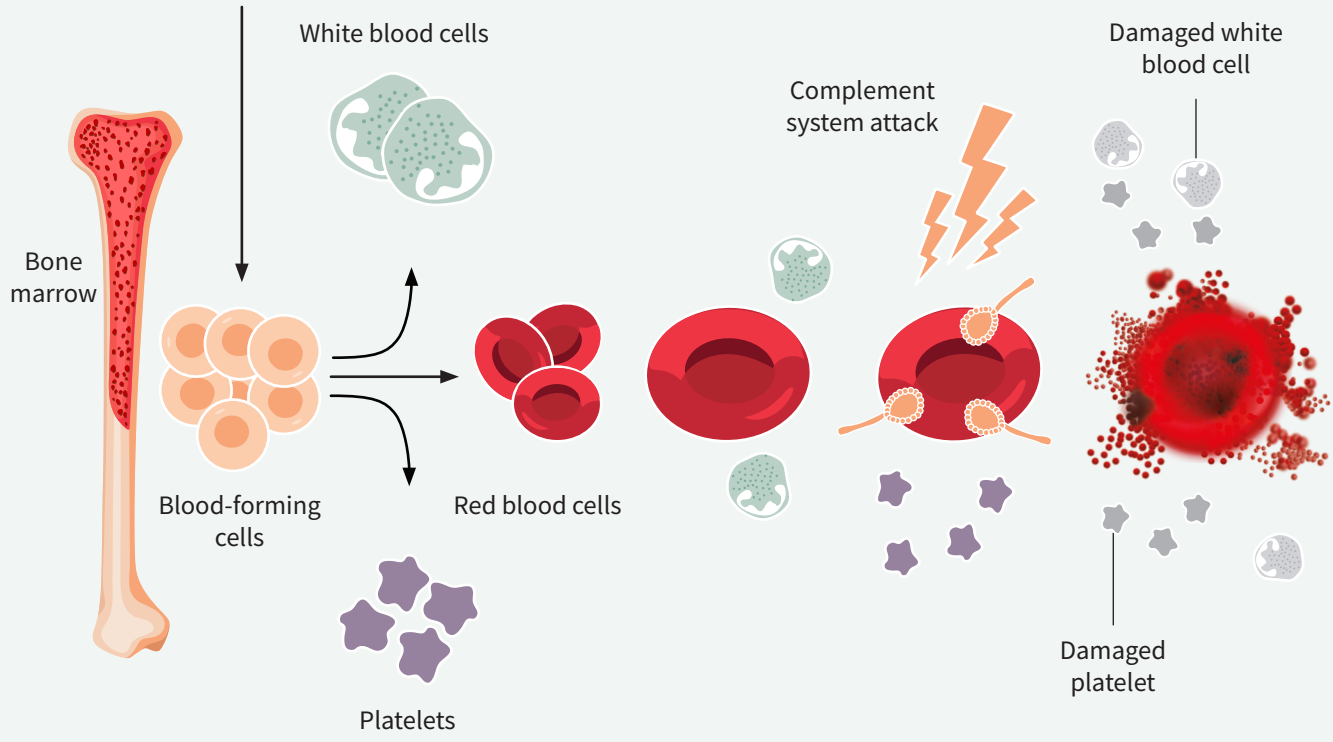
Intravascular hemolysis (IVH): The destruction of red blood cells within blood vessels. Red blood cells can also be destroyed in other places, such as the spleen or liver, but in IVH, this happens within the blood vessels.

Anemia: A condition where there aren't enough healthy red blood cells in the body. This can make you feel tired, weak, short of breath, or look pale, because your body isn't getting enough oxygen.

Thrombosis: Formation of blood clots that can block blood vessels.

How PNH damages blood cells



- The problem that causes PNH originates in the bone marrow, the spongy tissue inside long bones.
- The bone marrow functions as the body's blood cell factory.

- In PNH, a gene called *PIGA* mutates in one of the bone marrow stem cells (blood-forming cells).
- This results in the production of abnormal red and white blood cells and platelets.

- Healthy blood cells are protected by a protein shield that defends against attacks from the complement system.
- The *PIGA* gene is responsible for attaching a protective shield to blood cells.
- When the *PIGA* gene is mutated, blood cells lack this protective shield.

- The destruction of red blood cells, as well as the damage to white blood cells and platelets, contributes to most of the symptoms of PNH.
- This includes anemia, increased risk of blood clots, and reduced ability to fight infections.

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What are the symptoms of PNH?

- PNH is primarily caused by the destruction of red blood cells (IVH). This ongoing process leads to a shortage of red blood cells in the blood (anemia), which can cause:

Fatigue

Weakness

Pale skin (pallor)

Shortness of breath (dyspnea)

Increased heart rate (tachycardia)

- Certain triggers, such as pregnancy, stress, infections, or surgery, can worsen symptoms, leading to sudden episodes of intensified hemolysis.
- A key symptom is dark-colored urine due to hemoglobin (hemoglobinuria). Hemoglobin is a protein released when red blood cells are destroyed. Hemoglobinuria is often most noticeable early in the morning when urine has become concentrated overnight.

- The breakdown of red blood cells can cause problems with the muscles that work automatically in the body (smooth muscles), such as those in the stomach and blood vessels. This can lead to symptoms like:

Stomach pain

Trouble swallowing (dysphagia)

Problems with erections (erectile dysfunction)

- Abnormal platelets and white blood cells in PNH can lead to complications, such as:

Blood clots (thrombosis), particularly in large veins in the abdomen (the body region between the chest and the pelvis)

Severe bleeding episodes (hemorrhage)

- In some cases, PNH is associated with bone marrow disorders, such as aplastic anemia, where the bone marrow does not produce enough healthy blood cells.
- Infections may occur due to a shortage of white blood cells but may also be linked to bone marrow disorders.

What medications or treatments are commonly used to treat PNH?

- In the past, treatment for PNH was mainly focused on treating symptoms rather than the underlying cause. Patients received **blood transfusions**, steroids (medications that reduce inflammation), anabolics (drugs that help build muscle), and iron supplements to manage recurring hemolysis and anemia.
- They would also receive medication to prevent blood clots from forming, such as blood thinners and drugs that prevent platelets from sticking together.
- In cases of bone marrow complications – meaning when the bone marrow was not able to make enough healthy blood cells – patients were offered a procedure called an **allogeneic bone marrow transplant**. In this procedure, healthy **stem cells** (blood-forming cells) from a matched donor are given to the patient. These new cells travel to the patient's bone marrow, where they start making new blood cells and help restore normal blood production.
- **Eculizumab**, released in 2007, changed the treatment and morbimortality (the rates of illness and death) of PNH patients. **Ravulizumab**, **FDA approved** in 2018, is a second-generation treatment option. This means it is a newer and improved version of eculizumab.

Blood transfusions: A medical procedure where a person receives blood through a vein. This is done to replace blood that has been lost or to treat certain health problems. The blood comes from a donor or a blood bank.

Allogeneic bone marrow transplant: A procedure where a person gets healthy blood-forming stem cells from a donor, usually a family member or someone with a similar tissue type. These new cells are given through a vein and travel to the bone marrow – the soft, spongy tissue inside bones that makes all the blood cells your body needs.

Stem cells: Special cells in the body that can make copies of themselves and turn into many different types of cells. These cells help the body repair itself and make new blood cells, tissues, and organs.

Eculizumab: A medication used to treat PNH.

Ravulizumab: An improved version of eculizumab that is given less frequently.

Food and Drug Administration: A United States government agency that protects and promotes public health by ensuring food, medicines, vaccines, and other health products are safe and work as they should. The agency is often referred to by its acronym, FDA.

FDA approved: The process by which the FDA reviews scientific data from studies to decide if a new medicine is safe and effective for its intended use. Approval means the drug's benefits outweigh its risks, and the medicine can be sold and used as described in its official labeling.

Treatments commonly used for PNH in the past

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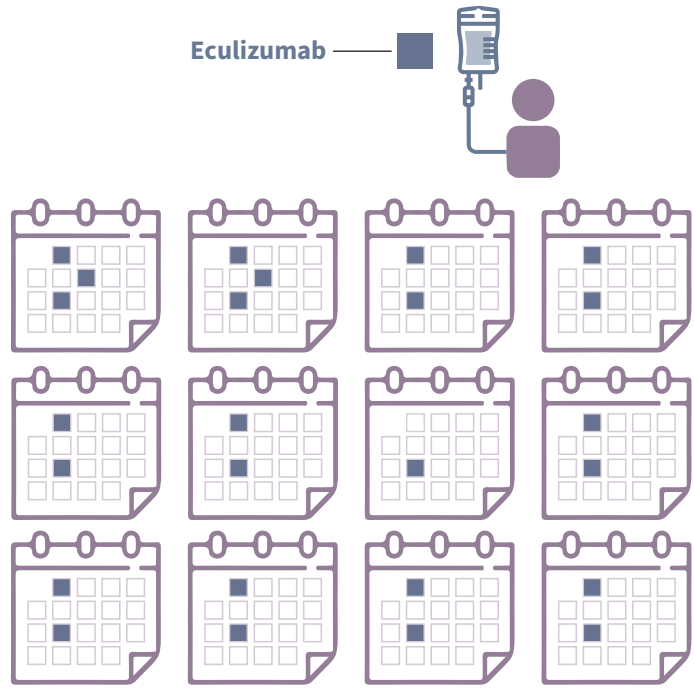
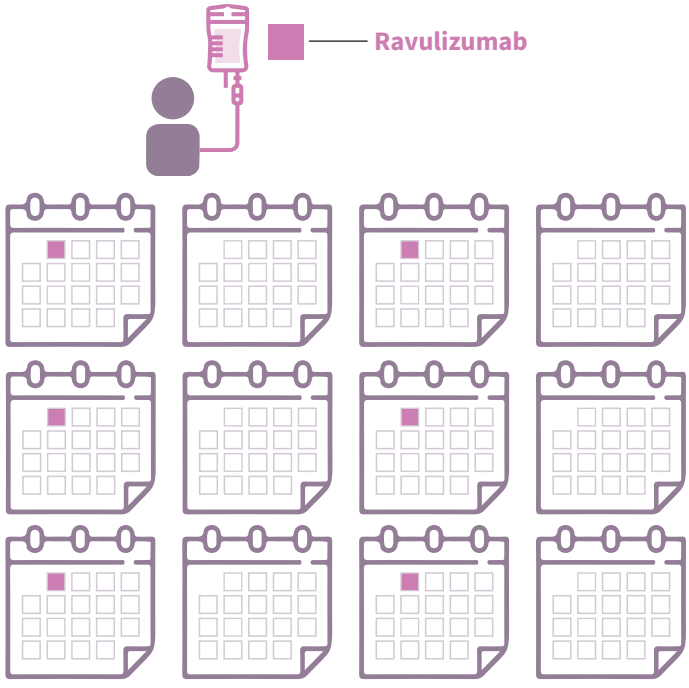
What are eculizumab and ravulizumab, and how do they work?

- Eculizumab is a treatment that can reduce the need for transfusions by over 50% and lower the risk of blood clots by nearly 70–85% in people with PNH.
- However, some people experience breakthrough intravascular hemolysis even when taking the approved eculizumab doses. This happens because the medication does not fully stop the body's immune system from attacking its blood cells. Sometimes this happens because there is insufficient medication at certain times, and sometimes it occurs due to other health problems, like infections.
- In addition, eculizumab has a short half-life (the time required for the quantity of medication in the body to be reduced to half its original amount), which means it needs to be taken frequently (every 2 weeks). Frequent dosing with eculizumab can negatively affect patients' quality of life by requiring regular clinic visits, disrupting daily routines, and adding logistical and emotional burdens for both patients and caregivers.

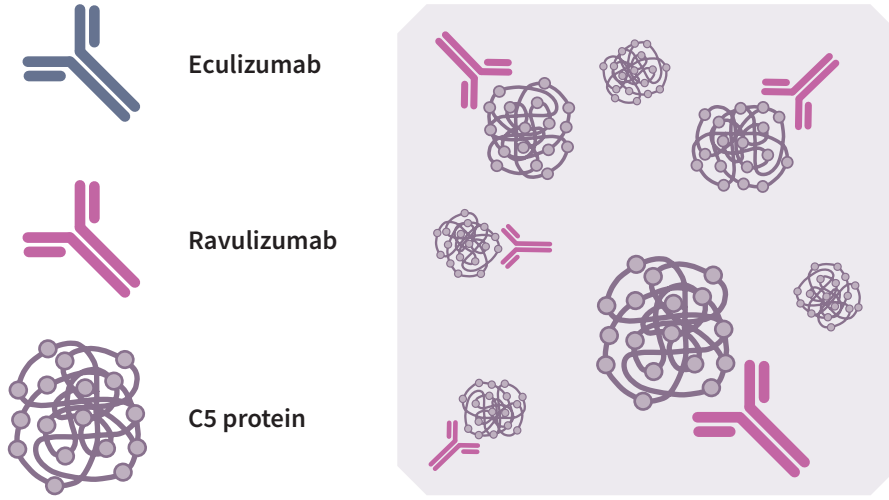




- In an attempt to overcome those limitations, a new drug, ravulizumab, was developed.
- Ravulizumab works differently from eculizumab because its molecular design allows it to remain in the bloodstream for a longer period, maintaining effective C5 inhibition with fewer infusions. This extended duration means that ravulizumab can provide continuous protection against hemolysis and only needs to be administered every 8 weeks, reducing the treatment burden compared to eculizumab, which requires dosing every 2 weeks.

Eculizumab and ravulizumab are monoclonal antibodies, a type of protein that is made in the laboratory and can stick on to certain targets in the body that cause diseases.

The **C5** protein is the target of eculizumab and ravulizumab. It is a protein from the complement system. By stopping this protein, the complement system cannot damage the red blood cells.



- Both eculizumab and ravulizumab are given through a vein (intravenous infusion), usually in an outpatient clinic:
  - Eculizumab infusions typically last 25 to 45 minutes (sometimes up to 2 hours if needed), with a volume of about 180 ml for the standard adult dose.
  - Ravulizumab infusions usually last about 1 to 2 hours (depending on the dose and body weight), with a volume between 120 and 360 ml.
- After the infusion, patients can usually go home the same day. However, the maintenance doses of these drugs differ:
  - Eculizumab needs to be given intravenously once every 2 weeks, which can be challenging for both patients and caregivers. This is because regular infusions require frequent trips to the clinic, can interfere with work or school, may involve travel costs, and can be uncomfortable or time-consuming for people and their families.
  - Ravulizumab is also given intravenously. It is derived from eculizumab and offers significant clinical advantages beyond its extended dosing schedule (every 8 weeks vs. every 2 weeks). It provides immediate, complete, and sustained complement inhibition, which:
    - Reduces **breakthrough intravascular hemolysis** events.
    - Lowers blood transfusion needs.
    - Improves patients' quality of life.

C5: A protein in the complement system (see below) that plays a crucial role in the body's immune defense by helping to fight infections. In PNH, C5 is also involved in the destruction of red blood cells. Eculizumab and ravulizumab work by blocking C5

Breakthrough intravascular hemolysis: When red blood cells suddenly break down due to insufficient medication or other stressors such as infections, fever, surgery, or physical or emotional stress. These stressors can trigger a return of PNH symptoms.

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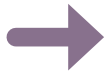
Why were studies 301 and 302 conducted?

- Studies 301 and 302 were large international studies that compared ravulizumab and eculizumab in people with PNH.
  - Study 301 included participants who had never received a **complement inhibitor** before. They received either ravulizumab (every 8 weeks) or eculizumab (every 2 weeks) for 26 weeks.
  - Study 302 included patients already stable on eculizumab, who either continued with eculizumab or switched to ravulizumab.
- Studies 301 and 302 showed that ravulizumab caused fewer episodes of breakthrough intravascular hemolysis. These studies also demonstrated the added benefit of immediate, complete, and long-lasting C5 inhibition and a longer dosing interval, reducing the treatment burden for patients.
- After 26 weeks, all patients could continue with ravulizumab to assess long-term results
- The studies we summarize here (301 and 302 extension studies) were done to describe the results of the 301 and 302 studies over a longer period, from week 27 to up to 2 years of follow-up. During this phase of the studies, patients receiving ravulizumab continued their treatment, while those receiving eculizumab switched to ravulizumab. This longer-term analysis, called the extension period, was planned from the beginning to determine if the benefits and safety of ravulizumab continued over time. It is common to include an extension period in clinical studies to provide more information about the effects of long-term treatment.
- Both studies 301 and 302 were conducted at multiple centers across America, Europe, and Asia. Study 301 included participants from 25 countries, while study 302 enrolled participants from 11 countries, ensuring a broad and internationally representative sample of patients with PNH.
- In addition, the other investigation we summarize was done to analyze breakthrough intravascular hemolysis events in studies 301 and 302.

Complement inhibitor: A type of medicine used to treat PNH that blocks part of the immune system called the complement system. By stopping the complement system from attacking blood cells, complement inhibitors like eculizumab and ravulizumab help prevent the destruction of red blood cells and reduce symptoms and complications of PNH.

How were the 301 and 302 extension studies carried out?

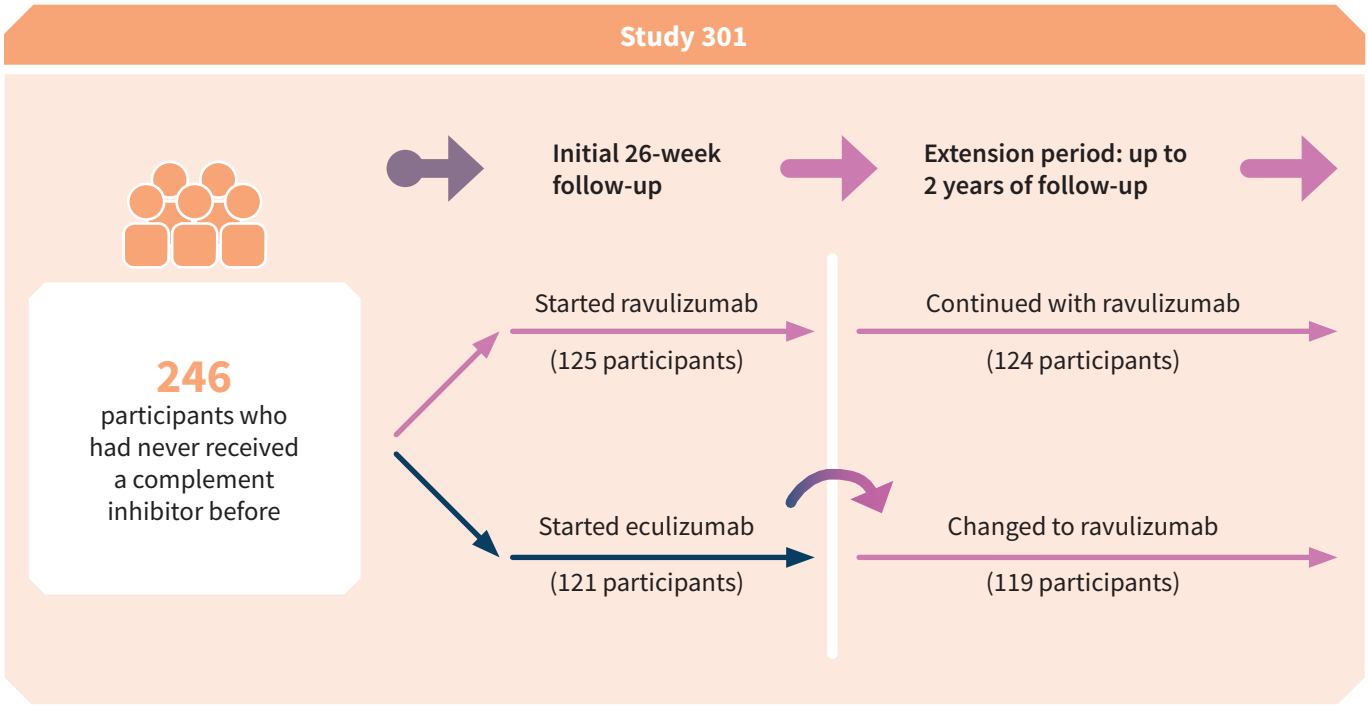
- In the 301 and 302 studies, ravulizumab proved to be just as effective as eculizumab after 26 weeks of treatment.
- Study 301 involved patients not previously treated with complement system inhibitors, while Study 302 involved patients whose PNH was already under control with eculizumab.

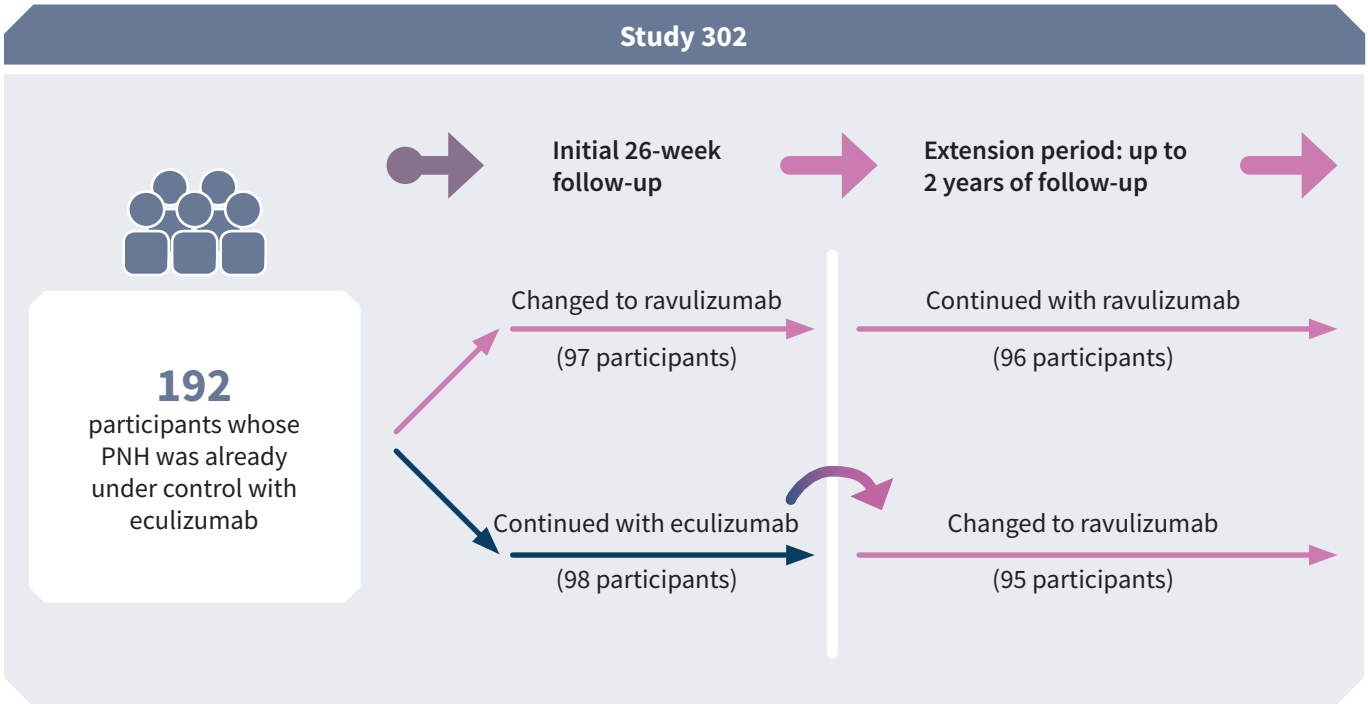


- The 301 and 302 **extension studies** aimed to report the results of both **trials** over a period of 27 weeks to 2 years, as patients either continued ravulizumab or switched from eculizumab to ravulizumab.

Extension study: An extension study is a component of a research study that occurs after the main study concludes. In an extension study, participants continue to receive the study treatment or are followed for a more extended period. This helps researchers gain a deeper understanding of the long-term effects and safety of the treatment.

Clinical trial: A research study that tests how well a new medical treatment works in people, in an environment that is as controlled as possible to try to isolate the effects of the treatment.





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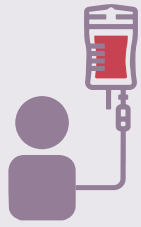
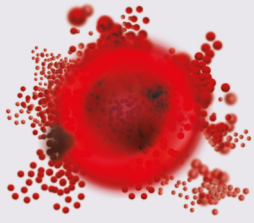
What were the characteristics of the participants included?

	Study 301 (participants who had never received complement inhibitors)	Study 302 (participants undergoing treatment with eculizumab)
Number of participants	246	195
Females	45.5%	50%
Age at PNH diagnosis	Around 39 years	Around 35 years
Age at the beginning of the study	Around 45 years	Around 48 years
Time on eculizumab at the beginning of the study	None received eculizumab	Around 6 years
Race		
Asian	52%	21.5%
Japanese	14%	6%
White	38%	57%
Black or African–American	2%	4%
American Indian or Alaska Native	1%	–
Other	3%	2%
Not reported	3%	15%
Blood transfusions received within 1 year prior to study entry		
0 transfusions	18%	Not reported
1 to 14 transfusions	64%	Not reported
More than 14 transfusions	18%	Not reported

What did studies 301 and 302 look at?

In the 301 and 302 studies, researchers were mainly looking for:

	What we're examining	Why we're examining it
	The proportion of participants who reached lactate dehydrogenase (LDH) levels at or below 1.5 times the upper limit of normal (ULN), and the percentage change in LDH levels. (LDH or lactate dehydrogenase is a protein found in red blood cells).	Normal LDH and stable hemoglobin levels in the blood indicate minimal hemolysis or breakdown of red blood cells. Hemoglobin stabilization was defined as avoiding a decrease of 2 grams per deciliter (g/dl) in the hemoglobin level from the baseline without the need for a transfusion during that time. A deciliter (dl) is a unit of volume equal to one-tenth (0.1) of a liter.
	**Stabilization of hemoglobin levels in the blood** (hemoglobin is a protein found in red blood cells that is responsible for carrying oxygen from the lungs to the rest of the body).	
	**Proportion of participants who avoid blood transfusion** (a medical procedure involving the transfer of blood from one person to another).	A low number of transfusions means that the treatment is working well and there is minimal breakdown of red blood cells.
	**Proportion of patients with breakthrough intravascular hemolysis** (an unexpected destruction of red blood cells despite ongoing treatment).	Allow number of breakthrough intravascular hemolysis events means that the treatment is working.
	**Participants quality of life**	Using questionnaires, we examined how living with PNH affects participants' daily lives and well-being in order to better understand the impact of the disease.

Side effect: Unwanted effects of a medication.
Lactate dehydrogenase (LDH): An **enzyme** that increases in the blood when red blood cells break down.
Enzyme: A protein that can speed up chemical reactions within the body.

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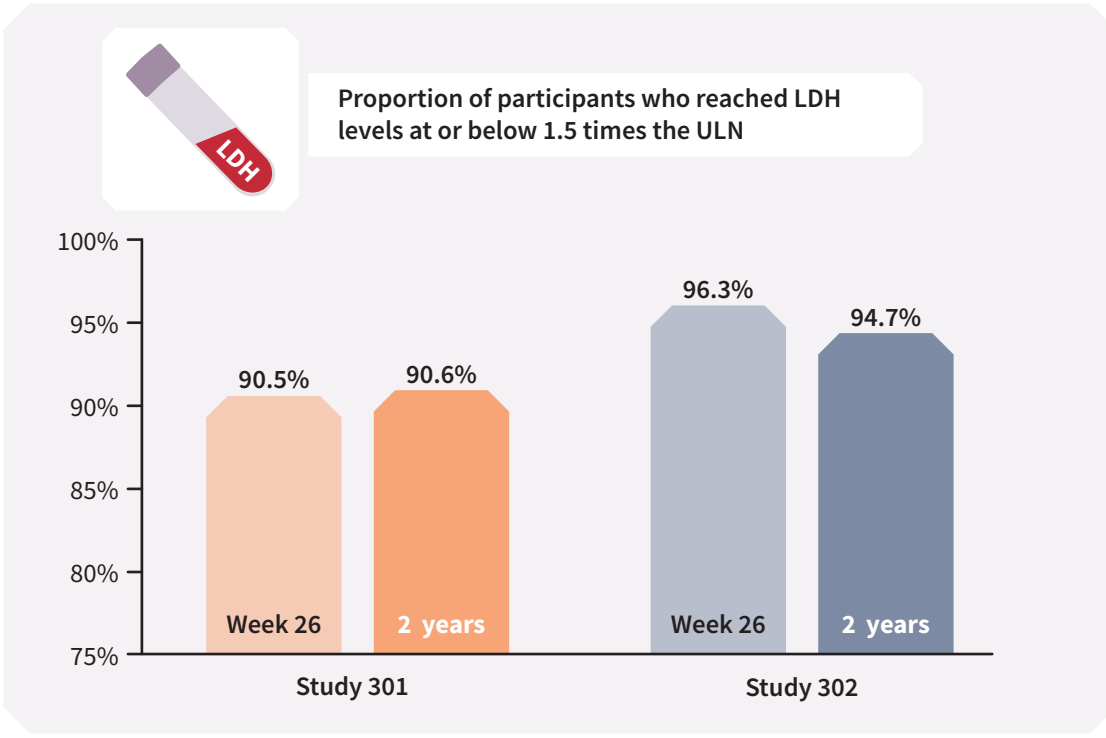
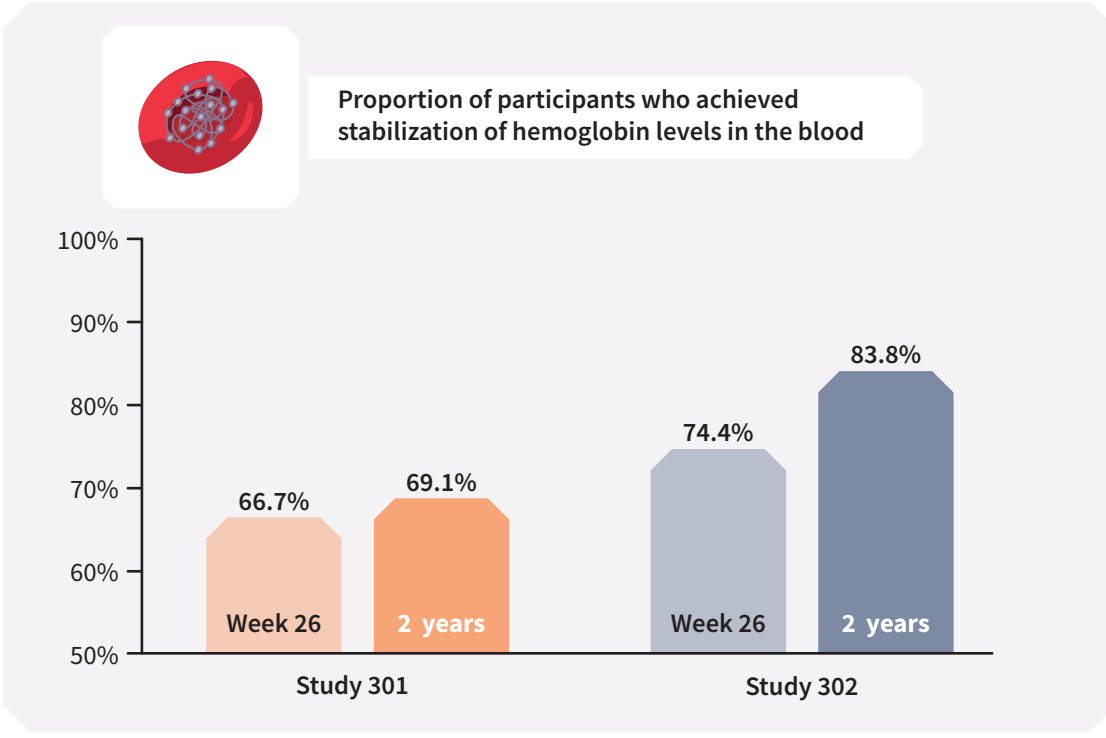
What were the main results relating to effectiveness?





Participants quality of life

We measured quality of life using two simple questionnaires

- One focused on how tired people felt and how this affected their daily lives. The higher the score, the less tired people felt.
- The other questionnaire asked about general health, ability to do everyday activities, and symptoms like fatigue. Higher scores for health and physical ability meant people were feeling well and active, while lower scores for symptoms meant fewer problems.

The quality-of-life improvement reported in studies 301 and 302 at week 26 was sustained throughout the 2-year extension period

- At 2 years, the average tiredness score was about 42 out of 52, showing low levels of fatigue.
- The average overall health score was around 71 out of 100, meaning most people felt well and satisfied with their health.
- Physical ability scores were high, about 87 out of 100, so people could do their usual daily activities and stay independent.
- Fatigue scores stayed low (about 21–28 out of 100), so tiredness did not stop people from enjoying life.

This means that over 2 years, most people were able to look after themselves, spend time with family and friends, and keep up with their normal routines.

None of the PNH patients stopped taking ravulizumab during the extension period because it wasn't working for them.

What were the main side effects that occured?

The most common side effects that occurred during treatment with ravulizumab in the extension period were:

- Infections of the upper part of the respiratory (breathing) system: 15.6%
- Nasopharyngitis (inflammation of the nose passages and throat): 16.3%
  - Headache: 11.3%
  - Pyrexia/fever (increase in body temperature): 7.9%
  - Fatigue (extreme tiredness or lack of energy): 10.6%

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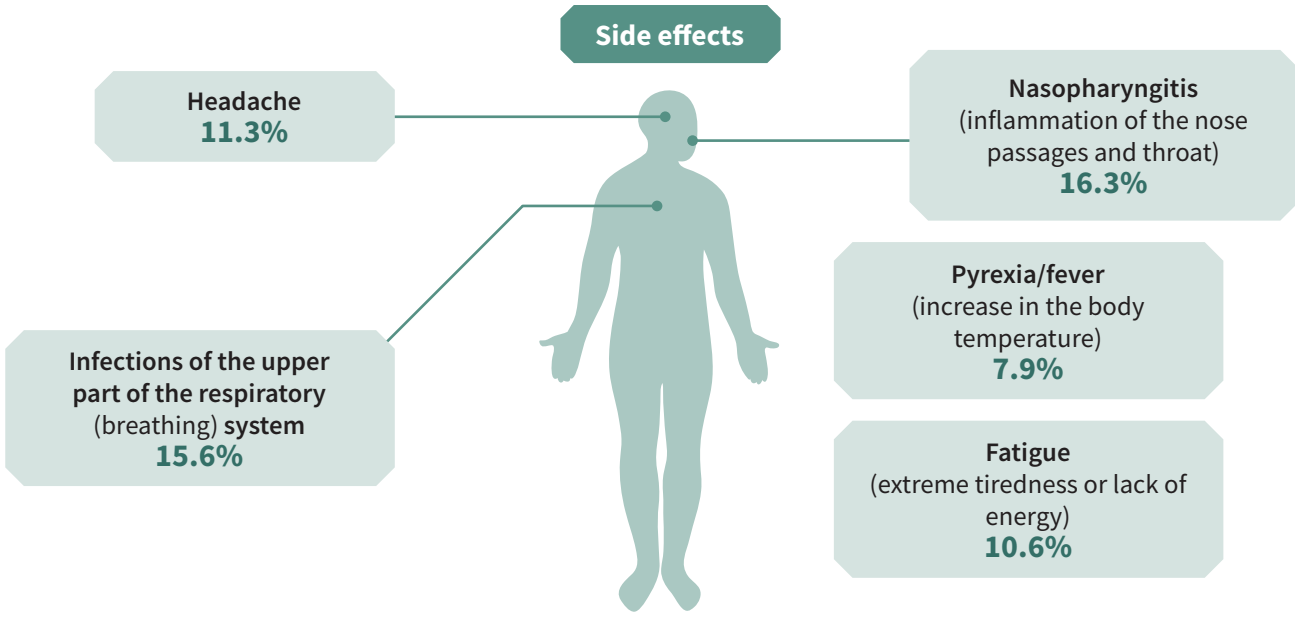

- The likelihood of serious side effects associated with ravulizumab treatment was low, at less than 3%.
- No cases of meningococcal infections were reported among individuals treated with ravulizumab. Meningococcal infections are rare but serious illnesses, like meningitis, that can affect the brain, spinal cord, and bloodstream.
- People taking medications like ravulizumab or eculizumab are at higher risk because these drugs weaken the immune system's ability to fight these bacteria. To reduce the risk, patients are enrolled in safety programs that include vaccination and close monitoring. Long-term studies have shown that these safety measures effectively prevent infections while allowing people to benefit from these treatments.

How were the breakthrough intravascular hemolysis events observed in the 301 and 302 studies of ravulizumab versus eculizumab?

- Breakthrough intravascular hemolysis occurs when, due to an unexpected event (such as missing a dose, an infection, or other stressors), the usual medication dose is insufficient to entirely block complement activation. This results in incomplete complement blockade for a short period, leading to the destruction of red blood cells and return of symptoms of PNH.
- This can cause symptoms like increased fatigue, shortness of breath, anemia, and complications such as blood clots.
- It is essential to avoid breakthrough intravascular hemolysis whenever possible, as it can lead to severe complications, including blood clots and, in some cases, death.
- Another publication analyzed in detail the breakthrough intravascular hemolysis events in studies 301 and 302 during the first 26 weeks of follow-up.
- In both studies, fewer patients experienced breakthrough intravascular hemolysis with ravulizumab compared to eculizumab:
  - Study 301: 4.0% vs 10.7%
  - Study 302: 0% vs 5.1%
- The results were not exactly the same in both studies because the groups of patients were different. Study 301 included patients who had never received complement inhibitor treatment before, while Study 302 included patients who were already stable on eculizumab.

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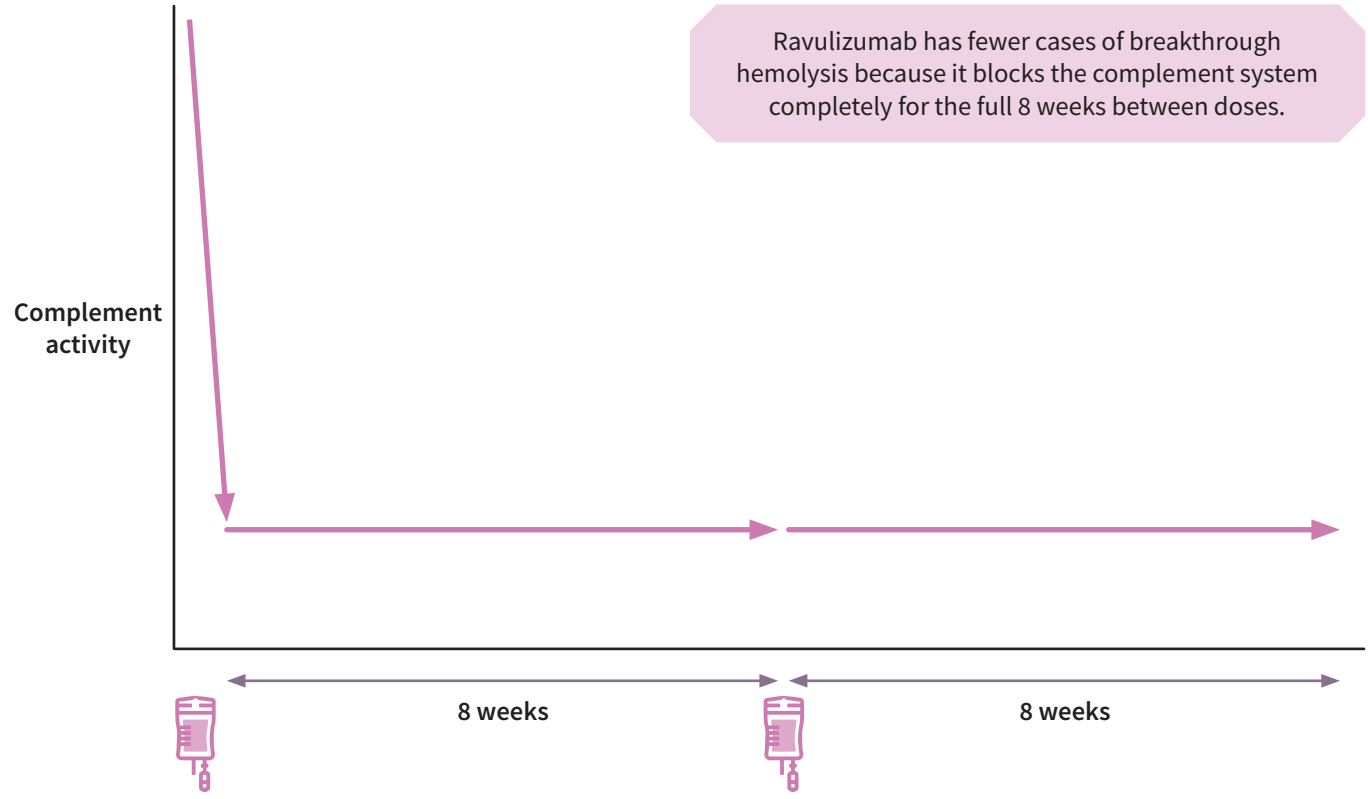
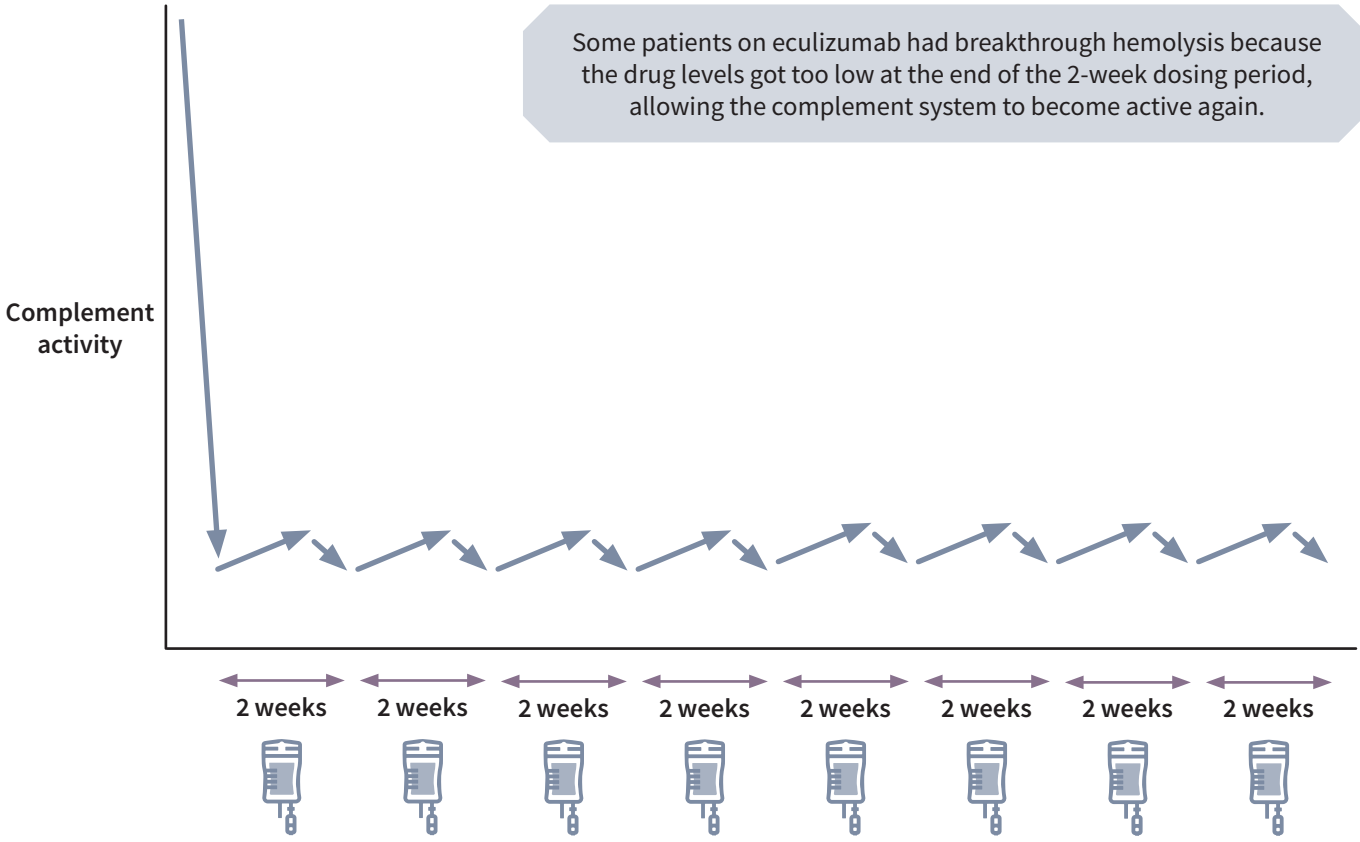
Complement blockade: Complement blockade means stopping part of the immune system called the complement system from working. In PNH, certain medicines block the complement system to protect blood cells from being destroyed by the body's own defenses





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How were the breakthrough intravascular hemolysis events observed in the 301 and 302 extension studies?

- In the extension period, 6.2% of the participants in study 301 and 5.8% in study 302 had breakthrough intravascular hemolysis events while they were on ravulizumab.
- Many cases of breakthrough intravascular hemolysis were connected to having an infection at the same time (e.g., the flu or upper respiratory infection). These infections can themselves be considered adverse events, since any medical issue that occurs while taking the medication is recorded as a possible side effect, regardless of its direct cause.

What do the results of these studies mean?

- These findings contribute to the evidence that complement inhibitors such as ravulizumab are effective and well tolerated in PNH patients.
- The results of this analysis suggest that ravulizumab quickly and completely stopped the complement system from working throughout the entire 26-week treatment period, lowering the overall risk of breakthrough intravascular hemolysis events.
- In any case, regardless of the results presented in these studies, treatment decisions should always be made jointly by patients and their healthcare providers, taking into account all available evidence and not relying solely on the results of a single study.

Where can readers find more information on these studies?

Readers can find more information in the original publication of the articles:

301 study

- Lee JW, *et al.* Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors: the 301 study. *Blood*. 133(6):530-539. doi:10.1182/blood-2018-09-876136 (2019).
  - https://ashpublications.org/blood/article/133/6/530/260550/Ravulizumab-ALXN1210-vs-eculizumab-in-adult

302 study

- Kulasekararaj AG, *et al*. Ravulizumab (ALXN1210) vs eculizumab in C5-inhibitor-experienced adult patients with PNH: the 302 study. *Blood*. 133(6):540-549. doi:10.1182/blood-2018-09-876805 (2019).
  - https://ashpublications.org/blood/article/133/6/540/260562/Ravulizumab-ALXN1210-vs-eculizumab-in-C5-inhibitor

Extension period of 301 and 302 studies

- Kulasekararaj AG, *et al*. Long-term safety and efficacy of ravulizumab in patients with paroxysmal nocturnal hemoglobinuria: 2-year results from two pivotal phase 3 studies. *Euro. J. Haematol.* 109(3):205-214. doi:10.1111/ejh.13783 (2022).
  - https://onlinelibrary.wiley.com/doi/10.1111/ejh.13783

Another article in simple language explaining the extension period of studies 301 and 302

- Kulasekararaj AG, *et al*. Ravulizumab is a suitable long-term treatment option for patients with paroxysmal nocturnal hemoglobinuria. *Future Rare Dis.* 3(2):FRD39. doi:10.2217/frd-2022-0024 (2023).
  - https://doi.org/10.2217/frd-2022-0024

Details on breakthrough hemolysis events

- Brodsky RA, *et al*. Characterization of breakthrough hemolysis events observed in the phase 3 randomized studies of ravulizumab versus eculizumab in adults with paroxysmal nocturnal hemoglobinuria. *Haematologica* 106(1):230-237. doi:10.3324/haematol.20 (2020).
  - https://haematologica.org/article/view/9614

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