Plain Language Summary of Publication

Future Rare Diseases

Ravulizumab is a suitable long-term treatment option for patients with paroxysmal nocturnal hemoglobinuria

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Summary

What is this summary about?
Eculizumab and ravulizumab are approved treatments for paroxysmal nocturnal hemoglobinuria (PNH), a rare blood disease which can cause potentially fatal complications if left untreated. Long-term ravulizumab treatment in patients with PNH is under investigation in two ongoing studies ('301' and '302'). This article describes the results at 2 years for both studies.

What were the results?
Ravulizumab continued to manage most patients' symptoms and less than 3% of patients experienced serious side effects related to treatment during this time.

What do the results mean?
This article highlights why eculizumab and ravulizumab are the usual treatments for PNH, where available. Long-term, ravulizumab controlled patients' PNH disease activity with few side-effects related to treatment.

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

- **Eculizumab:** ek-yoo-LIZ-oo-mab
- **Intravascular hemolysis:** in-TRA-vask-yoo lar HEE-mo-li-sys
- **Paroxysmal nocturnal hemoglobinuria:** par-ok-sys-mul nok-tur-nul hee moh glow bin yoo-ree-ah
- **Ravulizumab:** RAV-yoo-LIZ-oo-mab

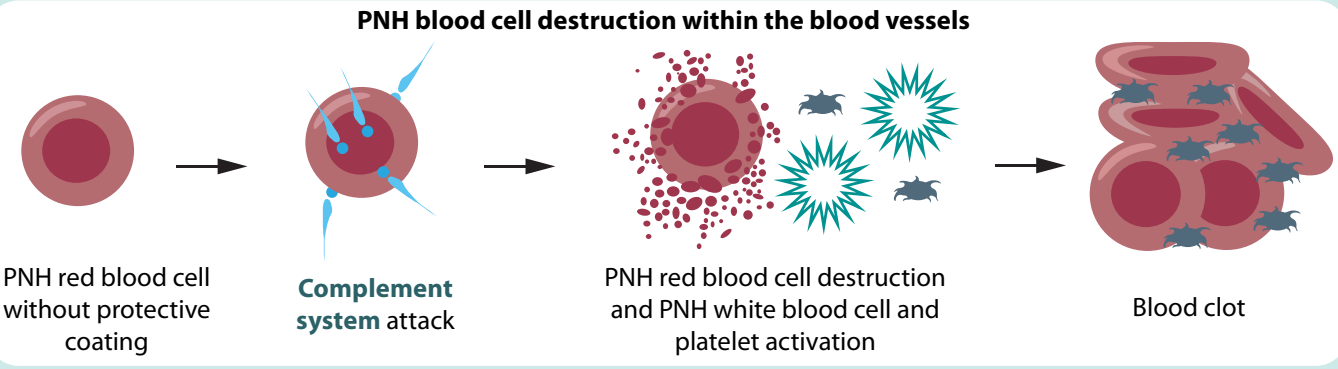
Who is this article for?

This summary was developed for people with paroxysmal nocturnal hemoglobinuria, their caregivers, patient advocacy organizations and healthcare professionals to help them understand the results of this study.

Why were these studies carried out?

What is paroxysmal nocturnal hemoglobinuria?
Paroxysmal nocturnal hemoglobinuria (PNH) is a rare blood disease characterized by the destruction of **red blood cells (RBCs)** within blood vessels – also known as **intravascular hemolysis (IVH)** – and activation of **white blood cells** and **platelets** which may cause blood clots (thrombosis).

Future Medicine part of fsg



What are the symptoms of PNH?

Symptoms include:

- Anemia (low levels of blood **hemoglobin**, or '**Hb**').
- Tiredness (fatigue).
- Difficulty swallowing.
- Stomach (abdominal) pain.
- Red or black urine.
- Erectile dysfunction.

If left untreated, PNH can lead to serious medical complications such as organ damage and blood clots, the leading cause of death in patients with PNH.

How is PNH diagnosed and tested?

- Blood samples are taken to check for anemia, IVH and other complications of PNH (e.g. kidney damage).
- Hb levels are measured to check for anemia, and the levels of a protein called **lactate dehydrogenase (LDH)** are used to measure IVH.
- In patients with PNH, Hb levels are usually too low and LDH levels are usually too high.
- As there is a link between high levels of LDH and the risk of thromboses, it is important that IVH is properly managed in patients with PNH.

Definitions

Hemoglobin (Hb): a red blood cell protein which carries oxygen

Intravascular hemolysis (IVH): the destruction of red blood cells within the blood vessels

Lactate dehydrogenase (LDH): a protein found throughout the body. Normally, LDH levels in the blood are low; however, when cells are damaged or destroyed, LDH is released into the bloodstream

Paroxysmal nocturnal hemoglobinuria (PNH): a rare blood disease characterized by the destruction of red blood cells, organ damage and potentially life-threatening blood clots

Platelets: blood cells that form clots to stop bleeding

Red blood cell (RBC): a type of blood cell which transports oxygen throughout the body and removes carbon dioxide (via the lungs)

White blood cells: blood cells to protect the body from infection

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

Ravulizumab and eculizumab are types of **monoclonal antibodies** known as **complement component** 5 (C5) inhibitors.

- These bind to the C5 protein in the blood, reducing IVH, organ damage and thromboses, as well as improving patient quality of life.

Both treatments are administered to the patient through a vein (intravenous infusion); however, depending on the treatment received, the time until retreatment is different.

- Eculizumab is given to patients every 2 weeks.
- Ravulizumab is given to patients every 8 weeks.

What are studies 301 and 302?

Studies 301 and 302 are two ongoing, phase 3 clinical studies.
In both studies, patients with PNH were randomly assigned to receive treatment with either ravulizumab or eculizumab for up to 26 weeks (the 'randomized treatment period').

- The aim of the randomized treatment period was to understand how effective ravulizumab treatment is for patients with PNH and whether these patients had any side effects when using ravulizumab compared with eculizumab.

Definitions

Complement system: a group of proteins in the immune system that help protect the body against infection, promote healing and kill bacteria and viruses

Complement component: a protein involved in the complement system

Monoclonal antibody: a protein that binds to specific targets in the body

After 26 weeks, depending on the treatment received, patients either continued treatment with ravulizumab or switched from eculizumab treatment to ravulizumab for up to 5 years (the 'extension period').

- The aim of the extension period was to understand the long-term effect of ravulizumab treatment in patients with PNH, regardless of their previous experience with eculizumab.

This article describes the long-term outcomes of studies 301 and 302 of ravulizumab-treated patients with PNH for up to 2 years.

What do we know so far?

Both studies have completed the 26-week randomly assigned treatment period.

- Ravulizumab provides the same benefits to patients with PNH as eculizumab, regardless of whether or not patients had received eculizumab before.

Both studies have completed the first year of the 5-year extension period.

- Ravulizumab is effective in managing PNH for up to 1 year, even after switching treatment from eculizumab.

Key research questions

In patients who are either new to C5 inhibitor treatment or have previously received C5 inhibitor treatment with eculizumab:

- Is long-term treatment with ravulizumab effective at controlling PNH disease activity?
- What are the side-effects associated with long-term treatment with ravulizumab?

What were the main outcomes of interest?

The key outcomes for both studies included:

- The change in markers for PNH disease activity over time, specifically LDH and Hb.
- The number of patients who needed blood transfusions.
- Changes in fatigue over time.
- The number of patients experiencing episodes during which IVH returned (also known as 'breakthrough hemolysis' or 'BTH'), including the number of BTH events.
- The number (and type) of side-effects related to ravulizumab treatment.

Who took part in these studies?

Together, these studies included 434 patients who received weight-based doses of ravulizumab every 8 weeks for up to 2 years. Of these patients, 243 had never received C5 inhibitors before (study 301) and 191 had previously received eculizumab (study 302).

Summary of studies 301 and 302

This study of long-term treatment of ravulizumab used data from **study 301** and **study 302**

Patients in **study 301** had:

- Never received a C5 inhibitor before (*newly treated*).

Patients in **study 302** had:

- Previously received a C5 inhibitor (*previously treated*).

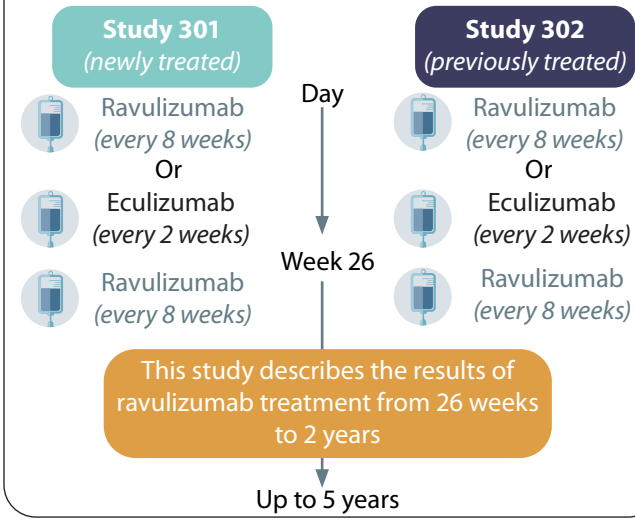
Patients in both studies had:

- A confirmed diagnosis of PNH.
- Been vaccinated against meningitis infection.

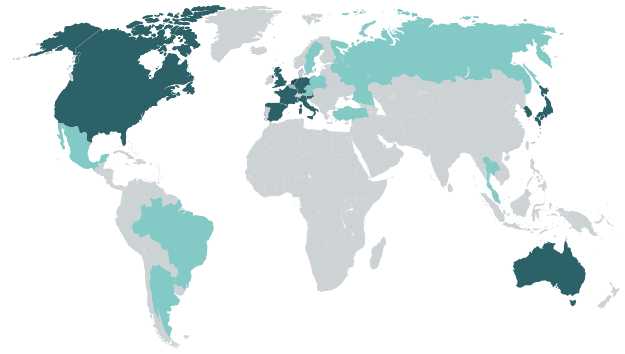
Patients in both studies did not have:

- Body weight below 40 kg at the screening stage of the trial.
- A history of bone marrow transplantation.
- A history of meningitis infection.

Study design



Study locations

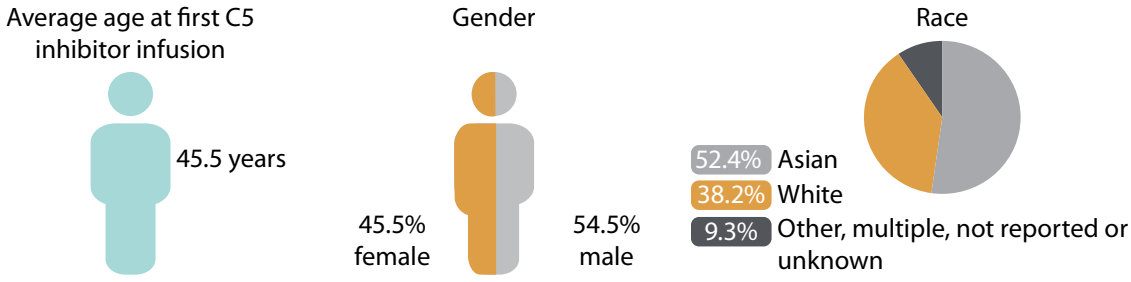


Study 301: 25 countries

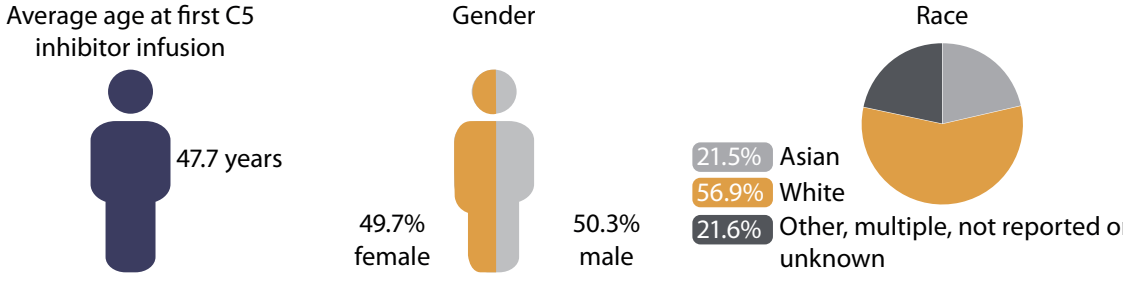
Study 302: 11 countries

Studies 301 and 302

Study 301 (newly treated)



Study 302 (previously treated)



Patients included in studies 301 and 302

Patients in study 301 had never received C5 inhibitors before (they were *newly treated*).
Patients enrolled into study 302 had previously received eculizumab before joining the study (they were *previously treated*).

Patients in both studies had:
- A confirmed diagnosis of PNH.
- Been vaccinated against meningitis infection.

These patients did not have:
- Body weight below 40 kg at the screening stage of the trial.
- History of bone marrow transplantation.
- History of meningitis infection.

Definitions

***Newly treated* patients:** patients who had never received C5 inhibitors before (patients included in study 301)

***Previously treated* patients:** patients who had previously received eculizumab before joining the study (patients included in study 302)

Current analysis includes 434 patients

243 *newly treated* — Study 301

191 *previously treated* — Study 302

Had LDH levels low enough to prevent severe PNH complications

90.6% of ***newly treated* patients**

94.7% of ***previously treated* patients**

Had normal LDH levels

48.2% of *newly treated* patients

56.5% of *previously treated* patients

Did not need blood transfusions

73.3% of *newly treated* patients

85.3% of *previously treated* patients

Had stabilized hemoglobin levels

69.1% of *newly treated* patients

83.8% of *previously treated* patients

Improvements in fatigue score made during the randomized treatment period were maintained

Newly treated patients

+1.6%

change in score

Previously treated patients

-1.2%

change in score

Experienced BTH

6.2% of *newly treated* patients

5.8% of *previously treated* patients

As infection can also cause BTH (and not just lack of treatment effect), infection was linked to...

36.0%

of the BTH events reported in *newly treated* patients

63.6%

of the BTH events reported in *previously treated* patients

10.2217/frd-2022-0024

What were the most common side effects?

Overall, 391 patients (90.1%) had **treatment-emergent adverse events (TEAEs)**.

The most common TEAEs were:
- Upper respiratory tract infection, 80 people (18.4%).
- Cold, 70 people (16.1%).
- Headache, 56 people (12.9%).
- Fever, 44 people (10.1%).
- Fatigue, 39 people (9.0%).

In total, 98 patients (22.6%) had treatment-related TEAE and six patients (1.4%) had a TEAE that was considered a **major adverse vascular event**.
Less than 3% of patients had **serious adverse events** related to treatment.
Three patients (0.7%) experienced treatment-emergent serious adverse events which were considered major adverse vascular events.
Serious adverse events that led to stopping the study were reported in three patients (0.7%).

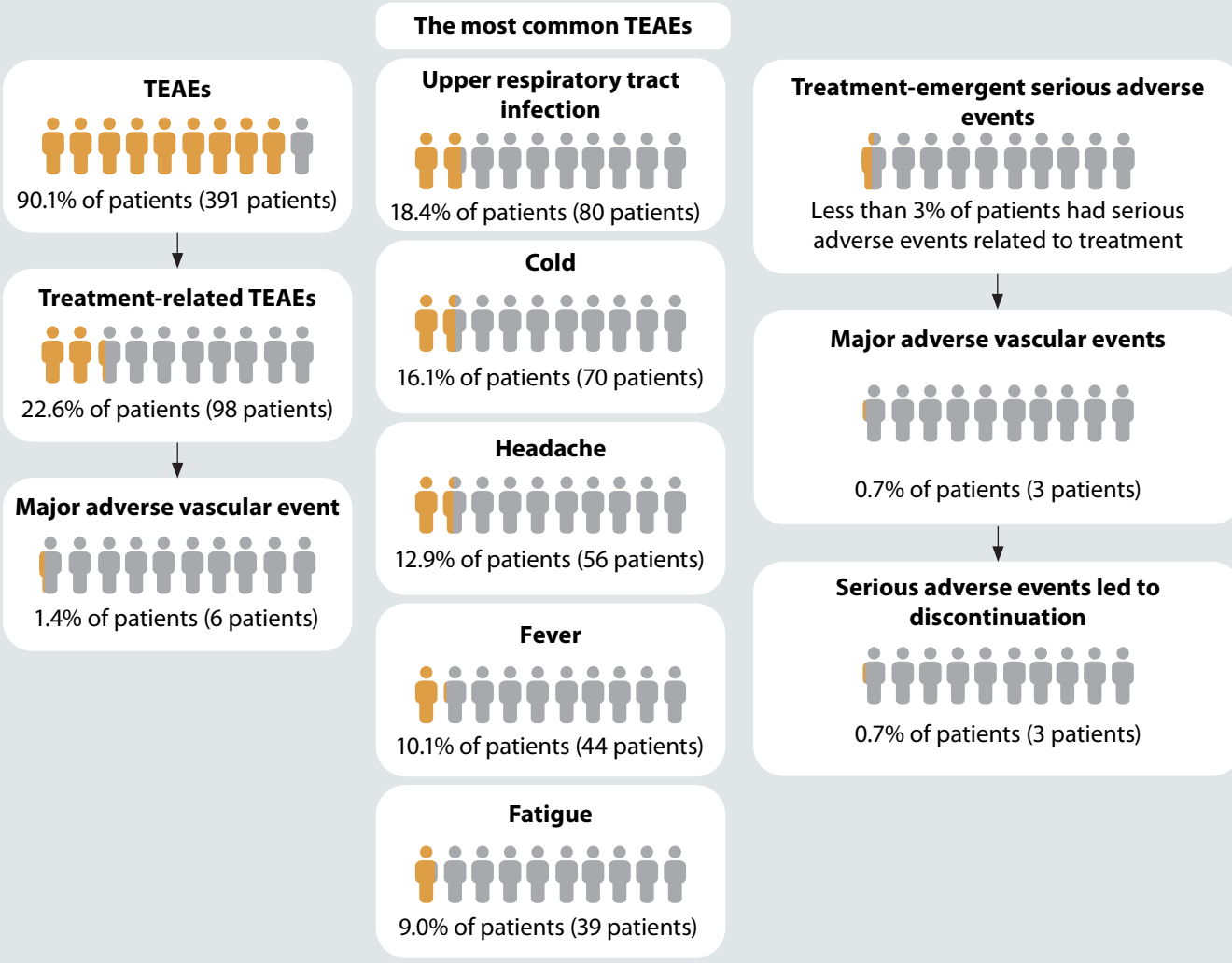
Definitions

Major adverse vascular events: side effects that affect the blood vessels, for example deep vein thrombosis, myocardial infarction (heart attack), angina (chest pain) and cerebrovascular accident (bleeds or blood clots occurring in the brain).

Serious adverse events: side effects considered to be life threatening.

Treatment-emergent adverse events: side effects that happened on or after the treatment was started.

Treatment-related treatment-emergent adverse events (TEAEs): side effects that happened on or after treatment was started that are related to treatment.



What do the results mean?

These results show that patients with PNH receiving ravulizumab continued to have improved symptoms of PNH and disease activity was controlled.

Overall:

- The combined results of these studies represent the longest period of ravulizumab treatment data in more than 400 patients with PNH.
- More than 90% of patients had LDH levels (used to measure RBC damage) which were low enough to limit severe PNH complications, and nearly half of the patients' LDH levels were kept within normal range while receiving ravulizumab.
  - This, along with the low number of patients having an episode of BTH, shows continued long-term control of PNH activity when patients were treated with ravulizumab.
- Hb levels, which are used to check for anemia, were maintained within the normal range in over 60% of patients and over 80% of patients did not need blood transfusions to recover from their anemia.
- Less than 3% of patients experienced serious side effects related to ravulizumab treatment.

These results show that long term ravulizumab treatment of up to 2 years was effective with little side effects in patients with PNH and disease activity was well controlled.
This study highlights why eculizumab and ravulizumab are the usual treatments for PNH, where available.
We will continue to collect and analyze data for the remainder of the 5-year extension period.

Were there any study limitations to consider?

A key limitation of this study was that patient free C5 data was not available for all of the BTH events that happened during the extension period.
These data would have been useful because they could have ruled out lack of treatment effect due to ravulizumab as the cause of these events.
Fortunately, data from the randomized treatment period showed that the number of BTH events linked to free C5 levels were low, and that all C5-associated BTH events occurred in patients who were assigned to eculizumab treatment.

Where can readers find more information on these studies?

Original article
This is a summary of an article titled 'Long-term safety and efficacy of ravulizumab in patients with paroxysmal nocturnal hemoglobinuria: 2-year results from two pivotal phase 3 studies', originally published in the *European Journal of Haematology*.
The full original article is freely available and can be read at: https://onlinelibrary.wiley.com/doi/epdf/10.1111/ejh.13783

Previous studies of interest
Publications on studies 301 and 302 can be found at:
Study 301: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6367644/,
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7592174
Study 302: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6368201/,
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8246907/

Trial registration site
You can read more about studies 301 and 302 at https://clinicaltrials.gov/.
The trial identifiers for these studies are:
Study 301: NCT02946463
Study 302: NCT03056040

Where can readers find more information on PNH?

Please visit the following national patient organizations for more information on PNH:

- PNH Global Alliance: https://www.pnhglobalalliance.org
- Aplastic Anemia and MDS International Foundation (USA): https://www.aamds.org/
- Canadian Association of PNH Patients: http://www.pnhca.org/

Who sponsored these studies?

These studies were sponsored by Alexion, AstraZeneca Rare Disease.

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