# CLINICAL STUDY RESULTS

A Study about Ravulizumab and Eculizumab in Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) who were being Treated with Eculizumab

## THANK YOU!

Alexion would like to thank all of the patients, their families, and caregivers who took part in this clinical study. Taking part in studies like this one contributes directly to the discovery of new medicines for people with PNH.

### STUDY IDENTIFICATION INFORMATION

TREATMENTS STUDIED: 1) ravulizumab, also known as ALXN1210 (trade name: Ultomiris®)
2) eculizumab (trade name: Soliris®)

STUDY TITLE: A Phase 3, Randomized, Open-Label, Active-Controlled Study of ALXN1210 Versus Eculizumab in Adult Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) Currently Treated with Eculizumab.

STUDY NUMBERS: Europe, 2016-002026-36 | United States, NCT03056040 | Protocol, ALXN1210-PNH-302

ALEXION

# BACKGROUND

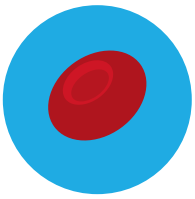
## What are clinical studies?

Clinical studies aim to answer specific questions about new or existing treatments, procedures, or vaccines and involve patients with health conditions or healthy volunteers. Clinical studies happen in several phases from phase 1 to 4.

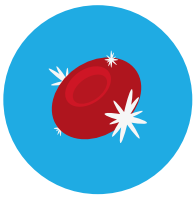
This study was a phase 3. Phase 3 studies look at the overall risks and benefits of a new treatment compared to the routine treatment or care for the condition studied. In this study, ravulizumab was compared with eculizumab in adult patients with PNH who were being treated with eculizumab and doing well.

## What is paroxysmal nocturnal hemoglobinuria?

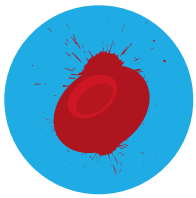
Paroxysmal nocturnal hemoglobinuria, also called PNH, is a very rare, life-threatening, lifelong blood disorder. In PNH, some or all of the red blood cells lack important protective proteins. Without these protective proteins, the body's natural defense system, also called the immune system, destroys the red blood cells. This process is known as hemolysis.



Red blood cell missing protective proteins



Red blood cell attacked



Red blood cell destroyed

For people living with PNH, hemolysis is always happening and can result in serious health problems.

## What are the symptoms of PNH?

The most common symptoms of PNH include feeling tired, difficulty swallowing, trouble concentrating or thinking, shortness of breath, stomach pain, dark-colored urine, and, for men, difficulty keeping an erection. The lack of healthy red blood cells, known as anemia or being anemic, is a serious complication of PNH, which often results in patients needing blood transfusions.

Life-threatening complications from PNH can include blood clots, kidney failure, and other organ damage.



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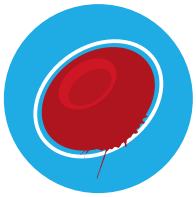
## What treatments are available for PNH?

Ravulizumab and eculizumab (trade name: Soliris®), known as complement inhibitors, aim to prevent the destruction of the red blood cells, improve common symptoms of PNH, and prevent life-threatening complications.

Complement inhibitors work by sticking to a protein in the blood called C5, which helps stop the red blood cells from breaking down.

Complement inhibitor treatment given directly into the bloodstream

Protective protein shields red blood cell from attack



Less destruction happening to red blood cell

## What were the treatments used in this study?

There were 2 treatment groups in this study: ravulizumab and eculizumab. The treatments were given by an infusion, which means it was administered directly into the bloodstream via a drip.

A computer selected at random who got ravulizumab and who got eculizumab.

### RAVULIZUMAB

Up to 3000* mg infusion for the first dose, up to 3600* mg on Day 15, and up to 3600* mg once every 8 weeks after that.

Each infusion was around 2 hours.

97 patients got ravulizumab infusions.

*Exact dose based on body weight.

### ECULIZUMAB

900^ mg infusion once every 2 weeks.

Each infusion was around 35 minutes.

98 patients got eculizumab infusions.

^Exact dose not based on body weight.



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# PURPOSE OF THE STUDY

## What were the researchers trying to find out in this study?

The researchers wanted to see if ravulizumab worked as well as eculizumab at treating symptoms of PNH in patients who had been treated with eculizumab for at least 6 months. The side effects of both treatments, which is called the safety of the study, were also looked at. The study was not designed to see if one treatment was better than the other.

The study had 2 parts. Part 1 started in June 2017 and ended in March 2018. **This summary provides the results of Part 1, which is when all patients had received 26 weeks of treatment.** The plan is for Part 2 to finish in 2021 and the results made available within 12 months.

## What was the main question?

### How did hemolysis compare between patients who got ravulizumab and patients who got eculizumab after 26 weeks of treatment?

## Were there any other important questions?

What percentage of patients in each treatment group had breakthrough hemolysis after 26 weeks of treatment?

How did tiredness levels compare between the 2 treatments after 26 weeks of treatment?

What percentage of patients who got ravulizumab did not need a blood transfusion compared to patients who got eculizumab after 26 weeks of treatment?

What percentage of patients in each treatment group had stable hemoglobin levels after 26 weeks of treatment?

How did the patients' overall quality of life compare between the 2 treatments after 26 weeks of treatment?



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# STUDY PARTICIPANTS

## Who could take part?

To be able to take part in the study, patients had to meet the following requirements:

Male or female, 18 years of age or older

Confirmed diagnosis of PNH with 1 or more related sign or symptom

Taken eculizumab for at least 6 months, and doing well

Hemolysis confirmed by a blood test

Any patient who never had eculizumab treatment or had been unwell due to a fever or infection could not take part. Any patient who had a hemolysis blood test result that was more than 2 times higher than the normal level could not take part.

Complement inhibitors increase a patient's risk of meningococcal infection. A meningococcal infection is caused by a bacteria called *Neisseria meningitidis*. This results in swelling around the brain and spinal cord or infections in the blood. To help prevent meningococcal infection, all patients needed to have had a meningococcal vaccination no more than 3 years before taking part. If they previously had a meningococcal infection, they could not take part.

## How many patients took part?


98
men

97
women

195
patients

Patients were aged between 18 and 79 years.

## Where was the study done?

The study took place in 52 study centers in 12 countries across North America, Europe, Asia, and Australia.




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# STUDY RESULTS

## Answer to the main question:

### How did hemolysis compare between patients who got ravulizumab and patients who got eculizumab after 26 weeks of treatment?

During hemolysis, the destruction of red blood cells causes the release of an enzyme called lactate dehydrogenase, or LDH, into the blood. LDH levels show how much hemolysis is happening in the body. Both ravulizumab and eculizumab aim to block hemolysis. If the treatment is working and blocking hemolysis, then the patient's LDH level should decrease.

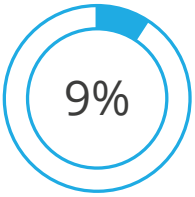
The researchers wanted to know the average amount the LDH levels changed in patients getting ravulizumab and eculizumab after 26 weeks of treatment. If the difference in the change in LDH levels between patients who got ravulizumab and patients who got eculizumab was less than 15%, then that meant that ravulizumab worked as well as eculizumab in decreasing LDH levels.

RAVULIZUMAB

The patients who received ravulizumab had an average decrease in their LDH levels of 1%.

ECULIZUMAB

The patients who received eculizumab had an average increase in their LDH levels of 8%




The difference in the change in LDH levels between the patients who got ravulizumab and the patients who got eculizumab was 9%



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## Answers to the other important questions:

### What percentage of patients in each treatment group had breakthrough hemolysis* after 26 weeks of treatment?

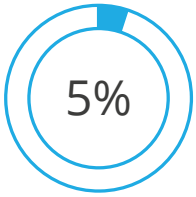
If the difference in the percentage of patients who had breakthrough hemolysis between those who got ravulizumab and those who got eculizumab was less than 20%, then that meant that ravulizumab worked as well as eculizumab in preventing breakthrough hemolysis.

RAVULIZUMAB


None of the 97 patients (0%) had breakthrough hemolysis.

ECULIZUMAB


5 of the 98 patients (5%) had breakthrough hemolysis.




The difference in the percentage of patients who had breakthrough hemolysis between those who got ravulizumab and those who got eculizumab was 5%.

*Breakthrough hemolysis means an increase in LDH levels and a new or worsening symptom or a serious complication.

### How did tiredness levels compare between the 2 treatments after 26 weeks of treatment?

Patients were asked to complete a questionnaire designed to understand how tiredness is affecting their quality of life. The researchers compared the results from the beginning of the study to the end of 26 weeks of treatment.

Patients in both treatment groups reported feeling less tired. Patients who got ravulizumab had a greater improvement in tiredness levels compared with those patients who got eculizumab.



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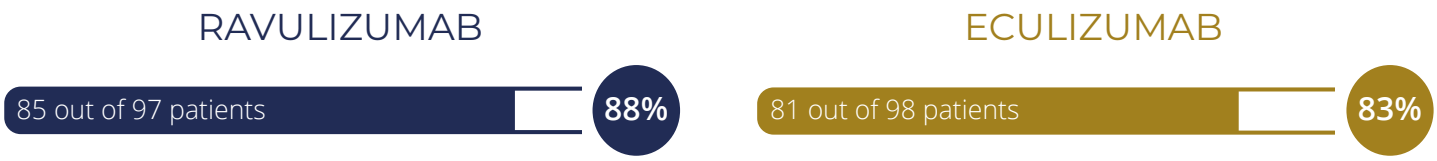
## What percentage of patients who got ravulizumab did not need a blood transfusion compared to patients who got eculizumab after 26 weeks of treatment?

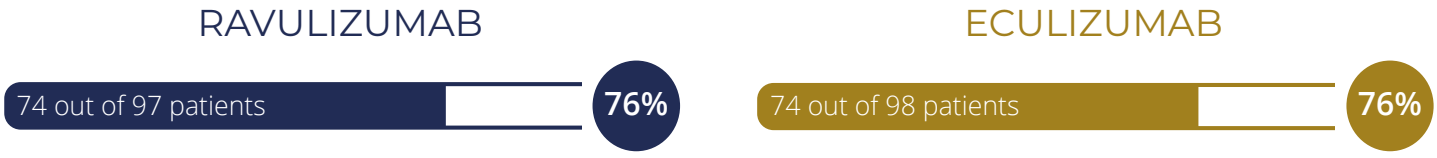
The researchers wanted to see if ravilizumab worked as well as eculizumab at reducing the need for a blood transfusion during the 26-week treatment period.




The results showed that 88% of patients who got ravulizumab did not need a blood transfusion compared to 83% of patients who got eculizumab.

## What percentage of patients in each treatment group had stable hemoglobin levels after 26 weeks of treatment?

During hemolysis, the destruction of red blood cells causes the release of hemoglobin, which is then free to enter the bloodstream. Free hemoglobin can lead to serious health problems, such as blood clots and damage to organs. The researchers checked each patient's hemoglobin level during the study to see if it remained stable on treatment.




The results showed that 76% of patients in both treatment groups had stable hemoglobin levels.



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## How did the patients' overall quality of life compare between the 2 treatments after 26 weeks of treatment?

Each patient rated their health, ability to function, and symptoms of PNH on a questionnaire. An improvement in their questionnaire score of 10 or more indicated a change in quality of life.

More patients who got ravulizumab had a change in their quality of life at the end of the treatment period compared with patients who got eculizumab.

### Summary of answers:

Following 26 weeks of treatment ravulizumab was considered to work as well as eculizumab as it:

- Lowered LDH enzyme levels
- Blocked the destruction of the red blood cells
- Reduced breakthrough hemolysis
- Reduced tiredness
- Reduced the need for a blood transfusion
- Stabilized hemoglobin levels
- Improved the patients' overall quality of life

# SIDE EFFECTS

## How is the safety of participants in clinical studies monitored?

A side effect is any symptom or clinical finding that occurs during the study. For example, a participant might get a headache or have abnormal blood test results. Side effects can vary from person to person. A lot of research is needed to see which side effects the study treatment causes and which side effects happen by chance. So, researchers keep a record of all the side effects participants have when new treatments are studied.

Any side effect thought to be an important medical event, requires a person to go to the hospital, could be life-threatening, or causes death, is called a serious side effect. A serious side effect may or may not be related to the treatment the participant was taking.



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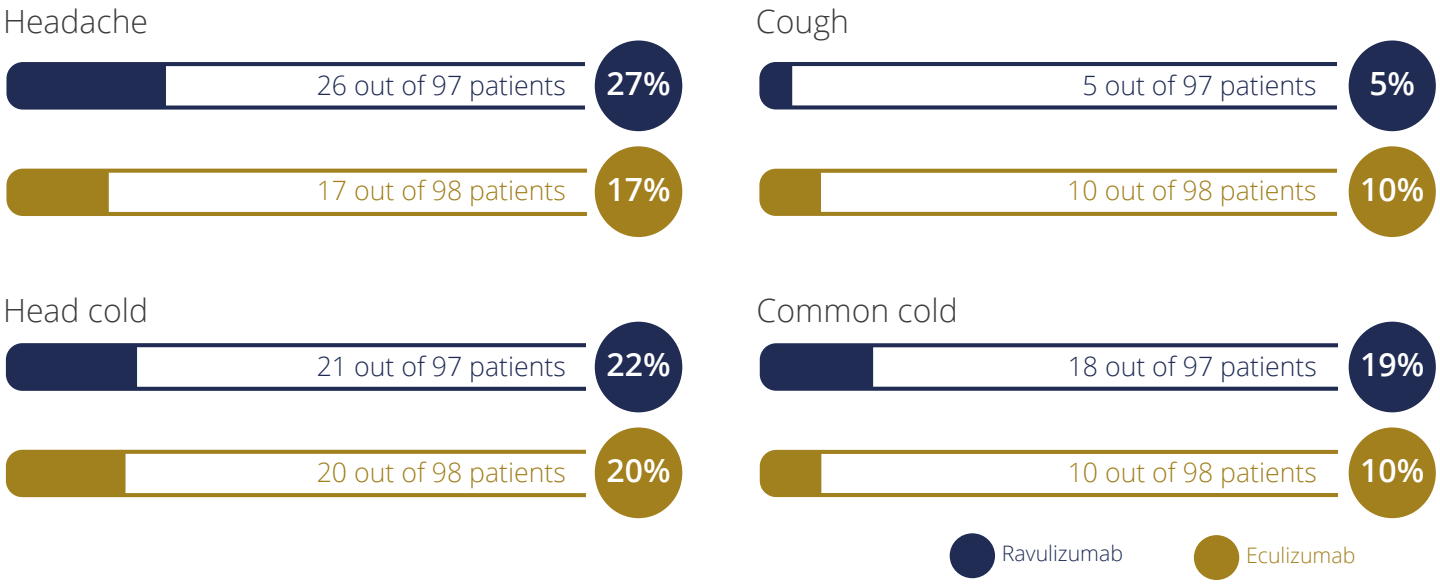
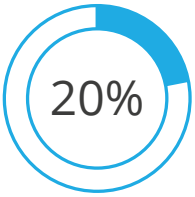
## What side effects did patients have in this study?

The most common side effects, which happened in more than 10 out of 100 patients (10%) in either treatment group, are shown below:

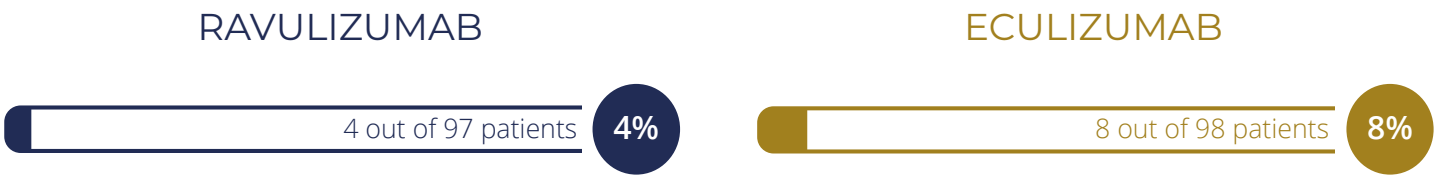



20% of patients in both treatment groups had a side effect that was thought by the study doctor to be related to the study treatment.

## What serious side effects did patients have in this study?

Overall, 12 out of 195 patients (6%) had a serious side effect.




The most commonly reported serious side effect was a fever. 3 patients experienced this: all 3 patients were on eculizumab.



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## Were there any other important safety findings in this study?

Complement inhibitors increase a patient's risk of meningococcal infection. An independent group was in place to monitor all patients for any cases of meningococcal infection. There were no meningococcal infections reported in either treatment group.

None of the patients who got either treatment stopped taking part because of the side effects they had. No patients died during their participation in Part 1 of this study.

# OUTCOME OF THE STUDY

The results showed that ravulizumab worked **as well as** eculizumab at treating patients with PNH who previously had treatment with eculizumab. The side effects experienced were similar in both treatment groups. Ravulizumab was considered safe and well tolerated.

## How has this study helped patients and researchers?

The information collected in this study was from patients with PNH who were getting eculizumab for at least 6 months. From a patient and healthcare perspective, patients who were getting eculizumab could safely switch to ravulizumab. Being able to take ravulizumab once every 8 weeks, compared to eculizumab once every 2 weeks, may reduce the burden of treatment.

Before a treatment can be approved for patients to use, researchers look at the results of many studies to decide which treatments work best and are safe. If you have any questions about ravulizumab or eculizumab for the treatment of PNH, please talk to your doctor. You should not change your treatment based on the results of this study without talking to a doctor first.

# MORE INFORMATION

## Useful clinical study websites

This document provides a summary of the main results of the study. It includes information about the side effects that happened in the study and the results of the questions the researchers wanted to answer.

A full report may be available to read at one of the following clinical trial registers:

**www.clinicaltrials.gov**
Use the study number NCT03056040 to search for more information on this website.

**www.clinicaltrialsregister.eu**
Use the study number 2016-002026-36 to search for more information on this website.

## Further studies

Several studies investigating ravulizumab for the treatment of PNH are either currently running or completed. Please follow the links below to find out more information.

PNH Registry

ALXN1210-PNH 103 Dose-escalation study of ravulizumab in adults with PNH

ALXN1210-PNH-201 Multiple ascending-dose study of ravulizumab in adults with PNH

ALXN1210-PNH-301 Ravulizumab versus eculizumab in adults with PNH

ALXN1210-PNH-303 Ravulizumab administered subcutaneously versus intravenously

ALXN1210-PNH-304 Children and adolescents with PNH




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