# CLINICAL STUDY RESULTS

A Study about 2 Different Doses of Ravulizumab in Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) who Never had Treatment with a Complement Inhibitor

## 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

| | |
|---|---|
| TREATMENT STUDIED: | Ravulizumab, also known as ALXN1210 (trade name: Ultomiris®) |
| STUDY TITLE: | An Open-Label, Intrapatient, Dose-Escalation Study to Evaluate the Safety, Tolerability, Efficacy, Pharmacokinetics, and Pharmacodynamics of ALXN1210 Administered Intravenously to Patients with Paroxysmal Nocturnal Hemoglobinuria. |
| STUDY NUMBERS: | United States, NCT02598583 \| Protocol, ALXN1210-PNH-103 |

ALEXION

# BACKGROUND

## What are clinical studies?

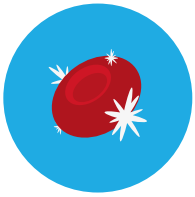
Clinical studies aim to answer specific questions about new or existing treatments, procedures, or vaccines and involve patients with health conditions or healthy volunteers. Clinical studies happen in several phases from phase 1 to 4.

This study was a phase 1b. Phase 1b studies aim to find what dose of a new drug causes the fewest side effects. In this study, a new drug called ravulizumab was tested in a small group of patients. If it is found to be safe, then it can be tested in a larger group.

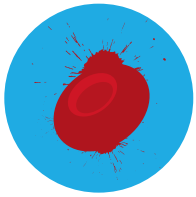
## What is paroxysmal nocturnal hemoglobinuria?

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. During hemolysis, an enzyme called lactate dehydrogenase, or LDH, is released into the blood. LDH levels can be measured by a blood test to know how much hemolysis is happening in the body.

## 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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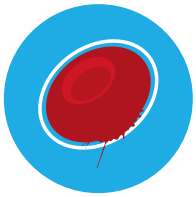
## What treatments are available for PNH?

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 groups in the study. Each group was given different doses of ravulizumab by an infusion. An infusion means it was administered directly into the bloodstream via a drip.

### GROUP 1

400 mg or 600 mg on Day 1,
400 mg on Day 8*, 600 mg on Day 15,
then 900 mg on Day 29
and once every 4 weeks after that.

### GROUP 2

600 mg on Day 1,
900 mg on Day 15,
then 1800 mg on Day 29
and once every 4 weeks after that.

Patients in both groups had an end of treatment visit on Day 169, which was around 24 weeks of treatment.

*Not all patients in Group 1 got a 400 mg infusion on Day 8.

# PURPOSE OF THE STUDY

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

The researchers wanted to see if 2 different doses of ravulizumab worked at treating symptoms of PNH in patients who had never had treatment with a complement inhibitor. They also wanted to see if different doses of ravulizumab lowered the patients' LDH level and reduced hemolysis. The side effects of ravulizumab and how patients tolerated the different doses were also looked at.

This study had 2 parts. Part 1 started in November 2015 and ended in July 2016. **This summary provides the results of Part 1, which is when all patients had received at least 24 weeks of treatment.** The plan is for Part 2 to finish in 2022 and the results made available in 2023.

## What was the main question?

Did 24 weeks of treatment lower the patients' LDH level?

## Were there any other important questions?

Did ravulizumab have an effect on the patients' red blood cells?

Were there any changes in the patients' symptoms of PNH?

Did any of the patients need a blood transfusion?

Did the patients' tiredness reduce or worsen?

Did ravulizumab improve the patients' overall quality of life?

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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

PNH confirmed by blood or bone marrow sample

High levels of LDH confirmed by 2 blood tests

Patients were unable to take part if they had previously had treatment with ravulizumab or eculizumab, or if they were unwell due to a fever or infection.

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 had previously had a meningococcal infection, they could not take part.

## How many patients took part?

GROUP 1

6
patients

+

GROUP 2

7
patients

=

13
patients

Patients were aged between 25 and 62 years.

## Where was the study done?

The study took place in 3 study centers in Australia and 7 study centers in South Korea.




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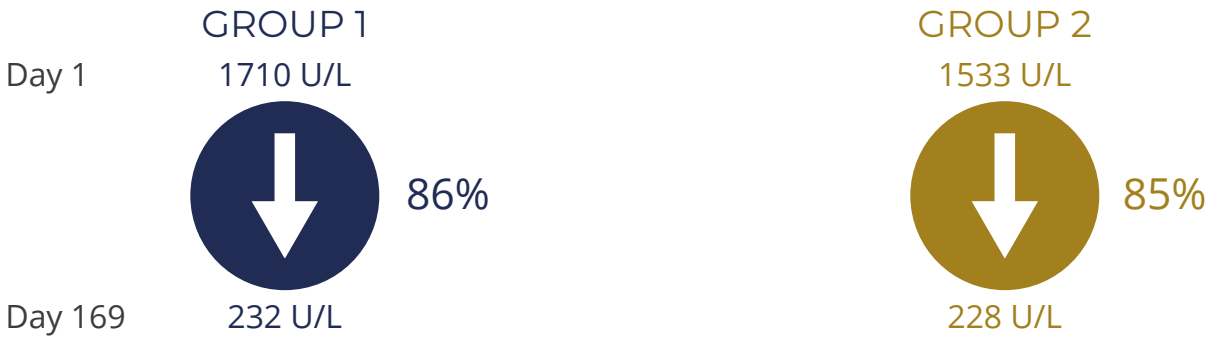
# STUDY RESULTS

## Answer to the main question:

### Did 24 weeks of treatment lower the patients' LDH level?

LDH levels show how much hemolysis is happening in the body. LDH levels are measured by a blood test as enzyme unit per liter, also called U/L. The normal level of LDH is 234 U/L or lower. Ravulizumab aims to prevent hemolysis. If the treatment is working and preventing hemolysis, then the patient's LDH level should fall back to a normal range.

The diagram below shows the average LDH level for patients in each group before and at the end of ravulizumab treatment. The average reduction in LDH level in each group is shown as a percentage.




This study found that both doses of ravulizumab lowered the patients' LDH level during 24 weeks of treatment.

## Answers to the other important questions:

### Did ravulizumab have an effect on the patients' red blood cells?

During the study, the researchers took several blood samples from each patient and performed specific tests. These tests helped the researchers understand more about red blood cells, blood clotting, and specific blood proteins in patients with PNH.

The results from these specific tests confirmed that ravulizumab helped to reduce hemolysis.

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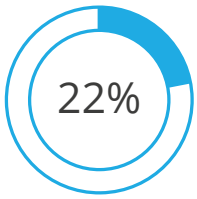
## Were there any changes in the patients' symptoms of PNH?

At the beginning of the study, all patients were asked whether they were experiencing tiredness, stomach pain, shortness of breath, difficulty swallowing, or chest pain. Men were also asked if they had difficulty keeping an erection.

Those patients who had symptoms of PNH were asked again after 24 weeks of treatment if they continued to experience these symptoms or not. The results below show the combined responses of both Group 1 and Group 2.

### TIREDNESS

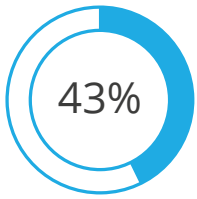



of patients no longer reported feeling tired

### STOMACH PAIN


of patients no longer reported having stomach pain

### SHORTNESS OF BREATH

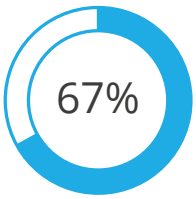



of patients no longer reported shortness of breath

### DIFFICULTY SWALLOWING

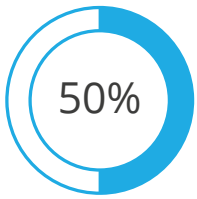

of patients no longer reported difficulty swallowing

### CHEST PAIN




of patients no longer reported chest pain

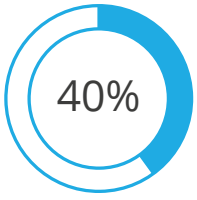
### DIFFICULTY KEEPING AN ERECTION




of men no longer reported difficulty keeping an erection

## Did any of the patients need a blood transfusion?

The researchers wanted to know how many patients had a blood transfusion before the start of the study. They then looked at how many of those patients needed a blood transfusion during 24 weeks of treatment. Overall, 5 out of 13 patients had a blood transfusion within 12 months before the start of the study.




Of those patients requiring a blood transfusion before the start of the study, 40% needed a further blood transfusion during the treatment period and 60% did not.

## Did the patients' tiredness reduce or worsen?

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 24 weeks of treatment.

Patients in both treatment groups reported feeling less tired. Patients in Group 2 had a greater improvement in tiredness levels.

## Did ravulizumab improve the patients' overall quality of life?

Each patient rated their health, ability to function, and symptoms of PNH on a questionnaire. The researchers compared the scores from the beginning of the study to the end of 24 weeks of treatment.

Patients in both groups had improved health, ability to function, and symptoms of PNH.

## Summary of answers:

Following 24 weeks of treatment, both doses of ravulizumab:

- Lowered the patients' LDH level
- Reduced hemolysis
- Reduced the need for a blood transfusion in some patients
- Improved the patients' common symptoms of PNH
- Reduced the patients' tiredness 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.

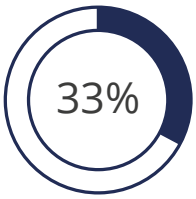
Any side effect thought to be an important medical event, requires a person to go to the hospital, could be life-threatening, or causes death, is called a serious side effect. A serious side effect may or may not be related to the treatment the participant was taking.

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

The most common side effects in both groups, which happened in 3 or more patients overall, were headache and the common cold.

### Headache

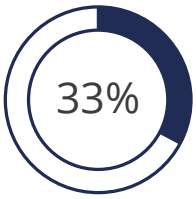
GROUP 1



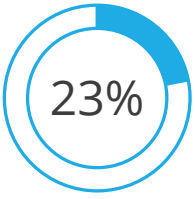

GROUP 2


### Common cold

GROUP 1




GROUP 2


3 out of all 13 patients who took part in the study had a side effect that was thought by the study doctor to be related to ravulizumab.

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

None of the patients had a serious side effect.

## 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 during 24 weeks of treatment.

None of the patients stopped taking part because of the side effects they had. No patients died during their participation in this study.

# OUTCOME OF THE STUDY

The results showed that both doses of ravulizumab lowered the patients' LDH level and reduced hemolysis. Patients experienced improved symptoms of PNH and overall quality of life. Ravulizumab was considered safe and well tolerated.

## How has this study helped patients and researchers?

This was the first study of ravulizumab in patients with PNH. The information collected from this study helped the researchers plan a further study to determine the most appropriate dose of ravulizumab for patients with PNH.

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 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.

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# 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 the following clinical trial register:

**www.clinicaltrials.gov**
Use the study number NCT02598583 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-201 Multiple ascending-dose study of ravulizumab in adults with PNH

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

ALXN1210-PNH-302 Adults with PNH currently treated with eculizumab

ALXN1210-PNH-303 Ravulizumab administered subcutaneously versus intravenously

ALXN1210-PNH-304 Children and adolescents with PNH




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