# Danicopan as Add-On to Ravulizumab or Eculizumab in Patients With Paroxysmal Nocturnal Hemoglobinuria and Clinically Significant Extravascular Hemolysis: A Phase 3 Randomized Trial

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## INTRODUCTION TO PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH)

- PNH is a lifelong rare blood disease that leads to the premature breakdown of the body's red blood cells (RBCs) within blood vessels, which is called intravascular hemolysis (IVH). The breakdown of RBCs is caused by the dysregulation of the complement system.
- The complement system normally helps defend the body against invading organisms such as bacteria.
- In patients with PNH, important proteins that help to regulate complement activity are missing on the surface of their RBCs.

## WHY WAS THIS STUDY NEEDED?

- The C5 inhibitors ravulizumab and eculizumab, which will be called RAV and ECU for the rest of this summary, are standard, approved drugs for treating PNH. These drugs are called C5 inhibitors because they block, or inhibit, the complement protein C5, which is involved in the destruction of RBCs by IVH.
  - C5 inhibitors are very effective for reducing IVH, which increases survival, reduces risk of blood clots (thromboembolic events or TEs), improves quality of life, and helps to reduce the need for blood transfusions in patients with PNH.
- Some patients with PNH also have extravascular hemolysis (EVH), which is RBC destruction that takes place outside of blood vessels.
- About 10%-20% of patients with PNH who take RAV/ECU have EVH, which can cause anemia that is severe enough that they need ongoing blood transfusions.
- Danicopan is an oral drug designed to inhibit factor D, a complement system protein that plays an important role in a branch of the complement system called the alternative pathway.
- Danicopan is an investigational drug, which means that it was not approved as add-on treatment of PNH when the study started.
- This study was done to see if danicopan as an additional treatment to RAV/ECU is more effective for reducing anemia due to EVH than RAV/ECU alone in patients with PNH.

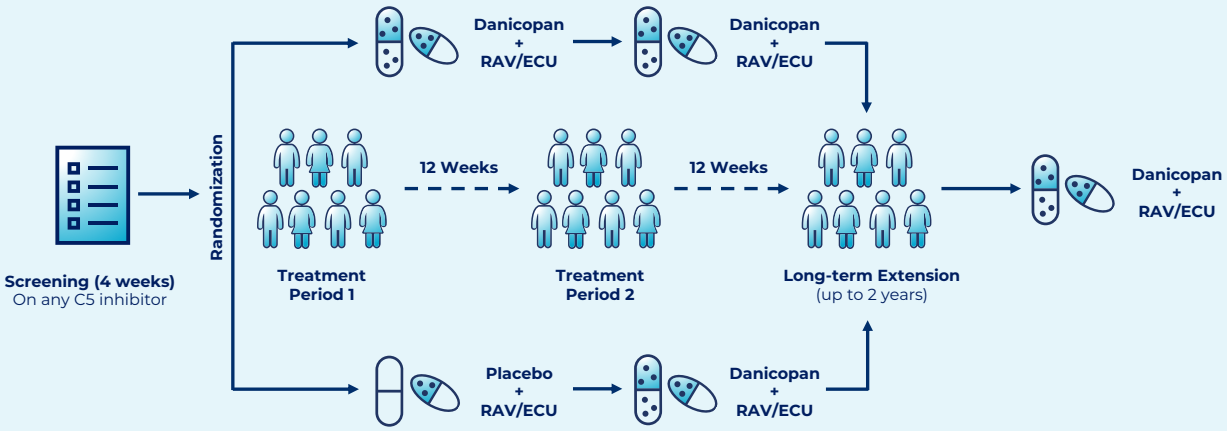
## HOW WAS THIS STUDY DONE?

- Researchers are testing danicopan in the ALPHA clinical trial to find out if participants taking danicopan orally 3 times a day for 3 months have increased hemoglobin compared to the hemoglobin levels in participants not taking danicopan. Hemoglobin is a protein in RBCs that carries oxygen throughout the body.

- All participants in the study are adults (aged ≥18 years) who were receiving treatment with either RAV or ECU for PNH before the study began, and all participants are continuing with their same dose of RAV or ECU (in other words, their prestudy RAV/ECU regimen) during the study.
  - Participants had to have clinically significant EVH, meaning that their prestudy tests showed that they had anemia (hemoglobin level ≤9.5 g/dL) and absolute reticulocyte count (also called ARC, to measure RBC production) ≥120 × $10^9$/L.
- Participants are assigned to 1 of 2 treatment groups
  - Danicopan 150 mg (the dose can be increased to 200 mg by their study doctor based on their clinical response to the drug) plus the participant's prestudy RAV/ECU regimen
  - Placebo, a pill that contains no medicine but appears identical to danicopan, plus the participant's prestudy RAV/ECU regimen

- The ALPHA trial is divided into 2 treatment periods, each lasting 12 weeks, for a total of 24 weeks (**Figure**). This is followed by a long-term extension where participants can choose to take danicopan plus RAV/ECU for up to 2 more years.

**ALPHA Phase 3 Clinical Trial Study Design**




- Researchers looked at the following to see if patients who took danicopan plus RAV/ECU saw greater improvement than patients who took placebo plus RAV/ECU
  - Hemoglobin levels
  - Percentage of participants with a clinically meaningful increase in hemoglobin (≥2 g/dL) without a blood transfusion
  - Percentage of participants who do not need to have blood transfusions
  - Amount of fatigue that participants feel, based on their responses to a questionnaire called the FACIT-Fatigue Scale that asks how much fatigue the participants felt during the previous week. Higher FACIT-Fatigue scores mean less fatigue.
  - ARC levels; high levels of ARC in patients with PNH may indicate loss of RBCs due to EVH. A reduction in ARC level is a sign there is less occurrence of EVH; thus, fewer RBCs are made to replace the cells destroyed during hemolysis

## WHAT DID THIS STUDY FIND?

- 63 participants completed the 12-week primary treatment phase; the cut-off date for this interim analysis was June 28, 2022

- **A total of 37 women participated**
- **A total of 26 men participated**
- **All participants were between the ages of 25 years and 82 years**

- After 12 weeks of treatment, danicopan plus RAV/ECU compared to placebo plus RAV/ECU resulted in increased hemoglobin levels (2.94 g/dL compared to 0.50 g/dL).
- By week 12, other improvements in participants treated with danicopan plus RAV/ECU compared to placebo plus RAV/ECU included
  - More participants with a clinically meaningful increase in hemoglobin (≥ 2 g/dL) without a blood transfusion (over half compared to none)
  - More participants who remained transfusion-free (80% compared to 40%)
  - Reduced fatigue (FACIT-Fatigue score increase of 7.97 points compared to 1.85 points)
  - Improved ARC (average change of –83.8 × $10^9$/L compared to 3.5 × $10^9$/L)

## WERE THERE ANY SIDE EFFECTS?

- Headache was the most common side effect in participants who took danicopan (reported by about 10%) compared to participants who took a placebo (reported by about 4%).
    - Nausea (reported by about 8%) and joint pain (reported by about 8%) were similar between danicopan and placebo groups, but diarrhea was reported by more participants in the placebo group (12.5%) than in the danicopan group (8.2%).
- No serious side effects (in other words, problems that are life-threatening, need hospital care, or cause lasting problems) that were seen during the study were considered to be caused by danicopan or placebo.
    - Non-serious liver-related events were reported by about 12% of participants taking danicopan and about 8% taking placebo.
- One participant each in the danicopan and placebo groups dropped out of the study due to non-serious abnormal liver laboratory values.
- No participants died or had a meningococcal infection during the study, and no participants dropped out of the study because of hemolysis.

## WHAT DOES THIS MEAN FOR PATIENTS?

- Participants with PNH and EVH who took danicopan as an add-on to their standard therapy with RAV/ECU had better results than participants who took placebo plus RAV/ECU.
- Participants taking danicopan had increased hemoglobin, less fatigue, and were less likely to need blood transfusions.
- Most of the side effects with danicopan were mild, and no participants had serious side effects that were caused or made worse by danicopan.

- These positive results are very encouraging about the potential for danicopan to improve the health and quality of life of patients with PNH who require blood transfusions due to EVH while taking RAV/ECU.
- However, it is important to remember that ALPHA is just 1 study, and that it is continuing. Several studies are usually needed to decide which medicines work best for patients.
- A full analysis of all the study information will be done when once ALPHA is finished to see if the results still show that danicopan add-on to RAV or ECU is effective and safe in patients with PNH and EVH.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## GLOSSARY

- Intravascular hemolysis (IVH): premature breakdown of the body's red blood cells within blood vessels
- Extravascular hemolysis (EVH): premature breakdown of the body's red blood cells outside of blood vessels
- Complement pathway: part of the innate immune system, which responds to infection by pathogens such as bacteria