ForPatients
by Roche

paroxysmal nocturnal hemoglobinuria (PNH) Healthy Volunteers

A clinical study to look at how safe crovalimab is at different doses and how well it works to reduce certain signs of paroxysmal nocturnal hemoglobinuria (PNH)

Study to Assess Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics of RO7112689 in Healthy Volunteers and Participants With Paroxysmal Nocturnal Hemoglobinuria

Trial Status	Trial Runs In	Trial Identifier
Active, not recruiting	7 Countries	NCT03157635 2016-002128-10 BP39144

The source of the below information is the publicly available website ClinicalTrials.gov. It has been summarised and edited into simpler language.

Trial Summary:

This is a Phase I/II, first-in-human study consisting of four sequential parts and an open-label extension (OLE). The safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of single doses of crovalimab will be evaluated in healthy volunteers (HV) during part 1. The safety, tolerability, PK and PD of multiple doses of crovalimab will be evaluated in participants with paroxysmal nocturnal hemoglobinuria (PNH) in parts 2, 3, 4, and OLE of the study. Efficacy of crovalimab will be evaluated in Parts 2, 3, and 4.

Hoffmann-La Roche Sponsor	**Phase 1/Phase 2** Phase

NCT03157635 2016-002128-10 BP39144
Trial Identifiers

Eligibility Criteria:

Gender	Age	Healthy Volunteers
All	>= 18 Years & <= 75 Years	Accepts Healthy Volunteers

1. Why is the COMPOSER clinical study needed?

Paroxysmal nocturnal haemoglobinuria (PNH) is a rare genetic blood disorder that leads to the breakdown of red blood cells (‘haemolysis’) causing anaemia (low levels of

haemoglobin). This can lead to symptoms like tiredness, headaches, trouble breathing, less appetite, difficulty exercising or concentrating, and stomach or chest pain. If too many red blood cells are destroyed, a person may need to receive blood from a donor (a blood transfusion). People with PNH also have a higher risk of blood clots, which can be life-threatening. PNH is usually treated with medicines called C5 inhibitors (such as eculizumab) which reduce the destruction of blood cells. However, this treatment often means life-long regular injections or drip infusions into a vein. Only some people benefit from this treatment, and better treatment options are needed. Crovalimab is also a C5 inhibitor but works in a different way to eculizumab and is designed to be given less often. Crovalimab is an experimental drug, which means it has not been approved by health authorities for treating PNH.

This clinical study aims to test the safety of crovalimab at different doses and when given by infusion (into a vein) or injection (under the skin), to understand how the body processes and reacts to it, and to see how well it works for people with PNH.

2. How does the COMPOSER clinical study work?

This clinical study recruited healthy people and people with PNH. People with PNH could take part if they had not been previously treated or had been treated with eculizumab. The trial is in 4 parts, plus an ‘Open Label Extension’ period, or OLE. The trial is no longer recruiting participants, and Parts 1–4 have been completed.

Part 1 looked at how safe different doses of crovalimab are in healthy people without PNH. Part 1 was ‘placebo-controlled’, which means that one of the groups was given a substance with no active ingredients (also known as a ‘placebo’); it looked like the drug being tested but did not contain any real medicine. Comparing results from the different groups helps the researchers know whether any changes seen result from the drug or occur by chance. Parts 2, 3 and 4 looked at how safe different doses of crovalimab were in people with PNH and how well it worked. Researchers used the results of Parts 1–3 to decide the best dose of crovalimab to use in Part 4.

People who took part in this clinical study (participants) were given the clinical study treatment crovalimab OR placebo once only (Part 1) or crovalimab regularly for up to 5 months (Parts 2, 3 and 4). The clinical study doctor saw them regularly. These hospital visits included checks to see how the participant responded to the treatment and any side effects they had. Participants with PNH who benefited from treatment with crovalimab are able to continue treatment for up to 10 years in the OLE. The total time of participation in the clinical study was about 6 months for healthy participants and about 8 months for participants with PNH plus up to 10 years if they are taking part in the OLE. Participants can stop study treatment and leave the clinical study at any time.

3. What are the main endpoints of the COMPOSER clinical study?

The main clinical study endpoints (the main results measured in the study, including the OLE) are the number and seriousness of any side effects, and the effect of crovalimab on the body in participants with PNH.

The other clinical study endpoints include:

- How crovalimab affects the body
- How the body breaks down and gets rid of crovalimab
- How much crovalimab can be used by the body when given as an injection under the skin
- For participants with PNH only:
    - how well different doses of crovalimab work when given as injections (Part 3 only)
    - the number of participants achieving control of their haemolysis
    - how often blood transfusions are needed per month, and the amount of blood units given
    - how often uncontrolled haemolysis is seen, or blood transfusions are avoided per person, per year
    - changes in tiredness, quality of life from the start of treatment and how satisfied participants are with how the treatment is given (injection under the skin vs infusion into the vein)

4. Who can take part in this clinical study?

People could join Part 1 of this study if they were male, healthy and between 21–55 years old. People could join Parts 2, 3 or 4 of this study if they had been diagnosed with PNH, were between 18–75 years old and had not been given treatment for PNH before (Parts 2 and 4) or were being given eculizumab (Parts 3 and 4).

People could not take part in this study if they had infections or certain uncontrolled infections, they smoked within the 2 months before the study (Part 1 only), had certain kidney, heart, liver or lung diseases, or had other medical conditions such as cancer within the last 5 years, were pregnant or breastfeeding, or were planning to become pregnant during or shortly after the study.

5. What treatment will participants be given in this clinical study?

Everyone who joined Part 1 of this clinical study were split into 2 groups randomly (like flipping a coin), and given either:

- Crovalimab OR placebo, as an infusion (into the vein) or as an injection (under the skin) once only

Participants had a 6 in 10 chance (60%) of being given crovalimab and a 4 in 10 chance (40%) of being given placebo. Part 1 was blinded, which means that neither the participant nor the clinical study doctor could choose or know the group the participant was in. This

helps to prevent bias and expectations about what will happen. However, the participant's clinical study doctor could find out which group the participant is in, if their safety is at risk.

Everyone who joined Parts 2, 3 and 4 were given, and participants in the OLE continue to be given:

- Crovalimab, as an infusion (into the vein) and as an injection (under the skin)

Parts 2, 3, 4 and the OLE are open label, which means everyone involved, including the participant and the clinical study doctor, know the participant has been given crovalimab.

6. Are there any risks or benefits in taking part in this clinical study?

The safety or effectiveness of the experimental treatment or use may not be fully known at the time of the study. Most studies involve some risks to the participant. However, it may not be greater than the risks related to routine medical care or the natural progression of the health condition. People who would like to participate will be told about any risks and benefits of taking part in the clinical study, as well as any additional procedures, tests, or assessments they will be asked to undergo. All of these will be described in an informed consent document (a document that provides people with the information they need to decide to volunteer for the clinical study).

Risks associated with the clinical study drug

Participants may have side effects (an unwanted effect of a drug or medical treatment) from the drug used in this clinical study. Side effects can be mild to severe, even life-threatening, and vary from person to person. Participants will be closely monitored during the clinical study; safety assessments will be performed regularly.

Crovalimab was given to people for the first time in this study. For this reason, this drug's side effects were not known when the study started. Participants were told about the possible side effects based on laboratory studies or knowledge of similar drugs. Participants were told about any known side effects of infusions into the vein (intravenous infusions) or injections under the skin (subcutaneous injections).

Potential benefits associated with the clinical study

Participants' health may or may not improve from participation in the clinical study. Still, the information collected may help other people with similar medical conditions in the future.