ForPatients
by Roche

paroxysmal nocturnal hemoglobinuria (PNH)Paroxysmal Nocturnal HemoglobinuriaHealthy 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 information is taken directly from public registry websites such as ClinicalTrials.gov, EuClinicalTrials.eu, ISRCTN.com, etc., and has not been edited.

Official Title:

An adaptive phase I/II study to assess safety, efficacy, pharmacokinetics and pharmacodynamics of RO7112689 in healthy volunteers and patients with paroxysmal nocturnal hemoglobinuria (PNH)

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

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.

Inclusion Criteria:

Part 1 (HVs only):

- Healthy male volunteers, aged between 21 and 55 years inclusive
- Participants with a negative hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), hepatitis C antibody, and human immunodeficiency virus (HIV) test result
- Participants who have been vaccinated against hepatitis B
- No evidence of Neisseria meningococci in nasopharyngeal swab
- Neisseria meningitidis vaccination against serogroups B and A, C, W, and Y
- Non-smokers, or former smokers, who have not smoked for at least 60 days prior to screening

Parts 2, 3 and 4 (PNH participants only):

- Male or female participants with PNH between 18 and 75 years of age
- Neisseria meningitidis vaccination in accordance with most current local guidelines or standard of care (SOC) for participants at increased risk for meningococcal disease (Part 2 and 4)
- Participant has been vaccinated with Neisseria meningitidis vaccine(s) in accordance with most current local guidelines or SOC for participants at increased risk for meningococcal disease or is being revaccinated if applicable (Part 3 and 4)
- Antibiotic prophylaxis for meningococcal infection must be initiated prior to initiation of crovalimab therapy if the time period between initial Neisseria meningitidis vaccination and first dose of crovalimab is less than 2 weeks (Part 2 and 4)
- Antibiotic prophylaxis of meningococcal infection may be initiated prior to initiation of crovalimab therapy based on local guidelines or SOC for participants at increased risk for meningococcal disease e.g., splenectomized patients (Parts 2 and 4)
- Stable dose for greater than or equal to (>/=) 28 days prior to screening of other therapies (immunosuppressant therapy, corticosteroids, iron supplements)

Part 2 and 4 (currently untreated PNH participants who are candidates for treatment with complement inhibitors only):

- PNH participants who have not been treated with any complement inhibitor or if previously treated stopped treatment due to lack of efficacy based on a single missense C5 heterozygous mutation
- Serum LDH levels at least 1.5-fold above the ULN at screening
- Hepatitis B participants can be enrolled if their liver function test values are less than 2 x ULN and there is no liver function impairment

Part 3 and 4 (PNH participants currently treated with eculizumab only):

- PNH participants who have been treated continuously with eculizumab for at least 3 months preceding enrollment in the trial
- Participants receive regular infusions of eculizumab
- Subjects with a negative hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), hepatitis C antibody, and HIV test result

OLE only - PNH participants:

- PNH participants who have completed Parts 2, 3 and 4 respectively
- PNH participants who derived, in the investigator's opinion, benefit from treatment with crovalimab
- Vaccination currency for Neisseria meningitidis serotypes A, C, W, Y and B should be maintained throughout the OLE

All Parts:

- Female participants should use proper means of contraception

Exclusion Criteria:

Part 1 (HVs only):

- Any clinically relevant history or the presence of moderate to severe respiratory, renal, hepatic, gastrointestinal, hematological, lymphatic, neurological, cardiovascular, psychiatric, musculoskeletal, or connective tissue disease
- Any major illness within 1 month before the screening
- Prior splenectomy
- History of clinically significant hypersensitivity (example: drugs, excipients) or allergic reactions
- History or presence of clinically significant electrocardiogram (ECG) abnormalities or cardiovascular disease
- Any contra-indication for receiving Neisseria meningitides vaccination and antibiotic prophylaxis therapy as required in the study
- Congenital or acquired complement deficiency
- Carriers of Neisseria meningitides based on cultures from nasopharyngeal swabs
- Known active viral, bacterial or fungal infection including herpes, herpes zoster or cold sores, during the last 14 days prior to first study drug administration
- Signs of parasitic infection (example: eosinophilia, diarrhea)
- History of significant recurrent infections in the opinion of the investigator

Parts 2, 3 and 4 - PNH participants only:

- Evidence of moderate to severe concurrent renal, liver, cardiac, pulmonary or gastrointestinal disease not related to PNH as determined by the investigator
- History of an illness that, in the opinion of the study investigator, might confound the results of the study or that poses an additional risk to the participant by his or her participation in the study
- History of bone marrow transplantation
- Treatment with azathioprine or erythrocyte-stimulating agents within 14 days prior to first study drug administration
- Splenectomy <1 year before start of crovalimab.

Part 3 and 4 - PNH patients only:

- Any evidence of sero-positive auto-immune connective tissue diseases (such as systemic lupus erythematosus, or rheumatoid arthritis)
- Any evidence of active inflammatory conditions (including inflammatory bowel disease, or cryoglobulinemia)

All Parts:

- Under active therapy with intravenous immunoglobulin (IVIG)
- Mentally incapacitated or history of a clinically significant psychiatric disorder over the previous 5 years
- Known or suspected hereditary complement deficiency
- History of meningococcal meningitis
- History of allergic or anaphylactic reactions to human, humanized, or murine monoclonal antibodies or known hypersensitivity to any constituent of the product

- Any major episode of infection requiring hospitalization or treatment with intravenous (IV) antibiotics within 28 days prior to screening or oral antibiotics within 2 weeks prior to screening and up to first study drug administration
- History of or currently active primary or secondary immunodeficiency, including known history of human immunodeficiency virus (HIV) infection
- Evidence of chronic active hepatitis C infection
- Evidence of malignant disease including myelodysplastic syndrome, or malignancies diagnosed within the previous 5 years
- Pregnant or breastfeeding, or intending to become pregnant during the study, including the OLE period, within 46 weeks (approximately 10.5 months) after the final dose of crovalimab