PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROLLED, MULTICENTER STUDY EVALUATING THE EFFICACY AND SAFETY OF CROVALIMAB VERSUS ECULIZUMAB IN ADULT AND ADOLESCENT PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA NOT PREVIOUSLY TREATED WITH COMPLEMENT INHIBITORS**
PROTOCOL NUMBER:	BO42162
VERSION NUMBER:	1
EUDRACT NUMBER:	2019-004931-21
IND NUMBER:	131343
TEST PRODUCT:	Crovalimab (RO7112689)
PHASE:	Phase III
INDICATION:	Paroxysmal Nocturnal Hemoglobinuria
SPONSOR:	F. Hoffmann-La Roche Ltd Chugai Pharmaceutical Co. Ltd

Objectives and Endpoints

This is a Phase III, randomized, open-label, active-controlled, multicenter study designed to evaluate the efficacy and safety of crovalimab compared to eculizumab in patients with PNH who have not been previously treated with a complement-inhibitor therapy.

Specific objectives and corresponding endpoints for the study are outlined below.

Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of crovalimab compared to eculizumab, based on the non-inferiority assessment of the following co-primary endpoints:

- Proportion of patients who achieve transfusion avoidance (TA) from baseline through Week 25 (after 24 weeks on treatment)

  TA is defined as patients who are packed RBC (pRBC) transfusion-free and do not require transfusion per protocol-specified guidelines.
- Proportion of patients with hemolysis control, measured by LDH ≤1.5 × upper limit of normal (ULN) from Week 5 through Week 25 (as measured at the central laboratory)

The superiority of crovalimab vs. eculizumab will be evaluated provided that non-inferiority has first been demonstrated.

Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate non-inferiority of crovalimab compared to eculizumab on the basis of the following endpoints:

- Proportion of patients with breakthrough hemolysis (BTH) from baseline through Week 25

  BTH is defined as at least one new or worsening symptom or sign of intravascular hemolysis (fatigue, hemoglobinuria, abdominal pain, shortness of breath [dyspnea], anemia [hemoglobin <10 g/dL], a major adverse vascular event [MAVE, including thrombosis], dysphagia, or erectile dysfunction) in the presence of elevated LDH ≥2 × ULN after prior reduction of LDH to ≤1.5 × ULN on treatment.
- Proportion of patients with stabilization of hemoglobin from baseline through Week 25

  Stabilized hemoglobin is defined as avoidance of a ≥2 g/dL decrease in hemoglobin level from baseline, in the absence of transfusion.
- Mean change from baseline to Week 25 in fatigue, as assessed by the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue (for adults aged ≥ 18 years)

The superiority of crovalimab vs. eculizumab will be evaluated provided that non-inferiority has first been demonstrated.

Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to evaluate the treatment effect of crovalimab compared to eculizumab on the basis of the following endpoints:

- Total number of units (based on local equivalent) of pRBCs transfused per patient by Week 25
- Proportion of patients with LDH ≤1 ULN from Week 5 through Week 25
- Time from baseline to the first time LDH ≤1 ×ULN
- Time from baseline to the first time LDH ≤1.5 ×ULN
- Percent change from baseline to Week 25 in LDH levels
- Proportion of patients who reach a hemoglobin level of at least 10 g/dL, without subsequent decrease below 9 g/dL, in the absence of a transfusion
- Proportion of patients experiencing MAVE from baseline through Week 25
- Mean change from baseline to Week 25 in Physical Functioning, Role Functioning, and Global Health Status/Quality of Life (QoL) scales of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life–Core 30 (QLQ-C30), and select disease-related symptoms (abdominal pain, headaches, dyspnea, dysphagia, chest pain, and erectile dysfunction) of the EORTC Item Library (for adults aged ≥18 years)
- Mean change from baseline to Week 25 in Pediatric Quality of Life (PedsQL) Multidimensional Fatigue Scale (MFS), and the Physical Functioning scale of the PedsQL Core (for adolescents aged 12–17 years)
- Mean treatment satisfaction with crovalimab or eculizumab, as assessed by the Treatment Satisfaction Questionnaire for Medication-9 (TSQM-9) at Week 25 (for adults aged ≥18 years)
- Proportion of patients with preference for crovalimab or eculizumab at Week 41, for patients randomized to eculizumab who switch to crovalimab after 24 weeks of eculizumab treatment, as assessed through use of the Patient Preference Questionnaire developed by the Sponsor
- Mean change over time in quality of life, as assessed by Quality of Life Questionnaire – Aplastic Anemia/Paroxysmal Nocturnal Hemoglobinuria (QLQ-AA/PNH), and in overall health status, as assessed by Patient Global Impression of Severity Survey (PGIS) (for adults aged ≥ 18 years)

Study Design

Description of Study

This randomized, multicenter, open-label, active controlled Phase III clinical study will enroll patients aged 12 years or older, with a body weight ≥40 kg, diagnosed with PNH, who have not been previously treated with a complement-inhibitor therapy. Approximately 200 patients will be randomized in a 2:1 ratio to the following regimens:

- Crovalimab