



Management of Acute Hemolytic Events in Paroxysmal Nocturnal Hemoglobinuria Patients Taking Pegcetacoplan

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Trial-in-Progress Objective

Evaluate the long-term safety and efficacy of pegcetacoplan dose adjustments for acute hemolysis in adult patients with Paroxysmal Nocturnal Hemoglobinuria

Background

- Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired, life-threatening disease characterized by hemolysis and thrombosis^{1,2,3}

- Current C5-inhibitors, such as eculizumab and ravulizumab, block complement-mediated intravascular hemolysis (IVH)

- These therapies, however, do not prevent C3-mediated extravascular hemolysis (EVH), manifesting as persistent anemia in up to 72% of treated patients and transfusion dependence in up to 36% of patients⁴

- Pegcetacoplan (PEG) is a C3-inhibitor recently approved by the Food and Drug Administration that controls IVH and prevents EVH

- In the PEGASUS Phase 3, multi-center, active-comparator controlled, randomized trial (NCT03500549), improvements in hemoglobin levels from baseline to Week 16 demonstrated the superiority of PEG over eculizumab⁵ (**Fig. 1**)

- 85% of patients receiving PEG achieved transfusion independence compared to 15% of patients on eculizumab in the PEGASUS study⁵

Main Study Objectives

Determine the long-term safety and efficacy of PEG dose adjustments in treated patients with PNH exhibiting acute hemolysis

Acute Hemolysis Sub-Study Rationale

- Patients experiencing acute hemolysis while participating in previous PEG trials had lower than projected PEG serum concentrations

- Therefore, increasing exposure to a higher and sustained PEG regimen is posited to help with immediate management of hemolysis and minimize the recurrence of acute hemolysis (**Fig. 2**)

Methods

This is a multicenter, open-label, nonrandomized extension study (NCT03531255) using PEG in patients with PNH who have completed a prior PEG study (**Fig. 2**).

1) Main Study Enrollment Criteria

The **main study** will determine long-term safety and efficacy of PEG dosing via subcutaneous infusion on complement-mediated hemolytic activity, hemoglobin levels, and transfusion independence in patients with PNH (**Table 1**).

- Adult patients (≥ 18 years of age) who have completed a previous PEG trial were eligible for enrollment (**Fig. 2**)

2) Acute Hemolysis Sub-Study and Enrollment Criteria

Approximately 11-27% of patients with PNH receiving complement inhibitors experience a return of hemolytic activity, defined as breakthrough hemolysis (BTH),⁶ characterized by new or worsening symptoms of acute hemolysis and dysregulated lactate dehydrogenase (LDH) levels.⁶

This **sub-study** will address the safety and efficacy (**Table 1**) of intensive intravenous or subcutaneous infusions of PEG treatments during acute hemolytic events and was devised with the following patient inclusion criteria:

- Patients from the main study (described above) could exercise the option to participate in this sub-study

- Lactate dehydrogenase (LDH) >2 times the upper limit of normal (ULN)

- Presence of at least one new or deteriorating sign or symptom of acute hemolysis (e.g., decrease in hemoglobin, hemoglobinuria, fatigue)

Management of Intravascular and Extravascular Hemolysis

- PEG controls both intravascular hemolysis (IVH) and extravascular hemolysis (EVH), leading to an increased PNH clonal red blood cell (RBC) population and reduced residual normal RBCs

- Consequently, BTH may lead to a larger drop in hemoglobin and potentially severe acute anemia

- It is therefore recommended to closely monitor patients switching from C5-inhibitors to PEG who are at high risk of developing BTH

- Physicians should consider immediate RBC transfusion, PEG dose adjustment, or acute administration of eculizumab to control IVH in such patients with PNH

The Need for C3-Inhibition

- Prompt identification and treatment of any underlying complement amplifying conditions are warranted

- Emergence of ubiquitous EVH and persistent anemia with C5-inhibitor eculizumab constitute more the rule than the exception^{3,4}

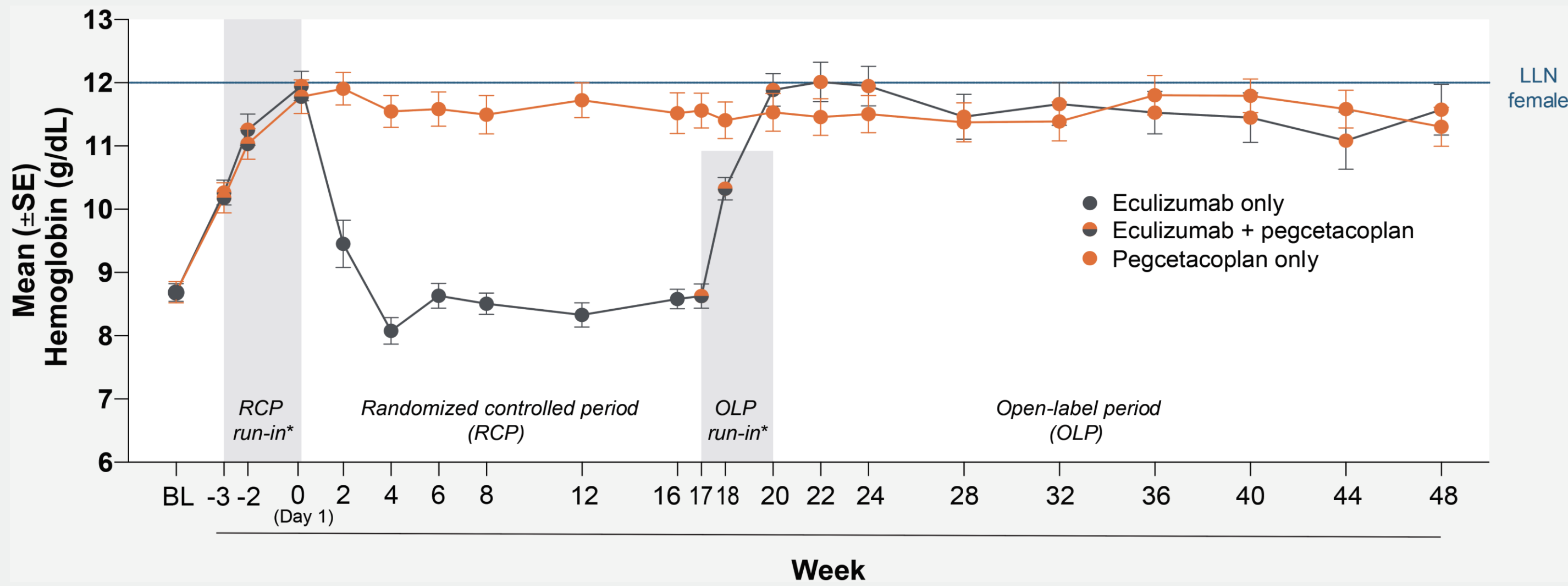
- In the Phase 3 PEGASUS trial which examined PEG vs. eculizumab in patients with suboptimal response to eculizumab, patients receiving PEG were more effectively managed compared to eculizumab (**Fig. 1**)

- In the PEGASUS study, PEG patients had less than half as many hemolytic events, and an improvement in mean hemoglobin of 3.8g/dL at Week 16⁵

- Thus, there is a critical need for proximal complement C3-inhibition via PEG, given that 85% of patients achieve transfusion independence with PEG, as compared to only 15% with eculizumab, along with improved fatigue scores and reticulocyte counts⁵

- The 48-week PEGASUS trial data also demonstrate durable efficacy and acceptable safety profiles for PEG⁷

Figure 1: Hemoglobin Levels Over 48 Weeks (PEGASUS Study)



*Pegcetacoplan run-in periods: 1) before randomization, for both PEG-to-PEG and ECU-to-PEG treatment groups; and 2) before the open-label period, for the ECU-to-PEG treatment group only. All observed/uncensored for transfusion data
BL, baseline; LLN, lower limit of normal; OLP, open-label period; RCP, randomized controlled period; SE, standard error

Fig. 1. Hemoglobin Improvements with Pegcetacoplan Treatment in the PEGASUS Study

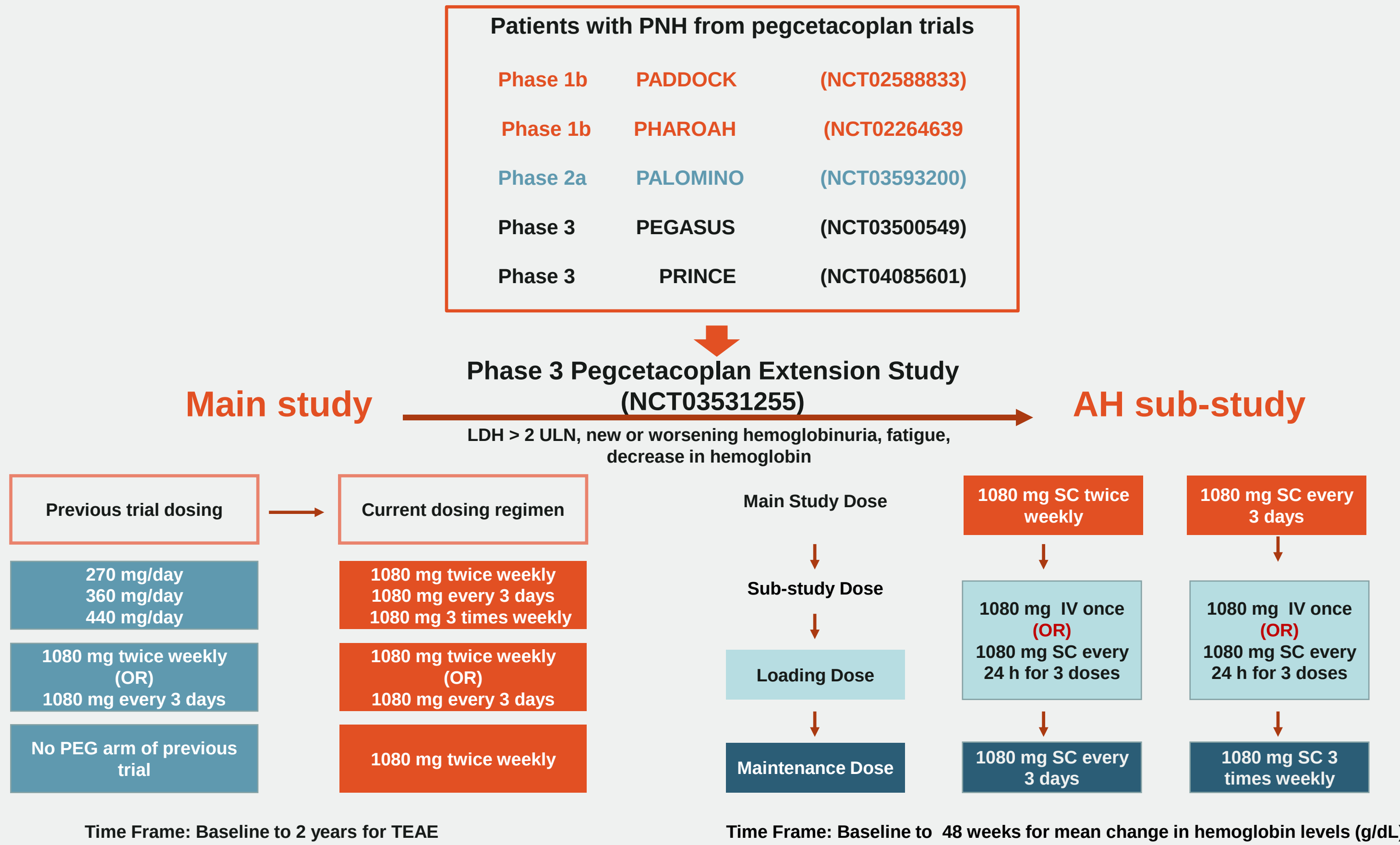
- Sustained improvements in hemoglobin levels from Week 16 through Week 48 were seen in patients on a PEG-PEG regimen (**Fig. 1**; no significant difference in hemoglobin levels between Week 16 and Week 48 in the PEG-to-PEG group; $p=0.14^a$)

- Hemoglobin levels measured improved after switching to pegcetacoplan; patients switching from eculizumab to PEG after Week 16 demonstrated significant improvements ($p<0.0001^a$) at Week 48 compared to Week 16 (**Fig. 1**)

^aUncorrected/nominal p-value

Study Design

Figure 2: Schematic of Study Design



PNH, paroxysmal nocturnal hemoglobinuria; AH, acute hemolysis; LDH, lactate dehydrogenase; ULN, upper limit of normal; PEG, pegcetacoplan; IV, intravenous; SC, subcutaneous; TEAEs, treatment-emergent adverse events

Table 1: Main and Sub-Study Outcome Measures

2-Year Endpoints	
Safety Endpoints	• Incidence and severity of TEAEs: mild, moderate, and severe
	• Incidence of thromboembolic events, lab, and ECG parameters
Week 48 Endpoints	
Efficacy Endpoints	• Change from baseline in hemoglobin levels, LDH levels, indirect bilirubin levels, ARC, FACIT-Fatigue score
	• Freedom from RBC transfusions
Week 16 Endpoints	
Pharmacodynamic Endpoints	• Complement levels, absolute changes in C3
	• Absolute values and relative changes in baseline percentages for CH 50, AH 50
Pharmacokinetic Endpoints	• C3 coating on RBC
	• Changes in baseline distribution of clonal PNH RBC types II and III
Pharmacokinetic Endpoints	• Detection of anti-PEG antibodies and anti-PEG peptides
	• PEG concentrations

TEAEs, treatment-emergent adverse events; ECG, electrocardiogram; LDH, lactate dehydrogenase; ARC, absolute reticulocyte count; FACIT, Functional Assessment of Chronic Illness Therapy; CH 50, classical pathway hemolytic activity; AH 50, alternative pathway hemolytic activity; RBC, red blood cells; PEG, pegcetacoplan

Results

- Initial trial results are anticipated upon study completion in 2022

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