Pegcetacoplan PNH – Biliary Sepsis in PEGASUS

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Apellis recommends the use of its products only as directed in the approved Prescribing Information. Please refer to the EMPAVELI Prescribing Information including the Boxed WARNING and Risk Evaluation and Mitigation Strategy (REMS) program for complete product information.

EMPAVELI® (pegcetacoplan) injection for subcutaneous use, is a complement inhibitor indicated for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH).[1]

Apellis has not conducted controlled studies to evaluate the appropriate management of gastrointestinal adverse events following the subcutaneous (SC) administration of pegcetacoplan. Therefore, appropriate therapy for managing treatment-related adverse events should be determined by the treating physician.

RELEVANT PRESCRIBING INFORMATION

Study in Complement-Inhibitor Experienced Adult Patients with PNH (Study APL2-302)

The data described reflect the exposure of EMPAVELI in 80 adult patients with PNH who received EMPAVELI (n=41) or eculizumab (n=39) at the recommended dosing regimens for 16 weeks.[1] Serious adverse events were reported in 7 (17%) patients with PNH receiving EMPAVELI. The most common serious adverse reaction in patients treated with EMPAVELI was infections (5%). The most common adverse reactions (≥10%) with EMPAVELI were injection-site reactions, infections, diarrhea, abdominal pain, respiratory tract infection, viral infection, and fatigue.

Clinically relevant adverse reactions in less than 5% of patients include:

- Intestinal ischemia
- Biliary sepsis
- Hypersensitivity pneumonitis

DEFINING BILIARY SEPSIS

Although biliary sepsis is diagnosed clinically when there are systemic signs of infection combined with features of biliary tract disease, organisms may be cultured from bile in the absence of symptoms.[2] Thus, the ideal definition of biliary infection should be based on the number of organisms isolated from bile. Such a definition is impracticable, though, because bile is difficult to collect.

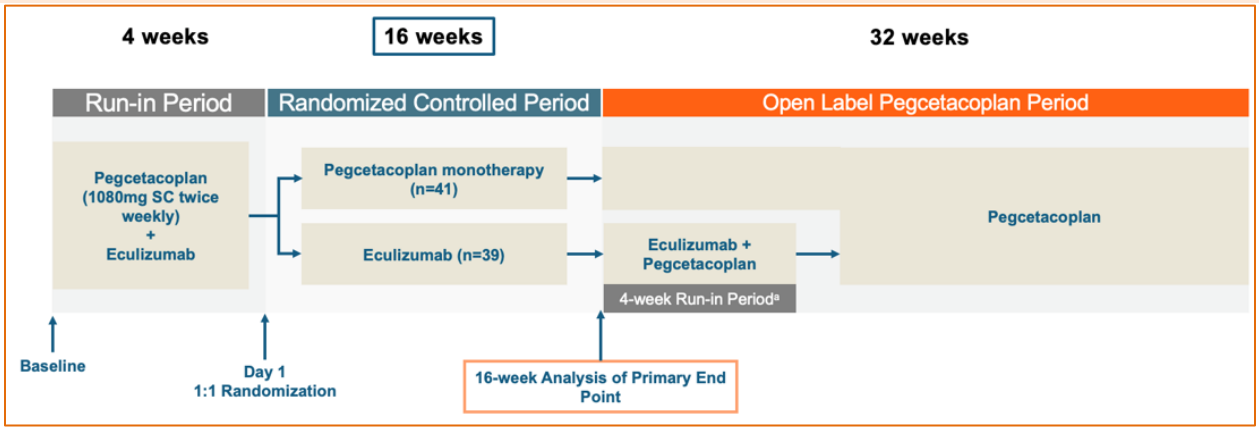
PEGASUS

Study Design

PEGASUS (NCT03500549), a Phase 3, randomized, multicenter, open-label, active-comparator controlled study sought to establish the efficacy and safety of SC pegcetacoplan compared with those of eculizumab in patients with PNH who continued to have hemoglobin levels <10.5 g/dL while on treatment with eculizumab for ≥3 months.[3] Patients completed a run-in period of 4 weeks with pegcetacoplan plus eculizumab before 1:1 randomization to monotherapy with pegcetacoplan (41 patients, 1080 mg SC, twice weekly) or eculizumab (39 patients, continuing current dosing regimen) for 16 weeks (**Figure 1**).

All patients (n=77) who completed the randomized controlled period entered the 32-week open-label period (Week 17 to Week 48) and received pegcetacoplan (1080 mg SC, twice weekly).[4] Patients who received eculizumab in the randomized controlled period received pegcetacoplan in addition to eculizumab for 4 weeks (Week 17 to Week 20) before starting pegcetacoplan monotherapy. Increasing the dosage of pegcetacoplan to 1080 mg every third day was allowed if a patient's LDH level was >2 times the upper limit of normal (ULN).

Figure 1. PEGASUS Study Design[3]



Occurrence of Biliary Sepsis

At Week 48, the end of the open-label period, biliary sepsis occurred in one patient.[4]

The patient experiencing biliary sepsis was a 70-year-old man (height: 183 cm; weight: 83 kg; body mass index: 24.78 kg/m^2) who had been diagnosed with PNH in 2017.[5] The patient's relevant medical history included inguinal hernia (2004), hypertension (2017), ischemic stroke (2017), asthenia (2018), orchitis (2019), benign prostatic hyperplasia (2019), iron overload (2019), cholangitis (2019), hemianopia (2019), dyspnea (2019), Budd-Chiari syndrome (2017), and hepatic vein thrombosis (2017).

On Study Day 182 during the open-label study period, the patient experienced severe biliary sepsis, severe hemolysis, and severe acute kidney injury and presented with mild pancreatitis, moderate pyrexia, and severe hyperbilirubinemia.[5] There was no gallstone migration on imaging. Treatment included intravenous (IV) ceftriaxone for fever and IV metronidazole for fever and hyperbilirubinemia. Also, glucose 5% was administered as needed for acute kidney injury (stopped on Study Day 221). Blood cultures performed before and after antibiotics initiation were negative. One urinary culture was positive for *Escherichia coli* (possible contamination; there was no leukocyturia). A second urinary culture was negative.

On Study Day 183, severe acute respiratory failure was reported.[5] The patient experienced life-threatening hypoxia following a coughing crisis, which required an ICU admission and up to 12 L/min of oxygen therapy. The hypoxia was quickly reversed, and the event of severe acute respiratory failure was reported as resolved on the same day. The hypoxia was deemed as probably related to sepsis because no pulmonary lesion was found.

On Study Day 184, the patient started IV heparin 46,000 IU once daily for thrombosis prevention.[5] The patient had 3 packed red blood cell (PRBC) transfusions (1 unit each day) on Study Days 185, 188, and 189 with pretransfusion hemoglobin (Hb) levels of 6.4 g/dL, 7 g/dL, and 7.3 g/dL, respectively.

On Study Day 188, the antibiotics ceftriaxone and metronidazole were discontinued.[5] Fever, pancreatitis, and hyperbilirubinemia resolved; however, the patient remained hospitalized because of persistent hemolysis and only partial recovery from kidney failure.

On Study Day 189, the patient's SAE of biliary sepsis was downgraded to moderate in severity.[5] The event of acute kidney injury improved to moderate severity on Study Day 197 and resolved on Study Day 221. In total from Study Day 185 to 214, 15 units of PRBC was received. On Study Day 219 the SAE of hemolysis resolved. The dosage of pegcetacoplan was increased to every 3 days because of the events of severe biliary sepsis, hemolysis, acute kidney injury, and hyperbilirubinemia.

The investigator assessed the event of biliary sepsis as related to pegcetacoplan and not applicable to eculizumab, whereas the events of hemolysis, acute respiratory failure, and acute kidney injury were not related to pegcetacoplan and not applicable to eculizumab.[4,5] The patient completed the open-label period.

REFERENCES

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2. Dooley JS, Hamilton-Miller JM, Brumfitt W, Sherlock S. Antibiotics in the treatment of biliary infection. *Gut*. 1984;25(9):988-998.
3. Hillmen P, Szer J, Weitz IC, et al. Pegcetacoplan versus eculizumab in paroxysmal nocturnal hemoglobinuria. *N Engl J Med*. 2021;384:1028-1037.
4. Peffault de Latour R, Szer J, Weitz IC, et al. Pegcetacoplan versus eculizumab in patients with paroxysmal nocturnal haemoglobinuria (PEGASUS): 48-week follow-up of a randomised, open-label, phase 3, active-comparator, controlled trial. *Lancet Haematol*. 2022;9(suppl):e648-e659.
5. Data on File: DOF-PEG-PNH-0035.