Efficacy and safety of intensive pegcetacoplan dosing for the treatment of acute hemolysis in patients with paroxysmal nocturnal hemoglobinuria

P812

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AIM

Examine efficacy and safety of intensive subcutaneous (SC) or intravenous (IV) pegcetacoplan dosing to manage acute hemolysis (AH) in a subset of patients from the pegcetacoplan open-label extension (OLE) study.

INTRODUCTION

Paroxysmal nocturnal hemoglobinuria (PNH) is characterized by complement-mediated hemolysis and increased thrombosis risk.[1] Pegcetacoplan is the first complement C3 and C3b inhibitor approved by the EMA/FDA for treatment of adults with PNH, and targets both intravascular and extravascular hemolysis.[2,3]

The ongoing OLE APL2-307 study (NCT03531255) evaluates the long-term safety and efficacy of pegcetacoplan in patients with PNH who had completed previous Phase 1–3 pegcetacoplan trials.

All patients with PNH on complement inhibitors are at risk of AH events. As expected, some pegcetacoplan-treated patients in the OLE study experienced AH events. We hypothesized that intensive pegcetacoplan dosing may help manage AH by achieving an immediate increase in pegcetacoplan concentration.

METHODS

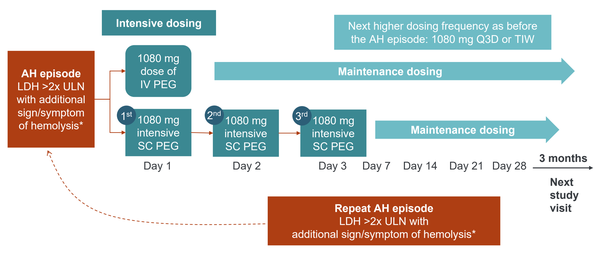
Patients enrolled in the OLE study who experienced AH events warranting immediate intervention were offered intensive pegcetacoplan (**Figure 1**).[4]

Eligibility criteria for intensive dosing included lactate dehydrogenase (LDH) >2× the upper limit of normal (ULN) and 1 new or worsening sign/symptom of hemolysis (e.g. decreased hemoglobin [Hb], hemoglobinuria, thrombosis, or fatigue).

Patients with AH on a steady-state pegcetacoplan dose of 1080 mg SC twice weekly received intensive pegcetacoplan treatment: a single dose of 1080 mg IV, or 1080 mg SC on 3 consecutive days. After this, an increased maintenance regimen was administered at the next higher dosing frequency as before the AH episode (1080 mg SC every 3 days or 3 times weekly). A patient may receive repeated rounds of intensive dosing with a minimum gap of 14 days between rounds.

Changes in Hb, LDH, and Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) score were described, and adverse events were evaluated.

Figure 1. Intensive pegcetacoplan treatment regimens[4]



* Decreased Hb, hemoglobinuria, thrombosis, or fatigue.
AH, acute hemolysis; Hb, hemoglobin; IV, intravenous; LDH, lactate dehydrogenase; PEG, pegcetacoplan; Q3D, every 3 days; SC, subcutaneous; TIW, 3 times weekly; ULN, upper limit of normal.

RESULTS

Baseline characteristics

- As of data cutoff (31/1/2023), 22 of 137 patients who entered the OLE study received intensive pegcetacoplan to manage an AH event
- **Table 1** summarizes the baseline characteristics of the OLE study; patients enrolled in the AH substudy had similar baseline characteristics as the overall OLE study population
- **Table 2** shows patient baseline characteristics at the start of intensive pegcetacoplan dosing in the AH substudy
  - Median (interquartile range [IQR]) LDH/ULN ratio was 6.9 (4.3, 11.6); mean (standard deviation, [SD]) Hb level and FACIT-Fatigue score were 9.0 (1.9) g/dL and 31.4 (15.9), respectively
- Dosing prior to the start of intensive pegcetacoplan was twice weekly (n=11), every 3 days (n=6), and 3 times weekly (n=5)

Table 1. OLE study baseline characteristics

Baseline characteristics	AH substudy population (N=22)	OLE study total population (N=136)
Age, mean (SD), years	45.7 (17.2)	46.4 (14.6)
Female, n (%)	10 (45.5)	76 (55.9)
Weight, mean (SD), kg	69.9 (13.8) n=20	70.2 (15.4) n=131
BMI, mean (SD), kg/m^2	25.7 (5.0) n=18	25.7 (5.2) n=124
LDH level, median (range), U/L	190.0 (123, 2089)	184.0 (69, 3459)
Hb level, mean (SD), g/dL	11.1 (2.1)	11.6 (2.2)
ARC, mean (SD), 10^9 cells/L	82.9 (23.6)	88.3 (40.4)
Indirect bilirubin level, mean (SD), µmol/L	11.5 (6.5)	11.6 (7.5)
Total FACIT-Fatigue score, mean (SD)	44.4 (11.0)	42.9 (8.7)

AH, acute hemolysis; ARC, absolute reticulocyte count; BMI, body mass index; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue; Hb, hemoglobin; LDH, lactate dehydrogenase; OLE, open-label extension; SD, standard deviation.

Table 2. Intensive pegcetacoplan for AH substudy baseline characteristics

Patient characteristics prior to the start of intensive pegcetacoplan	AH substudy population (N=22)
Time since diagnosis of PNH to Day 1 of AH substudy, mean (SD), years	11.0 (6.6)
LDH/ULN ratio, median (IQR)	**6.9 (4.3, 11.6)**
Hb level, mean (SD), g/dL	**9.0 (1.9)**
ARC, mean (SD), 10^9 cells/L	153.6 (65.9)
Indirect bilirubin level, mean (SD), µmol/L	30.6 (19.9)
Total FACIT-Fatigue score, mean (SD)	**31.4 (15.9)**

AH, acute hemolysis; ARC, absolute reticulocyte count; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue; Hb, hemoglobin; IQR, interquartile range; LDH, lactate dehydrogenase; OLE, open-label extension; PNH, paroxysmal nocturnal hemoglobinuria; SD, standard deviation.

Efficacy outcomes

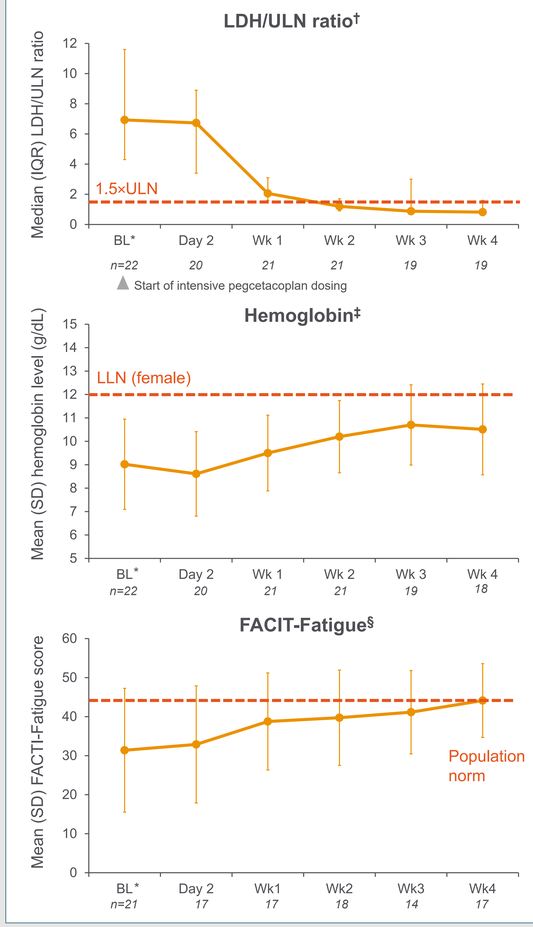
- 22 AH events (9 severe, 10 moderate, 3 mild) led to initiation of Round 1 of intensive pegcetacoplan dosing (SC n=15, IV n=7)
  - In the 28 days prior to the AH events, 2 patients received a vaccination and 8 patients experienced an infection, which were potential complement-amplifying conditions

Efficacy outcomes (continued)

- **After 1 round of intensive dosing, AH events resolved in 77% of patients (17/22)**; and after 2 rounds of intensive dosing, AH events resolved in 4 additional patients and did not resolve in 1 patient*
- **Median time to AH resolution was 14.5 days**, as reported by investigators

* Severe adverse event hemolysis started on day 1 of pegcetacoplan treatment in the antecedent study 308 and lasted for 1174 days till discontinuation; in the AH study patient demonstrated a transient LDH reduction with nadir after day 7 after both rounds of intensive treatment. Pegcetacoplan treatment in this patient relieved transfusion requirement from 1 unit of packed red blood cells every 14 days prior the 1st pegcetacoplan dose to every 25 days onwards.

Figure 2. LDH/ULN ratio, Hb, and FACIT-Fatigue score from first dose of intensive pegcetacoplan dosing in Round 1.



* Baseline of substudy. † LDH reference range: 113–226 U/L. ‡ Hb LLN (female): 12 g/dL. § FACIT-Fatigue score US population norm[5]: 44. BL, baseline; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue; IQR, interquartile range; LDH, lactate dehydrogenase; LLN, lower limit of normal; SD, standard deviation; ULN, upper limit of normal; Wk, Week.

Efficacy outcomes (continued)

- **Within 1 week of initiating intensive dosing,** there was a **rapid decrease in median LDH level** and **concomitant improvements in Hb** and **FACIT-Fatigue score (Figure 2)**
  - By Week 2, median (IQR) LDH/ULN ratio decreased from 6.9 (4.3, 11.6) at baseline to 1.2 (0.9, 1.7)
  - Mean (SD) Hb increased from 9.0 (1.9) g/dL at baseline to 10.5 (1.9) g/dL at Week 4
  - Mean (SD) FACIT-Fatigue score improved steadily from 31.4 (15.9) at baseline to 44.1 (9.5) at Week 4, reaching the population norm[5]
  - In 1 patient a C5 inhibitor was used to treat an AH event contemporaneously with Round 1 of intensive pegcetacoplan dosing

Safety outcomes

- During intensive dosing of the 22 AH patients in the substudy, **most treatment-emergent adverse events (TEAEs) were mild/moderate** (**Table 3**); there were **no new safety signals**
  - **There were no cases of meningitis, thrombosis, or death**
  - There was 1 TEAE (aplastic anemia) leading to pegcetacoplan discontinuation during the overall substudy follow up

Table 3. Safety summary in the AH substudy

Category	Round 1 Day 1–21 (N=22)	Overall substudy follow-up* (N=22)
Any TEAEs, n (%)	9 (40.9)	20 (90.9)
Total number of TEAEs, n	14	117
Pegcetacoplan-related TEAEs, n (%)	2 (9.1)	7 (31.8)
Injection site-related TEAEs, n (%)	0	4 (18.2)
Serious TEAEs, n (%)	3 (13.6)†	7 (31.8)
TEAEs leading to pegcetacoplan discontinuation, n (%)	**0**	**1 (4.5)§**
TEAEs leading to death, n (%)	**0**	**0**
TEAEs of special interest, n (%)	5 (22.7)	15 (68.2)
Hemolytic disorders	4 (18.2)	11 (50.0)
Hypersensitivity	1 (4.5)	3 (13.6)
Infections	0	10 (45.5)
Sepsis	1 (4.5)‡	2 (9.1)
Meningitis	**0**	**0**
Thrombosis	**0**	**0**

*As of 31/1/2023, patients have received up to 4 rounds of intensive pegcetacoplan in the substudy; median (range) pegcetacoplan exposure: 277 (96, 475) days. †Considered pegcetacoplan-related in 1 patient (sepsis‡). ‡Sepsis with no further infections. §One patient discontinued pegcetacoplan due to aplastic anemia. AH, acute hemolysis; TEAE, treatment-emergent adverse event.

CONCLUSIONS

- Preliminary data suggest that **intensive SC or IV pegcetacoplan dosing was effective, safe, and well-tolerated in the management of AH events** in patients receiving pegcetacoplan
  - **Median time to AH resolution was 14.5 days** from the date of the 1st intensive dosing as reported by the investigator
  - There were **timely improvements in LDH, Hb, and FACIT-Fatigue score** following intensive pegcetacoplan dosing
  - There were **no events of thrombosis** and **no pegcetacoplan discontinuations due to an AH event**; most TEAEs were mild/moderate and there were **no new safety signals**

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CONTACT INFORMATION

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ABBREVIATIONS: AH acute hemolysis; ARC, absolute reticulocyte count; BL, baseline; C3, complement protein 3; FACIT-Fatigue: The Functional Assessment of Chronic Illness Therapy – Fatigue; Hb, hemoglobin; IQR, interquartile range; IV, intravenous; LDH, lactate dehydrogenase; LLN, lower limit of normal; OLE, open-label extension; PEG, pegcetacoplan; PNH, paroxysmal nocturnal hemoglobinuria; Q3D, every 3 days; SC, subcutaneous; SD, standard deviation; TEAE, treatment-emergent adverse event; TIW, 3 times weekly; ULN, upper limit of normal; Wk, Week.

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