Characterization of clinically significant breakthrough hemolysis in patients with paroxysmal nocturnal hemoglobinuria treated with pegcetacoplan

P819

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Aim

Characterize **clinically significant breakthrough hemolysis** (cs-BTH) events during pegcetacoplan treatment in terms of **incidence, duration, potential concomitant complement-amplifying conditions** (CACs), and **management strategies**

INTRODUCTION

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

All patients with PNH on complement inhibition are **at risk of breakthrough hemolysis** (BTH). BTH can be **triggered by CACs**, such as infection or vaccination.[4,5] If a BTH occurs on pegcetacoplan, experts recommend **red blood cell (RBC) transfusion, pegcetacoplan dose adjustment**, or **short-term** administration of **eculizumab** to control the acute episode.[6-9] Emerging evidence suggests BTH on pegcetacoplan can be **effectively managed by intensive pegcetacoplan dosing**.[6]

The **integrated analysis** of data from the PEGASUS (NCT03500549) and PRINCE (NCT04085601) trials and the subsequent open-label extension (OLE) 307 study (NCT03531255) **confirmed the long-term efficacy and safety of pegcetacoplan for PNH patients for up to 3 years**.[10]

METHODS

The **integrated analysis data set** (data cutoff 31/1/2023) was used for this post-hoc analysis. **Safety baseline** was defined as **time of initiation of pegcetacoplan monotherapy** in the 2 pivotal pegcetacoplan trials.

Patients initially received **pegcetacoplan 1080 mg subcutaneously twice weekly** but **dose escalations to once every 3 days or 3 times weekly were permitted.**

An event of **cs-BTH** was defined post-hoc as an **adverse event (AE) report of hemolysis** by investigators in the presence of all the following: **lactate dehydrogenase (LDH) >2x upper limit of normal (ULN), prior LDH <1.5x ULN, and a decline in hemoglobin (Hb) by ≥2 g/dL** from a patient's prior median Hb*.

Events of cs-BTH were **evaluated from safety baseline up to Weeks 132 (2.5 years, PRINCE) and 156 (3 years, PEGASUS).**

* Patient's median of all prior Hb lab values while on pegcetacoplan.

RESULTS

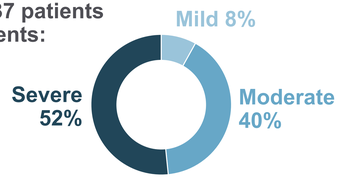
Integrated analysis of PEGASUS, PRINCE, and OLE 307 study data for **up to 3 years.**

Incidence of cs-BTH

37/132* patients experienced cs-BTH during the integrated analysis follow-up of up to 3 years

34/37 entered the 307 OLE study

62 cs-BTH in 37 patients
Severity of events:



24/37 (65%) patients experienced **only 1 hemolysis event**

The exposure-adjusted **incidence** was **0.19 events/year**

Characterization of cs-BTH

Mean (SD) Hb decreased by **4.4 (1.7) g/dL**†

Median (IQR) LDH during the events reached **1850 (464, 5055) U/L**‡

Potential CAC associated with **21/62 (34%) cs-BTH** (vaccination n=5, infection n=16)

Management of cs-BTH§

RBC transfusions to manage anemia

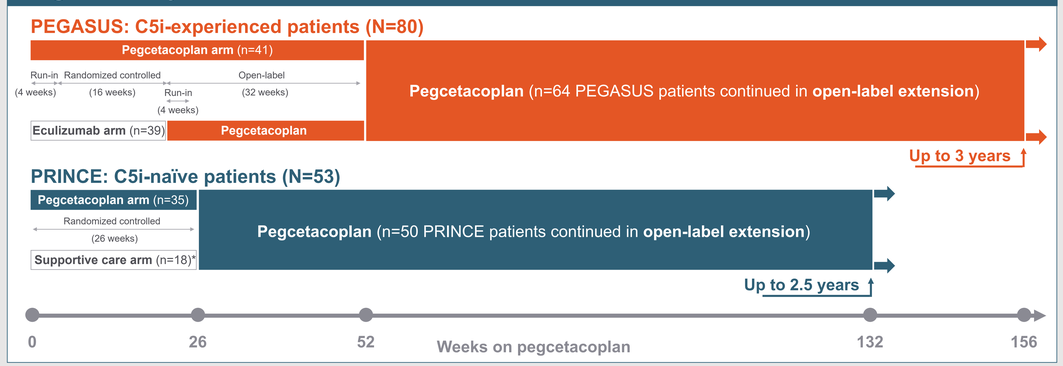
Average of **1.5 units** used **per transfusion**

C5 inhibitor rescue

Median **duration** of the **reported hemolysis AEs**: **26 days**¶

* One patient in the PRINCE study was lost to follow-up. † Compared to subjects' mean Hb prior to the cs-BTH event. ‡ LDH ULN: 226 U/L. § In addition to transfusions and C5 inhibitor administration, cs-BTH events were managed with supportive care according to local guidance and patients risks. ¶ Hemolysis AE median duration ranged from 2 to 654 days and is based on an interim analysis. AE, adverse event; CAC, complement-amplifying condition; cs-BTH, significant breakthrough hemolysis; Hb, hemoglobin; IQR, interquartile range; LDH, lactate dehydrogenase; OLE, open-label extension; RBC, red blood cell; SD, standard deviation; ULN, upper limit of normal.

Integrated analysis data set[10]



* Patients in the PRINCE supportive care arm could escape to the pegcetacoplan arm before the end of the 26 weeks if they experienced a qualifying event of anemia or thrombosis. C5i, complement C5 inhibitor.

CONCLUSIONS

- In this post-hoc analysis, among patients with PNH treated with pegcetacoplan in 2 pivotal Phase 3 clinical trials and a follow-up long-term OLE study, the **exposure-adjusted incidence of cs-BTH was 0.19 events/year and considered infrequent**
- Around **half of the hemolysis events** were reported as **mild or moderate**
- During cs-BTH events, pronounced declines in Hb were **managed with RBC transfusions and C5 inhibitor rescue** in 53% and 10% of events, respectively

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ABBREVIATIONS: AE, adverse event; BTH, breakthrough hemolysis; C5i, complement C5 inhibitor; CAC, complement-amplifying condition; cs-BTH, significant breakthrough hemolysis; Hb, hemoglobin; IQR, interquartile range; LDH, lactate dehydrogenase; OLE, open-label extension; PNH, paroxysmal nocturnal hemoglobinuria; RBC, red blood cell; SD, standard deviation; ULN, upper limit of normal.

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