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POSTER ABSTRACTS

508.BONE MARROW FAILURE: ACQUIRED

Categorization of Hematological Responses to Oral Iptacopan Monotherapy in Anti-C5-Treated Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) and Persistent Anemia in the Phase III APPLY-PNH Trial and Complement Inhibitor-Naïve Patients in the Phase III APPOINT-PNH Trial

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Background: PNH is an ultrarare disease characterized by complement-mediated hemolysis and consequent anemia. Iptacopan is the first oral, selective complement inhibitor that targets factor B to inhibit the alternative pathway proximally in the complement system. Iptacopan monotherapy led to normal/near normal hemoglobin (Hb) values and transfusion avoidance in the majority of complement inhibitor-naïve patients and anti-C5-treated patients with persistent anemia in the Phase III APPOINT-PNH (NCT04820530) and APPLY-PNH (NCT04558918) trials, respectively, with iptacopan achieving its primary endpoints and demonstrating superiority to anti-C5 treatment in APPLY-PNH.

Aim: To apply hematological response categories, adapted from Risitano *et al.* in *Front Immunol* 2019, to the data from APPLY-PNH (baseline and Week 24 data) and APPOINT-PNH (Week 24 data).

Methods: APPLY-PNH enrolled adult PNH patients with a mean Hb level <10 g/dL who had been receiving eculizumab or ravulizumab for \geq 6 months. Patients were randomized 8:5 to receive iptacopan monotherapy 200 mg twice daily or to continue their anti-C5 regimen for 24 weeks. APPOINT-PNH enrolled complement inhibitor-naïve adult PNH patients, with a mean Hb level <10 g/dL and lactate dehydrogenase (LDH) >1.5 × upper limit of normal (ULN); patients received iptacopan monotherapy 200 mg twice daily. Using central laboratory data, hematological responses were categorized primarily based on Hb levels (at baseline and between Days 126 and 168) and the need for packed red blood cell transfusions (in the 6 months prior to baseline and between Days 14 and 168). LDH levels and absolute reticulocyte counts were ancillary indicators to discriminate between complete and major responses. In the original definition of the response categories, absolute reticulocyte count was used to rule out patients with bone marrow failure; however, for this analysis, as patients with laboratory evidence of bone marrow failure were excluded from APPLY-PNH and APPOINT-PNH, absolute reticulocyte count was not used to define the suboptimal categories (ie good, partial, minor and no response categories). Week 24 categories were defined as follows: complete response - median Hb \geq 12 g/dL, no transfusions, and both median LDH \leq 1.5 × ULN and median absolute reticulocyte count \leq 150,000/µL between Days 1 and 168; major response - median Hb \geq 12 g/dL, no transfusions, and either LDH >1.5 × ULN or absolute reticulocyte count >150,000/µL between Days 1 and 168; major response - median Hb \geq 10 and <12 g/dL and no transfusions; partial response - median Hb \geq 8 and <10 g/dL and \leq 2 transfusions; minor response - median

POSTER ABSTRACTS

Hb <8 g/dL and ≤2 transfusions; or median Hb <10 g/dL and 3-6 transfusions; or median Hb <10 g/dL and a reduction in transfusions by \geq 50% between Days 14 and 168 compared with the number of transfusions received in the 6 months prior to baseline; no response - median Hb <10 g/dL and >6 transfusions.

Results: Sixty-two patients received iptacopan and 35 patients received anti-C5 treatment in the APPLY-PNH trial; 40 patients received iptacopan in the APPOINT-PNH trial. There were no baseline differences between patients in the iptacopan arm and patients in the anti-C5 arm of the APPLY-PNH trial, with most patients having a partial hematological response to complement inhibitor treatment at baseline (62.9% [39/62] of patients in the iptacopan arm and 62.9% [22/35] in the anti-C5 arm; Figure 1). At Week 24, most iptacopan-treated patients in the APPLY-PNH trial achieved a complete response (71% [44/62] of patients versus 0% in the anti-C5 arm; Figure 1). Most patients in the APPOINT-PNH trial also achieved a complete response to iptacopan (62.5% [25/40] of patients; Figure 2). As expected, at Week 24, none of the patients in the anti-C5 arm of APPLY-PNH achieved complete or major hematological responses, with most continuing to maintain a partial hematological response (54.3% [19/35] of patients).

Conclusions: This *post hoc* analysis of the APPLY-PNH and APPOINT-PNH trial data demonstrates that the majority of patients achieved complete or major hematological responses during treatment with iptacopan monotherapy, highlighting the ability of both complement inhibitor-naïve patients and anti-C5-treated patients with persistent anemia to achieve transfusion avoidance and improvement of Hb to normal/near normal levels with iptacopan.

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Figure 1. Hematological responses of patients in the APPLY-PNH trial at baseline and Week 24 of the treatment period







*The criteria for complete response at baseline were no transfusions in the last 6 months, Hb \geq 12 g/dL, LDH \leq 1.5 × ULN and absolute reticulocyte count \leq 150,000/µL. The criteria for complete response at Week 24 were no transfusions between Days 14 and 168, median Hb \geq 12 g/dL between Days 126 and 168, median LDH \leq 1.5 × ULN between Days 1 and 168 and median absolute reticulocyte count \leq 150,000/µL. The criteria for major response at Week 24 were no transfusions in the last 6 months, Hb \geq 12 g/dL between Days 126 and 168, inter LDH \geq 1.5 × ULN between Days 126 and 168, median LDH \leq 1.5 × ULN between Days 1 and 168 or median absolute reticulocyte count \geq 150,000/µL. The criteria for major response at Week 24 were no transfusions between Days 14 and 189, median Hb \geq 12 g/dL between Days 126 and 168, and 168 or median absolute reticulocyte count \geq 150,000/µL. The criteria for good response at Week 24 were no transfusions between Days 1 and 168; if the criteria for good response at baseline were no transfusions between Days 1 and 168 and median Hb \geq 10 g/dL. The criteria for good response at Week 24 were no transfusions between Days 14 and 168 and median Hb \geq 10 g/dL. The criteria for good response at Week 24 were no transfusions between Days 14 and 168 and median Hb \geq 10 g/dL. The criteria for good response at Week 24 were at transfusions in the last 6 months and Hb \geq 8 and <10 g/dL. The criteria for minor response at Week 24 were either s2 transfusions in the last 6 months and Hb <8 g/dL; or 3-6 transfusions between Days 14 and 168 and median Hb <8 g/dL. The criteria for minor response at Week 24 were either s2 transfusions between Days 14 and 168 and median Hb <8 g/dL. The criteria for minor response at Week 24 were either s2 transfusions between Days 14 and 168 and median Hb <8 g/dL were there and 168 and median Hb <10 g/dL between Days 126 and 168; "The criteria for no response at baseline were \geq 6 transfusions between Days 14 and 168 and median Hb <8 g/dL; or 3-6 transfusions be

Figure 1

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