Sustained long-term control of terminal complement activity with ravulizumab or danicopan add-on to ravulizumab in patients with paroxysmal nocturnal hemoglobinuria

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INTRODUCTION

- Paroxysmal nocturnal hemoglobinuria (PNH) is a chronic, progressive disease characterized by uncontrolled terminal complement activity with potentially life-threatening consequences.[1]
- Ravulizumab, a complement component 5 inhibitor (C5i) with immediate, complete and sustained effect, has shown effective long-term control of terminal complement activity and intravascular hemolysis (IVH), reduced thrombosis and improved survival in patients with PNH for up to 6 years.[1]
- Approximately 20–25% of patients treated with ravulizumab or eculizumab experience clinically significant extravascular hemolysis (csEVH),[2] characterized by symptomatic anemia and increased transfusion need.[3]
- The addition of danicopan, a first-in-class oral factor D inhibitor, to background ravulizumab or eculizumab has shown a favorable benefit–risk profile and sustained control of terminal complement activity, IVH and csEVH in patients with PNH and csEVH for up to 72 weeks.[2,4]

OBJECTIVE

- To characterize long-term outcomes, including breakthrough IVH (BT-IVH) events, of ravulizumab and add-on danicopan to ravulizumab or eculizumab alone in patients with PNH, using pivotal phase 3 trial data.

METHODS

- Long-term ravulizumab efficacy data for up to 6 years in adult (≥18 years of age) C5i-naive and eculizumab-experienced patients with PNH were available from studies 301 (NCT02946463) and 302 (NCT03056040), respectively.[1]
- Long-term add-on danicopan to ravulizumab or eculizumab efficacy data for up to 72 weeks in adult patients with PNH and csEVH were available from the ALPHA study (NCT04469465).
  - In ALPHA, csEVH was defined as hemoglobin (Hb) concentration ≤ 9.5 g/dL with absolute reticulocyte count ≥ 120 × 10^9/L.[2,4]
- The long-term efficacy outcomes assessed included: change in lactate dehydrogenase (LDH) level over time; change in Hb concentration over time (ALPHA data only); and the proportion of patients who avoided transfusion.
  - BT-IVH events were also assessed (per-protocol definitions [**Table 1**]).

Table 1. Per-protocol definitions of BT-IVH during ravulizumab treatment (studies 301 and 302) and treatment with add-on danicopan (ALPHA study)

Study	BT-IVH definition
301 and 302[1]	≥ 1 new or worsening symptom or sign of IVH[a] in the presence of elevated LDH ≥ 2 × ULN, and after prior reduction of LDH level to < 1.5 × ULN on therapy[b]
ALPHA[4]	Reported based on clinical judgment of the investigator (no per-protocol definition applied)

[a]Including fatigue, hemoglobinuria, abdominal pain, dyspnea, anemia (hemoglobin < 10 g/dL), major adverse vascular event (including thrombosis), dysphagia or erectile dysfunction; [b]Defined as 246 U/L.
BT-IVH, breakthrough intravascular hemolysis; IVH, intravascular hemolysis; LDH, lactate dehydrogenase; ULN, upper limit of normal.

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CONCLUSIONS

- **Ravulizumab effectively controls terminal complement activity and IVH in patients with PNH over a long-term period (1468 PYs of exposure).**
- **Add-on danicopan to ravulizumab is effective in managing csEVH while controlling terminal complement activity and IVH for up to 72 weeks.**
- **BT-IVH events experienced during long-term ravulizumab or add-on danicopan were infrequent, mostly non-severe and resolved without dose modification or treatment withdrawal, and none were associated with thrombosis.**
- **These findings highlight the benefits of dual inhibition in patients with residual and symptomatic anemia due to EVH, without compromising on the survival benefit associated with the control of terminal complement activity and IVH with ravulizumab.**

RESULTS

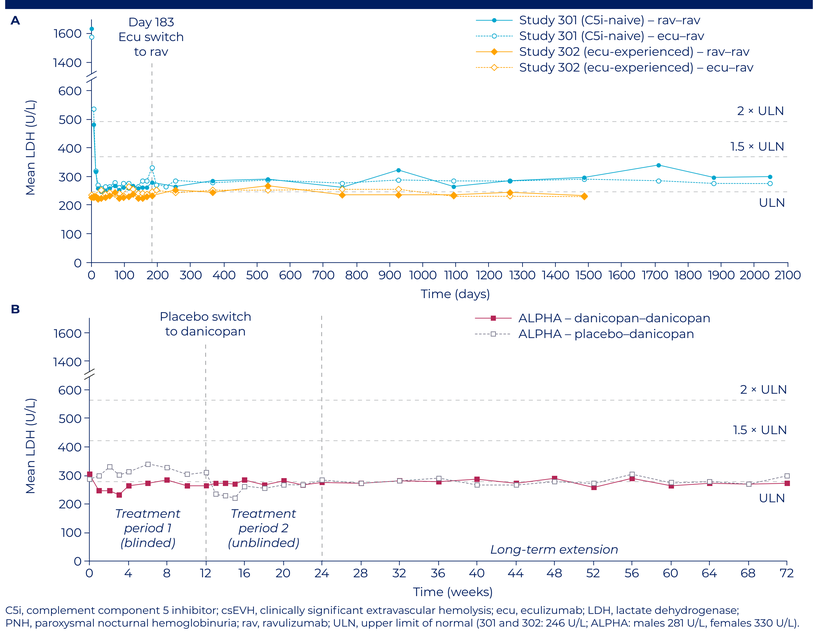
Studies 301 and 302

- Ravulizumab efficacy data were available for up to 6 years for 243/246 C5i-naive and 191/195 eculizumab-experienced patients with PNH.
- During ravulizumab treatment, mean LDH levels remained near normal in both patient groups (**Figure 1A**) and most patients avoided transfusion (**Figure 2A and 2B**).
- For up to 6 years, a total of 112 BT-IVH events were reported in 36 C5i-naive patients (14.8%; 94 events; event rate, 1.0 per 10 person-years [PYs]) and 15 eculizumab-experienced patients (7.9%; 18 events; event rate, 1.0 per 30 PYs) treated with ravulizumab.
  - Two events (1.8%) were associated with suboptimal inhibition of C5 (e.g. serum free C5 ≥ 0.5 µg/mL), 43 events (38.4%) were associated with infection or other complement-amplifying conditions, and no cause was reported for 67 events (59.8%).
  - None of the reported events were associated with thromboembolic events and all resolved without modification or discontinuation of ravulizumab.
- Ravulizumab was well tolerated for up to 6 years demonstrating improved survival (survival rates were 97.7% and 98.4% for studies 301 and 302, respectively),[1] and no new safety signals were identified.

ALPHA study

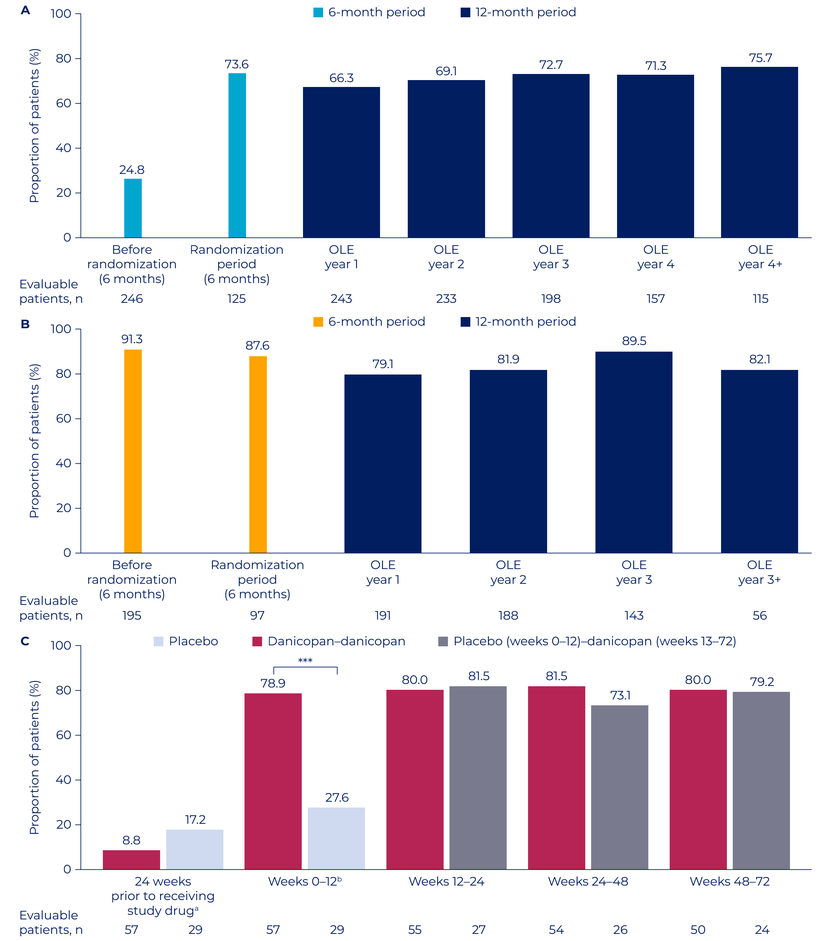
- Long-term add-on danicopan data were available for up to 72 weeks for 74/84 patients with PNH and csEVH (50/57 danicopan–danicopan; 24/27 placebo–danicopan).
- During add-on danicopan, LDH levels remained near normal in both treatment arms (**Figure 1B**), and most patients avoided transfusion (**Figure 2C**).
  - Overall, 53.7% (danicopan–danicopan) and 46.2% (placebo–danicopan) of patients achieved a ≥ 2 g/dL increase in Hb in the absence of transfusion at week 72.
- In total, 7 BT-IVH events were reported in 5/84 patients (event rate: 6 per 100 PYs).
  - Most events (5/7; 71.4%) were reported with concurrent adverse events, including anemia, COVID-19 infection, fever, food poisoning and skin infection.
  - One event was associated with LDH ≥ 2 × upper limit of normal (ULN) and decreased Hb concentration, which was linked with COVID-19 infection.
  - All events resolved rapidly without transfusion, dose modification or treatment withdrawal.
- Add-on danicopan was well tolerated for up to 72 weeks; no new safety signals were identified and no meningococcal infections were reported.

Figure 1. Mean LDH level over time in (A) C5i-naive and eculizumab-experienced patients with PNH treated with ravulizumab in studies 301 and 302 and (B) patients with PNH and csEVH treated with add-on danicopan to ravulizumab or eculizumab in the ALPHA study



C5i, complement component 5 inhibitor; csEVH, clinically significant extravascular hemolysis; ecu, eculizumab; LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal hemoglobinuria; rav, ravulizumab; ULN, upper limit of normal (301 and 302: 246 U/L; ALPHA: males 281 U/L, females 330 U/L).

Figure 2. Transfusion avoidance in (A) C5i-naive patients, (B) eculizumab-experienced patients with PNH treated with ravulizumab and (C) patients with PNH and csEVH treated with add-on danicopan



*** indicates $p \leq 0.001$.
[a]Participants who were RBC transfusion free during the 24 weeks before receiving the study drug.
[b]p values are only available for week 12 or treatment period 1.
C5i, complement component 5 inhibitor; csEVH, clinically significant extravascular hemolysis; OLE, open-label extension; PNH, paroxysmal nocturnal hemoglobinuria; RBC, red blood cell.

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