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Ravulizumab provides durable control of intravascular hemolysis and improves survival in patients with paroxysmal nocturnal hemoglobinuria: long-term follow-up of study 301 and comparisons with patients of the International PNH Registry

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INTRODUCTION

- Complement component 5 (C5) inhibitors, ravulizumab and eculizumab, are approved treatments for patients with paroxysmal nocturnal hemoglobinuria (PNH),[1] a life-threatening disease characterized by uncontrolled terminal complement activation, intravascular hemolysis (IVH) and major adverse vascular events (MAVEs, including thromboses [TEs]).[2–5]
- In study 301 (NCT02946463),[6] ravulizumab demonstrated non-inferiority to eculizumab with no new safety signals in C5 inhibitor-naïve patients with PNH,[7] and durable control of IVH with ravulizumab has been reported for up to 2 years.[8]
- Because of the chronic nature of PNH, data on long-term treatment outcomes and disease progression are essential.
- The International PNH Registry (NCT01374360; PNH Registry) is the largest global registry of patients with PNH and prospectively collects real-world data on patients with PNH, irrespective of treatment.[9]

OBJECTIVES

- To report ravulizumab treatment outcomes for up to 6 years in C5 inhibitor-naïve patients with PNH from study 301 and to compare survival with untreated patients in the PNH Registry.

METHODS

- The design of study 301 is outlined in **Supplementary Figure 1**.
- Outcomes included change from baseline lactate dehydrogenase (LDH) level, proportions of patients who experienced MAVEs (including TEs), breakthrough IVH or achievement of transfusion avoidance, and treatment discontinuations.
- Cox proportional hazards regression analyses compared survival of patients in study 301 with untreated patients in the PNH Registry.
  - To ensure that populations were balanced, patients in the PNH Registry included for survival analysis reported high disease activity (LDH level ≥ 1.5 × upper limit of normal [ULN; 246 U/L] and ≥ 1 sign or symptom of PNH), PNH clone size ≥ 5% and no history of bone marrow transplantation at registry enrollment (baseline).

Supplementary material

Please scan this quick response (QR) code with your smartphone camera or app to obtain a copy of these materials.

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CONCLUSIONS

- **Study 301 reports the longest period of follow-up for C5 inhibitor-naïve patients with PNH treated with ravulizumab (925.7 patient-years [PYs]), and demonstrated effective control of IVH, as evidenced by the maintenance of LDH levels ≤ 1.5 × ULN and low incidence of MAVEs (including TEs) and death.**
- **No new safety signals were identified, and ravulizumab improved survival compared with untreated patients in the PNH Registry, further supporting the use of ravulizumab as the first-line treatment of choice for patients with PNH, where available.**

RESULTS

Patient population

- Long-term ravulizumab treatment data and survival data were available for 244/246 patients in study 301 (median [range] follow-up: 46.8 [0.4–69.3] months), and 414 patients in the PNH Registry (**Supplementary Table 1**).
  - Differences in patient medical histories for MAVEs (including TEs), bone marrow disorders and transfusions were reported, owing to the pre-specified inclusion criteria for study 301.

Change from baseline LDH level

- IVH was controlled because most patients maintained LDH levels ≤ 1.5 × ULN during the open-label extension period (**Figure 1**).

MAVEs

- The incidence of MAVEs (including TEs) was low (rate: 1.4 per 100 PYs), with no observable trends in rates of MAVEs across study periods.

Breakthrough IVH

- Over the entire observation period of up to 6 years, 36/244 patients experienced breakthrough IVH (rate: 10.2 per 100 PYs).
  - Two of these events (one in the eculizumab to ravulizumab arm and one in the ravulizumab to ravulizumab arm) were related to suboptimal inhibition of C5 (C5 concentration ≥ 0.5 µg/mL).

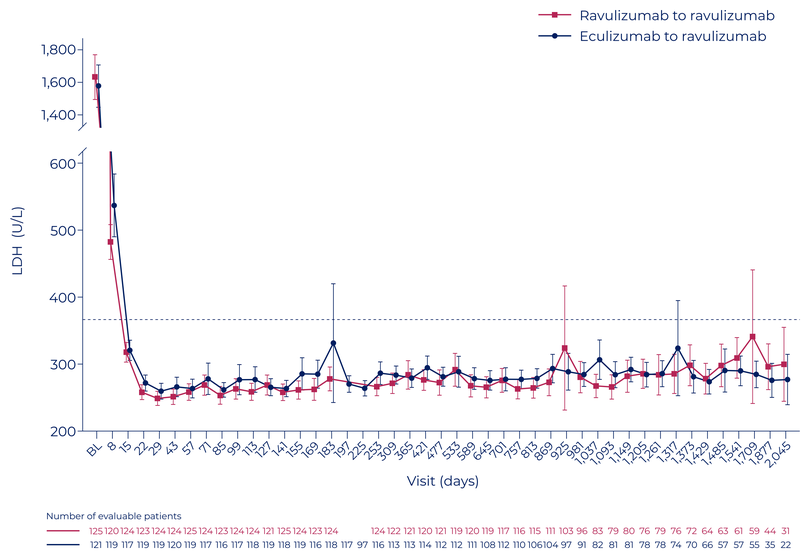
Transfusion avoidance

- Transfusion avoidance was maintained in the majority of patients throughout the open-label extension period, with the proportion of patients needing transfusion gradually decreasing over time (**Figure 2**).

Discontinuations

- Reasons for deaths and discontinuation due to adverse events are described in the **Supplementary material**.

Figure 1. Mean (95% CI) change in LDH level over time, by treatment sequence

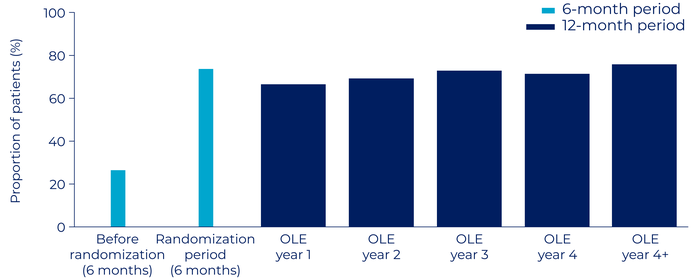


Dashed horizontal line indicates 1.5 × ULN (369 U/L).
BL, baseline; CI, confidence interval; LDH, lactate dehydrogenase; ULN, upper limit of normal.

Survival analysis

- Compared with untreated patients, ravulizumab was associated with significantly improved survival probability at 4 years ($p < 0.001$; **Figure 3**).
  - All-cause mortality was 5-fold lower than that observed in untreated patients in the PNH Registry.

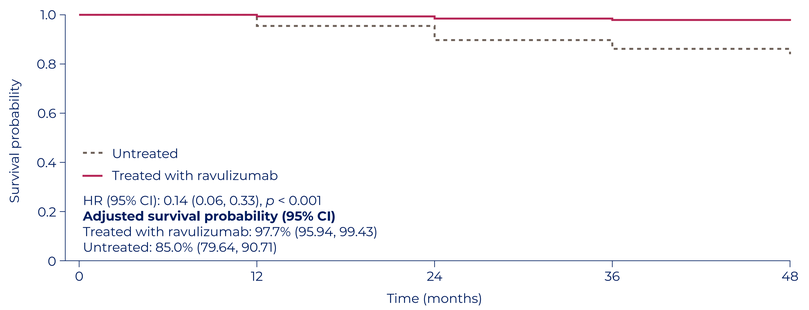
Figure 2. Proportion of patients who achieved transfusion avoidance



	Before randomization (6 months)	Randomization period (6 months)	OLE year 1	OLE year 2	OLE year 3	OLE year 4	OLE year 4+
Evaluable patients receiving ravulizumab, n	125	125	243	233	198	157	115
Time on ravulizumab, months	NA	6	18	30	42	54	> 54
Patients avoiding transfusion, n (%)	33 (26.4)	92 (73.6)	161 (66.3)	161 (69.1)	144 (72.7)	112 (71.3)	87 (75.7)
Number of transfusions, n	399	107	397	362	184	114	92
Number of units transfused, n	532	155	627	577	298	177	110

OLE, open-label extension period.

Figure 3. Adjusted survival analysis of ravulizumab-treated patients with PNH



Covariates included in the adjusted model included patient transfusion history ($p = 0.05$), age at PNH diagnosis and gender.
CI, confidence interval; HR, hazard ratio; PNH, paroxysmal nocturnal hemoglobinuria.

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