One-year Efficacy of Ravulizumab (ALXN1210) in Adult Patients with Paroxysmal Nocturnal Haemoglobinuria Naive to Complement Inhibitors

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INTRODUCTION

In a large, multicentre, phase 3 study in complement inhibitor therapy–naïve adults with PNH (NCT02946463; Study 301), ravulizumab, when administered every 8 weeks, was noninferior to eculizumab given every 2 weeks, across all primary end points and key secondary end points at 26 weeks.[1]

This study demonstrated ravulizumab provides immediate, complete, and sustained C5 inhibition through the entire dosing interval.

After completing the 26-week primary evaluation period, all participants had the opportunity to enter the extension period, wherein participants are receiving weight-based dosing of ravulizumab for up to 2 years.

OBJECTIVES

• To characterise the durability of efficacy responses to ravulizumab through 52 weeks
• To evaluate the efficacy of ravulizumab after switching from eculizumab
• To evaluate the safety profile in each treatment regimen

METHOD

Study Design

• Comparative study powered to show noninferiority of ravulizumab compared to eculizumab
• 246 patients who had not previously received eculizumab were randomised to receive the approved dose of eculizumab (900 mg every 2 weeks) or weight-based dosing of ravulizumab (every 8 weeks) for 26 weeks

Figure 1. Study Design
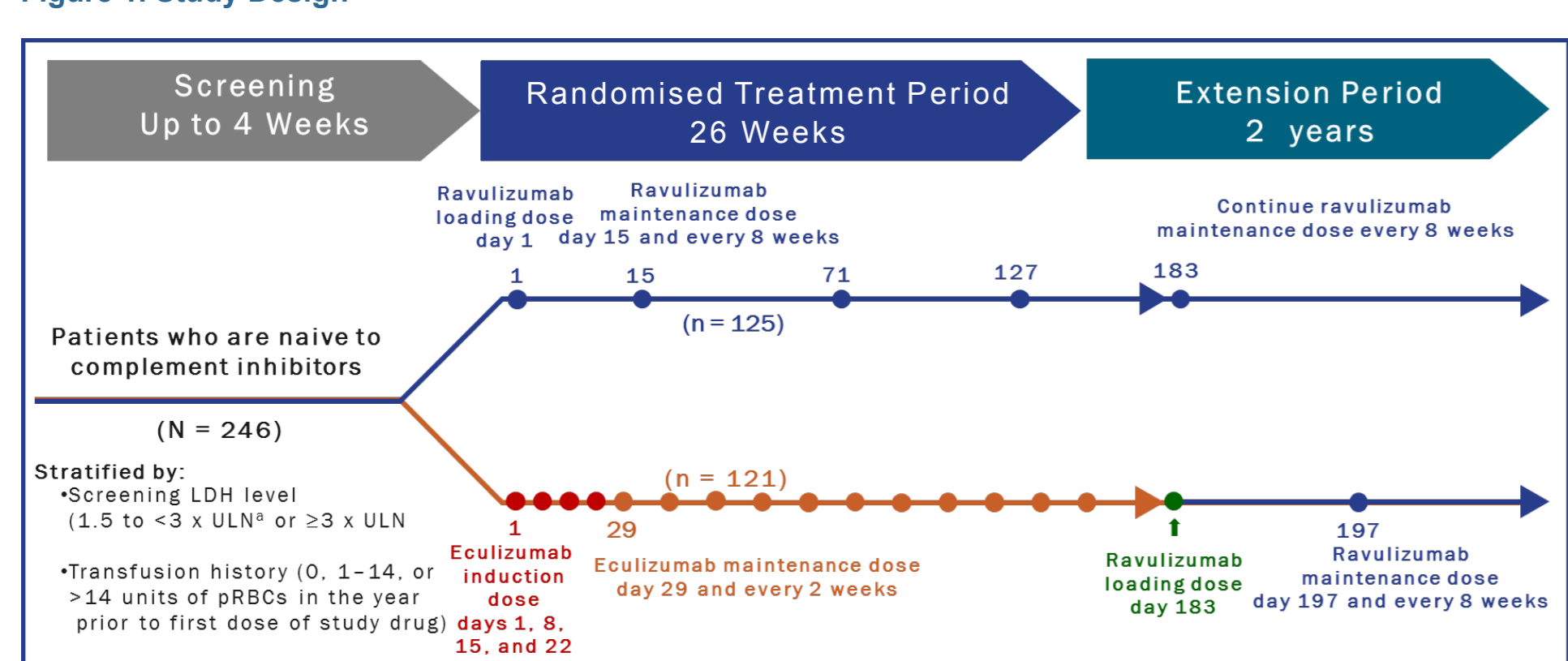
Dosages – Ravulizumab: Loading dose = 2400 mg for patients weighing ≥40 <60 kg, 2700 mg for ≥60 to <100 kg, and 3000 mg for ≥100 kg; maintenance dose = 3000 mg for patients weighing ≥40 to <60 kg, 3300 mg for ≥60 to <100 kg, and 3600 mg for ≥100 kg. Eculizumab: Induction dose = 600 mg; maintenance dose = 900 mg.ᵃULN for LDH was 246 U/L.

Key Enrollment Criteria

Inclusion:
• Male or female patients with PNH
• Aged ≥18 years
• Naïve to complement inhibitors
• LDH levels ≥1.5 × ULN (246 U/L)
• ≥1 PNH-related sign or symptom within 3 months of screening
  – Fatigue, haemoglobinuria, abdominal pain, shortness of breath (dyspnea), anemia (Hb <10 g/dL), history of MAVE (including thrombosis), dysphagia, or erectile dysfunction; or
  – History of packed red blood cells (pRBC) transfusion due to PNH

Exclusion:
• Current or previous exposure to a complement inhibitor
• Weight <40 kg
• History of bone marrow transplantation
• History of meningococcal or unexplained, recurrent infection
• Platelet count <30 × 10⁹/L
or
• ANC <0.5 x 10⁹/L at screening

ANC, absolute neutrophil count; Hb, haemoglobin; LDH, lactate dehydrogenase; MAVE, major adverse vascular event; PNH, paroxysmal nocturnal hemoglobinuria; ULN, upper limit of normal.

Patient demographics

• No noteworthy differences between treatment groups, with similar proportions of patients in each treatment group based on sex, age and race.

Table 1. Patient demographics

	Ravulizumab (n = 125)	Eculizumab (n = 121)	Total (N = 246)
Sex, n (%)			
Male	65 (52.0)	69 (57.0)	134 (54.5)
Female	60 (48.0)	52 (43.0)	112 (45.5)
Race, n (%)			
Asian	72 (57.6)	57 (47.1)	129 (52.4)
Non-Japanese	53 (42.4)	42 (34.7)	95 (38.6)
Japanese	19 (15.2)	15 (12.4)	34 (13.8)
White	43 (34.4)	51 (42.1)	94 (38.2)
Other	7 (5.6)	9 (7.4)	16 (6.5)
Not reported	3 (2.4)	4 (3.3)	7 (2.8)
Ethnicity (not Hispanic/Latino), n (%)	116 (92.8)	102 (84.3)	218 (88.6)
Body weight, mean (SD), kg	68.2 (15.6)	69.2 (14.9)	68.7 (15.2)
Age at first infusion, mean (SD), y	44.8 (15.2)	46.2 (16.2)	45.5 (15.7)

SD, standard deviation.

Baseline and clinical characteristics

• The study population was well-balanced with respect to baseline disease and clinical characteristics.
• Mean LDH levels were about 1600, indicative of high haemolytic activity. Granulocyte clone sizes were large, at 88% on average

Table 2. Baseline and clinical characteristics

	Ravulizumab (n = 125)	Eculizumab (n = 121)	Total (N = 246)
Age at PNH diagnosis, mean (SD), y	37.9 (14.9)ᵃ	39.6 (16.7)ᵇ	38.7 (15.8)ᶜ
Time from PNH diagnosis to consent, mean (SD), y	6.7 (8.1)ᵃ	6.4 (7.5)ᵇ	6.6 (7.8)ᶜ
LDHᵈ at baseline, mean (SD), U/L	1634 (778.8)	1578 (727.1)	1606 (752.7)
Transfusions received within 1 year prior to study, n (%)			
0 units	23 (18.4)	21 (17.4)	44 (17.9)
1–14 units	79 (63.2)	78 (64.5)	157 (63.8)
>14 units	23 (18.4)	22 (18.2)	45 (18.3)
PNH clone size, mean (SD), %			
Type II RBC	12.4 (20.5)ᵉ	13.7 (17.7)ᶠ	13.0 (19.2)ᵍ
Type III RBC	26.3 (17.2)ᵉ	25.2 (16.9)ᶠ	25.8 (17.1)ᵍ
Total RBC	38.4 (23.7)	38.7 (23.2)	38.6 (23.4)
Granulocytes	84.2 (21.0)	85.3 (19.0)	84.7 (20.0)
Monocytes	86.9 (18.1)	89.2 (15.2)	88.0 (16.7)
FACIT-Fatigue, mean (SD)	36.7 (9.7)	36.9 (10.3)	36.8 (10.0)
History of MAVE, n (%)	17 (13.6)	25 (20.7)	42 (17.1)

FACIT, functional assessment of chronic illness therapy; LDH, lactate dehydrogenase; MAVE, major adverse vascular event; PNH, paroxysmal nocturnal hemoglobinuria; RBC, red blood cell; SD, standard deviation; ULN, upper limit of normal. aⁿ = 123; bⁿ = 118; cⁿ = 241; dULN for LDH was 246 U/L; eⁿ = 124; fⁿ = 120; gⁿ = 244.

METHOD (continued)

52-week outcome measures

Co-primary efficacy end points
• The percentage of patients who achieved transfusion avoidance
• The proportion of patients with haemolysis as measured by normalisation of LDH levels

Key secondary end points
• The percentage change from baseline in LDH levels
• The proportion of patients with breakthrough haemolysisa

Safety
Serum free C5 levels

ᵃDefined as ≥1 new or worsening PNH-related sign or symptom (fatigue, hemoglobinuria, abdominal pain, dyspnea, anemia, major adverse vascular event [including thrombosis], dysphagia, or erectile dysfunction) in the presence of LDH ≥2 x ULN, after prior LDH reduction to <1.5 x ULN on therapy.

RESULTS

Co-primary endpoint
Transfusion avoidance: stable over time

• 77% and 67% of patients in the ravulizumab-ravulizumab arm and eculizumab-ravulizumab arm, respectively, avoided transfusion during Weeks 27–52 of treatment
• Responses were maintained for the majority of patients in each arm

Table 3. Transfusion avoidance

n (%)	Ravulizumab-ravulizumab (n = 124)		Eculizumab-ravulizumab (n = 119)	
	0–26 Weeks	27–52 Weeks	0–26 Weeks	27–52 Weeks
TA response	92 (74)	95 (77)	79 (66)	80 (67)
Maintained response from Weeks 0–26 to Weeks 27–52ᵃ	—	83 (90)	—	69 (87)

ᵃPatients maintaining TA response = patients who avoided transfusion during the initial 26 weeks and maintained response through Week 52

• 38% (n=12) in the ravulizumab-ravulizumab arm, who required transfusion in the 0–26 wk period avoided transfusion in wks 27–52
• 28% (n=11) who required transfusion during the 26 wks while on eculizumab avoided it through 52 wks after the switch to ravulizumab

Co-primary endpoint
LDH normalisation: stable over time

Of patients who entered the extension:

• LDH-N was achieved in 48% (n = 60) and 42% (n = 50) of patients administered ravulizumab and eculizumab, respectively, on Day 183
• LDH-N was achieved in 44% (n = 54) and 40% (n = 48) of patients in the ravulizumab-ravulizumab and eculizumab-ravulizumab arm, respectively, on Day 365

Figure 2. LDH normalisation*
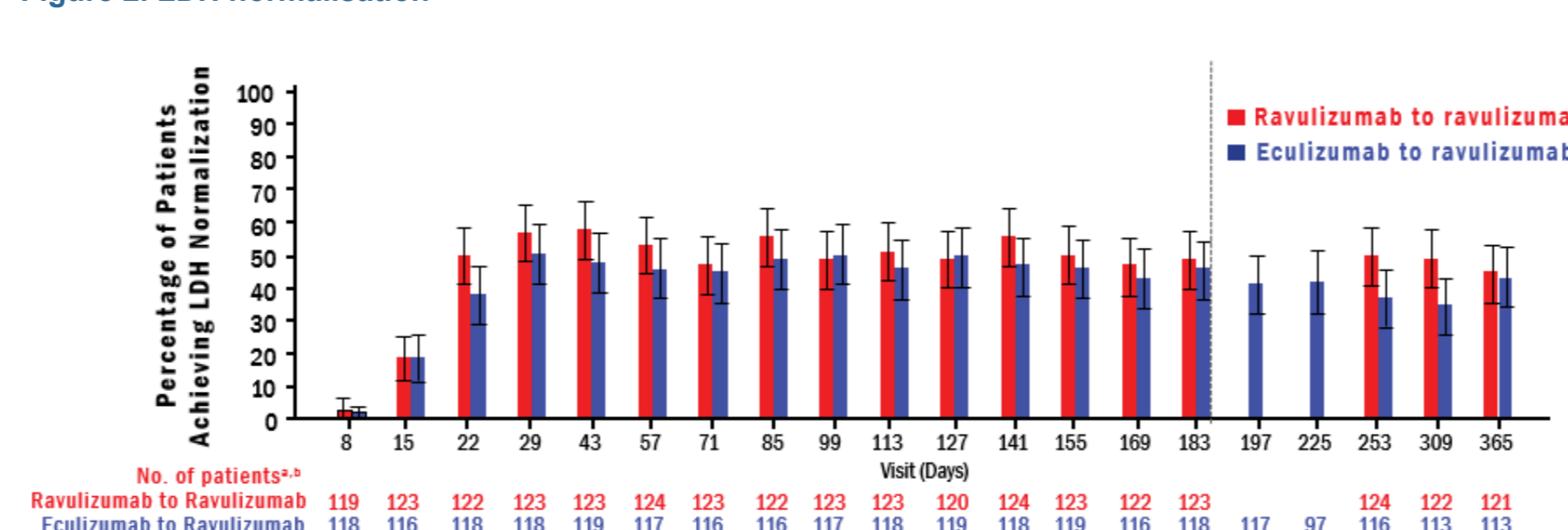
*LDH normalisation through 52 weeks, is defined as proportion of patients who achieved LDH level ≤1X ULN (246 U/L).

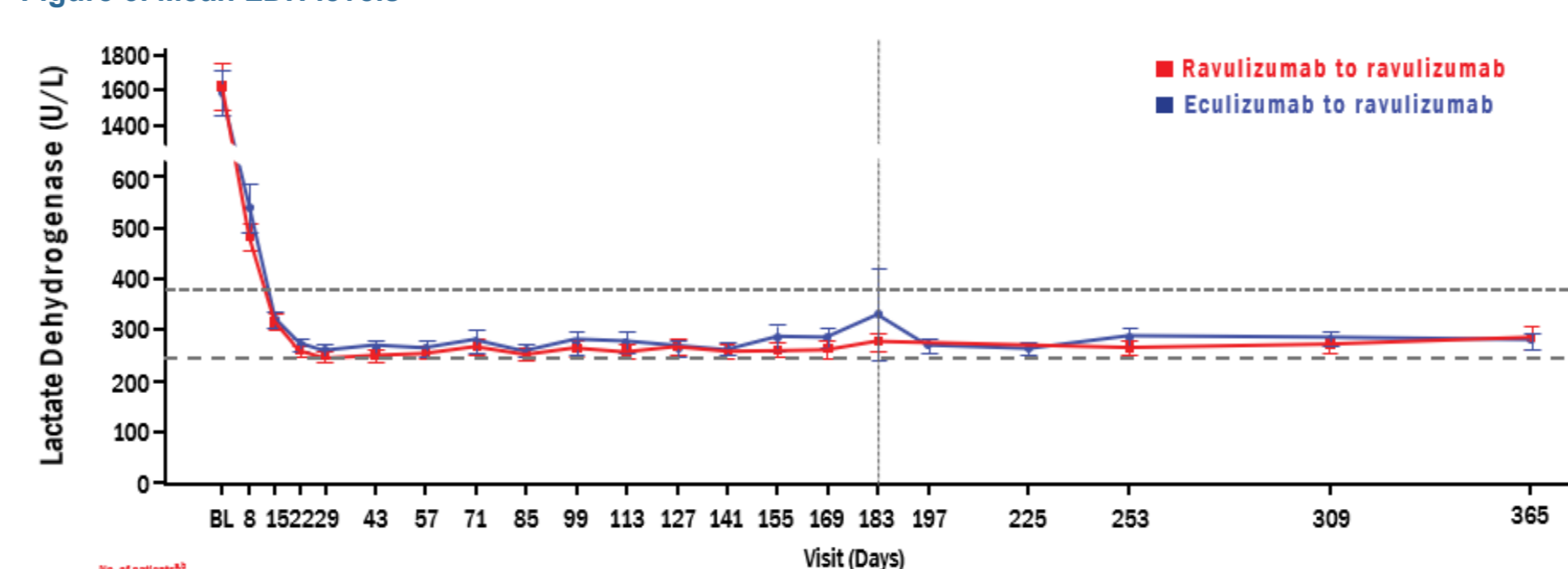ᵃNumber of patients may be lower than number enrolled at time point due to exclusion of samples having serum potassium ≥ 6 mmol/L and LDH ≥ 2x ULN); the sample might be missing (due to site error or for any other reason); and the patient discontinuations during the extension. bData cut-off date September 4, 2018.

Key secondary endpoint
Mean LDH levels: stable over time

• Mean LDH levels decreased rapidly after initiation of treatment and were sustained throughout the treatment period
• At the end of 26 wks, patients on ravulizumab had a 77% mean reduction in LDH from baseline and this was maintained through 52 wks (77%)

Figure 3. Mean LDH levels

ᵃNumber of patients may be lower than number enrolled at time point due to exclusion of samples having serum potassium ≥ 6 mmol/L and LDH ≥ 2x ULN); the sample might be missing (due to site error or for any other reason); and the patient discontinuations during the extension. ᵇData cut-off date September 4, 2018.

Key secondary endpoint
Breakthrough haemolysis

• Patients treated with ravulizumab had a low incidence of BTH
  – Fewer patients experienced BTH after patients switched from eculizumab to ravulizumab
  – No BTH events were associated with free C5 ≥ 0.5 µg/mL while on ravulizumab

Table 4. LDH normalisation

n (%)	Ravulizumab-ravulizumab (n = 124)		Eculizumab-ravulizumab (n = 119)	
	0–26 Weeks	27–52 Weeks	0–26 Weeks	27–52 Weeks
BTH, n (%)	5 (4)	4 (3)	13 (11)	2 (2)
Free C5 ≥0.5 µg/mL	0	0	7 (6)	0
Infection (with no free C5 elevation)	1 (1)	1 (1)	4 (3)	1 (1)
Unknownᵃ	4 (3)	3 (2)	4 (3)	1 (1)

ᵃWithout elevated free C5 or reported infection.

Free C5 levels through 52 weeks

• All patients in the ravulizumab treatment group continued to maintain free C5 <0.5 µg/mL at all time points through 52 weeks
• In patients initially randomised to eculizumab, the switch to ravulizumab showed improved free C5 control

Figure 4. Free C5 levels

Safety through 52 weeks
Ravulizumab was well-tolerated

• The most common treatment-emergent adverse events decreased in frequency with increased treatment duration

Table 5. Safety

Variables, n (%)	Ravulizumab-ravulizumab (n = 125)		Eculizumab-ravulizumab (n = 121)	
	0–26 Weeks (n = 125)	27–52 Weeks (n = 124)	0–26 Weeks (n = 121)	27–52 Weeks (n = 119)
Any TEAE	110 (88.0)	79 (63.7)	105 (86.8)	89 (74.8)
TEAE considered as a MAVE	2 (1.6)	0 (0)	1 (0.8)	1 (0.8)
TEAE leading to study drug discontinuation	0 (0)	0 (0)	1 (0.8)	1 (0.8)
Any SAE	11 (8.8)	9 (7.3)	9 (7.4)	7 (5.9)
SAE leading to study drug discontinuation	0 (0)	0 (0)	1 (0.8)	1 (0.8)
Death	0 (0)	0 (0)	1 (0.8)ᵃ	0 (0)
Common TEAEs				
Headache	45 (36.0)	6 (4.8)	40 (33.1)	10 (8.4)
Upper respiratory tract infection	13 (10.4)	10 (8.1)	7 (5.8)	5 (4.2)
Nasopharyngitis	11 (8.8)	8 (6.5)	19 (15.7)	15 (12.6)
Pyrexia	6 (4.8)	7 (5.6)	13 (10.7)	0 (0)

ᵃPatient withdrew from the study during the extension period due to an adverse event of lung cancer onset during the randomised treatment period. The patient died 35 days after the withdrawal.

CONCLUSIONS

In complement-inhibitor-naïve adult patients with PNH, ravulizumab demonstrated consistent and durable efficacy through 52 weeks of treatment.

Patients switching from eculizumab to ravulizumab after 26 weeks of treatment had outcomes comparable to those who received continuous ravulizumab.

All patients who had free C5 levels ≥0.5 µg/mL when treated with eculizumab had free C5 suppressed (levels <0.5 µg/mL) after switching to ravulizumab.

Ravulizumab decreased the incidence of BTH by eliminating free C5-associated BTH.

Ravulizumab was well-tolerated by all patients through 52 weeks.

REFERENCES

1. **Lee JW et al.** Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors: the 301 study. *Blood* 2019; 133: 530–539.

BL, baseline; BTH, breakthrough haemolysis; EOI, end of infusion; FACIT, Functional assessment of chronic illness therapy; LDH, lactate dehydrogenase; LDH-N, lactate dehydrogenase normalisation; PNH, paroxysmal nocturnal haemoglobinuria; MAVE, major adverse vascular event; RBC, red blood cell; SD, standard deviation; SAE, serious adverse event; TEAE, treatment-emergent adverse event; ULN, upper limit of normal.

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