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Patient Preferences For the Treatment of Paroxysmal Nocturnal Haemoglobinuria: Results of a Patient Survey of Ravulizumab (ALXN1210) and Eculizumab in the UK

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INTRODUCTION

- Paroxysmal nocturnal haemoglobinuria (PNH) is a rare hematopoietic stem cell disorder primarily caused by somatic mutations in the phosphatidylinositol glycan class A (PIGA) gene and is characterized by uncontrolled complement activation, resulting in hemolytic anemia and thrombosis[1]
- Eculizumab (administered every 2 weeks, q2w), which has been the standard care for PNH since its approval,[1-3] improves overall quality of life (QoL) in patients with PNH; however, the biweekly dosing regimen remains a high treatment burden[4-5] and potentially influences treatment adherence
- Ravulizumab (administered every 8 weeks, q8w) was recently approved for the treatment of PNH in the United States (December 2018),[6] Japan (June 2019),[7] Europe (July 2019),[8] Canada (August 2019),[9] and Brazil (September 2019)[10]
- Ravulizumab has demonstrated noninferior efficacy relative to eculizumab in two phase 3 trials, and its safety and tolerability are comparable with eculizumab[5,11]
- In regions where two treatment options are available for PNH, it is important to consider patient preference when determining a treatment plan

OBJECTIVE

- To evaluate UK patient preference for ravulizumab or eculizumab treatment in clinical trial substudy ALXN1210-PNH-302s using an 11-item PNH Patient Preference Questionnaire (PNH-PPQ©)

METHODS

Study Design and Inclusion Criteria

- Study ALXN1210-PNH-302 (NCT03056040), the parent study, is an ongoing phase 3, open-label, randomised, active-controlled, multicenter study to evaluate the safety and efficacy of ravulizumab versus eculizumab in adult patients with PNH who were clinically stable on eculizumab ≥6 months prior to the start of the study
  - The study included a 26-week primary evaluation period in which patients received either the approved dose of eculizumab (900 mg, q2w) or weight-based dosing of ravulizumab (q8w), followed by an extension period during which patients in the ravulizumab arm continued to receive ravulizumab maintenance therapy and patients in the eculizumab arm were switched to ravulizumab
- Substudy ALXN1210-PNH-302s (study 302s) was a noninterventional, noninvasive, nonrandomised, multicenter study that enrolled patients who had received a minimum of 2 maintenance doses of ravulizumab during the extension period of the parent study
- The 11-item PNH-PPQ© has been previously presented and described12 and comprises one question assessing overall treatment preference (Q1), nine questions (Q2a-2i) evaluating treatment preference based on treatment characteristics, one question (Q3) asking patients to indicate which treatment characteristic was most important for their overall medication preference, and four questions evaluating aspects of treatment with eculizumab and four matching questions for ravulizumab (Q4–11)
- The PNH-PPQ© was administered to the patients at a single time point

Statistical Analysis

- Statistical analyses were performed for each item in the PNH-PPQ©
  - Q1: Involved testing the null hypothesis that 50% of patients would prefer ravulizumab to eculizumab or have no preference, using an exact binomial test
  - Q2a–2i: Proportions and frequencies of patients preferring ravulizumab, eculizumab, and those who had no preference were calculated
  - Q3: The frequency of patients choosing each treatment characteristic as most important for determining treatment preference was calculated
  - Q4–11: Mean responses to matching questions were compared with paired t tests, and standardised effect sizes (d) were calculated as the difference in mean responses divided by the standard deviation of the difference in mean responses (Q4 vs Q8, Q5 vs Q9, Q6 vs Q10, and Q7 vs Q11)
  - Effect sizes (absolute value) were defined as small (0.20 to <0.50 points), medium (0.50 to <0.80 points), or large (≥0.80 points)

RESULTS

Patient Characteristics

- Of 98 patients enrolled in the substudy across 8 countries, 35 patients from the United Kingdom completed Q1 of the PNH-PPQ© (**Table 1**)

Table 1. Characteristics of the Study Population

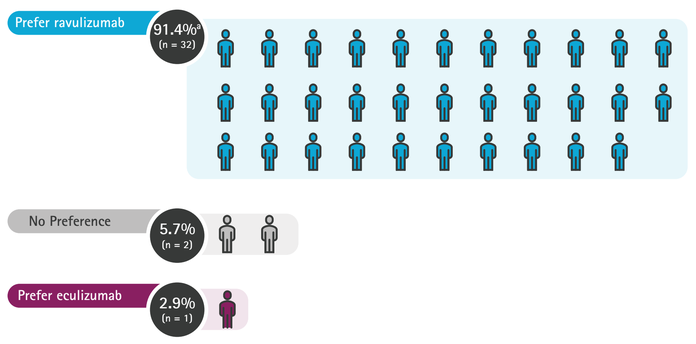
	Total N = 35	Ravulizumab n = 20	Switched from Eculizumab to Ravulizumab[a] n = 15
Age, mean years (SD, range)	53.0 (13.19, 27–76)	54.0 (13.54, 30–76)	51.8 (13.06, 27–67)
Sex			
Female, n (%)	19 (54.3)	10 (50.0)	9 (60.0)
Male, n (%)	16 (45.7)	10 (50.0)	6 (40.0)
Years since diagnosis, mean (SD, range)	13.7 (11.7, 2–46)	14.7 (11.5, 3–39)	12.2 (12.2, 2–46)
Years on eculizumab before study, mean (SD, range)	5.3 (3.75, 1–16)	5.0 (3.69, 1–15)	5.7 (3.91, 1–16)
Days between last randomized study treatment and PNH-PPQ©, mean (SD, range)	278.1 (38.45, 196–337)	296.6 (31.27, 236–337)	253.5 (33.58, 196–308)
History of major adverse vascular events, n (%)	7 (20.0)	5 (25.0)	2 (13.3)

PNH-PPQ©, Paroxysmal Nocturnal Hemoglobinuria Patient Preference Questionnaire; SD, standard deviation.
[a]Patients initially randomized to eculizumab were switched to ravulizumab at the end of the 26-week primary treatment period.

Treatment Preferences

- Overall, a significantly higher proportion of patients preferred ravulizumab (**Figure 1**)

Figure 1. Overall Treatment Preference (N = 35)

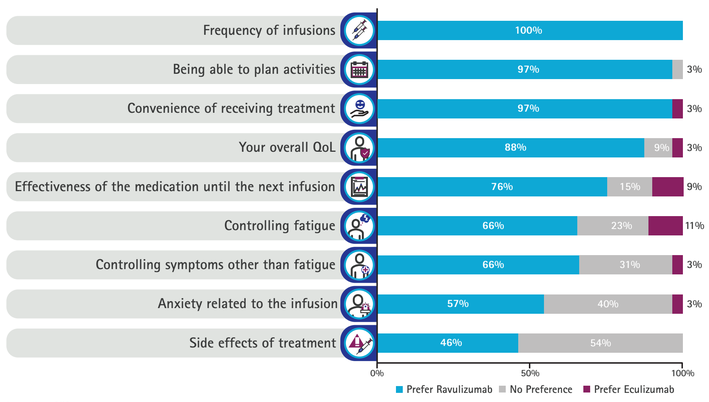


[a]$P < 0.001$ (prefer ravulizumab vs prefer eculizumab or no preference).

Factors Determining Treatment Preference

- Ravulizumab was widely preferred vs eculizumab across multiple factors (**Figure 2**)

Figure 2. Factors Driving Patients' Treatment Preference[a,b] (N = 35)

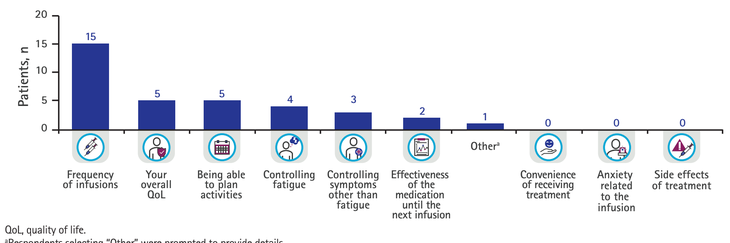


QoL, quality of life.
[a]Preference response was defined as responding "Strongly" or "Somewhat" prefer respective drug.
[b]One missing response for "Effectiveness of the medication until the next infusion" and "Your overall QoL."

Patients' Most Important Treatment Factor For Deciding Medication Preference

- "Frequency of infusions" was selected by the most respondents as the most important determinant of treatment preferences (**Figure 3**)

Figure 3. Patients' Most Important Factor For Deciding Medication Preference (N = 35)



QoL, quality of life.
[a]Respondents selecting "Other" were prompted to provide details.

Impact of Treatment on Patient QoL

- Moderate to large effect sizes were observed for factors differentiating ravulizumab and eculizumab, including the frequency of infusions disrupting everyday life, feeling fatigued after infusions, being able to enjoy life while receiving treatments (**Table 2**)

Table 2. Impact of Treatment on Measures of Patient QoL

	Ravulizumab[a] Mean	Eculizumab[a] Mean	Mean of Differences[b] (Ravulizumab–Eculizumab)	SD	Effect Size[c]	*P* Value[d]
The frequency of infusions disrupted my life	0.23	2.51	−2.29	1.07	−2.14	<0.001
After receiving infusions, I had fatigue	0.66	1.46	−0.80	1.13	−0.71	<0.001
Effective in treating symptoms of PNH	3.57	3.14	0.43	0.95	0.45	0.01
While I was receiving treatments, I was able to enjoy life	3.66	2.91	0.74	0.78	0.95	<0.001

PNH, paroxysmal nocturnal hemoglobinuria; QoL, quality of life; SD, standard deviation.
[a]Mean of responses on an agreement scale of 0 = "Not at all" to 4 = "Very much." Higher means indicate greater agreement. For this reason, lower scores on negatively worded questions are more favorable and higher scores on positively worded questions are more favorable.
[b]Difference in means of responses between identical questions for ravulizumab and eculizumab.
[c]Effect sizes are calculated as the difference in mean scores divided by the standard deviation of the mean differences. Normative standards for absolute effect sizes are small, 0.20 to <0.50; medium, 0.50 to <0.80; large ≥0.80.
[d]*P* value from paired *t* test; *P* values calculated using Wilcoxon signed-rank test gave similar findings.

Limitations

- The amount of time between patients' last randomised treatment and completion of the PNH-PPQ© presents a potential bias in time-based recall of their experiences

CONCLUSIONS

- In this clinical substudy of eculizumab-experienced PNH patients, a majority of UK patients preferred ravulizumab compared to eculizumab
  - The findings in this subgroup of patients are consistent with the results for the overall population in the 302s study, in which 92.6% (88/95) of patients reported an overall preference for ravulizumab[13]
- Ravulizumab was preferred because of reduced infusion frequency (q8w vs q2w), better ability to plan activities, more convenience of treatment, improved overall QoL, better control of fatigue and other symptoms, and effectiveness of medication until the next infusion
- These findings provide an important patient perspective on treatment preferences for PNH when there is more than one treatment option

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