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Composite endpoint to evaluate complement inhibition therapy in patients with paroxysmal nocturnal hemoglobinuria

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Abstract

This study developed and explored a novel composite endpoint to assess the overall impact that treatment can have on patients living with paroxysmal nocturnal hemoglobinuria (PNH). Candidate composite endpoint variables were selected by a group of experts and included: lactate dehydrogenase levels as a measure of intravascular hemolysis; complete terminal complement inhibition; absence of major adverse vascular events, including thrombosis; absence of any adverse events leading to death or discontinuation of study treatment; transfusion avoidance; and improvements in fatigue-related quality of life as determined by the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score. From these variables, a novel composite endpoint was constructed and explored using data collected in the ravulizumab PNH Study 301 (NCT02946463). Thresholds were defined and reported for each candidate variable. Five of the six candidate variables were included in the final composite endpoint; the FACIT-Fatigue score was excluded. Composite endpoint criterion was defined as patients meeting all five selected individual component thresholds. All patients in the ravulizumab arm achieved complete terminal complement inhibition and a reduction in lactate dehydrogenase levels; 51.2% and 41.3% of patients in the ravulizumab arm and eculizumab arm, respectively, achieved all composite endpoint component thresholds (treatment difference: 9.4%; 95% confidence interval: −3.0, 21.5). The composite endpoint provided a single and simultaneous measurement of overall benefit for patients receiving treatment for PNH. Use of the composite endpoint in future PNH research is recommended to determine clinical benefit, and its use in health technology assessments should be evaluated.

KEYWORDS
endpoint, paroxysmal nocturnal hemoglobinuria, rare disease, ravulizumab

1 | INTRODUCTION

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, chronic, and potentially life-threatening hematologic disorder caused by uncontrolled activation of the terminal complement pathway, leading to intravascular hemolysis (IVH), thrombosis, and organ damage.[1-4]

PNH occurs following a somatic gene mutation in the phosphatidylinositol glycan class A gene in bone marrow stem cells, resulting in the disruption of glycosyl phosphatidylinositol regulatory proteins, including CD55 and CD59, on the surface of blood cells.[5] This genetic mutation causes increased cellular sensitivity to terminal complement activation, IVH, promotion of inflammatory mediators, and systemic free hemoglobin release.[6] An analysis of the International PNH Registry showed that 23% of patients with PNH had been hospitalized owing to disease-related complications.[7] Thrombosis is the most common cause of mortality in patients with PNH,[3] accounting for approximately 40%–67% of deaths with known causes.[8] Approximately 35%–43% of patients with PNH have multiple thromboembolic events.[4,9] Terminal complement-mediated IVH, as measured by elevated lactate dehydrogenase (LDH) levels ($\geq 1.5 \times$ upper limit of normal [ULN]), is associated with an increased risk of thromboembolism and mortality.[4,10,11] Therefore, LDH is considered an important clinical biomarker in patients with PNH. Patients with PNH experience symptoms such as severe fatigue, abdominal pain, headache, shortness of breath, dysphagia, and erectile dysfunction, all of which are associated with a high burden of disease and impaired quality of life (QoL).[12]

Eculizumab was the first treatment to be approved for patients with PNH; it is a humanized monoclonal antibody that blocks terminal complement activation at complement component 5 (C5).[6] Since its approval in 2007, eculizumab has become established as a global standard of care for the management of PNH. However, 11%–27% of patients experience breakthrough intravascular hemolysis related to suboptimal C5 inhibition on approved dosages of eculizumab.[13-15] In addition, the usual eculizumab dosing regimen of every 2 weeks (q2w) may be challenging for some patients. These factors may negatively affect some patients' QoL, and increase the overall treatment burden of eculizumab.[16,17]

Ravulizumab is a long-acting C5 inhibitor that provides immediate, complete, and sustained C5 inhibition with an 8-week (q8w) dosing interval. It is approved for adult and pediatric patients with PNH who are naïve to complement inhibitors or who were previously treated with eculizumab,[18] and is the current standard of care for PNH in countries where it is commercially available. In the two largest phase 3 studies of PNH, ravulizumab was noninferior to eculizumab, with a safety profile similar to eculizumab.[19,20] A recent patient preference study has shown that the majority of patients prefer ravulizumab over eculizumab owing to reduced infusion frequency (q8w vs q2w), better ability to plan activities, improved overall health-related QoL, more convenient treatment, and effectiveness of the medication until the next infusion.[17]

What is the new aspect of your work?

This study developed and explored a novel composite endpoint to assess the overall impact that treatment can have on patients living with paroxysmal nocturnal hemoglobinuria (PNH).

What is the central finding of your work?

The composite endpoint provided a single and simultaneous measurement of overall therapeutic benefit for patients receiving treatment for PNH.

What is (or could be) the specific clinical relevance of your work?

Composite endpoints are increasingly used in chronic and complex diseases to demonstrate better control of disease and to assess the net benefit of a treatment when there is more than one endpoint to be considered; the use of this composite endpoint in future PNH research is recommended to determine the clinical benefits of a treatment.

Significance statement

A composite endpoint involves the combined assessment of multiple measures of improvement in patients with a disease. A group of experts in treating patients with paroxysmal nocturnal hemoglobinuria (PNH) selected and tested a number of measures important in assessing the therapeutic benefit of treatments to patients with PNH. The measures selected included levels of key blood markers for treatment effectiveness (lactate dehydrogenase and terminal complement inhibition) and the number of adverse events and blood transfusions avoided after treatment. When tested in a study where patients with PNH were treated with ravulizumab versus eculizumab, the composite endpoint provided a single and simultaneous measurement of overall benefit.

Clinical studies have traditionally used single, separate endpoints that capture several outcomes to describe the benefits of PNH treatment.[20] An alternative analytic approach for evaluating the benefits of PNH treatment is to combine multiple relevant clinical PNH variables into a single composite endpoint. Composite endpoints are widely used as primary endpoints in clinical trials across multiple disease areas[21,22]; however, a composite endpoint for use in PNH research has not been previously developed.

The rationale and benefits of developing a composite endpoint for clinical research are manifold.[23-25] First, a composite endpoint can provide a single measurement for evaluating overall impact and encompassing key clinical benefits in a complex, multifaceted

disease. Second, composite endpoints can create a more integrated assessment of treatment effects that cover relevant morbidities and are possibly less selective. In addition, a composite endpoint can consider all variables of major clinical relevance without the need to adjust for multiplicity.[26] A composite endpoint may also generate an increase in power to detect a meaningful difference between treatments, to help to inform treatment decisions and ultimately improve patient outcomes and health status. Furthermore, a composite endpoint can be utilized as a tool to compare outcomes across clinical trials, can offer a more practical approach for future PNH clinical trials, and can potentially improve the comparability of clinical trials.

The objective of this study was to explore and develop a composite endpoint for PNH that could be used by physicians, and that has the possibility to further clinical development, health economic evaluation, and research.

2 | METHODS

Components of a composite endpoint were chosen for their relevance to PNH based on advice from a working group of hematologists who are experts in the research and treatment of PNH, composite endpoint experts, and patients with extensive knowledge of PNH who are members of the PNH Global Alliance.[27] The process for selecting composite endpoint components by the working group is presented in Figure 1.

Detailed analyses of all clinical parameters, including laboratory values and QoL parameters for PNH, were reviewed for inclusion in the overall composite endpoint. Several noncritical and overlapping variables were eliminated in the overall composite endpoint. For example, the number of transfusions, number of packed red blood cells (pRBCs), hemoglobin levels requiring transfusion, and frequency of transfusions were captured under transfusion reductions or avoidance. Haptoglobin and reticulocyte count were excluded for the benefit of LDH level, which was considered to be more representative of the hemolytic state of PNH. Final clinical variables selected for the overall composite endpoint evaluation included: LDH levels as a measure of IVH; complete terminal complement inhibition; absence of major adverse vascular events (MAVEs) including thrombosis; absence of any adverse events (AEs) leading to death or discontinuation of study treatment; transfusion avoidance; and reduction of fatigue as determined by the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score.[28] Thresholds for binary assessment of the selected components were considered and defined by consensus of a multidisciplinary panel of experts based on existing literature and results from clinical trials (Table S1). It was determined that each component of the composite endpoint would act as a binary indicator, and each component indicator must hold true for patients to meet the overall composite endpoint indicator. Therefore, the composite endpoint can be interpreted as a special case of a binary composite endpoint.[25]

The composite endpoint was then applied to analyze the clinical benefits of the two approved drugs for PNH evaluated in Study 301. Study 301 (NCT02946463) was a phase 3, open-label, interventional study evaluating the effects of ravulizumab versus eculizumab in complement inhibitor-naïve patients with PNH,[20] and is the largest study of complement inhibitor-naïve patients to date. The proportion of patients meeting the threshold for each composite endpoint component at 26 weeks was assessed using descriptive statistical analysis. The percentages and confidence intervals (CIs) for treatment-effect difference were calculated using the stratified Newcombe CI method. Stratification factors are observed stratification groups of pRBCs/whole blood units transfused in the year before the first dose of study drug (0, 1–14, or >14 units of pRBCs) and screening LDH levels (1.5 to <3 or ≥3 × ULN). For the components of complete terminal complement inhibition (serum free C5 <0.5 μg/ml) and absence of any AEs leading to death or discontinuation of study treatment, the 95% CI was calculated using the exact method because the stratified Newcombe CI was noncalculable owing to a high event rate.

FIGURE 1 Composite endpoint component selection process. [a]Complete terminal complement inhibition (serum free C5 levels <0.5 μg/ml). [b]Leading to death or discontinuation from study treatment, including meningococcal infections. Purple text indicates noncritical variables. Red text indicates overlapping variables. AE, adverse event; BTH, breakthrough hemolysis; C5, complement component 5; LDH, lactate dehydrogenase; MAVE, major adverse vascular event; PNH, paroxysmal nocturnal hemoglobinuria; QoL, quality of life; TE, thrombotic event
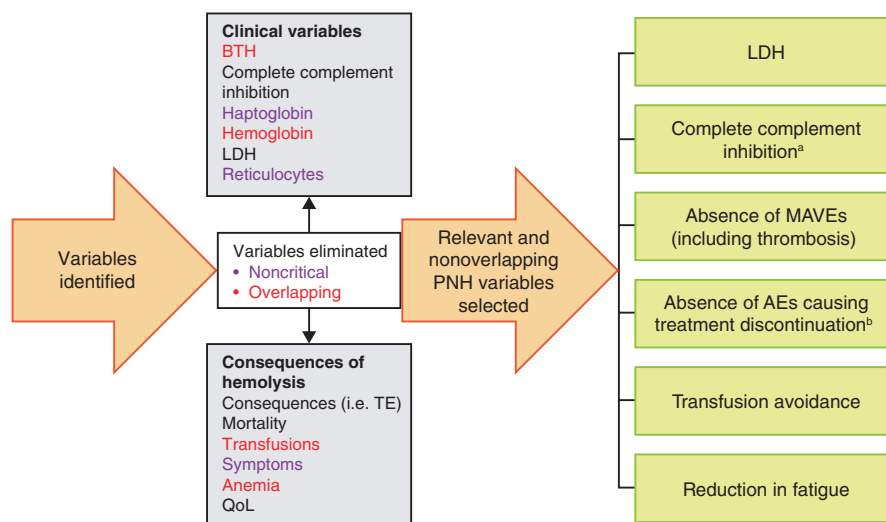
3 | RESULTS

3.1 | Patients

Thresholds for individual components in a PNH composite endpoint were applied to data from 246 complement inhibitor-naïve adult patients with PNH who were treated with ravulizumab (n = 125) or eculizumab (n = 121) during the 26-week primary evaluation period in Study 301.[20]

3.2 | Defined thresholds and proportion of patients meeting the threshold for each component of the composite endpoint

3.2.1 | LDH levels

The primary goal when a patient is started on a complement inhibitor is to reduce LDH levels below 1.5 × ULN.[29] During the primary evaluation period of Study 301, from week 4 to 26, the proportion of patients achieving median LDH values <1.5 × ULN was 92.8% and 98.3%, in the ravulizumab and eculizumab arms, respectively.

The chosen threshold for LDH levels in the composite endpoint was for all LDH measurements to be <1.5 × ULN after 4 weeks from initiation of treatment. At baseline, most patients had LDH values ≥3 × ULN in both the ravulizumab arm (85.6%) and eculizumab arm (86.8%) (Table 1). From weeks 4 to 26 of the treatment period, 12 LDH assessments were scheduled per the study protocol: 68.0% of patients in the ravulizumab arm and 57.0% of patients in the eculizumab arm had all LDH values <1.5 × ULN, a treatment-effect difference of 11.0% (95% CI: −1.2, 22.6). In addition, mean LDH values were similar between treatment groups throughout the 26-week treatment period (Figure 2).

3.2.2 | Complete terminal complement inhibition

It is key for a composite endpoint to include a measure of treatment effectiveness. Given that uncontrolled terminal activation is the main driver of PNH, and the measurement of C5 was appropriate in this trial study used to test the composite endpoint, the threshold of serum free C5 measurements <0.5 μg/ml was chosen to define complete terminal complement inhibition on this occasion. For evaluation of complement blockade of non-C5 inhibitors another biomarker other than free C5 levels could be considered, although terminal blockade would need to be evaluated due to its link to PNH disease pathology. At baseline, no patient in either treatment arm had serum free C5 levels <0.5 μg/ml (Table 1). At 26 weeks, every patient in the ravulizumab arm (100.0%) and most patients in the eculizumab arm (87.6%) had all serum free C5 levels <0.5 μg/ml from after the first infusion through week 26, corresponding to a treatment-effect difference of 12.4% (95% CI: 7.1, 19.6). This shows that ravulizumab provides immediate, complete, and sustained terminal complement inhibition (Figure S1).[30]

3.2.3 | Absence of MAVEs including thrombosis

The chosen threshold to define this variable was patients who did not have any MAVEs including thrombosis. At baseline, some patients had a history of MAVE (any experience of a MAVE before initiating treatment) in both the ravulizumab arm (13.6%) and eculizumab arm (20.7%) (Table 1). At 26 weeks, almost all patients reached the threshold and demonstrated absence of MAVEs from the first infusion through week 26 in both the ravulizumab arm (98.4%) and eculizumab arm (99.2%), a treatment-effect difference of −0.8% (95% CI: −6.1, 5.7).

3.2.4 | Absence of any AEs leading to death or discontinuation of study treatment

The chosen threshold to define this variable was patients who did not have any AEs leading to death or discontinuation from the study treatment. All patients in the ravulizumab arm (100.0%) and almost all patients in the eculizumab arm (99.2%) met this threshold and demonstrated an absence of any AEs leading to death or discontinuation of study treatment, corresponding to a treatment-effect difference of 0.8% (95% CI: −2.3, 4.6) (Table 1). Meningococcal infections were evaluated, and no patients reported meningococcal infection during the 26-week treatment period.

3.2.5 | Transfusion avoidance

Transfusion avoidance has been selected as an endpoint in clinical trials as this is a clinically meaningful endpoint for patients with PNH.[20] The chosen threshold for transfusion avoidance in the composite endpoint was for patients to remain transfusion free and not meet protocol-specified transfusion guidelines (hemoglobin value of ≤9 g/dl with signs or symptoms of sufficient severity to warrant a transfusion, or a hemoglobin value of ≤7 g/dl regardless of clinical signs or symptoms) throughout the 26-week study treatment period. In the year before study entry, a majority of patients required a transfusion of at least one unit of pRBC in both the ravulizumab arm (81.6%) and the eculizumab arm (82.7%) (Table 1). Throughout the 26-week treatment period, a majority of patients in both groups met the composite endpoint threshold by remaining transfusion free and not requiring any transfusions of pRBC units, 73.6% in the ravulizumab arm and 66.1% in the eculizumab arm.

3.2.6 | Reduction in fatigue as determined by FACIT-Fatigue score

The chosen threshold to define this variable was an increase of FACIT-Fatigue score by ≥3 points from baseline,[31] although this threshold was derived from prior studies not related to PNH. More than half the patients in both the ravulizumab arm (61.6%) and

TABLE 1 Baseline and 26-week data for components of the composite endpoint

	Ravulizumab (n = 125)	Eculizumab (n = 121)
LDH levels[a]		
Baseline		
LDH ratio, n (%)		
1.5 to <3 × ULN	18 (14.4)	16 (13.2)
≥3 × ULN	107 (85.6)	105 (86.8)
Baseline to 26 weeks		
Patients who had all LDH values from day 28 to 183 <1.5 × ULN, n (%; 95% CI)	85 (68.0; 59.8, 76.2)	69 (57.0; 48.2, 65.9)
Treatment-effect difference, % (95% CI)		11.0 (−1.2, 22.6)
Complete terminal complement inhibition (serum free C5 levels <0.5 μg/ml)		
Baseline		
Patients with serum free C5 levels <0.5 μg/ml, n (%)	0 (0)	0 (0)
Serum free C5 levels, mean μg/ml (SD)	104.1 (27.9)	144.4 (33.2)
Baseline to 26 weeks		
Patients who had all serum free C5 levels <0.5 μg/ml after first infusion/dose through week 26, n (%; 95% CI)[b]	125 (100.0; 97.1, 100.0)	106 (87.6; 80.4, 92.9)
Treatment-effect difference, % (95% CI)[b]		12.4 (7.1, 19.6)
Absence of MAVEs, including thrombosis		
Baseline		
History of MAVE, n (%)	17 (13.6)	25 (20.7)
Baseline to 26 weeks		
Absence of MAVE; proportion of patients who had no MAVE event (including thrombosis) after first infusion/ dose through week 26, n (%; 95% CI)	123[c] (98.4; 96.2, 100.0)	120[d] (99.2; 97.6, 100.0)
Treatment-effect difference, % (95% CI)		−0.8 (−6.1, 5.7)
Absence of AEs leading to death or discontinuation from study treatment		
Baseline to 26 weeks[e]		
Absence of any AEs leading to death or discontinuation from study treatment, n (%; 95% CI)[b]	125 (100.0; 97.1, 100.0)	120[f] (99.2; 95.5, 100.0)
Treatment-effect difference, % (95% CI)[b]		0.8 (−2.3, 4.6)
Transfusion avoidance		
Baseline pRBC units transfused in the year before study entry, randomization strata, n (%)		
0 units	23 (18.4)	21 (17.4)
1–14 units	79 (63.2)	78 (64.5)
>14 units	23 (18.4)	22 (18.2)
Baseline to 26 weeks		
Patients who received pRBC transfusions, n (%)	32 (25.6)	40 (33.1)
Patients who remained transfusion free, n (%; 95% CI)[g]	92 (73.6; 65.9, 81.3)	80 (66.1; 57.7, 74.6)
Treatment-effect difference, % (95% CI)[g]		6.8 (−4.7, 18.1)

Abbreviations: AE, adverse event; C5, complement component 5; CI, confidence interval; LDH, lactate dehydrogenase; MAVE, major adverse vascular event; pRBC, packed red blood cell; SD, standard deviation; ULN, upper limit of normal.

[a]The ULN for LDH is 246 U/L.

[b]95% CI was calculated using exact method because stratified Newcombe CI is noncalculable owing to high event rate.

[c]Lower-leg deep vein thrombosis occurred in two patients. One of the two patients was receiving concomitant oral contraceptive medication. The other patient had a history of right lower-leg pain and leg edema and was taking oral anticoagulants prior to the study, which were discontinued after starting the study drug.

[d]Mesenteric venous thrombosis with concurrent neutropenic colitis occurred in one patient with a history of aplastic anemia.

[e]Meningococcal infections were included in the data set; however, no patients had meningococcal infections during the 26-week treatment period.

[f]One patient developed symptoms of lung cancer during the 26-week treatment period and died owing to lung cancer (unrelated to treatment) during the extension phase of the study.

[g]Calculated using stratified Newcombe CI method. The stratification factors were observed stratification groups of pRBC/whole blood units transfused in the 1 year prior to first dose of study drug and screening LDH levels.
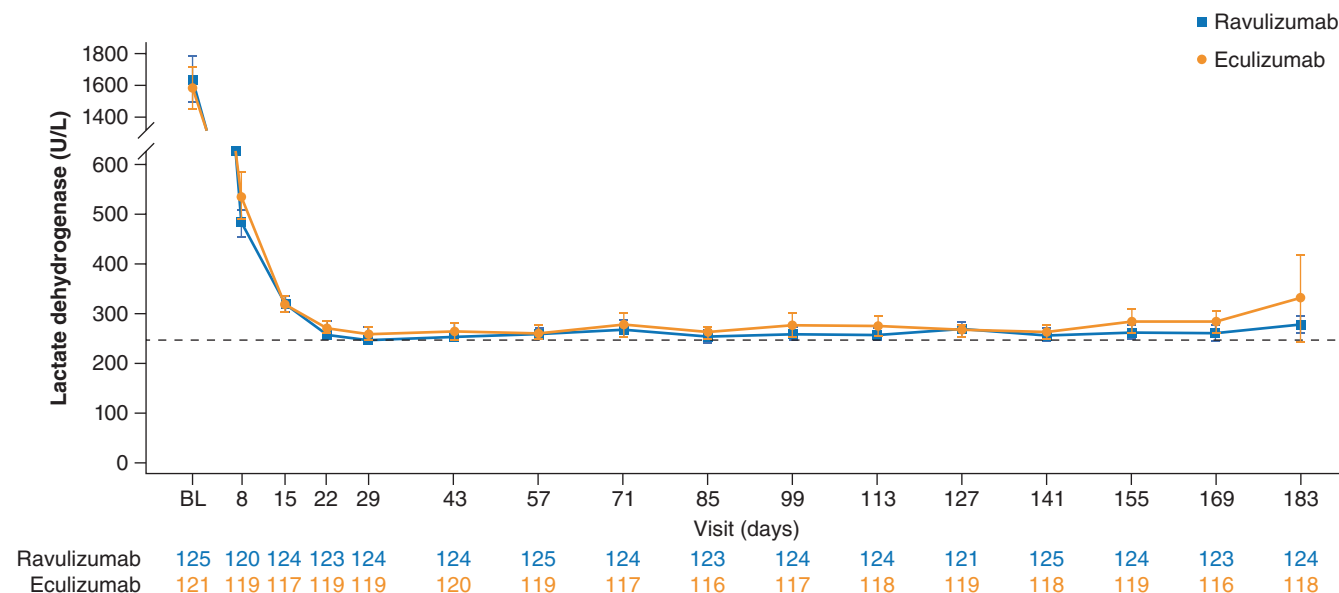
FIGURE 2 Mean LDH values over 26 weeks. BL is defined as the average of all available assessments prior to first study drug dose. Dotted horizontal lines indicate upper normal value. Error bars represent 95% confidence intervals. BL, baseline; LDH, lactate dehydrogenase
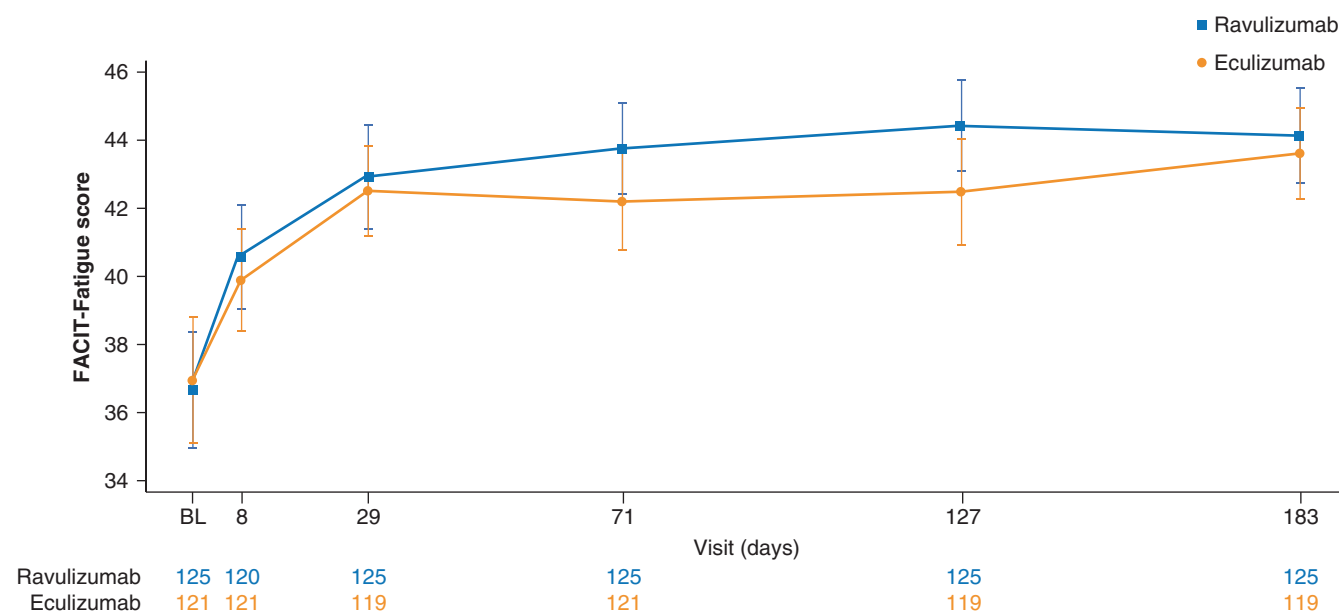

FIGURE 3 Mean FACIT-Fatigue scores over 26 weeks. FACIT score ranges from 0 to 52, with a higher score indicating less fatigue. BL was defined as the last non-missing assessment value prior to first study drug dose. Dashed horizontal line indicates threshold that delineates clinically meaningful improvement (≥3 points). Error bars represent 95% CIs. BL, baseline; CI, confidence interval; FACIT, Functional Assessment of Chronic Illness Therapy

eculizumab arm (59.7%) met the threshold for reduction in fatigue as determined by FACIT-Fatigue score improvement. The FACIT-Fatigue scale was used to measure and to quantify changes from baseline in fatigue-related QoL in patients with PNH who were treated with ravulizumab or eculizumab. Patients in both the ravulizumab and eculizumab treatment arms demonstrated improvements in FACIT-Fatigue scores over the 26-week treatment period

(Figure 3). Authors also evaluated other thresholds of FACIT-Fatigue (increase of ≥5, increase of ≥10 and overall score ≥44) and concluded not to select FACIT-Fatigue as a component of the composite endpoint owing to the difficulty in defining a normal score for this patient group. Thus, it was not possible to create a binary response criterion equivalent to the other criteria as more research is needed.

3.2.7 | Composite endpoint

The overall composite endpoint was defined as patients meeting all five of the selected individual component thresholds. In total, 51.2% of patients in the ravulizumab arm and 41.3% of patients in the eculizumab arm met the composite endpoint. The adjusted treatment difference between the two study arms for the overall composite endpoint was 9.4% (95% CI: −3.0, 21.5). Outcomes for the overall PNH composite endpoint and its individual components are shown in Figure 4.

Most patient demographics and baseline characteristics were similar for patients meeting and not meeting the composite endpoint threshold (Table 2). Despite these similarities, there were some numerical differences. First, the proportion of patients with high baseline LDH values ($>3 \times$ ULN) and the proportion of patients who received more transfusions (>14 units of pRBC) are numerically higher in individuals who did not meet the composite endpoint. Other trends observed were that the age of patients at both PNH diagnosis and first infusion who met the composite endpoint criteria was numerically lower than that of individuals who did not meet the criteria, and that total PNH RBCs at baseline was larger in patients who met the composite endpoint criteria than in those who did not (Table 2).

4 | DISCUSSION

Composite endpoints are increasingly used in chronic and complex diseases to demonstrate better control of disease and to assess the net benefit of a treatment when there is more than one endpoint to be considered.[24,32] From the clinical perspective, all the measures that form the composite endpoint are considered very important and provide a holistic goal encompassing efficacy and safety versus having a single primary endpoint (or co-endpoints), which may potentially overly emphasize only one parameter. PNH is a disease with a complex pathogenetic process that can lead to continuing health issues (e.g., MAVEs, chronic anemia, and transfusion dependence); therefore, a composite endpoint could provide a better assessment of clinical benefit as an overall, multifaceted measure of treatment effect versus single endpoints, which have traditionally been used in clinical trials. Nevertheless, composite endpoints come with interpretation challenges that must be adequately addressed.[33]

This study presents a composite endpoint for PNH as a novel and exploratory tool to provide a single measurement encompassing the sought for clinical benefits of complement inhibitor therapies for PNH. Components and thresholds for the composite endpoint were chosen for their relevance to PNH by PNH clinicians and patients with a diagnosis of PNH. The components chosen to define the composite endpoint incorporate a wide assessment of the PNH pathogenic process and have been recently validated as goals of complement inhibition (LDH levels as a measure of IVH, complete terminal complement inhibition, absence of MAVEs including thrombosis, PNH treatment safety variables [absence of any AEs leading to death or discontinuation of study treatment], and transfusion avoidance).[29] The composite endpoint was then evaluated by applying it to patient level data from a recent clinical trial. Overall, a majority of patients met the chosen threshold for each component of the composite endpoint, and more than half of patients met the overall composite endpoint in the ravulizumab arm.

Meeting the composite endpoint criteria is important for considering the overall benefit of therapeutic interventions, which seems appropriate as novel treatments offer differing benefits and should be measured accordingly. Not meeting the composite endpoint does not mean treatment failure or nonresponse; symptomatology is different for every patient and thus the management of PNH may vary accordingly. For example, management of patients with PNH who concomitantly experience bone marrow failure may differ to the management of patients with PNH alone, and it may not be possible
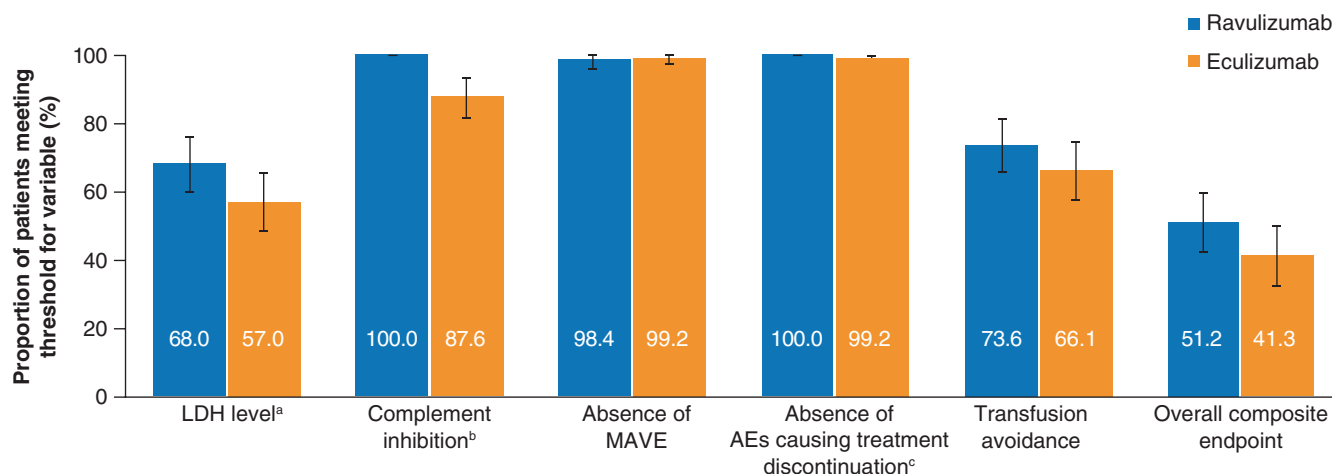

FIGURE 4 Evaluation of a PNH composite endpoint with ravulizumab and eculizumab at 26 weeks. [a]LDH values from day 28 to 183 $\leq 1.5 \times$ ULN. [b]Complete terminal complement inhibition (serum free C5 levels <0.5 µg/ml). [c]AEs leading to death or discontinuation from study treatment, including meningococcal infections. AE, adverse event; C5, complement component 5; LDH, lactate dehydrogenase; MAVE, major adverse vascular event; PNH, paroxysmal nocturnal hemoglobinuria; ULN, upper limit of normal
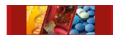
TABLE 2 Demographics and baseline characteristics by patients meeting and not meeting the composite endpoint threshold

	Met the composite endpoint		Did not meet the composite endpoint	
	Ravulizumab (n = 64)	Eculizumab (n = 50)	Ravulizumab (n = 61)	Eculizumab (n = 71)
Sex, n (%)				
Male	35 (54.7)	31 (62.0)	30 (49.2)	38 (53.5)
Female	29 (45.3)	19 (38.0)	31 (50.8)	33 (46.5)
Race, n (%)				
Asian	37 (57.8)	28 (56.0)	35 (57.4)	29 (40.8)
White	20 (31.3)	17 (34.0)	23 (37.7)	34 (47.9)
American Indian or Alaska Native	1 (1.6)	1 (2.0)	0 (0.0)	0 (0.0)
Black or African American	1 (1.6)	0 (0.0)	1 (1.6)	4 (5.6)
Other	3 (4.7)	1 (2.0)	1 (1.6)	3 (4.2)
Not reported	2 (3.1)	3 (6.0)	1 (1.6)	1 (1.4)
Age at PNH diagnosis (years)				
Mean (SD)	36.5 (14.5)	36.0 (15.1)	39.3 (15.3)	42.0 (17.3)
Age at first infusion (years)				
Mean (SD)	44.4 (15.1)	42.7 (15.3)	45.3 (15.4)	48.7 (16.5)
Baseline weight (kg)				
Mean (SD)	67.9 (14.8)	67.3 (13.1)	68.5 (16.5)	70.5 (16.0)
LDH stratification groups at randomization, n (%)				
1.5–<3 × ULN	11 (17.2)	10 (20.0)	7 (11.5)	6 (8.5)
>3 × ULN	53 (82.8)	40 (80.0)	54 (88.5)	65 (91.5)
pRBC stratification groups at randomization, n (%)				
0 units	14 (21.9)	17 (34.0)	9 (14.8)	4 (5.6)
1–14 units	42 (65.6)	29 (58.0)	37 (60.7)	49 (69.0)
>14 units	8 (12.5)	4 (8.0)	15 (24.6)	18 (25.4)
Total PNH RBC clone size (%)				
Mean (SD)	43.0 (24.2)	45.7 (23.9)	33.6 (22.5)	33.9 (21.5)
Total PNH granulocyte clone size (%)				
Mean (SD)	86.7 (17.4)	82.5 (22.8)	81.7 (24.0)	87.3 (15.6)
Total PNH monocyte clone size (%)				
Mean (SD)	88.7 (15.4)	86.6 (18.2)	84.9 (20.5)	91.0 (12.4)
Patients with any PNH conditions prior to informed consent, n (%)	63 (98.4)	49 (98.0)	58 (95.1)	71 (100.0)
Anemia	53 (82.8)	41 (82.0)	50 (82.0)	64 (90.1)
Hematuria or hemoglobinuria	39 (60.9)	28 (56.0)	42 (68.9)	47 (66.2)
Aplastic anemia	23 (35.9)	12 (24.0)	18 (29.5)	26 (36.6)
Renal failure	9 (14.1)	2 (4.0)	10 (16.4)	9 (12.7)
Pregnancy complication	1 (1.6)	3 (6.0)	2 (3.3)	1 (1.4)
Myelodysplastic syndrome	2 (3.1)	0 (0.0)	5 (8.2)	6 (8.5)
Other	12 (18.8)	5 (10.0)	15 (24.6)	8 (11.3)

Abbreviations: LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal hemoglobinuria; pRBC, packed red blood cell; RBC, red blood cell; SD, standard deviation; ULN, upper limit of normal.

for them to meet complete transfusion avoidance even if PNH is well treated and controlled. Reasons for requiring transfusions other than bone marrow failure may also occur and would be evaluated by this parameter. In order for the composite endpoint to be met, all LDH levels over time to be below 1.5 × ULN, complete terminal inhibition over time (all serum free C5 levels <0.5 μg/ml in our example) and complete avoidance of transfusions are required. This reflects an intensive suppression of disease activity and is more likely to result in increased clinical benefit than single endpoints. From a comparison of baseline demographics and characteristics, it appears

that patients with high disease burden at baseline were less likely to meet the composite endpoint criteria than those with low disease burden.

In accordance with previous research in other therapeutic areas, development of a composite endpoint as a primary endpoint for PNH can provide insight into meaningful PNH research endpoints for stakeholders such as clinicians, patients, investigators, and policy-makers.[24] Composite endpoints have previously been developed for use in several therapeutic areas including diabetes, heart failure, multiple sclerosis, rheumatoid arthritis, chronic obstructive pulmonary disease, oncology, orthopedics, and allogeneic hematopoietic cell transplantation.[34–41]

This novel, exploratory composite endpoint offers a more comprehensive evaluation of PNH treatment effect than any individual endpoint in the clinical trial, which can potentially allow for improved assessment of clinical benefit of PNH treatments.[24] The composite endpoint for PNH enables evidence generation of sufficient validity and generalizability for translation into practice and policy to improve health outcomes in patients with PNH.[24] Clinical trials of rare diseases such as PNH are restricted in capacity to detect treatment effect owing to the limited number of studies with small sample sizes that are performed.[42] There are also challenges associated with the use of composite endpoints such as planning and interpreting clinical trials, accounting for competing risks as a source of bias, and follow-up beyond the first event. If these challenges are not addressed, composite endpoints can bear risks for bias and misinterpretation. A well-defined composite endpoint guided by arguments of clinical relevance can importantly contribute to more efficient clinical trials.[33]

Fatigue is a common complaint reported by patients with PNH, and it can have substantial debilitating effects on patients' QoL.[43] The FACIT-Fatigue scale measures reduction in fatigue severity and related functional impairments in patients with chronic illness, and has been validated to assess fatigue levels in patients with PNH[43]; however, no specific QoL tool has been developed to assess the effectiveness of PNH treatment. Although reduction in fatigue as determined by the FACIT-Fatigue score is an important outcome and should be assessed as a secondary endpoint in PNH clinical trials, it is not recommended to include it in a composite endpoint for several reasons. First, there were uncertainties concerning threshold criteria for reduction in fatigue in PNH; there is no generally accepted level for minimal clinically important difference (MCID) in FACIT-Fatigue scores for this patient population, as well as for comparable healthy control populations.[44,45] In addition, it was not possible to determine the possible weight of a FACIT-Fatigue score versus the other elements of the composite endpoint. Furthermore, there are conceptual differences between a composite endpoint measuring biological markers and clinical events, and a composite endpoint measuring symptoms and QoL. Although it is methodologically preferable not to integrate FACIT-Fatigue score into this composite endpoint, it is strongly recommended to assess reduction of fatigue as a patient-reported outcome measure in addition to the composite endpoint in PNH research.

This study has several notable strengths. A group comprised of PNH and composite endpoint experts and patients with PNH developed the composite endpoint together. Overlapping and non-critical variables were eliminated from the composite endpoint, making it a robust tool to evaluate treatment benefit in PNH. A combination of the use of stringent criteria (e.g., LDH <1.5 × ULN) and carefully selected PNH endpoints enabled assessment of both complement inhibition (i.e., LDH and serum free C5 levels) and endpoints of clinical benefit to patients (e.g., absence of MAVEs/SAEs and transfusion avoidance). Furthermore, this study was based on a large, well-controlled, randomized comparison of two treatments in a homogeneous and representative patient group. Finally, results were reported for each individual component on the composite endpoint.

Despite the strengths of this study, several limitations must be considered. The definition of a composite endpoint compared with an isolated endpoint also bears several risks and limitations,[33] which we tried to address as well as possible. As we defined the components of the composite endpoints by argument of clinical relevance, this importantly contributes to overcoming such challenges. The design and analysis of the composite endpoint were exploratory in nature and evaluated utilizing data from one trial, and therefore the results should be interpreted with caution. The analysis of the composite endpoint was also *post hoc* in nature. In Study 301, discontinuations due to MAVEs and AEs (including meningococcal infections) were evaluated for a 26-week treatment period, which may be too short to evaluate them.[20] Furthermore, it is challenging to compare lifetime history of MAVEs with a reduction in MAVEs over a relatively short primary evaluation period of 6 months; however, the findings of this study are supported by recent data showing that MAVEs were reduced after 1 year of treatment with ravulizumab.[46] Terminal complement inhibition is the goal in PNH treatment owing to the role of complement-mediated intravascular hemolysis in morbidity and mortality.[2,4,47] In this example, serum free C5 was used as a measure of complete terminal complement inhibition; therefore, this composite endpoint may need some adaptation when evaluating other new PNH treatments for their ability to inhibit terminal complement activation, as per their own pharmacokinetic/pharmacodynamic standards.[48,49] Additionally, patients with PNH commonly have a history of bone marrow failure; therefore, results seen for PNH treatment may be affected by transfusions received for the treatment of bone marrow failure.

5 | CONCLUSIONS

A composite endpoint for PNH was designed and applied to patient data from Study 301, which allowed for an integrated and simultaneous assessment of the key clinical benefits of the two approved drugs for PNH (ravulizumab and eculizumab) evaluated in the study. Additionally, the composite endpoint provides a holistic goal offering a single measurement of therapeutic benefit.

Despite the fact that improvements in fatigue-related QoL as determined by FACIT-Fatigue score was not included in the composite endpoint, it is strongly recommended to assess fatigue severity and related functional limitations in addition to the composite endpoint in PNH research; however, further research is still needed in this area as it evolves. This composite endpoint is recommended for use in future PNH research to explore clinical benefit. Furthermore, its use in health technology assessments should be evaluated.

CONFLICT OF INTEREST

A.K. has served on advisory boards, received speaker fees and/or travel grants from Alexion, AstraZeneca Rare Disease, Amgen, Apellis, UCB/Ra Pharmaceuticals, Sobi, Celgene/BMS, Novartis, Roche, and Biocryst. A.G., G.R., and C.G. have received fees from Alexion. P.L. and J.R.S. are employees and stockholders of Alexion, AstraZeneca Rare Disease. J.S. has served on advisory boards and speaker bureaus and has received honoraria from Alexion, AstraZeneca Rare Disease, Apellis, Novartis, Pfizer, Sanofi, and Prevail Therapeutics. D.A. has served on Alexion advisory boards and has received speaker fees from Alexion. J.W.L. has received grants and honoraria from Alexion, AstraZeneca Rare Disease, and has served as a member of an advisory board for Alexion, AstraZeneca Rare Disease. The authors received no additional financial support or other form of compensation related to the development of this article.

AUTHOR CONTRIBUTIONS

A.G., A.K., C.G., G.R., J.R.S., J.S., J.W.L, and P.L. contributed to the concept and design of the study; D.A. also contributed to the study design. A.G. and J.R.S. developed the outline of the manuscript. P.L. performed the data analysis. A.G., A.K., C.G., D.A., G.R., J.R.S., J.S., and J.W.L contributed to the interpretation of the data. All authors contributed to the development and review of the article and approved the final version.

CLINICAL TRIAL REGISTRATION

This study was not a clinical trial.

PATIENT CONSENT STATEMENT

Patient consent was not applicable for this study.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

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Alexion will consider requests for disclosure of clinical study participant-level data provided that participant privacy is assured through methods like data de-identification, pseudonymization, or anonymization (as required by applicable law), and if such disclosure was included in the relevant study informed consent form or similar documentation. Qualified academic investigators may request participant-level clinical data and supporting documents (statistical analysis plan and protocol) pertaining to Alexion-sponsored studies. Further details regarding data availability and instructions for requesting information are available in the Alexion Clinical Trials Disclosure and Transparency Policy at https://alexion.com/our-research/research-and-development. Link to Data Request Form (https://alexion.com/contact-alexion/medical-information).

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