One-year efficacy and safety of ravulizumab in adults with paroxysmal nocturnal hemoglobinuria naïve to complement inhibitor therapy: open-label extension of a randomized study

Hubert Schrezenmeier, Austin Kulasekararaj, Lindsay Mitchell, Flore Sicre de Fontbrune, Timothy Devos, Shinichiro Okamoto, Richard Wells, Scott T. Rottinghaus, Peng Liu, Stephan Ortiz, Jong Wook Lee and Gérard Socié

Ther Adv Hematol

2020, Vol. 11: 1–14

DOI: 10.1177/2040620720966137

Correspondence to:
Jong Wook Lee
Department of Hematology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul, 06591, Republic of Korea
jwlee@catholic.ac.kr

Hubert Schrezenmeier
Institute of Transfusion Medicine, University of Ulm and Institute for Clinical Transfusion Medicine and Immunogenetics Ulm, German Red Cross Blood Transfusion Service and University Hospital Ulm, Ulm, Germany

Austin Kulasekararaj
Department of Haematological Medicine, King's College Hospital, NIHR/Wellcome King's Clinical Research Facility, London, UK

Lindsay Mitchell
Department of Haematology, University Hospital Monklands, Lanarkshire, UK

Flore Sicre de Fontbrune
Service d'Hématologie Greffe, Centre de Référence Aplasie Médullaire, Assistance Publique des Hôpitaux de Paris, Hôpital Saint-Louis, Paris, France

Timothy Devos
Department of Hematology, University Hospitals Leuven and Department of Microbiology and Immunology, Laboratory of Molecular Immunology (Rega Institute), KU Leuven, Leuven, Belgium

Shinichiro Okamoto
Division of Hematology, Keio University School of Medicine, Tokyo, Japan

Richard Wells
Division of Medical Oncology and Hematology, Sunnybrook Health Sciences Centre, Toronto, ON, Canada

Abstract

Background: Ravulizumab, the only long-acting complement C5 inhibitor for adults with paroxysmal nocturnal hemoglobinuria (PNH), demonstrated non-inferiority to eculizumab after 26 weeks of treatment in complement inhibitor-naïve patients during a phase III randomized controlled trial. We present open-label extension results with up to 52 weeks of treatment.

Methods: Patients assigned to ravulizumab every 8 weeks (q8w) or eculizumab every 2 weeks during the randomized primary evaluation period received ravulizumab q8w during the 26-week extension. Efficacy endpoints were lactate dehydrogenase (LDH) normalization, transfusion avoidance, breakthrough hemolysis (BTH), LDH levels, Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale, and stabilized hemoglobin. Serum free C5 levels and safety were assessed. Outcomes as of the data cut-off (4 September 2018) were summarized using descriptive statistics.

Results: Overall, 124 patients continued ravulizumab, and 119 switched from eculizumab to ravulizumab. During the extension, 43.5% and 40.3% of patients in the ravulizumab–ravulizumab and eculizumab–ravulizumab arms, respectively, achieved LDH normalization; 76.6% and 67.2% avoided transfusion. BTH decreased in the eculizumab–ravulizumab arm; no events were associated with free C5 $\geqslant$0.5 μg/mL while receiving ravulizumab. Overall, 73.4% and 65.5% of patients in the ravulizumab–ravulizumab and eculizumab–ravulizumab arms, respectively, achieved stabilized hemoglobin. Similar proportions of patients achieved $\geqslant$3-point improvement in FACIT-Fatigue at week 52 (ravulizumab–ravulizumab, 64.5%; eculizumab–ravulizumab, 57.1%). All patients maintained free C5 $<$0.5 μg/mL during the ravulizumab extension, including those who experienced C5 excursions $\geqslant$0.5 μg/mL while receiving eculizumab during the primary evaluation period. Adverse events were comparable between groups and decreased over time.

Conclusion: In adult, complement inhibitor–naïve patients with PNH, ravulizumab q8w for up to 52 weeks demonstrated durable efficacy and was well tolerated, with complete and sustained free C5 inhibition and a decreased incidence of BTH with no events associated with loss of free C5 control.

Trial registration: ClinicalTrials.gov identifier, NCT02946463

Keywords: breakthrough hemolysis, complement inhibitor, eculizumab, high disease activity, lactate dehydrogenase, paroxysmal nocturnal hemoglobinuria, ravulizumab, transfusion

Received: 29 May 2020; revised manuscript accepted: 18 September 2020.

Scott T. Rottinghaus
Global Medicine, Alexion Pharmaceuticals, Inc., Boston, MA, USA

Peng Liu
Biostatistics, Alexion Pharmaceuticals, Inc., Boston, MA, USA

Stephan Ortiz
Clinical Pharmacology, Alexion Pharmaceuticals, Inc., Boston, MA, USA

Gérard Socié
Hematology Transplantation, Hôpital Saint-Louis, Paris, France

Institut National de la Santé et de la Recherche Médicale, Université de Paris, Paris, France

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, lifelong blood disorder. Patients with PNH lack important proteins on the surface of their red blood cells, white blood cells, and platelets. Without these protective proteins, the complement system, which is part of the body's natural defense, attacks and destroys the body's own red blood cells as foreign invaders. This process is known as intravascular hemolysis (inside blood vessels). Hemolysis results in a loss of hemoglobin, which is responsible for transporting oxygen to all the cells of the body. Furthermore, patients may present with a variety of symptoms. These include stomach pain, difficulty swallowing, fatigue, shortness of breath, low levels of red blood cells (anemia), dark-colored urine, trouble concentrating and erectile dysfunction in men. PNH has serious complications, including blood clots, which may be fatal.

Eculizumab is an established treatment for adults with PNH. It works by blocking the complement system and protecting blood cells from the attack of the body's defense system. Eculizumab is given every 2 weeks by intravenous infusion (directly into the bloodstream through a vein). Some patients taking eculizumab have hemolysis even after starting treatment (i.e. breakthrough hemolysis). Breakthrough hemolysis is associated with an increase in lactate dehydrogenase levels (an enzyme which is released when red blood cells are destroyed due to hemolysis) and a new or worsening symptom or a serious complication.

Ravulizumab is the first treatment for PNH designed to last longer in the bloodstream and is given every 8 weeks. It works the same way as eculizumab, by blocking the complement system and protecting the patient's own blood cells from being attacked by the body's defense system.

In this study, adults with PNH took eculizumab or ravulizumab for 26 weeks. Then they either continued taking ravulizumab or switched from eculizumab to ravulizumab. Ravulizumab continued to be effective and well-tolerated through 52 weeks of treatment. In addition, patients who switched from eculizumab to ravulizumab after 26 weeks had consistent efficacy and safety outcomes when compared with patients who received ravulizumab for 52 weeks. The safety profile for patients treated with ravulizumab was similar to that previously shown for patients treated with eculizumab, with side effects decreasing over time. Importantly, there were fewer events of breakthrough hemolysis after patients switched to ravulizumab. In this study, patients were required to receive a vaccination against meningococcal infection, and no patients reported meningococcal infection during the 52 weeks of treatment.

These results show that (a) ravulizumab remains well-tolerated and effective over 1 year and (b) patients taking eculizumab can switch safely to ravulizumab without interruption of therapy.

Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare hematologic disorder that is characterized by intravascular hemolysis, bone marrow failure, and thrombosis.[1] Most patients with PNH have an acquired somatic mutation in the phosphatidylinositol glycan class A (*PIGA*) gene, leading to reduced or absent glycosylphosphatidylinositol (GPI) anchor proteins.[1,2] Deficiency of GPI-anchored complement regulatory proteins CD55 and CD59 results in complement-mediated intravascular hemolysis and other disease manifestations such as platelet, monocyte, and granulocyte activation.[1] Intravascular hemolysis is a significant contributor to morbidity and mortality in patients with PNH.[3,4]

Eculizumab, a humanized monoclonal antibody that inhibits terminal complement C5 activation,[5] was the first approved treatment for patients with PNH and has changed the paradigm of PNH management. Intravenous infusion of eculizumab every 2 weeks (q2w) reduced hemolysis and increased hemoglobin stabilization, improved the rate of transfusion independence, and enhanced patient quality of life (QoL).[6–8] Compared with pre-treatment rates, eculizumab is associated with an 82% relative reduction in thromboembolism,[8] which is an independent predictor of mortality in patients with PNH.[3] Despite established efficacy, up to 27% of patients continue to experience breakthrough intravascular hemolysis while receiving approved dosages of eculizumab that may require dosing intervals to be shortened to <14 days or individual dosages to be increased.[8,9] Breakthrough hemolysis (BTH) in patients with PNH typically occurs around the time of low serum concentrations of eculizumab or in the setting of infection, operative stress, or pregnancy,[10,11] but residual intravascular hemolysis may occur even when serum levels of eculizumab

are adequate.[12] The biweekly infusions and the risk of BTH represent a burden to patients. Thus, to further enhance the treatment for patients with PNH, providing complete C5 inhibition (by maintaining free C5 levels below a threshold of $<0.5\,\mu g/mL$) may help to minimize the occurrence of BTH and benefit patients with PNH.

Ravulizumab is the first long-acting C5 inhibitor approved for the treatment of PNH and was developed through targeted engineering of eculizumab to provide immediate, complete, and sustained C5 inhibition with 8-week dosing intervals.[10] In phase III studies in patients with PNH who were naïve to[13] or previously treated with a complement inhibitor,[14] ravulizumab was non-inferior to eculizumab with respect to normalization and percentage change in lactate dehydrogenase (LDH), transfusion avoidance, rates of BTH, and hemoglobin stabilization during the 26-week primary evaluation period. In patients naïve to complement inhibitor therapy, the rate of BTH was 4% with ravulizumab and 11% with eculizumab.[13] Ravulizumab was also non-inferior to eculizumab with respect to improvements in fatigue as measured by the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale[13,14] and was comparable to eculizumab for QoL outcomes as measured by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 Scale (EORTC QLQ-C30).[13]

The aim of this study was to assess, per protocol design, the efficacy and safety of ravulizumab for an additional 26 weeks following the primary evaluation period (i.e. 1 year of treatment) and to assess the efficacy and safety of ravulizumab after switching from eculizumab in adults with PNH naïve to complement inhibitor therapy who participated in the randomized controlled trial.

Methods

Study design

This was an open-label extension of a phase III, randomized, active-controlled trial conducted at 123 centers in 25 countries [ClinicalTrials.gov identifier: NCT02946463]. Detailed methods have been previously described.[13] The protocol was approved by the institutional review board or independent ethics committee at each participating center, and the study was conducted in accordance with the Declaration of Helsinki and the Council for International Organisations of Medical Sciences International Ethical Guidelines.

The study included a 4-week screening period, a 26-week randomized, primary evaluation period (1:1 ravulizumab/eculizumab), and an open-label extension period. During the primary evaluation period, patients in the ravulizumab arm received a weight-based loading dose ($\geq$40 to $<$60 kg, 2400 mg; $\geq$60 to $<$100 kg, 2700 mg; $\geq$100 kg; 3000 mg) on day 1 and subsequent maintenance doses ($\geq$40 to $<$60 kg, 3000 mg; $\geq$60 to $<$100 kg, 3300 mg; $\geq$100 kg, 3600 mg) on day 15 and every 8 weeks (q8w) thereafter, as previously described.[13] Patients in the eculizumab arm received induction doses (600 mg) on days 1, 8, 15, and 22 and subsequent maintenance doses (900 mg) on day 29 and q2w thereafter. During the extension period, patients who had previously received ravulizumab continued ravulizumab q8w, and patients who had previously received eculizumab were switched to weight-based ravulizumab treatment, receiving a loading dose on day 183, followed by maintenance doses on day 197 and q8w thereafter.

All patients entering the study must have received a meningococcal vaccine within 3 years before study drug initiation or at the time of study drug initiation. Patients who received a meningococcal vaccine $<$2 weeks before initiating study drug were required to receive appropriate prophylactic antibiotics until $\geq$2 weeks after vaccination.

Patients

Patients with PNH confirmed by flow cytometry who were $\geq$18 years old were eligible for inclusion if they were naïve to complement inhibitors and had high disease activity [LDH levels $\geq$1.5 times the upper limit of normal (ULN) and $\geq$1 PNH-related sign or symptom within 3 months of screening or history of packed red blood cell transfusion because of PNH]. Patients were excluded if they weighed $<$40 kg; had a history of bone marrow transplantation, meningococcal infection, or unexplained recurrent infection; had a platelet count $<30\times10^9$/L; or had an absolute neutrophil count $<0.5\times10^9$/L. All patients provided written informed consent.

Outcomes

The efficacy endpoints were the proportion of patients with normalized LDH (defined by LDH

levels ⩽1× ULN), the proportion of patients avoiding transfusion (i.e. remained transfusion free and did not require transfusion per protocol-specified guidelines), the proportion of patients with BTH, percentage change from baseline in LDH levels, change from baseline in QoL as assessed by the FACIT-Fatigue scale and EORTC QLQ-C30, and proportion of patients with stabilized hemoglobin levels. BTH was defined as ⩾1 new or worsening symptom or sign of intravascular hemolysis in the presence of elevated LDH ⩾2× ULN after prior LDH reduction to <1.5× ULN on treatment. Stabilized hemoglobin was defined as avoidance of a ⩾2-g/dL decrease in hemoglobin level from the period baseline in the absence of transfusion during that period. Additional endpoints included levels of free C5; safety, analyzed by adverse events (AEs), serious AEs (SAEs), and major adverse vascular events; and immunogenicity (measured by the development of antidrug antibodies) up to the 52-week cut-off.

Statistical analysis

Outcomes as of the data cut-off (4 September 2018) were summarized using descriptive statistics. Efficacy was analyzed in the extension set (all patients who entered the extension period), and safety was analyzed in the safety set (all patients who received ⩾1 dose of study drug). For transfusion avoidance, patients who withdrew from the study for lack of efficacy were considered non-responders and were included in the group requiring transfusions, as were patients who met protocol-specified guidelines for transfusion regardless of a transfusion being administered.

Results

Patients

A total of 285 patients were screened, and 246 were randomly assigned to receive ravulizumab ($n=125$) or eculizumab ($n=121$). All 125 patients in the ravulizumab arm completed the 26-week primary evaluation period, and 124 (99.2%) continued to ravulizumab in the open-label extension period (Figure 1). Of the 121 patients who received eculizumab during the primary evaluation period, 119 (98.3%) completed treatment and entered the open-label extension. As of the data cut-off (4 September 2018), eight patients discontinued, including three in the ravulizumab–ravulizumab arm (one each for physician decision, pregnancy, other) and five in the eculizumab–ravulizumab arm (two AE, two physician decision, one death). Patient baseline demographics and disease characteristics have been previously reported[13] and were generally similar between treatment groups. At baseline, overall mean LDH was 1606.4 (SD, 752.7) U/L, 86% of patients had LDH levels ⩾3× ULN, and mean granulocyte clone size was 84.7% (SD, 20.0%).[13]

Efficacy endpoints

At week 52, 43.5% of patients in the ravulizumab–ravulizumab arm and 40.3% in the eculizumab–ravulizumab arm had achieved LDH normalization (Table 1; Figure 2). During the extension period, 76.6% and 67.2% of patients in the ravulizumab–ravulizumab and eculizumab–ravulizumab arms, respectively, avoided transfusion (Table 1); 90.2% and 87.3%, respectively, of those who avoided transfusion during the primary evaluation period maintained the response during the extension period.

During the extension period, four patients in the ravulizumab–ravulizumab arm and two patients in the eculizumab–ravulizumab arm experienced BTH compared with five patients and 13 patients, respectively, during the primary analysis period (Table 1). None of the BTH events during the extension period was associated with free C5 ⩾0.5 μg/mL (Table 2). LDH levels at the end of the primary evaluation period were maintained throughout the extension period for both treatment groups (Figure 3). At 52 weeks, 64.5% and 57.1% of patients in the ravulizumab–ravulizumab and eculizumab–ravulizumab arms, respectively, experienced a ⩾3-point improvement in FACIT-Fatigue score (Table 1). Mean change in FACIT-Fatigue scores from study baseline to 52 weeks was 7.5 and 6.4 in the ravulizumab–ravulizumab arm and eculizumab–ravulizumab arm, respectively (Figure 4). Similar proportions of patients in the ravulizumab–ravulizumab arm and eculizumab–ravulizumab arm experienced a ⩾10-point improvement in the EORTC QLQ-C30 global health, physical functioning, and fatigue subscales at 52 weeks (Figure 5). A total of 73.4% and 65.5% of patients in the ravulizumab–ravulizumab arm and eculizumab–ravulizumab arm, respectively, achieved stabilization of hemoglobin during the extension period (Table 1). Of those who had achieved stabilized

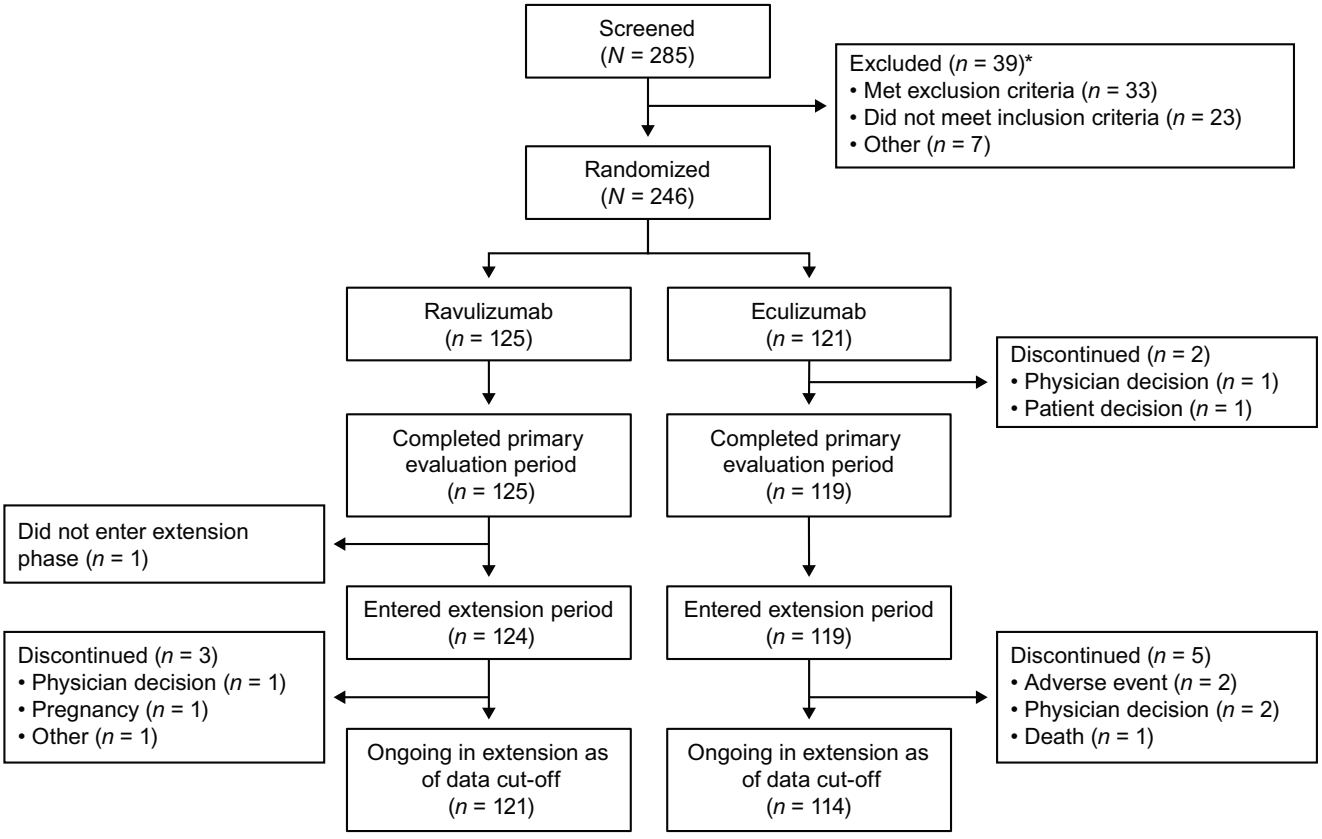

Figure 1. Patient disposition.
*Patients may be counted in more than one category.

Table 1. Summary of efficacy endpoints in the primary evaluation and extension periods.

Patients, *n* (%)	Ravulizumab–ravulizumab		Eculizumab–ravulizumab	
	Primary evaluation period* weeks 1–26 *n* = 125	**Extension period† weeks 27–52 *n* = 124**	**Primary evaluation period* weeks 1–26 *n* = 121**	**Extension period† weeks 27–52 *n* = 119**
LDH normalization	61 (48.8)	54 (43.5)	54 (44.6)	48 (40.3)
Transfusion avoidance	92 (73.6)	95 (76.6)	80 (66.1)	80 (67.2)
BTH	5 (4.0)	4 (3.2)	13 (10.7)	2 (1.6)
Stabilized hemoglobin	85 (68.0)	91 (73.4)	78 (64.5)	78 (65.5)
⩾3-point improvement in FACIT-Fatigue	77 (61.6)	80 (64.5)	71 (58.7)	68 (57.1)

*Full analysis set (all patients who received ⩾1 dose of study drug and had ⩾1 efficacy assessment after the first infusion).
†Extension set (all patients who entered the extension period).
BTH, breakthrough hemolysis; FACIT, Functional Assessment of Chronic Illness Therapy; LDH, lactate dehydrogenase.

hemoglobin levels during the primary evaluation period, 89.4% and 85.7%, respectively, maintained the response during the extension period.

Free C5 levels

Patients in the ravulizumab–ravulizumab arm continued to maintain complete terminal complement

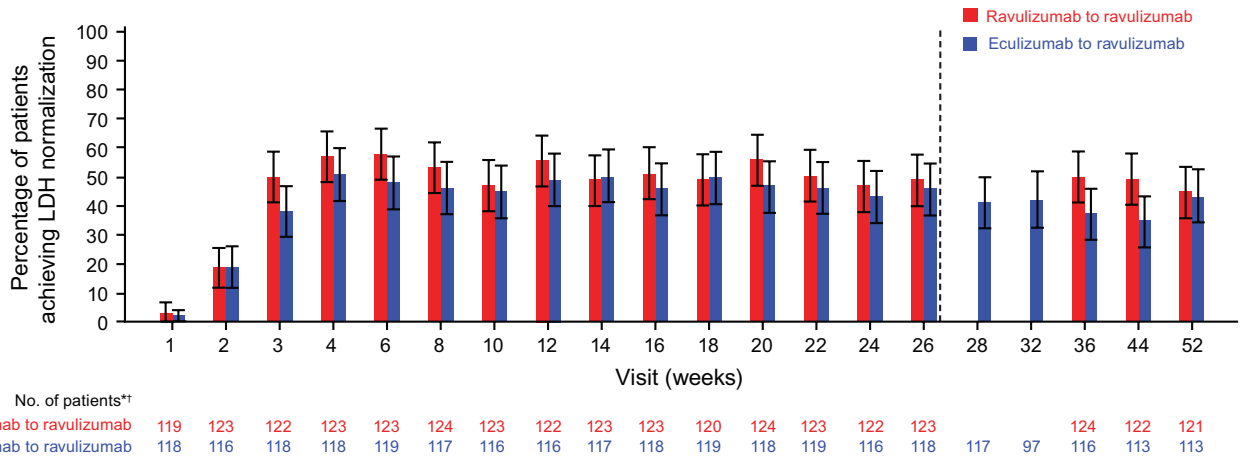

Figure 2. Proportion of patients achieving LDH normalization during the primary evaluation (weeks 1–26) and extension (weeks 27–52) periods.
*Number of patients may be lower than number enrolled at time point because of exclusion of samples having serum potassium ⩾6 mmol/L and LDH ⩾2× ULN, missing samples (because of site error or for any other reason), or patient discontinuations during the extension.
†LDH levels were not measured for patients in the ravulizumab–ravulizumab group on days 197 and 225.
BL, baseline; LDH, lactate dehydrogenase; ULN, upper limit of normal.

Table 2. Analysis of BTH events.

Events, *n*	Ravulizumab–ravulizumab		Eculizumab–ravulizumab	
	Primary evaluation period* weeks 1–26 *n* = 125	Extension period† weeks 27–52 *n* = 124	Primary evaluation period* weeks 1–26 *n* = 121	Extension period† weeks 27–52 *n* = 119
BTH	5	5‡	15§	2
Free C5 ⩾0.5 µg/mL	0	0	7	0
Infection (with no free C5 elevation)	4	1	4	1
Undetermined#	1	4	4	1

*Full analysis set (all patients who received ⩾1 dose of study drug and had ⩾1 efficacy assessment after the first infusion).
†Extension set (all patients who entered the extension period).
‡A total of four patients had five events; one patient with two events had one infection-related event and one event unrelated to free C5 ⩾0.5 µg/mL or infection.
§A total of 13 patients had 15 events; two patients with free C5 ⩾0.5 µg/mL had concomitant infection.
#Unrelated to known complement amplifying condition, infection, or loss of free C5 control.
BTH, breakthrough hemolysis.

inhibition (serum free C5 levels <0.5 µg/mL) through 52 weeks (Figure 6A). After switching from eculizumab to ravulizumab, no patient had serum free C5 ⩾0.5 µg/mL (Figure 6B).

Safety

Treatment with ravulizumab was well tolerated. The incidence of treatment-emergent AEs (TEAEs) decreased during the extension period in both arms (Table 3). The most common TEAEs were upper respiratory tract infection [*n* = 10 (8.1%)], nasopharyngitis [*n* = 8 (6.5%)], pyrexia [*n* = 7 (5.6%)], and headache [*n* = 6 (4.8%)] in the ravulizumab–ravulizumab arm and nasopharyngitis [*n* = 15 (12.6%)], headache[*n* = 10 (8.4%)], nausea [*n* = 6 (5.0%)], abdominal pain [*n* = 6 (5.0%)], and anemia [*n* = 6 (5.0%)] in the eculizumab–ravulizumab

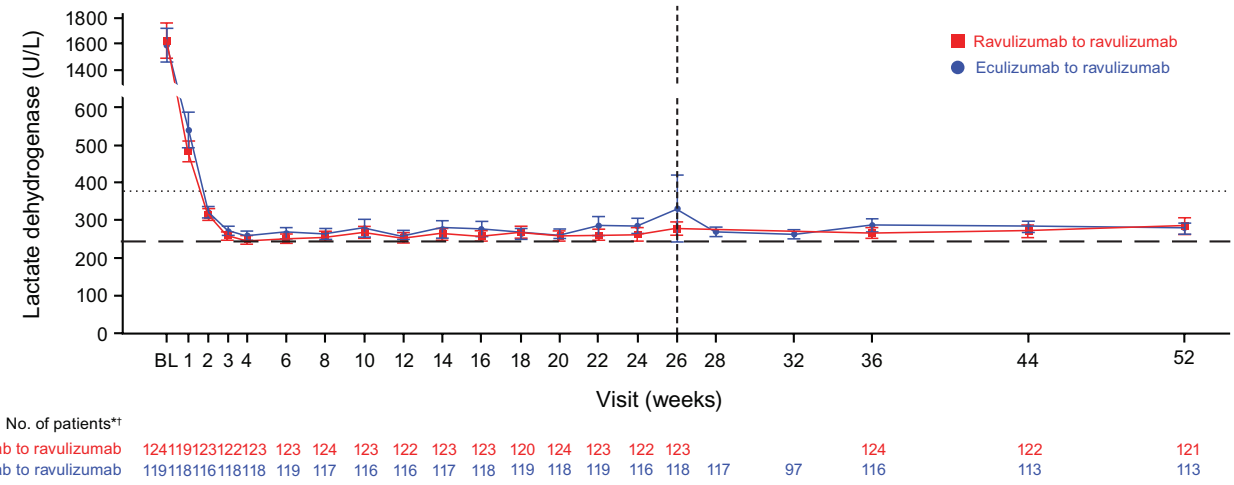

Figure 3. Mean lactate dehydrogenase (LDH) levels during the primary evaluation (weeks 1–26) and extension (weeks 27–52) periods. Dashed horizontal line indicates 1× upper limit of normal (ULN), and the dotted horizontal line represents 1.5× ULN.
*Number of patients may be lower than number enrolled at time point because of exclusion of samples having serum potassium ⩾6 mmol/L and LDH ⩾2× ULN, missing samples (because of site error or for any other reason), or patient discontinuations during the extension.
†LDH levels were not measured for patients in the ravulizumab–ravulizumab group on days 197 and 225.
BL, baseline.

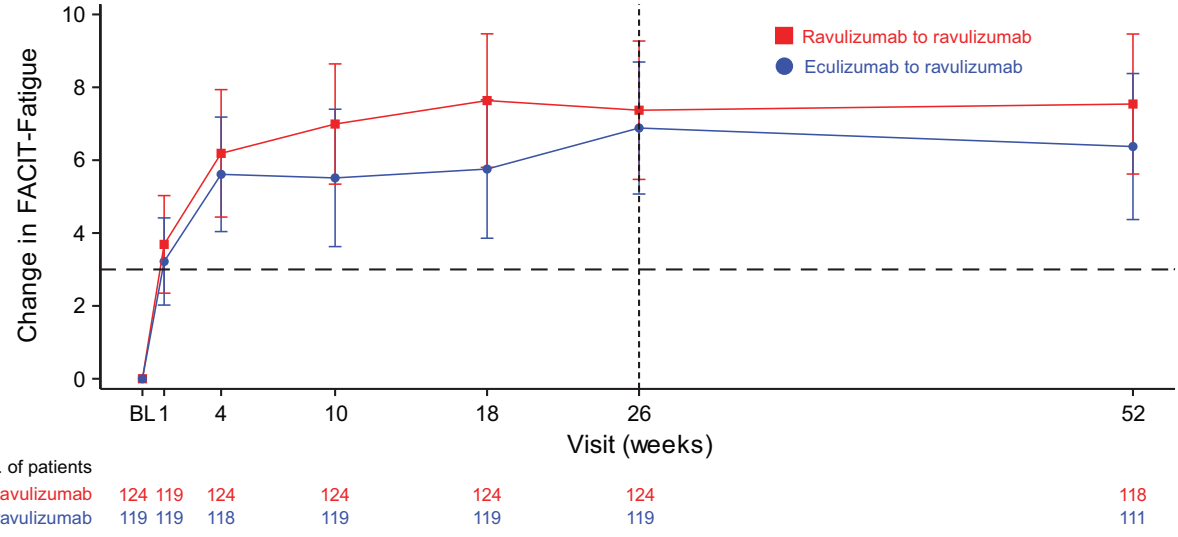

Figure 4. Mean (95% confidence interval) change from baseline to end of extension period in FACIT-Fatigue scale. FACIT scores range from 0 to 52, with a higher score indicating less fatigue. Dashed horizontal line indicates threshold that delineates clinically meaningful improvement (>3 points).
BL, baseline; FACIT, Functional Assessment of Chronic Illness Therapy.

arm (Table 4). No meningococcal infections were reported through 52 weeks.

The incidence of SAEs remained stable over time (Table 3). During the extension period, one patient in the eculizumab–ravulizumab arm experienced an SAE that was considered a major adverse vascular event (arterial embolism starting on day 327 and resolving on day 338); the event was considered unrelated to study treatment. One patient in the eculizumab–ravulizumab arm died during the extension period following an AE (lung adenocarcinoma) with onset during the primary evaluation period that

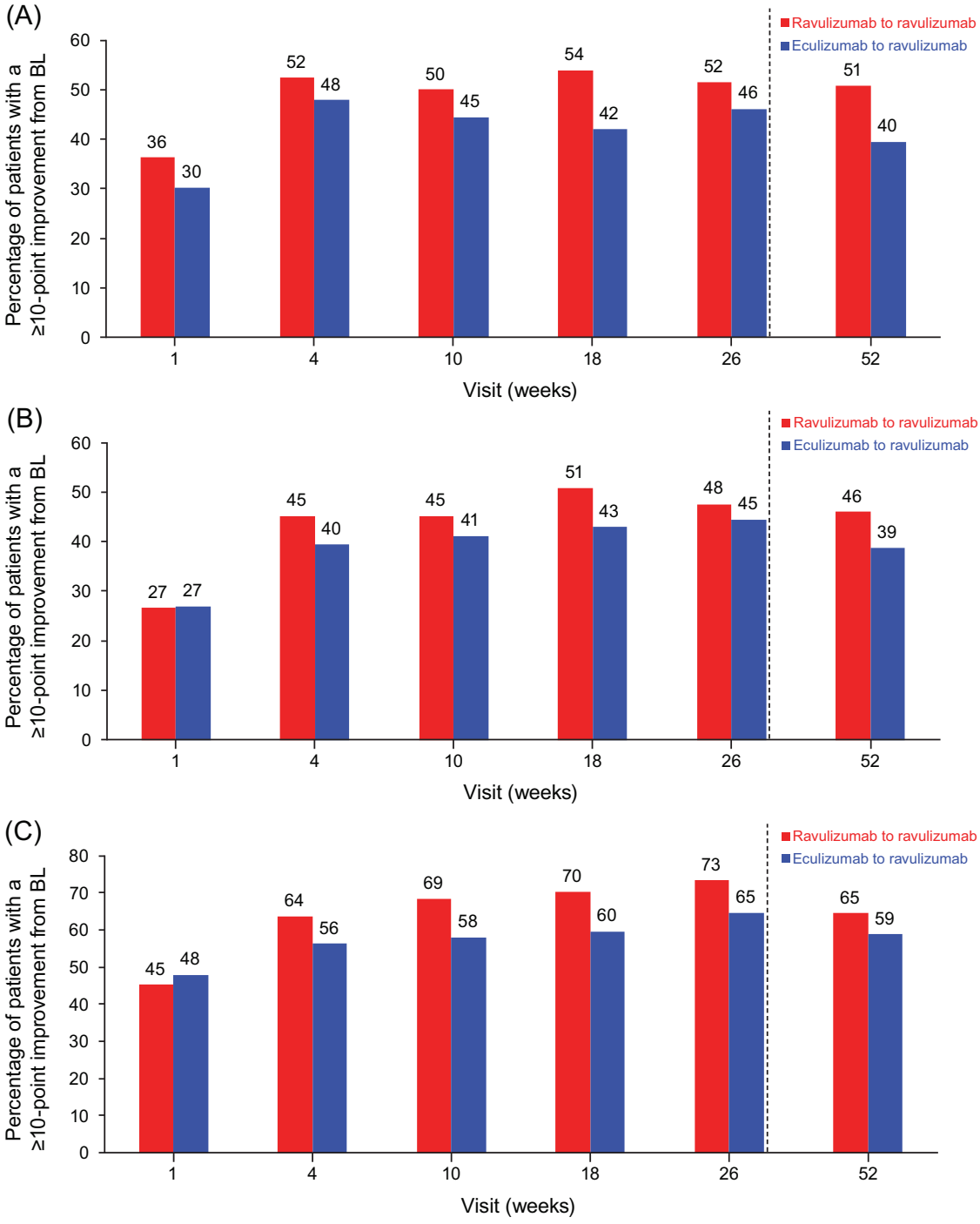

Figure 5. Proportions of patients maintaining ⩾10-point improvement in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 Scale: (A) Global Health Status, (B) Physical Functioning, and (C) Fatigue subscales.
BL, baseline.

was assessed by the investigator as unrelated to study medication. This patient withdrew during the extension period and died 35 days after study discontinuation. No new antidrug antibody-positive responses were observed in any patient during the extension period.

Discussion

In adult patients with PNH naïve to complement inhibitor therapy, ravulizumab demonstrated durable efficacy through 52 weeks of treatment, with patients in both treatment arms showing a durable response with respect to achieving LDH normalization and avoiding transfusion. Patients switching from eculizumab to ravulizumab after 26 weeks of treatment had outcomes comparable to those who received continuous ravulizumab treatment. Ravulizumab produced an immediate, complete, and sustained inhibition of terminal complement (defined as free C5 levels <0.5 µg/mL), accompanied by a decreased incidence of BTH, with no BTH events associated with suboptimal terminal complement inhibition (serum free C5 levels ≥ 0.5 µg/mL). During the primary evaluation period, seven patients had shown BTH accompanied by incomplete terminal complement inhibition while receiving eculizumab, but there were no such events after switching to ravulizumab.

Elevated levels of LDH, a marker for intravascular hemolysis, is an important factor to consider when determining severity of PNH and likelihood of experiencing a benefit from treatment with complement inhibitors.[15] Elevated levels of LDH ($\geq 1.5\times$ ULN), are associated with increased prevalence of PNH-related symptoms compared with LDH levels $<1.5\times$ ULN, as well as with an increased risk of complications associated with thromboembolism, mortality, and reduced QoL.[3,16] Transfusion is typically used as a supportive measure to manage hemolytic anemia,[2] or the underlying bone marrow failure, and 61.3% of patients enrolled in the International PNH Registry reported history of red blood cell transfustion.[16] Treatment with eculizumab has been shown to reduce transfusion dependence and rapidly decrease LDH levels.[6,7,17] During the primary evaluation period, ravulizumab demonstrated non-inferiority to eculizumab with respect to LDH normalization and transfusion avoidance,[13] and these benefits were maintained during the extension period for the majority of patients in both treatment arms. Mean LDH levels in both groups remained stable over 52 weeks and did not increase above $1.5\times$ ULN. Moreover, transfusion avoidance and LDH results for patients who switched from eculizumab to ravulizumab during the extension period were consistent with those seen in patients receiving continuous ravulizumab in this study. Further support for the efficacy of ravulizumab in patients previously treated with eculizumab was provided by a separate phase III study in which patients had previously been treated with eculizumab for a mean of 5.8 years before enrolling in the trial.[14] In that study, 87.6% of patients treated with ravulizumab avoided transfusion compared with 82.7% of patients treated with eculizumab; LDH normalization was achieved by 66.0% and 59.2% of patients in each group, respectively.[14]

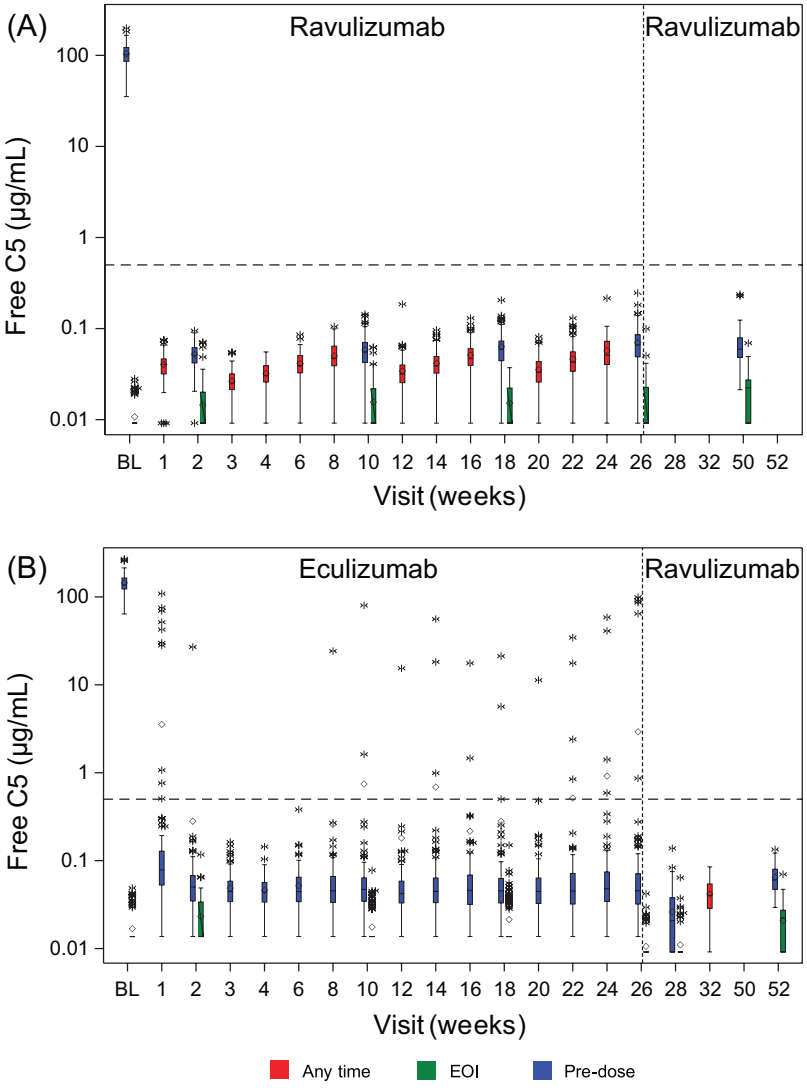

Figure 6. Free C5 levels through 52 weeks in patients in the (A) ravulizumab–ravulizumab arm and (B) eculizumab–ravulizumab arm. The horizontal line in the middle of each box indicates the median, and a diamond indicates the mean. The top and bottom borders of the box represent the 75th and 25th percentiles, respectively, and the whiskers represent the 1.5 interquartile range of the lower and upper quartile. Asterisks represent values outside the interquartile range. Dashed horizontal lines indicate serum free C5 concentration of 0.5 µg/mL.
BL, baseline; EOI, end of infusion.

Table 3. Summary of adverse events*.

Patients, *n* (%)	Ravulizumab–ravulizumab		Eculizumab–ravulizumab	
	Primary evaluation period weeks 1–26 *n* = 125	Extension period weeks 27–52 *n* = 124	Primary evaluation period weeks 1–26 *n* = 121	Extension period weeks 27–52 *n* = 119
Any TEAE	110 (88.0)	79 (63.7)	105 (86.8)	89 (74.8)
TEAE considered as a major adverse vascular event	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)†	0 (0)

*Safety set (all patients who received ⩾1 dose of study drug).
†Patient withdrew from the study during the extension period because of an adverse event of lung adenocarcinoma with onset during the primary evaluation period assessed by the investigator as unrelated to study medication and died 35 days after study withdrawal.
SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Although the introduction of eculizumab has substantially improved the management of PNH, some patients may still experience BTH.[8,9,18] During the primary evaluation period of the current study, 15 BTH events were reported in patients treated with eculizumab, seven of which were associated with free C5 levels ⩾0.5 μg/mL;[13] during the extension period, two BTH events were reported in patients who switched from eculizumab to ravulizumab. The decreased incidence of BTH in the eculizumab–ravulizumab arm appeared to be the result of improved C5 control, as neither BTH event was associated with free C5 ⩾0.5 μg/mL. Five patients experienced BTH with ravulizumab during the primary evaluation period, none of which was associated with free C5 ⩾0.5 μg/mL,[13] and four patients continuing q8w dosing of ravulizumab experienced five events of BTH during the extension. Throughout both the primary evaluation and extension periods, all patients receiving ravulizumab achieved complete terminal complement inhibition (free C5 <0.5 μg/mL).

Patients with PNH experience severe fatigue and reduced QoL,[19] which may be exacerbated in those who have other symptoms of PNH or a history of thromboembolism.[20] Improvements in fatigue and QoL seen during the primary evaluation period[13] were generally maintained throughout the extension period. At 52 weeks, 64.5% and 57.1% of patients in the ravulizumab–ravulizumab and eculizumab–ravulizumab arms, respectively, experienced a ⩾3-point improvement in FACIT-Fatigue score, which is considered a clinically meaningful improvement.[21] Although a slightly lower proportion of patients experienced a ⩾10-point improvement in the EORTC QLQ-C30 subscales, these changes also remained stable over time and were similar between treatment arms. In addition to improving fatigue and physical functioning, the extended dosing interval of ravulizumab (q8w *versus* q2w with eculizumab), resulting in six infusions per year as opposed to 26 infusions per year with eculizumab, has the potential to further improve patient QoL by minimizing the burden of repeated infusions and of hospitalization.

Ravulizumab was well tolerated through 52 weeks, with a comparable percentage of patients experiencing TEAEs and SAEs between treatment arms and only one patient experiencing a major adverse vascular event (arterial embolism considered unrelated to study treatment) during the first 26 weeks of the extension period. The safety profile was comparable to that previously reported for eculizumab, with reductions in the incidence of TEAEs over time.[6,8] For example, in the phase III trial of eculizumab, 94% of patients who

Table 4. Treatment-emergent adverse events occurring in ⩾5% of patients in either treatment group in either period by system organ class*.

Adverse event, *n* (%)	Ravulizumab–ravulizumab		Eculizumab–ravulizumab	
	Primary evaluation period weeks 1–26 *n* = 125	Extension period weeks 27–52 *n* = 124	Primary evaluation period weeks 1–26 *n* = 121	Extension period weeks 27–52 *n* = 119
Nervous system disorders				
Headache	45 (36.0)	6 (4.8)	40 (33.1)	10 (8.4)
Dizziness	9 (7.2)	0 (0)	7 (5.8)	0 (0)
Infections and infestations				
URTI	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)
Viral URTI	9 (7.2)	3 (2.4)	10 (8.3)	2 (1.7)
Musculoskeletal and connective tissue disorders				
Pain in extremity	9 (7.2)	0 (0)	7 (5.8)	3 (2.5)
Arthralgia	8 (6.4)	3 (2.4)	8 (6.6)	5 (4.2)
Back pain	8 (6.4)	1 (0.8)	6 (5.0)	3 (2.5)
Myalgia	8 (6.4)	1 (0.8)	9 (7.4)	3 (2.5)
Gastrointestinal disorders				
Nausea	11 (8.8)	2 (1.6)	10 (8.3)	6 (5.0)
Diarrhea	10 (8.0)	2 (1.6)	5 (4.1)	4 (3.4)
Abdominal pain	7 (5.6)	3 (2.4)	7 (5.8)	6 (5.0)
Dyspepsia	5 (4.0)	0 (0)	6 (5.0)	3 (2.5)
Respiratory, thoracic, and mediastinal disorders				
Oropharyngeal pain	8 (6.4)	0 (0)	6 (5.0)	1 (0.8)
Cough	4 (3.2)	2 (1.6)	8 (6.6)	4 (3.4)
Cardiac disorders				
Palpitations	7 (5.6)	0 (0)	2 (1.7)	0 (0)
General disorders and administration site conditions				
Pyrexia	6 (4.8)	7 (5.6)	13 (10.7)	0 (0)
Metabolism and nutrition disorders				
Hypokalemia	6 (4.8)	4 (3.2)	6 (5.0)	0 (0)
Blood and lymphatic system disorders				
Anemia	4 (3.2)	0 (0)	6 (5.0)	6 (5.0)
Psychiatric disorders				
Insomnia	2 (1.6)	3 (2.4)	6 (5.0)	4 (3.4)

*Safety set (all patients who received ⩾1 dose of study drug).
URTI, upper respiratory tract infection.

experienced headache had the event within the first 48 h of infusion and within the first 2 weeks of treatment.[7] In the current study, approximately one-third of patients experienced headache during the primary evaluation period,[13] whereas during the extension period, the incidence of headache was <10%. While headache is a well-recognized phenomenon associated with the initiation of complement inhibitor treatment,[7] the incidence of other AEs during the extension period—such as upper respiratory tract infection—was similar to or lower than the incidence observed during the primary evaluation period.

Meningococcal infections are serious and potentially fatal infections, and patients treated with eculizumab are at increased risk for developing meningococcal disease.[5,22] A long-term study of eculizumab for the treatment of PNH showed an overall rate of 0.25 meningococcal infections per 100 patient-years, with almost all patients having previously received meningococcal vaccination.[23] In this study, patients were required to be vaccinated against meningococcal infection within 3 years before, or at the time of, initiating study treatment. No cases of meningococcal disease were reported by the time of data cut-off.

This is the largest controlled, interventional study of patients with PNH; other strengths were the evaluation of efficacy and safety in patients after switching from eculizumab to ravulizumab and the inclusion of a range of clinically important endpoints, as well as patient-reported measures of fatigue and QoL. Limitations of the study include the open-label extension design, which may bias results; however, objective endpoints (e.g. defined guidelines for transfusion, laboratory values for LDH, and hemoglobin levels) were used to minimize potential bias. Finally, the efficacy and safety profile of ravulizumab beyond 52 weeks remains unknown.

Complement pathway inhibition is an active area of clinical development; newer molecules currently under investigation for the treatment of PNH include anti-C5 monoclonal antibodies and drugs with upstream targets such as complement C3, complement factor D, and complement factor B.[24] These drugs have the potential to expand treatment options for patients with PNH, and the future treatment landscape may include medications that can be self-administered and combination therapies.

Conclusion

In the primary evaluation period of this phase III randomized controlled trial, ravulizumab given every 8 weeks was well tolerated and demonstrated durable efficacy comparable with that of eculizumab in adult patients with PNH naïve to complement inhibitor therapy. Results from the first 26 weeks of the open-label extension show that improvements in LDH normalization, transfusion avoidance, BTH, hemoglobin stabilization, and patient-reported QoL seen with ravulizumab treatment during the 26-week primary evaluation period were generally maintained with up to 52 weeks of treatment. Importantly, all patients achieved complete free C5 control while receiving ravulizumab, including patients who had experienced loss of free C5 control while receiving eculizumab during the primary evaluation period. In addition, complete suppression of free C5 was accompanied by a decreased incidence of BTH, with no events of BTH associated with incomplete terminal complement inhibition. Results strengthen the evidence that patients on a prior fixed dose of eculizumab therapy can safely switch to weight-based dosing of ravulizumab without interruption of treatment while ensuring terminal complement inhibition is sustained, which is the primary goal for patient management.

Acknowledgments

Portions of this work were presented at the 24th Congress of the European Hematology Association, Amsterdam, Netherlands, 13–16 June 2019. The authors thank Arshad Mujeebuddin, MD, of Alexion Pharmaceuticals, Inc., for his support with defining the safety strategy for the study and for reviewing the manuscript. Medical writing and editorial support for development of this manuscript was provided by Krystina Neuman, PhD, and Nicole Strangman, PhD, at ICON plc (North Wales, PA). Editorial support/critical review was provided by Gabriela Marcheva, PharmD, at Alexion Pharmaceuticals, Inc.

Conflict of interest statement

Hubert Schrezenmeier: Honoraria and grants (to the University Hospital of Ulm) from Alexion Pharmaceuticals, Inc.; grants (to the University Hospital of Ulm) from Apellis, Ra Pharmaceuticals, and Sanofi; grants and other support (to the University Hospital of Ulm) from Roche; patent pending (PCT/EP2017/065979).

Austin Kulasekararaj: Travel grants from Achillion, Alexion Pharmaceuticals, Inc., Celgene,

and Ra Pharmaceuticals; advisory board fees (honoraria) from Alexion Pharmaceuticals, Inc., Celgene, Novartis, Ra Pharmaceuticals, and Regeneron.

Lindsay Mitchell: Honoraria from Alexion Pharmaceuticals, Inc.

Flore Sicre de Fontbrune: Honoraria and grants (to St. Louis Hospital) from Alexion Pharmaceuticals, Inc.

Timothy Devos: Consulting fees from Novartis, Alexion Pharmaceuticals, Inc., and Celgene.

Shinichiro Okamoto: Grants and personal fees from Alexion Pharmaceuticals, Inc., Astellas, Chugai, Daiichi Sankyo, JCR Pharma, Mochida, Novartis, Pfizer, and Takeda; grants from Asahi Kasei Pharma, Dainihon Sumitomo, Shionogi, and Teijin Pharma; and personal fees from Bristol-Meyers Squibb and Nihon Shinyaku.

Richard Wells: Honoraria and consulting fees from Alexion Pharmaceuticals, Inc.

Scott T. Rottinghaus: Employee and stockholder of Alexion Pharmaceuticals, Inc.; patent for "Dosage and administration of anti-c5 antibodies for treatment of paroxysmal nocturnal hemoglobinuria (pnh) and atypical hemolytic uremic syndrome (ahus)."

Peng Liu, **Stephan Ortiz:** Employees and stockholders of Alexion Pharmaceuticals, Inc.

Jong Wook Lee: Honoraria, consulting fees, and grants (to Seoul St. Mary's Hospital) from Alexion Pharmaceuticals, Inc.

Gérard Socié: Speaker fees and grants from, and a consultant for, Alexion Pharmaceuticals, Inc.

Data sharing and data accessibility

Alexion will consider requests for disclosure of clinical study participant-level data provided that participant privacy is assured through methods such as data deidentification, 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://alexionclinicaltrials.com/Disclosure-and-Transparency-Policy; the Data Request Form is available at https://alexion.com/contact-alexion/medical-information.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by funding from Alexion Pharmaceuticals, Inc. Medical writing and editorial support for development of this manuscript was provided by Krystina Neuman, PhD, and Nicole Strangman, PhD, at ICON plc (North Wales, PA) and funded by Alexion Pharmaceuticals, Inc.

ORCID iD

Jong Wook Lee https://orcid.org/0000-0003-2949-4166

References

1. Brodsky RA. Paroxysmal nocturnal hemoglobinuria. *Blood* 2014; 124: 2804–2811.
2. Parker C, Omine M, Richards S, *et al.* Diagnosis and management of paroxysmal nocturnal hemoglobinuria. *Blood* 2005; 106: 3699–3709.
3. Jang JH, Kim JS, Yoon SS, *et al.* Predictive factors of mortality in population of patients with paroxysmal nocturnal hemoglobinuria (PNH): results from a Korean PNH registry. *J Korean Med Sci* 2016; 31: 214–221.
4. Yenerel MN, Muus P, Wilson A, *et al.* Clinical course and disease burden in patients with paroxysmal nocturnal hemoglobinuria by hemolytic status. *Blood Cells Mol Dis* 2017; 65: 29–34.
5. SOLIRIS® [package insert]. Boston, MA: Alexion Pharmaceuticals, Inc., 2018.
6. Hillmen P, Young NS, Schubert J, *et al.* The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. *N Engl J Med* 2006; 355: 1233–1243.
7. Brodsky RA, Young NS, Antonioli E, *et al.* Multicenter phase 3 study of the complement inhibitor eculizumab for the treatment of patients with paroxysmal nocturnal hemoglobinuria. *Blood* 2008; 111: 1840–1847.
8. Hillmen P, Muus P, Röth A, *et al.* Long-term safety and efficacy of sustained eculizumab treatment in patients with paroxysmal nocturnal haemoglobinuria. *Br J Haematol* 2013; 162: 62–73.

9. Peffault de Latour R, Fremeaux-Bacchi V, Porcher R, *et al*. Assessing complement blockade in patients with paroxysmal nocturnal hemoglobinuria receiving eculizumab. *Blood* 2015; 125: 775–783.

10. Sheridan D, Yu Z-X, Zhang Y, *et al*. Design and preclinical characterization of ALXN1210: a novel anti-C5 antibody with extended duration of action. *PLoS One* 2018; 13: e0195909.

11. Brodsky RA. Eculizumab: another breakthrough. *Blood* 2017; 129: 922–923.

12. Harder MJ, Kuhn N, Schrezenmeier H, *et al*. Incomplete inhibition by eculizumab: mechanistic evidence for residual C5 activity during strong complement activation. *Blood* 2017; 129: 970–980.

13. Lee JW, Sicre de Fontbrune F, Wong Lee Lee L, *et al*. Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors: the 301 study. *Blood* 2019; 133: 530–539.

14. Kulasekararaj AG, Hill A, Rottinghaus ST, *et al*. Ravulizumab (ALXN1210) vs eculizumab in C5-inhibitor-experienced adult patients with PNH: the 302 study. *Blood* 2019; 133: 540–549.

15. Parker CJ. Update on the diagnosis and management of paroxysmal nocturnal hemoglobinuria. *Hematology Am Soc Hematol Educ Program* 2016; 2016: 208–216.

16. Schrezenmeier H, Roth A, Araten DJ, *et al*. Baseline clinical characteristics and disease burden in patients with Paroxysmal Nocturnal Hemoglobinuria (PNH): updated analysis from the international PNH registry. *Ann Hematol* 2020; 99: 1505–1514.

17. Hillmen P, Hall C, Marsh JC, *et al*. Effect of eculizumab on hemolysis and transfusion requirements in patients with paroxysmal nocturnal hemoglobinuria. *N Engl J Med* 2004; 350: 552–559.

18. Nakayama H, Usuki K, Echizen H, *et al*. Eculizumab dosing intervals longer than 17 days may be associated with greater risk of breakthrough hemolysis in patients with paroxysmal nocturnal hemoglobinuria. *Biol Pharm Bull* 2016; 39: 285–288.

19. Escalante CP, Chisolm S, Song J, *et al*. Fatigue, symptom burden, and health-related quality of life in patients with myelodysplastic syndrome, aplastic anemia, and paroxysmal nocturnal hemoglobinuria. *Cancer Med* 2019; 8: 543–553.

20. Schrezenmeier H, Muus P, Socie G, *et al*. Baseline characteristics and disease burden in patients in the International Paroxysmal Nocturnal Hemoglobinuria Registry. *Haematologica* 2014; 99: 922–929.

21. Cella D, Eton DT, Lai JS, *et al*. Combining anchor and distribution-based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy (FACT) anemia and fatigue scales. *J Pain Symptom Manage* 2002; 24: 547–561.

22. McNamara LA, Topaz N, Wang X, *et al*. High risk for invasive meningococcal disease among patients receiving eculizumab (Soliris) despite receipt of meningococcal vaccine. *MMWR Morb Mortal Wkly Rep* 2017; 66: 734–737.

23. Socie G, Caby-Tosi MP, Marantz JL, *et al*. Eculizumab in paroxysmal nocturnal haemoglobinuria and atypical haemolytic uraemic syndrome: 10-year pharmacovigilance analysis. *Br J Haematol* 2019; 185: 297–310.

24. Gembillo G, Siligato R, Cernaro V, *et al*. Complement inhibition therapy and dialytic strategies in paroxysmal nocturnal hemoglobinuria: the nephrologist's opinion. *J Clin Med* 2020; 9: 1261.