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Ravulizumab: a novel C5 inhibitor for the treatment of paroxysmal nocturnal hemoglobinuria

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***Abstract*:** Paroxysmal nocturnal hemoglobinuria (PNH) is a rare stem cell disorder characterized by hemolytic anemia, bone marrow failure, and thrombosis. Until recently, the complement inhibitor, eculizumab, was the only United States Food and Drug Administration (US FDA)-approved therapy for the treatment of PNH. Although effective, eculizumab requires a frequent dosing schedule that can be burdensome for some patients and increases the risk of breakthrough intravascular hemolysis. Ravulizumab, an eculizumab-like monoclonal antibody engineered to have a longer half-life, is intended to provide the same benefits as eculizumab but with a more convenient and effective dosing schedule. In two recently published phase III non-inferiority trials, ravulizumab was found to be non-inferior to eculizumab both in efficacy and safety for the treatment of patients with PNH. Based on these results, ravulizumab was approved by the US FDA on 21 December 2018 and is currently under regulatory review in both the European Union and Japan.

Keywords: complement inhibitor, eculizumab, paroxysmal nocturnal hemoglobinuria, ravulizumab

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Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare clonal hematopoietic stem cell disorder that is characterized by hemolytic anemia, bone marrow failure and thrombosis. Originally described by Paul Strübing in 1882, PNH has an annual incidence of only 1–10 new cases per 1 million individuals.[1–3] While it has been diagnosed in patients of all ages (including children primarily in their teenage years), PNH most often affects individuals in young adulthood with a median age of diagnosis in the early 30s.[4,5] It affects men and women in equal proportions and has no clear ethnic or geographic preferences.[6,7]

While great strides were made in understanding the pathophysiology of PNH in the 125 years following Strübing's original description of the disease, there were no United States Food and Drug Administration (US FDA)-approved therapies to treat PNH until the approval of the complement inhibitor, eculizumab, in March 2007.[8] Prior to eculizumab treatment, PNH management was primarily supportive with the estimated median survival ranging from 10 to 22 years.[9–11] Approximately 50% of patients died from their PNH, with thrombotic events as the primary cause of death.[9,10]

Eculizumab has changed the clinical course of PNH. Patients with PNH on long-term eculizumab therapy now have improved survival, close to that of normal age- and sex-matched controls.[12] Eculizumab is not a curative therapy, however, and with a half-life of approximately 11 days, patients must undergo maintenance infusions of eculizumab every 2 weeks.[13] The need for frequent dosing may be burdensome for some patients, increases the risk of breakthrough intravascular hemolysis, and is at least partially responsible for the high cost of eculizumab therapy. Ravulizumab,

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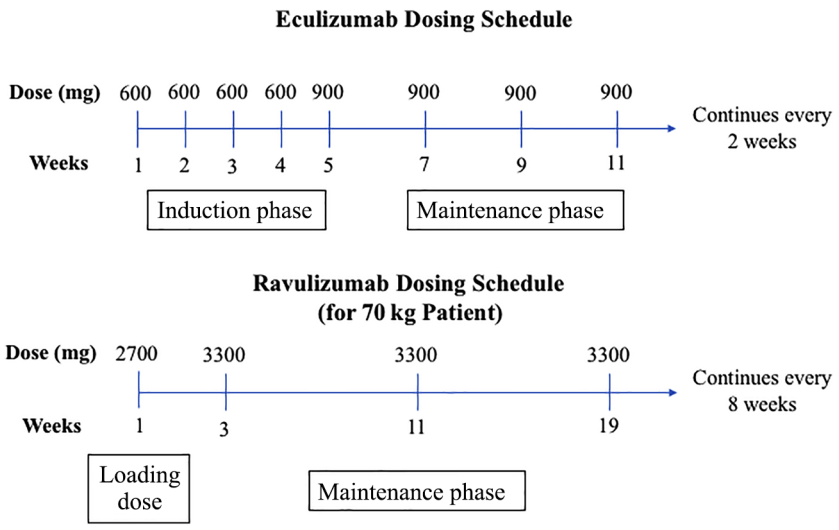

Figure 1. Comparative dosing schedules for Eculizumab and Ravulizumab.[17,18]

an eculizumab-like monoclonal antibody engineered to have a longer half-life, is intended to provide the same benefits as eculizumab with a more convenient and effective dosing schedule (Figure 1).[14] It was approved by the US FDA on 21 December 2018 and is currently under regulatory review in both the European Union and Japan.[15,16]

Pathophysiology of PNH

PNH arises when a somatic mutation in the phosphatidylinositol glycan class A (*PIGA*) gene develops in a self-renewing, hematopoietic stem cell.[19] The *PIGA* gene is found on the X chromosome and is responsible for producing one of the seven proteins involved in the first step of glycosylphosphatidylinositol (GPI) anchor biosynthesis.[20] While a number of different somatic mutations on *PIGA* have been described in patients with PNH, most mutations are small insertions or deletions arising on exon 2 that result in a severe deficiency or absence of GPI.[19] While the GPI moiety is responsible for anchoring more than 150 different proteins to the cell surface, the deficiency of complement-inhibitor proteins CD55 and CD59 leads to the primary clinical manifestations of PNH.[19]

CD55 and CD59 are specifically responsible for protecting red blood cells from complement-mediated lysis. In the alternative pathway of complement activation, C3 spontaneously hydrolyzes leading to the creation of C3 convertase (C3 convertase can also be formed through the lectin and classical pathways of complement). C3 convertase then cleaves C3 to C3a and C3b. Once formed, C3b joins with C5b and additional terminal complement proteins to form the membrane attack complex (MAC).[20–22] Under normal circumstances, this process is regulated by CD55 and CD59. CD55 accelerates the rate of destruction of membrane-bound C3 convertase while CD59 blocks the formation of the MAC. In patients with PNH, the absence of CD55 and CD59 results in increased C3 convertase activity, uncontrolled MAC formation, and continual complement-mediated intravascular hemolysis.[19,23,24] In the setting of infection, inflammation, or surgery, all of which increase complement activation, the rate of hemolysis further rises.[19]

Clinical manifestations and diagnosis of PNH

The primary clinical manifestations of PNH include anemia, thrombosis, smooth muscle dystonia, chronic kidney disease, hemoglobinuria and bone marrow failure.[9,19,25] These clinical findings arise from both complement-mediated hemolysis and deficiencies in GPI-linked proteins. The anemia in PNH, for example, results from a combination of a Coombs-negative intravascular hemolysis, C3- and opson-mediated extravascular hemolysis and bone marrow failure.[22] Similarly, the thrombophilia in PNH, which

disproportionately results in thrombosis in the intra-abdominal or cerebral vasculatures, is driven by the deficiency in GPI-linked fibrinolytic proteins as well as increased plasma-free hemoglobin, decreased nitric oxide and increased proinflammatory and prothrombic cytokines.[19] The decrease in nitric oxide also leads to smooth muscle dystonia and abdominal pain, esophageal spasm, dysphagia and erectile dysfunction.

PNH should be considered any time a patient presents with hemolytic anemia, thrombosis or bone marrow failure. Diagnostic flow cytometry for PNH utilizes monoclonal antibodies and a special reagent (FLAER) which binds directly to the glycan portion of the GPI anchor to detect a severe deficiency or absence of GPI-linked proteins. For the diagnosis of PNH, a severe deficiency or absence of GPI-linked proteins should be present in at least two different cell lineages.[19,22]

Treatment for PNH prior to eculizumab

Historically, once PNH was diagnosed, treatment options were limited. The only curative treatment was, and continues to be, a bone marrow transplant, and this is rarely performed due to the risks of transplant-related morbidity and mortality.[9] Additional treatments were supportive and nonstandardized as a result of an absence of outcomes data, limited treatment efficacy and significant treatment toxicity.[22] Treatment options included corticosteroids to manage hemolysis flares, androgen therapy, iron supplementation and red blood cell transfusions to alleviate anemia, and anticoagulation to treat thromboembolic disease.[9,19,22] In addition, while anticoagulation was used prophylactically to prevent the development of thromboses, there were no randomized, prospective studies to support this practice.[22]

The development of eculizumab

The absence of effective PNH therapy, along with the well-defined pathophysiology of the disease, created an opportunity for drug developers to use rational therapeutic design to develop a novel treatment for PNH. As previously described, the formation of the MAC from C3b, C5b and additional terminal complement proteins is the common endpoint to the alternative, lectin, and classical pathways of complement. Therefore, blocking C5 to prevent the conversion of C5 to C5a and C5b would effectively stop the complement cascade regardless of the stimulus.[26] In addition, C5 blockade is downstream in the pathway so as not to impair the immunoprotective and immunoregulatory functions of C3b-mediated opsonization and immune complex clearance.[13]

Once C5 was identified as an optimal target, panels of murine antihuman C5 monoclonal antibodies were created and screened for their ability both to inhibit complement-mediated lysis and to effectively block the generation of C5a.[13] From these panels, a single monoclonal antibody emerged. Its complementarity determining regions were cloned and grafted onto human heavy and light chain antibody frameworks creating the humanized monoclonal antibody eculizumab. Eculizumab subsequently demonstrated efficacy *in vivo* in murine models and safety in individuals with rheumatoid arthritis, systemic lupus erythematosus, or coronary artery disease.[13] The first clinical trial of eculizumab to inhibit complement in patients with PNH was launched in May 2002.[21]

Clinical trials of eculizumab in patients with PNH

This first trial enrolled 11 transfusion-dependent PNH patients into an open-label phase II study.[21] All 11 patients were treated with eculizumab 600 mg intravenously weekly for 4 weeks, followed by a 900 mg intravenous infusion on week 5 and then every 2 weeks thereafter for a total treatment duration of 12 weeks. As the terminal complement plays a role in preventing meningococcal infection, all trial participants were vaccinated against *N. meningitidis*. Following treatment with eculizumab, the trial participants were found to have a decrease in lactate dehydrogenase levels (LDH) from a mean of 3111 ± 598 IU/l pre-enrollment to a mean of 594 ± 32 IU/l during treatment ($p = 0.002$). In all patients, this decrease in LDH occurred after a single dose of eculizumab. In addition to the decline in LDH, patients were also found to have statistically significant improvements in global health and physical, emotional and cognitive functioning, as well as a statistically significant decrease in the need for red cell transfusions. Episodes of hemoglobinuria were also reduced by 96%. Based on these results, all 11 patients chose to continue eculizumab therapy through a 52-week extension

study with all statistically significant changes in both laboratory and clinical markers of hemolysis maintained throughout the extension study.[27]

Given the findings of this phase II trial, two phase III trials of eculizumab were conducted in 2005. The TRIUMPH trial (ClinicalTrials.gov identifier: NCT00122330) examined the safety and efficacy of eculizumab in patients with PNH who had undergone at least four transfusions in the prior 12 months. The SHEPHERD trial (ClinicalTrials.gov identifier: NCT001300000) assessed the safety and efficacy of eculizumab in a more heterogeneous group of patients with PNH, including those with minimal transfusion requirements and those with evidence of thrombocytopenia.[8,28]

The results of the TRIUMPH study were published in September of 2006. A total of 87 participants underwent randomization and were treated with either placebo or eculizumab for 6 months.[28] The eculizumab dosing schedule was unchanged from the phase II study and all participants were once again vaccinated against *N. meningitidis*. The two primary endpoints were prespecified as the stabilization of hemoglobin levels and the number of packed red blood cells transfused during the study period. Secondary endpoints included LDH levels and quality of life measures. For the primary endpoints, 49% of participants in the eculizumab group had stabilized hemoglobin values as opposed to 0% of participants in the placebo group ($p < 0.001$). Consistent with this, the median number of transfused red blood cell units in the eculizumab group was 0 compared with 10 in the placebo group ($p < 0.001$). For the secondary endpoints, participants in the eculizumab group had lower LDH values ($p < 0.001$) and greater improvement in their quality of life ($p < 0.001$). The primary adverse events experienced by the participants in the eculizumab group were headache, nasopharyngitis, back pain and nausea. There was one reported case of an alpha-hemolytic streptococcal bacteremia and no reported meningococcal infections.

In the open-label single-arm SHEPHERD trial, published in February 2008, a total of 97 patients were treated with eculizumab for 52 weeks.[8] The primary endpoints focused on safety and clinical efficacy. Like the TRIUMPH study, the primary adverse events of eculizumab therapy in the SHEPHERD study were headache and nasopharyngitis. Most headaches were classified as mild to moderate in severity and were limited to the first 2 weeks of therapy. A total of two patients also experienced new thrombotic events, the first while on eculizumab therapy and the second 1 month following completion of eculizumab. No patients experienced meningococcal infections. Regarding measures of clinical efficacy, approximately 92% of patients maintained complete inhibition of serum hemolytic activity while on eculizumab. The remaining 8% of patients experienced hemolysis during the last 1–2 days of the 14-day dosing interval.

Long-term results of eculizumab in the treatment of PNH

Based on the results of the TRIUMPH study, as well as the prespecified interim 26-week analysis of the SHEPHERD study, eculizumab was granted US FDA approval in March 2007 and European Medicines Agency approval in June 2007.[8] Subsequent studies have demonstrated eculizumab's long-term efficacy and safety. For example, in a study of 79 patients with PNH treated with long-term eculizumab therapy, the rate of thrombotic events dropped from 5.6 events per 100 patient-years prior to eculizumab to 0.8 events per 100 patient-years on eculizumab.[12] In addition, the mean number of transfusions per patient dropped by 74% (from 19.3 units annually pre-eculizumab to 5.0 units annually on eculizumab), with 66% of patients becoming transfusion-independent. Sustained improvements in hemolytic markers and prolonged increases in patient-reported quality of life measures have also been observed.[12,20]

Recent studies have also demonstrated the safety and efficacy of eculizumab for specialized populations with PNH, including pregnant women and children.[29,30] In a retrospective study of 75 pregnancies in 61 women treated with eculizumab for PNH during their pregnancies, there were no maternal deaths reported and only three fetal deaths. This is in contrast with a historic maternal mortality rate of 8–20% and fetal mortality rate of 4–9% for pregnant women with PNH prior to eculizumab treatment.[29] Similarly, in a prospective trial of eculizumab therapy in seven children diagnosed with PNH between ages 11–17, treatment with eculizumab led to complete inhibition of hemolysis and normalization of LDH levels in all seven children.[30]

Limitations to eculizumab therapy

Despite its benefits in the treatment of PNH, eculizumab therapy does have limitations. Up to 50% of patients experience headache following the first dose of eculizumab and approximately 0.5% of patients per year will develop meningococcal infection while on the therapy.[20,31] In addition, eculizumab's half-life of approximately 11 days necessitates indefinite intravenous dosing of eculizumab every 2 weeks.[12] This dosing schedule is burdensome for patients and has been shown to cause psychosocial strain for patients with PNH both in their relationships with friends and family and in their ability to function in the workplace.[32] Moreover, despite eculizumab infusions every 14 days, a small percentage of patients with PNH may experience fatigue and breakthrough hemolysis due to insufficient complement inhibition in the final 24–48 h before their next infusion.[20,31] Due to breakthrough hemolysis, as well as opson-mediated extravascular hemolysis and bone marrow failure, 25–35% of patients on eculizumab therapy continue to require red cell transfusions.[20]

The frequent and indefinite need for eculizumab dosing also plays a role in the high cost of eculizumab therapy. In 2017, with a cost of nearly US$18,000 per infusion in the United States, this amounts to an annual cost of nearly US$500,000 per patient with PNH.[33] A cost-effectiveness analysis of eculizumab for the treatment of PNH conducted in Canada in 2014 demonstrated that when compared with supportive therapies, eculizumab resulted in an incremental cost per life-year of CAN$4.62 million, and a cost per quality-adjusted life-year of CAN$2.13 million. The authors concluded eculizumab's cost would need to be reduced by 98.5% in order to be cost-effective for the treatment of PNH.[34]

Finally, although eculizumab is effective in the greater majority of patients with PNH, a small cohort of patients (~3.2%) have been found to have a single missense mutation on C5 that blocks eculizumab binding and results in a poor therapeutic response to eculizumab therapy.[35]

The development of ravulizumab

Ravulizumab was designed to address the limitations in eculizumab therapy, particularly eculizumab's short half-life and frequent dosing schedule.[14] As previously described, eculizumab binds to the complement protein C5 in the intravascular space. Once this occurs, the resulting eculizumab–C5 complex is taken up by endothelial cells through pinocytosis and degraded in the endosome by lysosomal enzymes. The endosomal degradation of eculizumab only occurs when eculizumab is associated with C5. When eculizumab is disassociated from C5, eculizumab is recycled from the endosome back to the intravascular space through the neonatal Fc receptor. To increase eculizumab's half-life, two changes were made to the antibody. First, two amino acid residues on eculizumab were substituted with histidine residues to facilitate eculizumab–C5 dissociation in the endosome. These two substitutions change the antibody's binding kinetics to C5, so that antibody and C5 continue to associate at a pH of 7.4 (the pH of the intravascular space) but disassociate at a pH of 6.0 (the pH of the endosome). Second, two amino acid substitutions were made to the Fc-binding portion of the antibody to enhance the antibody's affinity for the neonatal Fc receptor. This alteration in just four amino acid residues generates a new antibody, ravulizumab, with a half-life three to four times longer than eculizumab.[14,36]

Phase I and II clinical trials of ravulizumab

Ravulizumab was initially tested in 14 healthy people in a phase I randomized, blinded, placebo-controlled single-ascending dose study.[36] The goal of the study was to assess the safety of ravulizumab in healthy people and to characterize its pharmacokinetics (PK), pharmacodynamics (PD) and immunogenicity. The 14 participants were vaccinated against *N. meningitidis*, then treated with a single dose of ravulizumab at either 200 mg or 400 mg or with a placebo. All participants received prophylactic penicillin V and were followed up for a total of 150 days. Following treatment with ravulizumab, 70% of participants reported an adverse event, the majority of which were headaches of mild severity. No adverse events were deemed severe. Ravulizumab was found to have a half-life of 32 days and to have a low intersubject variability in PK parameters. In addition, in all participants, levels of C5 were reduced by >99%.

Following this phase I study of ravulizumab in healthy participants, two concurrent phase Ib/II

multicenter open-label studies of ravulizumab were performed in patients with PNH naïve to complement-inhibitor therapy.[37] The goals of both studies were to assess the efficacy and safety of different doses and dosing schedules of the antibody. The phase Ib study enrolled 13 participants who were treated with ravulizumab either once weekly or every 2 weeks for a 4-week induction, then every 4 weeks thereafter at a dose of either 900 mg or 1800 mg. The phase II study, in contrast, enrolled 26 participants who were treated with ravulizumab every 2, 3, or 4 weeks during induction, then every 4, 6, 8, or 12 weeks thereafter at doses ranging from 1000 mg to 5400 mg. All 39 participants enrolled in the two studies were required to have a confirmed diagnosis of PNH, a baseline LDH $\geq$3 times the upper limit of normal and a documented meningococcal vaccination. Key exclusion criteria included a platelet count $<30 \times 10^9$/l, an absolute neutrophil count $<0.5 \times 10^9$/l, history of bone marrow transplantation, history of major surgery <90 days prior to dosing on study day 1 or history of *Neisseria meningitidis* infection. At the time of enrollment, all participants were found to have mean baseline free hemoglobin levels and reticulocyte counts above the upper limit of normal and to have a mean plasma haptoglobin below the upper limit of normal. The participants' PNH clone size ranged from 78.3% to 91.1% at baseline.

In both studies, the assessed endpoints were similar. Change in mean plasma LDH levels from baseline to study completion was the primary endpoint; changes in laboratory markers of hemolysis (e.g. free hemoglobin, haptoglobin and reticulocyte levels) and clinical manifestations of PNH (e.g. fatigue, abdominal pain and dyspnea) were the key secondary endpoints. Change from baseline in blood transfusion requirements, major adverse vascular events and estimated glomerular filtration rate (eGFR) were exploratory endpoints.

Results of the two studies were published in September 2018.[37] For the primary endpoint, across all dose and dosing cohorts in both the phase Ib and phase II trials, treatment with ravulizumab led to a statistically significant drop in mean LDH levels from baseline. The mean LDH reduction ranged from 72.9% to 89.6% in the cohorts. For the key secondary endpoints, mean free hemoglobin levels decreased for all but one treatment cohort, while all cohorts had an improvement in total hemoglobin and a decrease in symptom burden. Mean haptoglobin levels and mean reticulocyte counts, in contrast, continued to be abnormal in all cohorts. Finally, for the exploratory endpoints, across all treatment cohorts, transfusion requirements decreased and there were no major adverse vascular events identified. The eGFR demonstrated a small but not clinically meaningful drop across all cohorts.

The primary adverse event in both studies was headache, occurring in 43.6% of participants, while two participants in the phase IIb study developed sepsis secondary to meningococcal infection. Both participants recovered following treatment with intravenous ceftriaxone and restarted ravulizumab therapy.

Phase III trials of ravulizumab

Based on the encouraging results of the phase Ib/II studies of ravulizumab, two phase III trials of ravulizumab were initiated. The first study, the 301 study (ClinicalTrials.gov identifier: NCT 02946463), assessed the non-inferiority of ravulizumab compared with eculizumab in adult patients with PNH naïve to complement inhibitors.[38] The second study, the 302 study (ClinicalTrials.gov identifier: NCT03056040), assessed the non-inferiority of ravulizumab compared with eculizumab in adult patients with PNH who had previously been treated with a C5 inhibitor.[39] Both studies were conducted across more than 40 centers and in 10 countries and were published in February 2019.

The 301 study enrolled a total of 244 participants who were stratified into six groups based on transfusion history and LDH screening level, then randomized in a 1:1 ratio to receive either ravulizumab or eculizumab.[38] Ravulizumab dosing was weight-based with a loading dose on day 1 (2400 mg for participants weighing $\geq$40 kg to <60 kg, 2700 mg for participants $\geq$60 kg to <100 kg, and 3000 mg for participants $\geq$100 kg) followed by maintenance doses on day 15 and every 8 weeks thereafter (3000 mg for participants weighing $\geq$40 kg to <60 kg, 3300 mg for participants $\geq$60 kg to <100 kg, and 3600 mg for participants $\geq$100 kg). Eculizumab was administered according to its approved dosing schedule. Inclusion criteria and exclusion criteria were similar to the prior phase

Table 1. Key endpoints from the ravulizumab phase III clinical trials.[38,39]

	Endpoints	Ravulizumab	Eculizumab	P_{inf}
301 study	Transfusion avoidance rate, %	73.6	66.1	<0.0001
	LDH normalization, %	53.6	49.4	<0.0001
	FACIT-fatigue score, mean change	7.07	6.40	<0.0001
	Breakthrough hemolysis rate, %	4.0	10.7	<0.0001
	Hemoglobin stabilization rate, %	68.0	64.5	<0.0001
302 study	LDH, mean % change	–0.82	8.4	<0.006
	Breakthrough hemolysis rate, %	0	5.1	<0.004
	FACIT-fatigue score, mean change	2.0	0.54	<0.0001
	Transfusion avoidance rate, %	87.6	82.7	<0.0001
	Hemoglobin stabilization rate, %	76.3	75.5	<0.0005

Ib/II studies of ravulizumab and demographic and baseline clinical characteristics were balanced between the treatment arms. Coprimary endpoints included transfusion avoidance and hemolysis as measured by LDH normalization. The key secondary endpoints were the percentage change from baseline in LDH levels, change from baseline in quality of life, the proportion of participants with breakthrough hemolysis and the proportion of participants with stabilized hemoglobin levels.

Participants on the 301 study were treated for a total of 26 weeks with 99.2% of participants receiving all planned infusions of the study medications. Ravulizumab was found to be non-inferior to eculizumab for both coprimary endpoints (Table 1). In the ravulizumab arm, 73.6% of participants avoided transfusion and 53.6% of participants had normalization of LDH. In contrast, in the eculizumab arm, 66.1% of participants avoided transfusion and 49.4% of participants had normalization of LDH. For the four key secondary endpoints, ravulizumab was also found to be non-inferior to eculizumab. This included 4% of participants on ravulizumab experiencing breakthrough hemolysis compared with 10.7% of participants on eculizumab. Adverse events were similar between the two arms. The most frequent adverse event in both arms was headache and occurred in 36% of participants on ravulizumab compared with 33.1% of participants on eculizumab (Table 2). Although no meningococcal infections occurred in either treatment arm, two participants had serious infections on ravulizumab and four participants had serious infections on eculizumab.

The 302 study enrolled 197 participants, 195 of whom received treatment in the study.[39] Participants were stratified by transfusion history, then randomized in a 1:1 ratio to receive either ravulizumab or to continue with eculizumab. Ravulizumab and eculizumab dosing were the same as in the 301 study. Inclusion criteria in the 302 study included eculizumab treatment for ⩾6 months before study entry, baseline LDH ⩽1.5 times the upper limit of normal and documented meningococcal vaccination. Key exclusion criteria included LDH level ⩾2 times the upper limit of normal, major adverse vascular events within 6 months before study day 1, platelet count $<30 \times 10^9$/l, an absolute neutrophil count $<0.5 \times 10^9$/l, history of bone marrow transplantation, body weight ⩽40 kg or history of *Neisseria meningitidis* infection. Demographic and baseline clinical characteristics were balanced between the treatment arms. The primary efficacy endpoint of the 302 study was hemolysis, as measured by a percentage change in LDH levels

Table 2. Reported adverse events from the ravulizumab phase III clinical trials.[38,39]

	Adverse event	Ravulizumab, %	Eculizumab, %
301 study	Total adverse events	88	86.8
	Headache	36.0	33.1
	Nausea	8.8	14.9
	Nasopharyngitis	8.8	8.3
	Upper respiratory tract infection	10.4	5.8
	Serious infection[a]	1.6	3.3
302 study	Total adverse events	87.6	87.8
	Headache	26.8	17.3
	Nasopharyngitis	21.6	20.4
	Upper respiratory tract infection	18.6	10.2
	Serious infection[a]	2.1	1.0

[a]Infections in the ravulizumab arms included: leptospirosis, influenza lower respiratory tract infection and a systemic infection. Infections in the eculizumab arm included: limb abscess, cellulitis, pneumonia, upper viral respiratory infection and pyelonephritis. No patients in either study had meningococcal infection.

from baseline to day 183. Key secondary endpoints included the proportion of participants with breakthrough hemolysis, change from baseline in quality of life, transfusion avoidance and the proportion of participants with a stabilized hemoglobin.

Participants in the 302 study were also treated for a total of 26 weeks with 100% of participants receiving all planned infusions of the study medications. Ravulizumab was once again found to be non-inferior to eculizumab for the primary endpoint (Table 1). Participants on ravulizumab experienced a 0.82% decrease in LDH levels on day 183 compared with participants on eculizumab who experienced an 8.39% increase in LDH levels on day 183. For the key secondary endpoints, ravulizumab was also non-inferior to eculizumab. In fact, none of the participants on ravulizumab experienced breakthrough hemolysis compared with 5.1% of participants on eculizumab. Adverse events were similar not only between both arms, but also to the 301 study. The most frequent adverse event in the 302 study was headache which occurred in 28.6% of participants on ravulizumab compared with 17.3% of participants on eculizumab (Table 2). Once again, no meningococcal infections occurred in either treatment group, but two participants had serious infections on ravulizumab and one participant had a serious infection on eculizumab.

Conclusion and future directions

The results of the 301 and 302 studies suggest that ravulizumab is indeed non-inferior to eculizumab in the short-term treatment of both complement-inhibitor-naïve patients with PNH and those previously treated with eculizumab. The two drugs also appear to have similar safety profiles, with both drugs leading to headache in up to one-third of treated patients and posing a small but clinically significant risk of meningococcal infection. With a dosing frequency of every 8 weeks, ravulizumab is likely to be less burdensome therapy for patients with PNH and may be associated with a decreased rate of breakthrough hemolysis. After being given priority review and orphan drug status by the US FDA, ravulizumab was officially granted approval as the second drug for adult patients with PNH on 21 December 2018.[16] While the estimated annual average cost of ravulizumab is still exceedingly high at approximately US$458,000, it is about 10% lower than the annual cost of eculizumab.[40]

At the current time, ravulizumab is too new for any long-term data assessing safety or efficacy. Long-term safety data are especially important, given that ravulizumab carries a black box warning for serious meningococcal infection based on the two patients in the phase II study who developed meningococcal infections. There are also no data to determine whether ravulizumab will be as well-tolerated and effective as eculizumab in special populations with PNH, including pregnant woman or children.

Moving forward, ravulizumab will likely have expanded indications. The two phase III studies of ravulizumab in complement-inhibitor-naïve patients with atypical hemolytic uremic syndrome are underway.[41,42] In addition, ravulizumab is currently being tested in clinical trials for children and adolescents with PNH and atypical hemolytic uremic syndrome and for adults with myasthenia gravis and immunoglobulin A nephropathy.[15] A subcutaneous formulation of ravulizumab is also under development to further improve ease of ravulizumab administration.[15]

At the time of writing, there are 18 studies assessing novel therapies for the treatment of PNH registered as recruiting, active and not recruiting, or recently completed on clinicaltrials.gov, so new therapies for PNH are on the horizon.[43] These therapies target a range of steps in the complement pathway including, but not limited to, C3, C5 and complement factor D.[44–46] We are hopeful that ravulizumab, together with these additional new therapies, will provide an assortment of options to treat PNH and will continue to improve the care of patients with PNH.

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Conflict of interest statement

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