



The cost-effectiveness, of pegcetacoplan compared with ravulizumab for the treatment of paroxysmal nocturnal hemoglobinuria, in a UK setting

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Aim: Paroxysmal nocturnal hemoglobinuria (PNH) is a rare blood disorder characterized by hemolytic anemia, bone marrow failure and thrombosis. We evaluated, the cost-effectiveness of pegcetacoplan, a novel proximal C3 inhibitor, versus ravulizumab in patients with PNH and hemoglobin levels <10.5 g/dl despite eculizumab treatment in the UK healthcare and social services setting. **Materials & methods:** A Markov cohort framework model, based on the data from the pivotal trial of pegcetacoplan (PEGASUS/NCT03500549), evaluated lifetime costs and outcomes. Patients transitioned through 3 PNH hemoglobin level/red blood cell transfusion health states. **Results:** Pegcetacoplan provides lower lifetime costs/greater quality-adjusted life years (£6,409,166/14.694QALYs, respectively) versus ravulizumab (£6,660,676/12.942QALYs). **Conclusion:** Pegcetacoplan is associated with enhanced anemia control, greater QALYs and reduced healthcare costs versus ravulizumab in the UK healthcare and social services setting.

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Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, potentially fatal blood disorder [1] characterized by hemolytic anemia, bone marrow failure and thrombosis [2,3]. In PNH, a proportion of hematopoietic stem cells lack various cell surface proteins due to an inability to produce the glycosylphosphatidylinositol anchor that is required for these proteins to be bound to the cell surface [4–6]. This defect is caused by somatic loss-of-function mutations in the *PIGA* gene [1]. CD59 and CD55 are glycosylphosphatidylinositol-linked complement regulatory proteins that protect blood cells when the complement system is activated [2]. However, in PNH, without these protective proteins, individuals experience complement-mediated destruction of blood cells and the subsequent symptoms of the disease [7].

PNH may present at any age, but it is most frequently diagnosed in people between 30 and 42 years of age [8,9] and affects males and females equally [9]. The global prevalence of the disease is approximately 1–1.5 cases per million [1,10,11]. In the UK, the incidence is estimated to be 1 in 770,000/year [12]. Untreated PNH is associated with considerable disease burden in terms of mortality (with 10-year rate of 24–29%) [13,14] and economic costs [15] especially given its high disease activity [16] and associated systemic complications, including smooth muscle dystonia

(presenting as chest and abdominal pain, dysphagia and erectile dysfunction) [1,17], impaired renal function and thrombotic events [18,19]. Disabling anemia-related fatigue is a leading symptom of PNH, and in addition to weakness [1,20–22], contributes to significant impairment in patient health-related quality of life (HRQoL), work productivity and everyday activities [1,23,24]. Thromboembolism is the most common cause of mortality in patients with PNH [14]. Moreover, disease paroxysms can be triggered by events such as physical exertion, vaccinations, infections, pregnancy, or after excessive alcohol consumption. Some patients may also pass dark-colored urine because of the excreted breakdown product of red blood cells (i.e., hemoglobinuria) [25].

Red blood cell transfusions can address anemia in PNH and improve daily functioning [26]; however, recipients face further risks of morbidity and mortality associated with transfusion-related iron overload [27]. The only curative treatment for PNH [19,26], allogeneic bone marrow transplantation, is also associated with considerable morbidity and mortality risk and is not recommended in countries where anti-complement therapy is available [28]. Therefore, therapeutic management of hemolytic disease and/or thromboembolic complications remain the key objectives across international clinical practice. In the UK, current treatment options comprise complement component 5 inhibitors (C5i), including eculizumab and ravulizumab [16,29]. These humanized monoclonal antibodies are specifically designed to target the complement protein C5, prevent its cleavage and thereby prevent the formation of the terminal complement complex, the membrane attack complex [26,30].

Available in Europe since 2007 [31], eculizumab has been the first anti-C5 monoclonal antibody treatment for adults and children that provides sustained inhibition of complement-mediated intravascular hemolysis (IVH) [1]. Eculizumab increases 5-year survival to 95.5% (95% CI: 87.6–98.5%) in the real world compared with survival rates associated with the untreated course of disease (66%; 95% CI: 41.4–85.1%) [32]. Ravulizumab is an eculizumab-like monoclonal antibody that has a half-life four-times longer than eculizumab [33]. Ravulizumab was first licensed by the European Medicines Agency (EMA) in 2019 for treatment in adults and paediatric patients (of body weight ≥ 40 kg) with PNH who present with hemolysis and clinical symptoms despite treatment with eculizumab for at least the past 6 months [34]. Ravulizumab is now recommended in the UK National Health System (NHS) setting within its marketing authorization as an option for treating PNH in adults [35].

Despite the important benefits that eculizumab provides in the management of PNH [32], the requirement for frequent dosing has limited its clinical utility, and thus been outmoded by ravulizumab given its reduced intravenous infusion frequency (every 8 weeks vs every 2 weeks for eculizumab) [36], facility for dosing individualization via therapeutic drug monitoring approaches and patient preferences [37,38]. However, further limitations remain for C5i due to the emergence of C3-mediated extravascular hemolysis (EVH) and its effect on patient HRQoL [7,39,40].

Pegcetacoplan is a recently available PNH treatment option in the UK. A novel proximal C3 inhibitor (C3i), pegcetacoplan targets the complement cascade, thereby controlling IVH without associated increases in EVH [41]. The self-administered twice weekly 1080 mg dose is delivered with a syringe system infusion pump [42]. Pegcetacoplan is approved by the US FDA for the treatment of adults with PNH [42] based on evidence from PEGASUS (NCT03500549), the pivotal phase 3, prospective, randomized, multicenter, open-label, active-comparator, controlled clinical trial of pegcetacoplan versus eculizumab. For UK prescribing, pegcetacoplan is approved by the European Medicines Agency [43] and the Medicines & Healthcare Products Regulatory Agency [44], and recently recommended by the National Institute for Health and Care Excellence (NICE) for adults with PNH and hemoglobin (Hb) levels <10.5 g/dl after treatment with a C5 inhibitor for at least 3 months.

In PEGASUS, pegcetacoplan provided significant improvement in the primary endpoint, serum Hb levels, and was non-inferior to eculizumab in reducing transfusion requirements and in reducing reticulocyte counts, with comparable safety to eculizumab [41]. In particular, the week 16 Hb levels between the 2 groups were significantly different (3.84 g/dl [95% CI: 2.33–5.34]; $p < 0.0001$) on least-squares mean change from baseline (CFB). Pegcetacoplan also provided substantial and clinically meaningful improvements in patient reported outcomes, including symptoms of fatigue (measured on the Functional Assessment of Chronic Illness Therapy–Fatigue scale), dyspnoea, and HRQoL (measured on the Linear Analog Scale Assessment and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 Scale [EORTC QLQ-C30]) [41,45].

Given the potential lifelong need for treatment and care, the funding of new healthcare technologies for orphan diseases with high unmet needs is as equally crucial as funding diseases with high prevalence; yet allowing patient access to new and highly specialized technologies for rare disease remains a global challenge for healthcare commissioners given ever-constrained budgets [46]. Hence, value assessment frameworks for rare diseases must balance such health policy factors as severity and unmet need with standard efficiency criteria such as cost-effectiveness [47]. Cost-utility analysis (CUA) is a form of cost-effective analysis (CEA) that weighs the incremental

Table 1. Base-case model inputs.

PEGASUS Trial data (n = 80)		
Variable	Value (mean/percentage)	Measurement of uncertainty - distribution ($\pm$ SE)
Baseline patient characteristics		
Age (years)	48.8	Normal ($\pm$ 1.79)
Sex (female)	61.3%	Beta
Weight (kg)	75.25	Normal ($\pm$ 1.97)
Time since diagnosis (years)	10.18	Normal ($\pm$ 0.96)
Treatment outcomes		
Intravenous hemolysis breakthrough and pegcetacoplan treatment discontinuation (at week 16)	2.44%	Beta
Intravenous hemolysis breakthrough requiring a single dose of pegcetacoplan continued thereafter	1.9%	Beta
Percentage of patients receiving chelation therapy (deferoxamine mesilate and deferasirox)	27.5%	Beta
Utilities		
Health states		
No transfusion and Hb $\geq$ 10.5	0.808	Beta
No transfusion and Hb <10.5	0.738	Beta
Transfusion required	0.695	Beta
Disutilities		
Iron overload	-0.03	Normal
Costs and utilization		
Medication		
Pegcetacoplan 1080 mg PAS price (£)	3100.00	Fixed
Ravulizumab 300 mg price (£)	4533.00	Fixed
Prophylactic antibiotic cost (£)	1.04	Gamma
Chelation therapy cost (per 4-week cycle) (£)	513.62	
Pegcetacoplan administration cost (£)	78.67	Normal
Ravulizumab administration cost (£)	0.00	Normal
Blood transfusion unit cost (£)	532.51	Gamma ($\pm$ 5.325a)
Mean number of transfusions per cycle	1.0	Fixed

Hb: (Serum) Hemoglobin; IV: Intravenous; SE: Standard error.

health economic benefits, including costs and HRQoL, associated with a new treatment modality in relation to best practice. Some healthcare reimbursement authorities across Europe mandate such analyses to inform health technology assessments for highly specialized technologies for rare diseases as well as non-orphan healthcare technologies [47–50].

This study evaluates the cost-effectiveness, in the UK setting, of pegcetacoplan compared with the newest C5i, ravulizumab, for the treatment of PNH in patients whose anemia was insufficiently controlled despite at least 3 months treatment with eculizumab.

Materials & methods

We conducted the CUA from the perspective of the UK NHS and social services. We developed a *de novo* Markov model in Microsoft Excel to estimate the long-term cost-effectiveness of the introduction of pegcetacoplan on the UK PNH treatment pathway. The model estimated the lifetime costs and quality-adjusted life years (QALYs) incurred in the pegcetacoplan label population of adults with PNH whose anemia was insufficiently controlled (ie, had Hb levels <10.5 g/dl) despite at least 3 months of treatment with eculizumab and were therefore candidates for switching to pegcetacoplan (Table 1) [41].

A comprehensive systematic literature review (SLR) enabled the identification of models and inputs to the CUA, with searches conducted on 30 July 2020 (updated on 11 March 2021) in MEDLINE, MEDLINE In-Process, Embase, BioScience Information Service of Biological Abstracts, EconLit and Cochrane Library. A single combined search identified existing cost- and clinical- effectiveness, HRQoL/utility and cost/resource use studies in PNH.

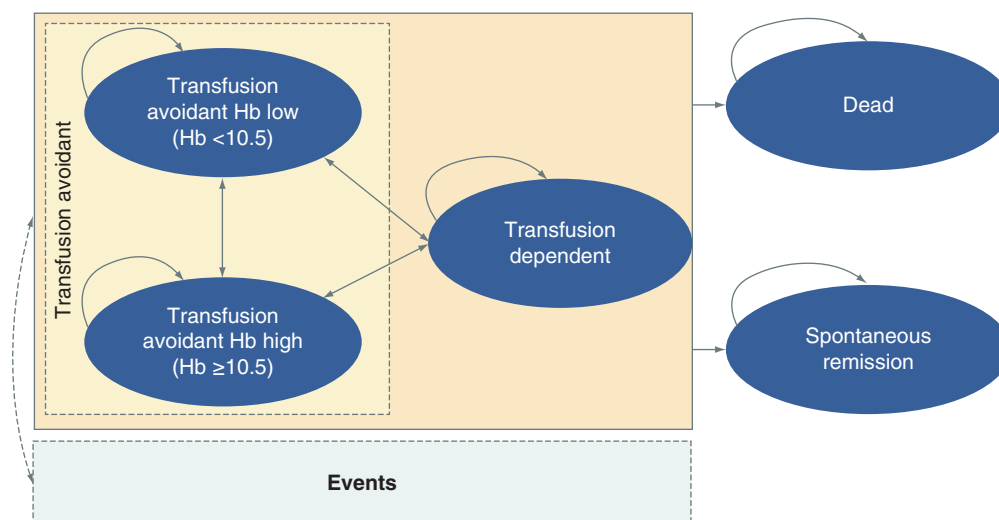


Figure 1. Markov model diagram.
Hb: (Serum) Hemoglobin.

Model structure

Informed by clinical data from PEGASUS, the pivotal trial of pegcetacoplan [41], the CUA model was based on a Markov cohort framework whereby patients transitioned between 3 PNH health states representing Hb level at a given trial visit and red blood cell transfusion requirements during the previous 4 weeks. Together, the health states represented different levels of disease status and impacts on PNH healthcare costs and QALYs. The model assumed a cycle length of 4 weeks, based on the length of time between clinical visits in PEGASUS [41]; consequently, health state transitions occurred every 4 weeks.

We stratified transfusion avoidance on patient Hb level above and below a threshold level of 10.5 g/dl; this threshold was consistent with the PEGASUS trial inclusion criteria of Hb <10.5 g/dl and validated by clinical opinion for capturing differences in HRQoL between PNH health states [51,52]. According to clinicians, although anemia is defined as Hb <13.5 g/dl in men and Hb <12 g/dl in women, patients with PNH may have a Hb lower than the general population but feel 'normal' because of symptom adaptation [51,52]. Given this, a lower threshold of Hb level of 10.5 g/dl was deemed appropriate for categorising patients as having 'controlled' or 'uncontrolled' anemia. Hence, the model represented 3 relevant health states including: transfusion-avoidant Hb high (Hb ≥10.5 g/dl); transfusion-avoidant Hb low (Hb <10.5 g/dl); and transfusion-dependent (Hb <10.5 g/dl). The model also allowed patients to enter the 'absorbing' state of death (Figure 1).

Based on clinical opinion, patients in better health states (ie, the transfusion-avoidant Hb high [Hb ≥10.5 g/dl]) would be expected to accumulate the lowest costs and greatest HRQoL benefits; patients in the transfusion-avoidant Hb low (Hb <10.5 g/dl) state would accumulate relatively higher costs and reduced HRQoL due to anemia, while patients in the transfusion-dependent (Hb <10.5 g/dl) health state would accumulate the highest costs and most impaired HRQoL as most of the negative health effects and costs associated with PNH are due to blood transfusions [3].

Clinical inputs

Treatment response

A *post hoc* analysis of PEGASUS informed patient baseline clinical status, demographics (Table 1) and transitions between health states for patients treated with pegcetacoplan in the model [41]. The treatment period of PEGASUS comprised a 4-week run-in period during which all patients received pegcetacoplan and concomitant eculizumab treatment; a 16-week controlled period where, after 1:1 randomization, patients received either pegcetacoplan (n = 41) at a dose of 1080 mg subcutaneously twice weekly, or eculizumab (n = 39) administered by intravenous (IV) infusion at the current and stable prescribed dosage [51,52]. A 32-week open-label pegcetacoplan-only period then followed.

PEGASUS trial data from the randomized controlled phase informing the model included, besides the primary efficacy endpoint of mean CFB in Hb level at Week 16: transfusion status, HRQoL based on the EORTC-QLQ-C30 and drug dosage. To inform clinical inputs we first considered anchored matching-adjusted indirect comparison (MAIC) to assess the comparative effectiveness of these treatments among patients previously treated with eculizumab [53,54]. The MAIC used individual patient-level data from PEGASUS and adjusted the trial population to match average aggregate baseline characteristics reported in the ALXN1210-PNH-302 (Study 302) trial for patients receiving ravulizumab [53]. An eculizumab control arm anchored comparisons across both studies [54].

The MAIC showed that, besides equivalent mean CFB in LDH levels, all other clinical, hematological and HRQoL endpoints for patients previously treated with eculizumab were better for patients who received pegcetacoplan compared with those who received ravulizumab [54]. However, there was also evidence to suggest heterogeneity between PEGASUS and the ravulizumab pivotal trial (Study 302), such as in the inclusion criteria (e.g., the 302 study enrolled eculizumab-stable patients), the randomized controlled periods (16 weeks + 4-week run-in phase in PEGASUS versus 26 weeks in Study 302) and the differing dosing of eculizumab between the 2 trials; therefore, we deemed that the results of the MAIC were subject to bias [54]. In lieu, we assigned values for efficacy and safety of ravulizumab based on the head-to-head non-inferiority trial data of ALXN1210-PNH-302 (Study 302) [53,55]. This assumption was also consistent with health technology assessments (HTAs) of ravulizumab conducted by the NICE in England and the Scottish Medicines Agency [16,56].

Iron overload

Blood transfusion therapy results in accumulated iron, a key component of Hb present in the red blood cells that the body cannot remove if at an excess level. Therefore, transfused patients can experience iron overload, which can lead to progressive damage of the liver, heart and endocrine system if not removed. Based on iron overload rates in PEGASUS, the model assumed that patients could experience iron overload with a probability of 0.0065 per cycle when in the transfusion dependent health state.

Breakthrough hemolysis

Patients in the model on pegcetacoplan could experience breakthrough hemolysis at a probability of 0.0315 per cycle if in the transfusion avoidant (Hb <10.5 g/dl health state) or at a probability of 0.1334 per cycle in the transfusion dependent health state, as based on the outcomes in PEGASUS. Moreover, for patients treated with pegcetacoplan, those experiencing breakthrough received a single dose of eculizumab or switched back to eculizumab treatment in PEGASUS [57]; this practice was applied to the model and validated by input from and expert panel of clinicians [57]. For ravulizumab patients, we applied a conservative assumption in the model of no breakthrough hemolysis.

Mortality

In the base-case, we assumed that the background mortality rate among patients receiving any complement inhibitor was comparable with the age- and sex-adjusted general population, as per published evidence [32]. However, we modeled PNH-specific mortality in scenario analyses.

Health state transitions

We calculated transition probabilities between health states for patients receiving pegcetacoplan from the PEGASUS patient-level data from the randomized control period (weeks 4–16) (Table 2). All patients entered the model in the transfusion-avoidant (Hb <10.5 g/dl) health state, with their baseline characteristics reflecting those of patients in PEGASUS. The model assumed a sustained treatment effect, and patients accumulated differential costs and QALYs until death. In the base-case, the model did not consider spontaneous remission, as we would not expect any remission to vary by treatment arm. However, we modeled spontaneous remission in the scenario analyses.

To estimate transition rates, we first classified patients by health states according to their Hb level and transfusion dependency during the planned visits during the PEGASUS randomized control period. A multinomial logistic regression model that included variables to adjust for the interactions between treatments and visit categories then allowed the calculation of transition probabilities between health states. With current health state as the dependent variable, covariates included the prior 4-weeks' health state, treatment, visit category and age. The regression also included a patient-level random intercept term [58]. Through interviews and an advisory board, clinical experts and health economists validated the final model structure and inputs [51,57].

Table 2. Transition probabilities applied in base-case (week 4 to week 16).

From	To		
	No transfusion and Hb <10.5 g/dl	No transfusion and Hb ≥10.5 g/dl	Transfusion required
Transition probabilities for patients receiving pegcetacoplan (%)			
No transfusion and Hb <10.5 g/dl	43.7	49.0	7.2
No transfusion and Hb ≥10.5 g/dl	3.1	96.6	0.3
Transfusion required	26.6	61.2	12.2
Transition probabilities for patients receiving ravulizumab (%)			
No transfusion Hb and <10.5 g/dl	65.2	0.1	34.7
No transfusion and Hb ≥10.5 g/dl	74.2	3.0	22.8
Transfusion required	40.4	0.1	59.5

Hb: (Serum) hemoglobin.

Utilities

For utilities, we applied the EORTC QLQ-C30 data collected in PEGASUS to map to EQ-5D-3L utility weights (in line with the NICE reference case [59]); this approach addressed the lack of data EQ-5D data collected in the PEGASUS clinical study. A mapping algorithm converted EORTC-QLQ-C30 scores from PEGASUS to EuroQol 5 Dimension 3 Level (EQ-5D-3L) utilities [60], and approach consistent with the UK HTAs for ravulizumab [16,56] and NICE HTA guidance overall [61]. We considered 2 mapping algorithms, by Longworth *et al.* [60,62] and McKenzie *et al.* [63], respectively. The Longworth algorithm, based on multinomial logistic regressions, has five separate regressions for the five dimensions of utility on the E5-5D-3L: mobility, self-care, usual activities, pain and anxiety/depression. We applied this algorithm to validate our mapping approach. The utilities applied in the model corresponded to the model health states, as per an analysis conducted to confirm the impact of Hb and transfusion status on utilities. We assumed that utilities remained constant over time; however, we adjusted the estimates for age [60].

IV infusion

Ravulizumab is given as an IV infusion every 8 weeks. A published targeted literature review reported that the frequent regular IV infusion of ravulizumab versus eculizumab was associated with a utility increment of 0.025 [64]. In addition, both NICE and Scottish Medicines Agency HTAs assumed a utility increment of 0.057 associated with the reduced administration frequency of ravulizumab [16,65]. Patients have also reported a preference for subcutaneous over IV delivery in other disease settings [64].

Adverse events

In the base-case, we assumed that the mapped EQ-5D-3L utilities accounted for adverse events. However, in the scenario analyses, we applied disutilities for adverse events as sourced from the SLR, adjusted for the probability of developing the effects per cycle (Supplementary Table 3) and the duration of the event.

Iron overload

To account for disutilities related to iron overloads, targeted literature searches identified a disutility of -0.03 associated with chelation therapy [66]. We applied this value for ravulizumab additively based on the proportion of patients who received chelation therapy in the eculizumab arm in PEGASUS to estimate disutility (-0.00789) (Table 1; Supplementary Table 4).

Costs

Direct costs considered in the model covered PNH treatments, prophylactic antibiotic treatment, blood transfusion, treatment monitoring and adverse events, iron overload and ravulizumab infusion (Table 1). We based dosing assumptions for pegcetacoplan on data from PEGASUS week 4 to week 16 visits.

Table 3. Paroxysmal nocturnal hemoglobinuria treatment costs.

Treatment	Dosing regimen				Split (%)	
Pegcetacoplan	Labeled dosing: ● 4-week run-in period: 1080 mg SC administration twice weekly + current dose of eculizumab ● Maintenance period: 1080 mg SC administration twice weekly				100	
	Dosing units				Cost per administration (£)	
	Initial dose (applied in cycle 1 only): first SC administration includes training for self-administration at home (20 min nurse specialist band 6 £147 per hour of contact time)				£49.00	
	Dose 2 and 3 (applied in cycle 1 only): at-home care assumed for doses 2 and 3 to check patients administering correctly (30 min community nurse £89 per hour of patient related work)				£29.67	
	Cost per dose (£)	Doses per week (n)	Drug cost per week (£)		Patients (%)	
	3100	2.00	6200		100%	
	Weighted average cost per week (£):				4600	
Ravulizumab	Body weight range (kg)		Loading dose (mg)		Maintenance dose (mg)	
	≥40 to <60		2400		3000	
	≥60 to <100		2700		3300	
	≥100		3000		3600	
	Maintenance dose: Weight-based IV infusion every 8 weeks starting 2 weeks after the loading dose					
	Labeled dosing ● 900 mg IV infusion every 14 ± 2 days				70	
	Dosing escalation ● IV 900 mg IV every 11 days				1.3	
	Dosing escalation ● IV 1200 mg every 11 days				26.3	
	Dose escalation ● IV 1500 mg every 11 days				2.5	
Eculizumab	Labeled dose	600 mg IV infusion every week	6300	1	6300	NA
	Labeled dosing	IV 900 mg every 2 weeks	9450	0.50	4725	70%
	Dose escalation	IV 900 mg every 11 days	9450	0.64	6014	1.3%
	Dose escalation	IV 1200 mg every 2 weeks	12,600	0.50	6300	26.3%
	Dose escalation	IV 1500 mg every 2 weeks	15,750	0.50	7875	2.5%
	Weighted average cost per week (£):				5233	
	Weighted average cost per cycle (£):				20,933	

IV: Intravenous; PNH: Paroxysmal nocturnal hemoglobinuria; SC: Subcutaneous.

IV: Intravenous; PNH: Paroxysmal nocturnal hemoglobinuria; SC: Subcutaneous.

PNH treatment

For ravulizumab treatment costs, we assumed patients were administered a maintenance weight-based dosing, as per the label [67]. We excluded administration costs in the base-case since the analytic population comprised those who would have been receiving C5i before switching to ravulizumab.

For pegcetacoplan treatment administration costs (Table 3), in the base case we assumed that patients had their first dose administered in a clinic where they also received training in subcutaneous self-administration (£49 assuming 20 min of specialist nurse time based on NHS salary band 6) [68] and self-administered subsequent doses at home. We assumed that nurses also provided support for administering the second and third doses (30 min per home visit; £29.67) [68]. We excluded one-off pump costs for pegcetacoplan at-home infusion in the base-case.

We applied the list price for pegcetacoplan (£3100 per 1080 mg; Table 3) and for ravulizumab based drug price (£4533 per 300 mg) on that assumed in the most recent UK HTAs [16,56]. We did not need to account for wastage costs in the model, as the required dosages for neither pegcetacoplan nor ravulizumab result in any wastage.

Blood transfusion

Patients incurred blood transfusion costs in the transfusion-dependent health state (Table 1) as based on unit cost per transfusion (£532.46) [69] and per cycle transfusion frequency.

Monitoring

Monitoring costs, applied at each cycle based on the health state of the patient, stemmed from hematologist visits (£110.61) [16] and blood tests (£32.18) [70]. We estimated these costs based on the number of visits/tests per cycle multiplied by the respective unit costs for each resource per health state, as based on clinical opinion (Table 1 & Supplementary Table 5).

Iron overload

To capture the costs of iron overload in patients administered ravulizumab, we considered the baseline (ie, pre-run in) proportion of patients in the PEGASUS trial receiving chelation therapy [41]. The baseline iron overload medication use (3.8% on deferoxamine mesilate and 23.8% on deferasirox) was multiplied by the cost of the treatments per cycle (Table 1 & Supplementary Table 6) [41].

For pegcetacoplan patients in PEGASUS, given sufficient increases in Hb levels due to the earlier inhibition of the complement cascade provided by treatment [41] blood removal (i.e., venesection), rather than iron chelation, provided a viable option to address iron accumulation at baseline or following any transfusions and for maintenance treatment (average of three venesections per year) [57]. For the cost estimate, we multiplied the unit cost of venesection (i.e., the cost of half an hour at a hematology day unit) [69] by the number of venesections occurring in a 4-week cycle, adjusted by the percentage of patients who received iron chelation therapy at baseline in PEGASUS.

Breakthrough hemolysis

For pegcetacoplan patients, we modeled breakthrough hemolysis costs based on the 1 out of 41 patients (2.4%) in the PEGASUS pegcetacoplan arm who experienced breakthrough [41] and estimated a per-cycle rate of 2.5% based on four episodes in the 16-week treatment period. The event was costed at £9450, the list price of eculizumab, in addition to costs of the associated transfusion-dependent health state [71]. The remaining three patients with breakthrough discontinued pegcetacoplan at week 16 and incurred medical costs of breakthrough treatment, was estimated at £392.86 (Table 1 & Supplementary Table 7).

Adverse events

The model did not include the cost of adverse events in the base-case, but only in the scenario analyses. Per the summaries of product characteristics, the adverse event rates are comparable for ravulizumab [34] and pegcetacoplan. Therefore, we estimated costs based on the probability of developing an event per cycle (Supplementary Table 3) and the corresponding unit cost per adverse event (Supplementary Table 8) per treatment arm. We calculated a sum product of the probabilities of events and their respective unit costs to obtain total adverse event costs per treatment respectively: £48.49 for pegcetacoplan; £46.49 for eculizumab (in those pegcetacoplan patients who revert back to eculizumab) and £6.87 for ravulizumab.

Analysis

We discounted costs and utilities at 3.5% per annum as mandated for the base-case by NICE in England [72] and adjusted costs to 2021 British pounds sterling. Clinically plausible scenarios within the deterministic analyses were characterized by assumptions of non-inferiority between treatments, in terms of breakthrough hemolysis incidence and blood transfusion requirements, various time horizons, discount rates, utilities and clinical effectiveness rates (Supplementary Table 2).

One-way sensitivity analysis (OWSA) demonstrated the level of uncertainty in the model results by varying one parameter at a time and assessing the subsequent impact on the incremental QALYs and incremental costs. We defined the low and high values for each parameter by lower and upper bounds of their 95% CI. In the absence of CI data, we altered the variable by $\pm 20\%$; a tornado diagram highlighted the parameters which had the greatest effect on the net monetary benefit (NMB; incremental benefit $\times$ threshold – incremental cost), with a positive incremental NMB indicating that the intervention is cost-effective compared with the alternative at the given willingness-to-pay (WTP) threshold. The NMB approach is an alternative to the incremental cost-effectiveness ratio (ICER) that avoids negative ICERs within the OWSA (in such a case that pegcetacoplan costs are lower and QALYs greater than ravulizumab). For this we applied a threshold of £10,000 per QALY, as specified by NICE to allow highly specialized technologies to be made more quickly and widely available within the NHS [73] and capped the upper and lower bounds for clinical plausibility [51,52].

Table 4. Base-case deterministic cost-effectiveness and probabilistic sensitivity analysis: pegcetacoplan vs ravulizumab.

Treatment	Total:			Incremental: pegcetacoplan vs comparators			ICER: pegcetacoplan vs ravulizumab
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	£/QALY gained
Deterministic analysis							
Ravulizumab	6,660,676	19.706	12.942	-251,510	0	1.75	Pegcetacoplan dominant
Pegcetacoplan	6,409,166	19.706	14.694	–	0	–	
Probabilistic sensitivity analysis							
Ravulizumab	6,665,853	19.706	12.999	-262,127	0	1.76	Pegcetacoplan dominant
Pegcetacoplan	6,403,726	19.706	14.759	–	0	–	

The bold stresses the results for pegcetacoplan.

ICER: Incremental cost-effectiveness ratio; LYG: Life-years gained; QALY: Quality-adjusted life year.

Finally, we used probabilistic sensitivity analyses (PSA) to explore the impact of model parameter uncertainty on the results, performing 1000 simulations with values randomly and simultaneously drawn for each variable from its probability distribution. For event rates and utilities, beta distribution parameters allowed restricting draws to between 0 and 1. The fitted gamma distribution parameters prevented values less than zero for costs, resource use estimates, and hazard ratios. Treatment costs remained fixed. Each iteration gave a distribution of incremental results, and the distributions provided an assessment of the robustness of the cost-effectiveness results. We graphically illustrated uncertainty with an incremental cost-effectiveness plane scatter plot. We conducted all analyses using Excel version 2013 (Microsoft, WA, USA).

Results

Systematic literature review

The searches within the SLR identified no relevant CEA model structures applicable to the given study objectives nor any head-to-head randomized control trial data for comparing pegcetacoplan and ravulizumab in patients previously treated with eculizumab. The SLR also did not identify published data reporting EQ-5D responses in PNH patients. Therefore, a *de novo* Markov model was developed with health states defined on Hb levels and transfusion status. For comparative effectiveness we aimed to apply data from the previously described MAIC [53,54].

Utility mapping

Estimated utilities at the patient level, using the Longworth algorithm, ranged between -0.14 and 0.97 and mean utilities ranged between 0.72 and 0.86 across the visits (Supplementary Table 1). The McKenzie algorithm, based on a single ordinary least-squares regression, provided individual utilities ranging between -0.21 and 1.06 and mean utilities ranging from 0.55 to 0.89 across the visits. However, at most visits, the McKenzie algorithm resulted in non-interpretable utility values above 1 for some patients. Based on this anomaly, we concluded that the Longworth algorithm was more appropriate for mapping EQ-5D-3L utilities.

Cost-effectiveness analysis

In the base-case CEA, (Table 4), patients receiving ravulizumab accrued 12.942 QALYs at a total cost of £6,660,676. Patients treated with pegcetacoplan accrued 14.694 QALYs at a total cost of £6,409,166. Therefore, pegcetacoplan was economically dominant (i.e., lower total costs, greater number of QALYs) versus ravulizumab in the base case and confirmed through PSA (Table 4).

In the scenario analysis, a variety of scenarios investigating variations in time horizons, discount rates, utilities, and clinical efficacy of pegcetacoplan were consistent with the base case (Supplementary Table 8).

The OWSA for pegcetacoplan versus ravulizumab (Figure 2) showed that the model was most sensitive to: the mean weight of patients, utility values for no transfusion and Hb ≥ 10.5 g/dl, the cost of blood transfusion and the mean units of blood transfusion. The NMB remained positive across all varied parameters, indicating that pegcetacoplan remained cost-effective compared with ravulizumab at a WTP threshold of £10,000 per QALY (Figure 3; Supplementary Table 10).

The incremental cost-effectiveness plane scatterplot (Figure 3) showed that 100% of results were in the southeast quadrant for pegcetacoplan versus ravulizumab, meaning that pegcetacoplan continued to dominate ravulizumab in each simulation (Figure 3) and was 100% cost-effective at all WTP thresholds.

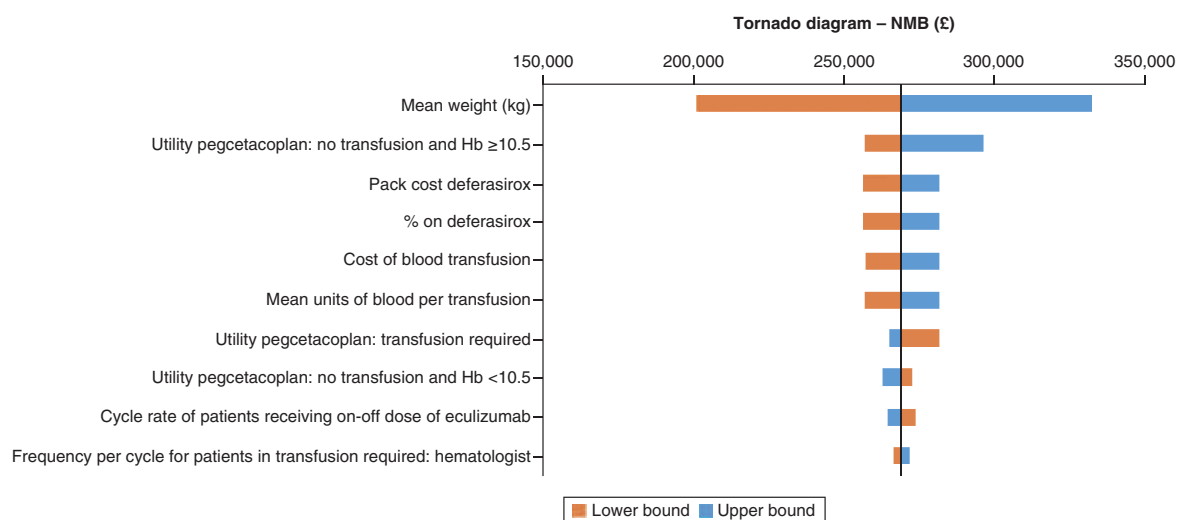


Figure 2. One-way sensitivity analysis tornado diagram for pegcetacoplan versus ravulizumab.
Hb: (Serum) Hemoglobin; NMB: Net monetary benefit.

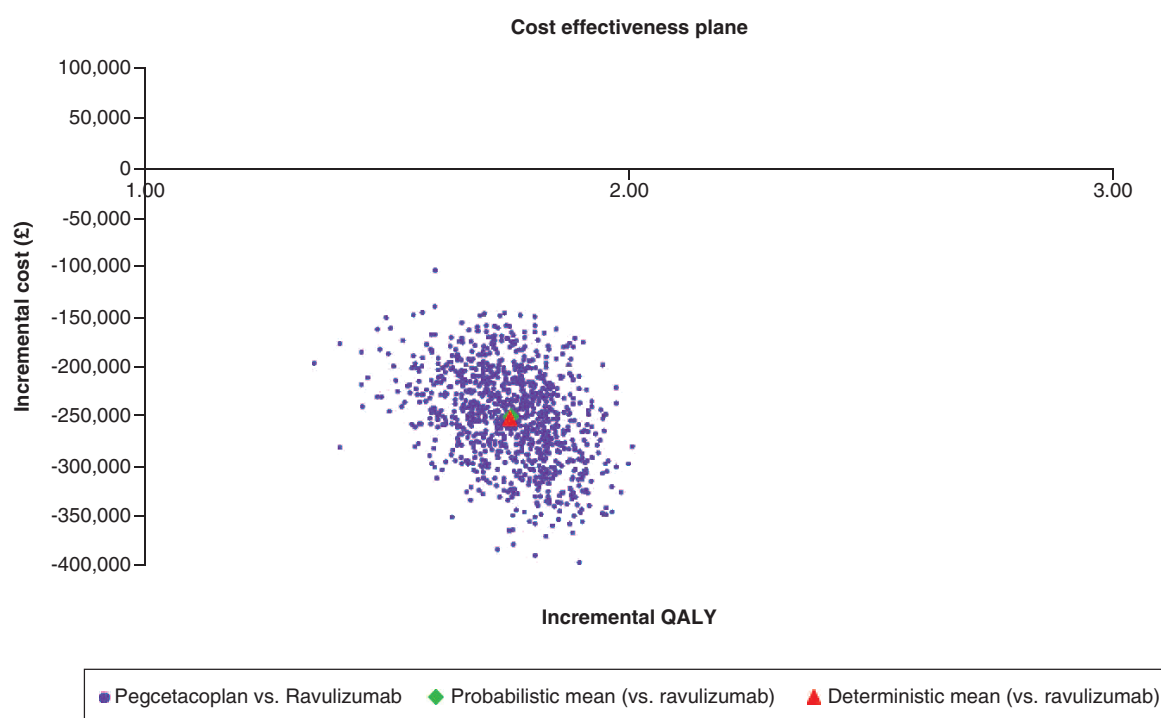


Figure 3. Incremental cost-effectiveness plane.
QALY: Quality-adjusted life year.

Discussion

Among patients with PNH and insufficiently controlled anemia despite eculizumab treatment, this CUA showed not only that pegcetacoplan compared with ravulizumab resulted in lower healthcare costs, but also enhanced patient HRQoL. The PSA confirmed 100% of probabilistic iterations remained within all WTP thresholds, including the £10,000 per QALY threshold set by NICE for highly specialized technologies dedicated to drugs for very rare, usually serious conditions. The findings were consistent and robust even after we varied key parameters; pegcetacoplan remained the economically dominant treatment option across scenarios.

Despite the vital therapeutic benefits offered by C5i in preventing IVH and improving patient symptoms and HRQoL outcomes [32,40], some clinical limitations have endured, including the reduced blood transfusion-sparing benefits of C5i, in particular due to C3-mediated EVH [32,33,74]. PEGASUS showed that in patients who had adequately controlled IVH at enrollment (i.e., LDH: mean 282.4 [$\pm$ 210.9] U/L), EVH had become the primary mechanism of hemolysis on C5i treatment, which continued to cause severe anemia. While all enrolled patients in PEGASUS had baseline Hb <10.5 g/dl, they also had a high rate of transfusion dependency (i.e., a mean of 6.5 transfusions in the preceding 12 months, with 55% of patients requiring over four transfusions in the preceding 12 months) [41].

Although transfusions may temporarily improve and elevate Hb levels in PNH patients, as the transfused cells express CD59 and CD55 on their cell surface and are resistant to complement-mediated lysis [26], patients may still experience long periods of suboptimal Hb level and resulting fatigue, besides the physiologic impact of iron overload [27]. These negative outcomes of transfusions further exacerbate patient burden because of work absenteeism resulting from transfusion-related hospital visits. As shown by a recent US real-world study, transfusion-dependent patients had significantly higher PNH-related and all-cause higher medical-related, hospital-related and outpatient-related work absenteeism compared with transfusion-free patients [9]. From the healthcare payer's perspective, the economic burden of transfusions is also substantial. A recent US study estimated that healthcare costs associated with hospitalizations and blood transfusions for a breakthrough hemolysis episode amounted to US\$51,716 per patient for events due to complement-amplifying conditions, US\$152,895 for events due to insufficient C5 inhibition, and US\$186,107 for events due to pregnancy [15].

Where prescribing of above-label doses of C5i to address breakthrough hemolysis was common (up to 60%) in PEGASUS enrolled patients at study initiation [41], we also observed alternative findings in the literature. The US real-world study that stratified patients by transfusion-dependency found that transfusion-dependent C5i users were not only more likely to be dosed lower than as recommended on the label but had a shorter median time to treatment discontinuation [9]. The investigators suggested that discontinuation of treatment among transfusion-dependent C5i users may have been attributed to complications resulting in adverse events, the development of comorbid diseases (i.e., aplastic anemia, myelodysplastic syndrome), or the high cost of the therapy, which may have initially contributed to the lower number of infusions (five vs eight infusions) [9].

PEGASUS has provided evidence that, because pegcetacoplan targets the complement cascade earlier than C5i, it achieves improvements across hematological parameters, including Hb, bilirubin, reticulocytes and HRQoL, with almost no/minimal treatment-associated safety issues [41]. Long-term results through week 48 in PEGASUS have further shown clinically meaningful improvements in fatigue among patients continuously administered pegcetacoplan, and in those who switched from eculizumab at week 16. The effect was consistent across all FACIT-F score items, demonstrating that pegcetacoplan significantly reduces fatigue levels and maintains this effect over time by increasing Hb levels and limiting the need for transfusions.

Finally, a feature that is of practical value to patients, providers and payers, the twice-weekly 1080 mg SC dose of pegcetacoplan is self-administered with a syringe system infusion pump that delivers volumes up to 20 ml [42]. While a 30–60 minute time commitment (depending on one versus two infusion sites accessed) is still necessary compared with IV cannulation and infusion [64], the flexibility of SC self-administration of pegcetacoplan may allow patients to feel more in control of their disease management [64]. Economically, this reduces the burden on healthcare systems beyond the initial training provided by nurses, compared with the IV infusion of C5i treatment [75]. However, with SC formulations typically needing a higher dosing frequency than IV formulations to enable administration of the relatively higher volume doses required [76], the mechanistic aspects of treatment have been shown across numerous studies to be generally over-ridden by preferences for the features of SC infusions versus IV infusions by patients and healthcare providers [77].

Limitations & strengths

An inherent limitation of this CUA was, because of the rarity of PNH, the small sample size of the PEGASUS clinical trial that informed the clinical and cost parameters. Therefore, some of the more extreme values may have introduced bias into the analysis. Another consideration is that there were no EQ-5D utilities data collected in PEGASUS; therefore, we mapped utilities using data collected on the EORTC-QLQ-30, although the approach was consistent with published NICE guidelines [61] and the HTA of ravulizumab compared with eculizumab [16]. While designed to measure the HRQoL of cancer patients, the EORTC-QLQ-C30 has demonstrated adequate reliability and validity PNH, with some additional items specific to PNH warranted for consideration in future

validation studies [78]. Where generic utility instruments may fall short of capturing the specific and important aspects of the condition in question, or when trial-based EQ-5D data are unavailable, validated mapping algorithms can transform disease-specific HRQoL data into patient-level utility values [62]. However, this may have introduced some level of uncertainty into the model as opposed to applying directly elicited EQ-5D-5L values.

For comparative effectiveness inputs, where there was a lack of direct comparison of efficacy for pegcetacoplan versus ravulizumab, given that ravulizumab became available within the NHS only as of May 2021, we filled the evidence gap by assuming identical efficacy between ravulizumab and eculizumab per head-to-head non-inferiority trial data [53,55], which may have only conservatively biased the results. For example, during clinical input [57], the key limitation noted for the ravulizumab versus eculizumab trial design was preclusion of up-dosing [58]. Hence, our assumption of equal efficacy in the model may have underestimated the total costs associated with ravulizumab, as those patients treated with eculizumab who experienced IVH breakthrough in the trial may have required up dosing in actual clinical practice.

Finally, RCT data on which the clinical efficacy inputs were based are considered gold-standard evidence, yet may not fully reflect real-world practice. However, while the UK sites in PEGASUS allowed some level of local clinical practice to be reflected in the analysis, other inputs to the economic analysis were validated with expert input [57]. These inputs included assumptions of Hb thresholds and management of such outcomes as breakthrough hemolysis and iron overload that were representative to UK practice.

According to clinical opinion, a key benefit for pegcetacoplan-treated patients is that they do not require costly life-long chelation therapy (such as deferasirox and deferoxamine mesilate) to treat iron overload as required by those patients on C5i who require regular blood transfusions and accumulate iron in the liver and spleen. Where pegcetacoplan can increase and normalize Hb levels by preventing IVH without an increase in EVH [41], patients do not require continued blood transfusions and as such, do not experience further iron overload [41]. However, prior to the initiation of pegcetacoplan in transfusion dependent patients, built-up iron from prior receipt of regular transfusions would have necessitated venesection to address iron overload in pegcetacoplan patients, as transpired in PEGASUS [57].

In terms of the Hb <10.5 g/dl threshold for anemia within the model health states, although clinical experts confirmed that there is no consensus on an exact Hb level which corresponds to anemia, we applied a threshold that was not only consistent with the inclusion criteria of PEGASUS, but deemed the most appropriate threshold to reflect differences in HRQoL and cost affects in the PNH population. Using a higher threshold (eg, 12 g/dl) as per other anemia thresholds, such as that defined by the WHO [79] for anemia (<13 g/dl in men and <12 g/dl in women) would have led to a wider interval for the anemia health state and which may not have accurately measured the impact of anemia on patient HRQoL. However, while these thresholds are appropriate for the general population, they cannot be generalized to PNH patients who have adjusted to functioning with lower Hb. Therefore, a Hb threshold of 12 g/dl or higher would have misrepresented the reality of uncontrolled anemia in patients with PNH. PNH clinical experts have also confirmed that there is no consensus on an exact Hb level which corresponds to anemia, and that this will vary on a patient-by-patient basis [57].

In the absence of such an accepted threshold, a level of <10.5 g/dl was selected for the PEGASUS trial based on evidence throughout the PNH literature. For example, Risitano *et al.* proposed a system to classify hematological response in PNH patients on eculizumab [7]. In this trial setting, a complete or major response to eculizumab was associated with Hb levels ≥ 12 g/dl, a good response with levels ≥ 10 to <12 g/dl, a partial response with levels ≥ 8 and <10 g/dl and a minor response with levels <8 g/dl [7]. Earlier, Schrezenmeier *et al.* also reported that the 1425 patients enrolled in the international PNH registry had a median Hb of 10.6 g/dl, while, McKinley *et al.* similarly found, from a review of 141 patients referred to the UK National PNH Service, a median Hb level for these patients of 10.9 g/dl. Finally, the pivotal TRIUMPH study, which investigated eculizumab versus placebo, excluded patients with a mean Hb level prior to transfusion over the previous 12 months of above 10.5 g/dl [80].

Conclusion

The base-case results of this CUA, all scenario analyses and sensitivity analyses revealed QALY gains and lifetime cost savings for pegcetacoplan versus ravulizumab in patients with PNH and low Hb levels despite eculizumab therapy. Therefore, by providing enhanced control of anemia, greater improvements in HRQoL and reduced healthcare costs, pegcetacoplan may provide considerable clinical and economic value within the UK PNH treatment pathway.

Future perspective

While curative options for PNH are yet to be developed, treatment with the proximal complement inhibitor pegcetacoplan, as shown in PEGASUS, provides patients with increased disease control through improved Hb levels and overall reduced disease burden gained through independence from transfusions. Real-world evidence will reveal the ongoing humanistic and economic benefits of pegcetacoplan in long-term use and actual practice settings.

Summary points

- Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, potentially fatal blood disorder caused by somatic mutations to hematopoietic stem cells.
- Characterized by hemolytic anemia, bone marrow failure and thrombosis and their clinical manifestations, PNH causes significant disease burden to patients due to chronic hemolysis and its consequences, including thrombotic events and the need for blood transfusions.
- Curative treatment for PNH is limited to bone marrow transplantation. This is an option in countries where anti-complement therapy is not available, although the procedure is associated with considerable morbidity and mortality risk.
- Therefore, therapeutic management of hemolytic disease and/or thromboembolic complications remains the key modality in current international and UK clinical practice, with standard of care based on treatment with complement component 5 inhibitor (C5i) humanized monoclonal antibodies.
- Ravulizumab is the newest C5i recommended by National Institute for Health and Care Excellence for the treatment of PNH.
- Pegcetacoplan is a novel self-administered proximal C3 inhibitor that targets the complement cascade earlier than C5i, controlling intravascular hemolysis without the emergence of C3-mediated extravascular hemolysis.
- PEGASUS, the pivotal trial of pegcetacoplan, showed that among patients with PNH and insufficiently controlled anemia despite eculizumab treatment, intravascular hemolysis was adequately controlled at enrollment (ie, lactate dehydrogenase [LDH]: mean 282.4 [$\pm$ 210.9] U/l); however, extravascular hemolysis had become the primary mechanism of hemolysis, which continued to cause severe anemia.
- At baseline, patients in PEGASUS had a mean of 6.5 transfusions in the preceding 12 months, with 55% of patients requiring ≥ 4 transfusions.
- Versus ravulizumab, pegcetacoplan provides significant overall improvement across PNH outcomes through increased serum hemoglobin levels, reduced levels of indirect bilirubin, and reticulocytes, and substantial and clinically meaningful improvements in patient fatigue, dyspnoea and health-related quality of life.
- To inform payer decision-making, we conducted a lifetime cost-utility study based on a Markov model in the UK setting of pegcetacoplan compared with ravulizumab for the treatment with PNH and insufficiently controlled anemia (ie., Hb <10.5 d/l) despite ≥ 3 months treatment with eculizumab.
- Results showed that in the base-case, patients receiving ravulizumab accrued 12.942 QALYs at a total cost of £6,660,676. Patients treated with pegcetacoplan accrued 14.694 Quality-adjusted life years at a total cost of £6,409,166.
- Therefore, by providing enhanced control of anemia, greater improvements in health-related quality of life and reduced healthcare costs as compared with ravulizumab in patients with PNH, pegcetacoplan may provide considerable clinical and economic value within the UK PNH treatment pathway.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/cer-2022-0076

Author contributions

All authors were involved in developing the content of the publication. E McAughey, M Pochopien, P Wojciechowski, and C Knight developed the analytic model and conducted EA conducted analysis for the pegcetacoplan in the UK setting.

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