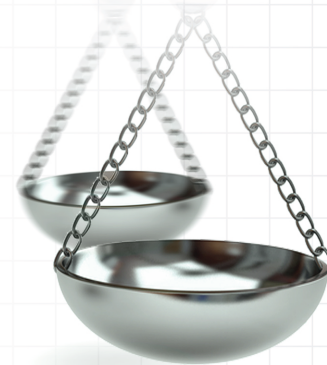




The cost-effectiveness of pegcetacoplan in complement treatment-naïve adults with paroxysmal nocturnal hemoglobinuria in the USA

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Aim: Paroxysmal nocturnal hemoglobinuria (PNH) is a rare blood disorder characterized by hemolytic anemia, bone marrow failure and thrombosis, and is associated with high healthcare burden. We evaluated the cost-effectiveness of pegcetacoplan, a proximal complement-3 inhibitor (C3i), compared with the C5i, eculizumab and ravulizumab, in complement treatment-naïve adults with PNH, from the US healthcare payer perspective. **Materials & methods:** A *de novo* cost-effectiveness model based on a Markov cohort structure evaluated lifetime (55-year) PNH costs and outcomes. The 6-month cycles of the model reflected the follow-up period of PRINCE (NCT04085601), an open-label trial of pegcetacoplan compared with eculizumab in C5i-naïve patients. Data from PRINCE informed the clinical, safety and health-related quality of life outcomes in the model. **Results:** Pegcetacoplan was associated with lifetime cost savings of \$1,176,808 and \$213,062 relative to eculizumab and ravulizumab, respectively (largely attributed to reduced drug costs and blood transfusions), and additional quality-adjusted life years (QALYs) of 0.25 and 0.24. **Conclusion:** In patients with PNH who are treatment-naïve, the base-case cost-effectiveness analysis, scenario analysis and sensitivity analysis showed both lifetime cost savings and increased QALYs associated with pegcetacoplan compared with eculizumab or ravulizumab in the USA.

Plain language summary

What is this article about? Paroxysmal nocturnal hemoglobinuria (PNH) is a rare disease that can lead to a high level of illness in individuals who are affected with the genetic disorder. In the USA, patients who have PNH and severe symptoms or complications can currently receive one of three licensed treatments: pegcetacoplan, ravulizumab or eculizumab.

However, in order to improve healthcare for these patients, some important information is needed to understand how well these treatments work and the total costs to the person or health insurer paying for the treatment. Therefore, this study measured the cost-effectiveness of the currently-available treatments for PNH.

How was the study carried out? Using information from clinical trials and other published sources, this study looked at whether patients could benefit from improvements in life-expectancy and health-related quality of life of pegcetacoplan compared with the other treatments. These benefits were weighed against the costs of each of the drugs and other various healthcare costs.

What do the results mean? The findings of this study suggest that pegcetacoplan is a treatment for PNH that is associated with more patient benefits and lower healthcare costs compared with ravulizumab and eculizumab.

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Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, potentially fatal blood disorder characterized by hemolytic anemia, bone marrow failure and a high risk of thrombosis [1,2]. Although the disease may manifest at any age, median age at diagnosis is around 30 years, and with a slight female preponderance [3]. Estimated global PNH prevalence is around 1–1.5 cases per million [4,5], but epidemiology varies regionally [6]. In the USA, epidemiological measurements of PNH are limited, however, a 2016/2017 prevalence rate of 12–13 PNH cases per million in insured populations has been reported, with 257 incident cases measured during that period [7]. Other data published in 2018 based on stochastic predictive models fitted to 2010 US age distribution data pointed to a prevalence of 1.76 cases of PNH per 100,000 individuals [8,9].

A hematopoietic stem cell disease, PNH is caused by a somatic X-linked genetic mutation [10] which causes a proportion of red blood cells (RBCs) to lack surface glycosylphosphatidylinositol (GPI)-linked complement regulatory proteins CD55 and CD59 [11]. Without these proteins on their surface, the RBCs cannot control complement activation, leading to the formation of the membrane attack complex and subsequent hemolysis [12]. The destruction of RBCs occur via two mechanisms, intravascular hemolysis (IVH) and extravascular hemolysis (EVH; occurring in liver and spleen), and presents clinically as chronic hemolytic anemia [8,13–15].

Despite the rarity of PNH, overall resultant disease burden is considerable. Outcomes related to the disease activity [16], coupled with the systemic complications of PNH, including smooth muscle dystonia [13,17–19], impaired renal function, complement-dependent thrombophilia [20] and bone marrow failure [18,19], weigh heavily on healthcare payer budgets [7,21]. Moreover, PNH symptoms such as fatigue, weakness, dyspnea, smooth muscle dystonia, dysphagia and erectile dysfunction greatly impair the health-related quality of life (HRQoL), work productivity, and day-to-day functioning of affected individuals [22–25].

Although symptoms of PNH are managed conventionally with frequent administration of packed RBC transfusions [26], allogeneic bone marrow transplantation remains the only curative option, but only for select patients with life-threatening PNH complications [19,27–29]. Therefore, hemolytic disease therapeutically managed with monoclonal antibodies targeting the complement cascade remains the current standard of care for PNH in USA [16,30]. Complement component 5 inhibitors (C5i) are specifically designed to target the complement protein C5, prevent its cleavage and thereby the formation of the terminal membrane attack complex [27,31].

Eculizumab was the first C5i therapy approved in USA for adults and children with PNH [32]. Ravulizumab, an eculizumab-like monoclonal antibody with a half-life four-times longer than the C5i predecessor [33], followed with a license in USA for treatment in adults with PNH [34]. Even as these treatments initially revolutionized the therapeutic prospects for PNH, the persistent anemia attributed to underlying bone marrow dysfunction, emergence of C3-mediated EVH [35], and breakthrough hemolysis (BTH) associated with free C5 concentrations of ≥ 0.5 mg/ml [36,37], along with increases in lactate dehydrogenase (LDH) levels [38], have limited their clinical benefits [26,39,40]. This failure to normalize patient hemoglobin (Hb) levels has meant the persistence of, or return to, PNH morbidity and associated healthcare costs, in addition to potentially life-threatening complications [36–38,41].

Pegcetacoplan (Empaveli®) is a treatment that targets C3 in the complement cascade (i.e., upstream of C5) [17] in PNH. Pegcetacoplan is approved in the USA [42], and across numerous healthcare systems [43–45] in this indication, as based on the results from the pivotal phase 3, PEGASUS (NCT03500549) [46] open-label, head-to-head trial demonstrating superiority for pegcetacoplan over eculizumab in achieving improvements in patient Hb levels.

Further evidence for pegcetacoplan has more recently been shown in PRINCE (NCT04085601), an open-label trial in C5i-naïve patients randomly assigned 2:1 to treatment with pegcetacoplan (added to best supportive care [BSC]) or BSC (excluding complement-inhibitors) [47]. PRINCE demonstrated meaningful hematologic and clinical improvements associated with pegcetacoplan following 26 weeks of treatment versus BSC, with a favorable safety profile [47].

In addition to the demonstrated clinical benefits for pegcetacoplan in the PNH treatment-naïve population, the value of pegcetacoplan to US patients and payers is also necessary for informing appropriate healthcare funding decisions on the early part of the PNH treatment pathway [48,49]. This study evaluated the cost-effectiveness, from the US healthcare payer perspective, of pegcetacoplan compared with eculizumab or ravulizumab in complement treatment-naïve adults with PNH.

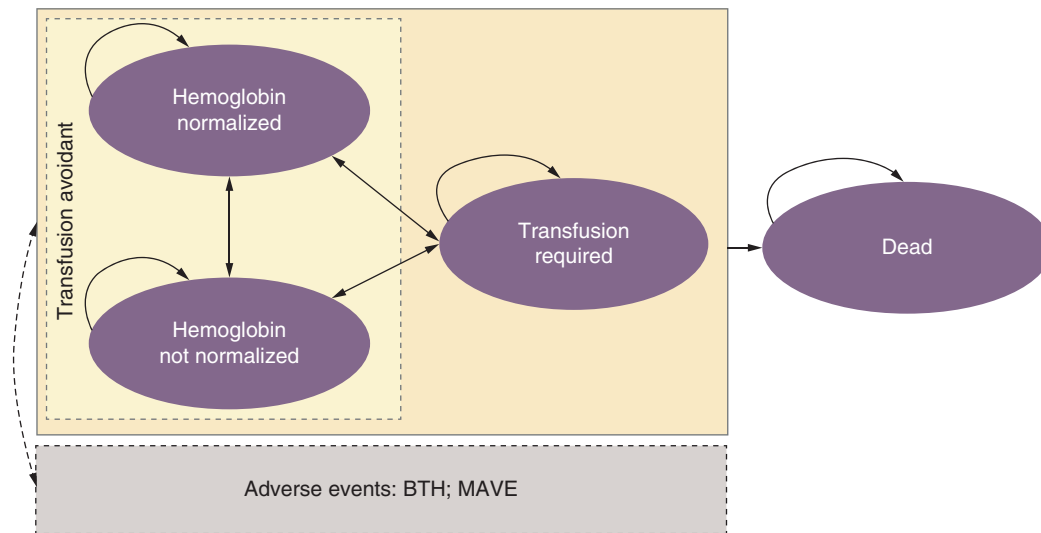


Figure 1. Markov model diagram.
BTH: Breakthrough hemolysis; MAVE: Major adverse vascular event.

Materials & methods

A comprehensive systematic literature review identified existing PNH cost-effectiveness models (CEM), with searches conducted on 11 December 2020, in Ovid MEDLINE® In-Process & Other Non-Indexed Citations and Ovid MEDLINE® databases and Embase (accessed via the OVID interface) database, National Health Service Economic Evaluation Database (NHS EED), websites of Health Technology Assessments [50–55] and Database of Abstracts of Reviews of Effects (DARE) databases [56]. Because none of the identified models [21,57–59] fully characterized the treatment pathway and outcomes of patients with PNH naïve to complement inhibitors, we deemed it necessary to develop a *de novo* CEM that was informed by the prior models. We validated all clinical assumptions of the model with clinical experts.

Model structure

The resulting CEM evaluated the lifetime (55-year) costs and quality-adjusted life-years (QALYs) of pegcetacoplan and its comparators (Table 1) and was based on a Markov cohort structure of 6-month (26-week) cycle length reflecting the follow-up period of the PRINCE trial [47]. The lifetime horizon of the model considered the chronicity of PNH and the current lack of a cure for the disease. This structure aligned with previously published PNH CEMs, striking good balance between the reduced complexity and maximal accuracy afforded by Markov cohort models [60], especially pertinent for such rare diseases as PNH whereby patient numbers would be insufficient to fulfil the requirements for microsimulation models [61].

Microsoft Excel and Microsoft Visual Basic for Applications enabled model construction and analyses; and the study followed The Professional Society for Health Economics and Outcomes Research (ISPOR) good research practices for measuring drug costs in cost-effectiveness analysis [71,72]. Reporting of the study followed The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement [73].

Clinical inputs

Patient characteristics

Patient baseline characteristics for pegcetacoplan assumed in the CEM were based on previously published patient-level data from the PRINCE trial [47]. Because the mean age of patients and male/female distribution of patients in the trial [47] reflected the overall epidemiology of the disease [3], we assumed that the clinical data could be transferable to US patients [5].

Health states

The CEM included two overall PNH health states (Figure 1), transfusion avoidant (representing the key aim of PNH treatment) [46,74,75] and transfusion required (for those patients who do not respond to treatment). The

Table 1. Model inputs: base-case, deterministic sensitivity analysis and probabilistic sensitivity analysis.

Parameter	Base-case value (mean / percentage)	Deterministic sensitivity analysis		Probabilistic sensitivity analysis	Source	Ref.		
		Low value	High value	Distribution and values				
Discount rates, %								
Discount rate for costs (per year)	3.0	0.0	6.0	Not included	ICER guidelines	[62]		
Discount rate for health outcomes (per year)	3.0	0.0	6.0		ICER guidelines	[62]		
Baseline patient characteristics								
Mean age (years)	44.5	35.6	53.4	Normal (μ = 44.5, σ = 4.54)	PRINCE trial baseline characteristics	[47,63]		
Proportion of females, %	45.28	32.23	58.67	Beta (α = 24, β = 29)	PRINCE trial baseline characteristics	[63]		
Mean weight (kg)	83.86	67.09	100.63	Normal (μ = 83.86, σ = 8.56)	CDC Vital and Health Statistics	[64]		
Health state utilities								
Hb normalized	0.869	0.782	0.956	Beta (μ = 0.869, σ = 0.039)	Calculations based on PRINCE trial patients’ level data			
Hb not normalized	0.820	0.738	0.902	Beta (μ = 0.820, σ = 0.037)				
Transfusion required	0.818	0.736	0.900	Beta (μ = 0.818, σ = 0.038)				
General population utilities								
Age 18–29 years	0.922	Not included		Not included	Sullivan, 2006	[65]		
Age 30–39 years	0.901							
Age 40–49 years	0.871							
Age 50–59 years	0.842							
Age 60–69 years	0.823							
Age 70–79 years	0.790							
Age 80+ years	0.736							
Treatment costs								
Price per package, \$								
Pegcetacoplan	4403.84	Not included		Not included	REDBOOK	[66]		
Eculizumab	6523.00							
Ravulizumab	6404.00							
Dosage distributions, %								
Pegcetacoplan – 1080 mg twice weekly	100	Not included		Dirichlet (x_1 = 100.00%, α_1 = 35, x_2 = 0%, α_2 = 0)	Prescribing information	[32,42]		
Pegcetacoplan – 1080 mg every 3 days	0							
Eculizumab – 900 mg every 2 weeks	100			Dirichlet (x_1 = 100.00%, α_1 = 121, x_2 = 0.00%, α_2 = 0, x_3 = 0.00%, α_3 = 0, x_4 = 0.00%, α_4 = 0)				
Eculizumab – 900 mg every 11 days	0							
Eculizumab – 1200 mg every 2 weeks	0							
Eculizumab – 1500 mg every 2 weeks	0							
Ravulizumab – 40–60 kg	30.23			21.61	45.34	Dirichlet (x_1 = 30.23%, α_1 = 3165, x_2 = 33.47%, α_2 = 3504, x_3 = 36.31%, α_3 = 3802)	Distribution based on mean weight	[24]
Ravulizumab – 60–100 kg	33.47			23.93	26.22			
Ravulizumab – 100+ kg	36.31			28.44	54.46			
Total cost per cycle, \$								
Supportive treatment	4137.55	3310.04	4965.06	Gamma (μ = 4137.55, σ = 445.86)	REDBOOK PRINCE trial	[47,63,66]		
AE: Adverse event; IV: Intravenous; QALY: Quality-adjusted life-year.								

AE: Adverse event; IV: Intravenous; QALY: Quality-adjusted life-year.

Table 1. Model inputs: base-case, deterministic sensitivity analysis and probabilistic sensitivity analysis (cont.).

Parameter	Base-case value (mean/ percentage)	Deterministic sensitivity analysis		Probabilistic sensitivity analysis	Source	Ref.
		Low value	High value	Distribution and values		
Administration costs						
Pegcetacoplan	134.96	107.97	161.96	Gamma (μ = 134.96, σ = 14.54)	CMS Fee Schedule	[67]
IV administration cost (first hour)	140.16	112.13	168.19	Gamma (μ = 140.16, σ = 15.10)		
IV administration cost (subsequent hours)	29.76	23.81	35.71	Gamma (μ = 29.76, σ = 3.21)		
Administration times, minutes						
Eculizumab – maintenance dose	35	Not included		Not included	Prescribing information	[32]
Eculizumab – additional observation time after administration	60					
Ravulizumab – loading dose, 40–60 kg	114				Prescribing information	[34]
Ravulizumab – loading dose, 60–100 kg	102					
Ravulizumab – loading dose, 100+ kg	108					
Ravulizumab – maintenance dose, 40–60 kg	140					
Ravulizumab – maintenance dose, 60–100 kg	120					
Ravulizumab – maintenance dose, 100+ kg	132					
Ravulizumab – additional observation time after administration	60					
Vaccine costs, \$						
Meningitis (A, C, Y, W–135)	70.97	56.78	85.17	Gamma (μ = 70.97, σ = 7.65)	CDC Vaccine Price List	[68]
Meningitis (B)	103.43	82.75	124.12	Gamma (μ = 103.43, σ = 11.15)		
PCV13	137.22	109.78	164.66	Gamma (μ = 137.22, σ = 14.79)		
PPSV23	149.90	119.92	179.88	Gamma (μ = 149.90, σ = 16.15)		
Monitoring						
Number of hematologist visits per cycle – hemoglobin normalized	1	Not included		Not included	Clinical experts	
Number of hematologist visits per cycle – hemoglobin not normalized	1					
Number of hematologist visits per cycle – transfusion required	13					
Hematologist visit cost, \$	134.96	107.97	161.96	Gamma (μ = 134.96, σ = 14.54)	CMS Fee Schedule	[67]
Blood tests related parameters						
Number of blood tests per cycle – hemoglobin normalized	2	Not included		Not included	Clinical experts	
Number of blood tests per cycle – hemoglobin not normalized	2					
Number of blood tests per cycle – transfusion required	4					
Blood test cost, \$	7.77	6.22	9.32	Gamma (μ = 7.77, σ = 0.84)	CMS Fee Schedule	[67]
Blood transfusions						
Total number – initial	2.65	2.12	3.18	Normal (μ = 2.65, σ = 0.27)	Calculations based on PRINCE trial data	[63]
Increment per cycle	0.2	0.16	0.24	Normal (μ = 0.20, σ = 0.02)	Clinical experts	
Maximum number in 1 cycle	8.17	6.54	9.80	Normal (μ = 8.17, σ = 0.83)	Calculations based on PRINCE trial data	[63]
AE: Adverse event; IV: Intravenous; QALY: Quality-adjusted life-year.						

AE: Adverse event; IV: Intravenous; QALY: Quality-adjusted life-year.

Table 1. Model inputs: base-case, deterministic sensitivity analysis and probabilistic sensitivity analysis (cont.).

Parameter	Base-case value (mean / percentage)	Deterministic sensitivity analysis		Probabilistic sensitivity analysis	Source	Ref.
		Low value	High value	Distribution and values		
QALY loss per transfusion	-0.002	-0.002621108	-0.001747405	Beta (μ, σ) ($\mu = -0.002$, $\sigma = 0.0004$)	Calculations based on PRINCE trial patients' level data	[63]
Cost per transfusion, \$	2744.32	2195.46	3293.19	Gamma ($\mu = 2744.32$, $\sigma = 295.73$)	Cheng, 2021	[2]
AEs						
AEs probability – pegcetacoplan – breakthrough hemolysis	4.3%	3.44%	5.15%	Beta ($\mu = 0.0429$, $\sigma = 0.0041$)	PRINCE trial data	
AEs probability – eculizumab – breakthrough hemolysis	10.7%	8.56%	10.27%	Beta ($\mu = 0.1070$, $\sigma = 0.0109$)	Matching adjusted indirect comparison	[69]
AEs probability – eculizumab – major adverse Vascular Events	0.8%	0.66%	0.80%	Beta ($\mu = 0.0083$, $\sigma = 0.0014$)		
AEs probability – ravulizumab – breakthrough hemolysis	4.0%	3.20%	3.84%	Beta ($\mu = 0.0400$, $\sigma = 0.0038$)		
AEs probability – ravulizumab – major adverse Vascular Events	1.6%	1.28%	1.54%	Beta ($\mu = 0.0160$, $\sigma = 0.0020$)		
AEs QALY lost – breakthrough hemolysis	0.0006	0.0005	0.0006	Beta ($\mu = 0.0006$, $\sigma = 0.0001$)	O'Connell, 2020	[58]
AEs QALY lost – major adverse vascular events	0.0006	0.0005	0.0006	Beta ($\mu = 0.0006$, $\sigma = 0.0001$)	Sullivan, 2006	[65]
AEs treatment cost – major adverse vascular events	\$24,190	\$19,352.18	\$23,222.62	Gamma ($\mu = 24,190.23$, $\sigma = 2,606.72$)	Dasta, 2015	[70]
AE: Adverse event; IV: Intravenous; QALY: Quality-adjusted life-year.						

transfusion avoidant health state further subdivided patients into either of two states based on Hb levels attained during the 26-week period — Hb normalized (defined as the Hb level of ≥ 12 g/dl; i.e., above the lower limit of normal range [female: 12.0 g/dl, male 13.6 g/dl]) [76] or Hb not normalized. Patients who required transfusions moved to the transfusion required state in the CEM irrespective of Hb level, and as more transfusions were needed they remained in the 'Transfusion required' state; 'tunnel states' tracked the time patients stayed in the health state (Supplementary Figure 1). If the patient moved out of the transfusion required state (during any cycle) and then required transfusion again, they transitioned back to transfusion required (Cycle 1). Patients could also move to the terminal state (i.e., death), from any health state.

Patients assigned to the transfusion required health state upon model entry comprised those who had experienced at least 1 transfusion during the 13 weeks prior to randomization (i.e., the screening period) in PRINCE. The other group comprised the remaining patients who were transfusion avoidant at baseline and assigned to the transfusion avoidant health state upon entering the model.

Health state transitions

Representative patients in the CEM had Hb levels allocated based on PRINCE baseline patient-level data for the pegcetacoplan treatment arm [47], whereas the head-to-head trial ALXN1210-PNH-301 (Study 301) [37] informed Hb levels for the eculizumab and ravulizumab arms of the CEM. Considering the small sample size of the transfusion avoidant patients in PRINCE ($n = 10$), we adjusted the probabilities that these patients would require transfusions by applying odds ratios (ORs) to the transition probabilities for transfusion avoidant and transfusion required for the pegcetacoplan group (Supplementary Figure 2A & Table 2). These ORs were calculated using the formula:

$$OR = (ProbTA \times [1 - ProbTR]) / (ProbTR \times [1 - ProbTA])$$

Where, ProbTR and ProbTA are the respective probabilities of the transfusion required and transfusion avoidant events occurring for patients in the trial.

Table 2. Rates of transfusion avoidance and hemoglobin normalization.

Patient-level data for transfusion avoidance from PRINCE trial [63], n (%)				
To:	From:			
	Transfusion required (pegcetacoplan only)	Transfusion avoidant (pegcetacoplan only)	Transfusion required (pegcetacoplan + BSC)	Transfusion avoidant (pegcetacoplan + BSC)
Transfusion avoidant and Hb normalized	10/21 (47.6)	7/10 (70.0)	10/32 (31.3)	7/14 (50.0)
Transfusion avoidant and Hb not normalized	9/21 (42.9)	3/10 (30.0)	9/32 (28.1)	4/14 (28.6)
Transfusion required	2/21 (9.5)	0/10 (0.0)	13/32 (40.6)	3/14 (21.4)
Sum of probabilities	100	100	100	100
Hb normalization probabilities for transfusion avoidant group (%)				
From:	To:			
		Transfusion required	Transfusion avoidant	
Transfusion avoidant	Hb normalized	90.5	96.0	49.9
	Hb not normalized			44.9
Transfusion required		9.5	4.0	4.0
Sum of probabilities		100	100	100
Calculated transition probabilities – Hb normalization				
From:	To:			
		Hb normalized (%)	Hb not normalized (%)	Transfusion required (%)
Hb normalized		50.51–53.41	45.46–46.59	0.00–4.03
Hb not normalized		47.62–50.51	44.33–45.46	4.03–8.05
Transfusion required		47.62	42.86	9.52

BSC: Best supportive care; Hb: Hemoglobin.

Since the transfusion avoidant state included both Hb normalized and Hb not normalized categories, based on the ORs we calculated additional probabilities of moving to each of these Hb states. These calculations then informed the probability of transfusion avoidant for the transfusion avoidant group (Table 2).

Taking the above assumptions into account, the probability of remaining in the Hb normalized health state was estimated to be in the interval:

$$[Prob_{TA}, Prob_{TA} + Prob_{TA} - Prob_{TR}]$$

where

$Prob_{TA}$: probability of moving to the Hb normalized state from transfusion avoidant,

$Prob_{TR}$: probability of moving to the Hb normalized state from transfusion required.

Similarly, the probability of transition from Hb normalized to transfusion required state was estimated to be in interval:

$$[Prob_{TA} + Prob_{TA} - Prob_{TR}, Prob_{TA}]$$

where

$Prob_{TA}$: probability of moving to transfusion required state from transfusion avoidant,

$Prob_{TD}$: probability of moving to transfusion required state from transfusion required;

In the base-case, we assumed that the transition probabilities from the Hb not normalized state to other states are equal to the average transition probability from states Hb normalized and transfusion required to each respective state, as Hb not normalized was considered an intermediate state (more beneficial than transfusion required, but worse than Hb normalized; Table 3).

For the C5i comparators, we calculated the transition probabilities based on those for pegcetacoplan and the respective ORs between the comparator and pegcetacoplan, calculated based on a matching-adjusted indirect comparison (MAIC) [69], using the formula:

$$OR = \frac{Prob_{comp} \times (1 - Prob_{peg})}{Prob_{peg} \times (1 - Prob_{comp})}$$

Table 3. Hemoglobin normalization transition probabilities for pegcetacoplan.

From:	To:		
Pegcetacoplan	Hb normalized (%)	Hb not normalized (%)	Transfusion required (%)
Hb normalized	51.48	46.33	2.19
Hb not normalized	49.55	44.59	5.86
Transfusion required	47.62	42.86	9.52

Hb: Hemoglobin.

Table 4. Hemoglobin normalization efficacy odds ratios and transition probabilities for comparators.

Efficacy odds ratios			
Outcome	Probability		Odds ratio (comparator vs pegcetacoplan)
	Pegcetacoplan	Comparator	
Eculizumab – normalization distribution: Normal			
Hb normalized	48.1%	16.1%	0.21
Transfusion required	7.8%	33.9%	6.09
Eculizumab – normalization distribution: Weibull			
Hb normalized	48.1%	21.3%	0.29
Transfusion required	7.8%	33.9%	6.09
Ravulizumab – normalization distribution: Normal			
Hb normalized	47.8%	16.9%	0.22
Transfusion required	5.6%	26.4%	5.99
Ravulizumab – normalization distribution: Weibull			
Hb normalized	47.8%	22.2%	0.31
Transfusion required	5.6%	26.4%	5.99
Transition probabilities			
From	To		
	Hb normalized, %	Hb not normalized, %	Transfusion required, %
Eculizumab – normalization distribution: Normal			
Hb normalized	18.0	70.0	12.0
Hb not normalized	16.9	55.6	27.5
Transfusion required	15.8	45.1	39.0
Eculizumab – normalization distribution: Weibull			
Hb normalized	23.6	64.4	12.0
Hb not normalized	22.2	50.3	27.5
Transfusion required	20.9	40.0	39.0
Ravulizumab – normalization distribution: Normal			
Hb normalized	5.1	69.1	11.9
Hb not normalized	17.9	54.9	27.2
Transfusion required	16.8	44.5	38.7
Ravulizumab – normalization distribution: Weibull			
Hb normalized	24.8	63.3	11.8
Hb not normalized	23.4	49.4	27.2
Transfusion required	22.1	39.3	38.7
Hb: Hemoglobin.			

Hb: Hemoglobin.

Where $Prob_{peg}$ and $Prob_{comp}$ are probabilities of transition for pegcetacoplan and comparator, respectively.

As the exact data for the number of patients achieving normalization were not available in Study 301, we estimated ORs and transition probabilities using mean and SD data and assuming two statistical distributions: Normal and Weibull (Table 4).

Adverse events

We considered BTH to be an adverse event, and also captured major adverse vascular events (MAVE; Table 1) in the costing of adverse outcomes. In PRINCE, there were two instances of BTH among 35 pegcetacoplan patients during a mean 244.8 days of follow-up [47]. To inform the input for the model, the rate for each event was adjusted to the 26-week cycle length. The probability of BTH associated with eculizumab and ravulizumab were sourced from the published MAIC [69]. For MAVE events, there were none among patients in the pegcetacoplan arm of the PRINCE trial.

Mortality

In the long-term study of eculizumab [35], the survival of patients treated with eculizumab was not different from age- and sex-matched normal controls, but was significantly ($p < 0.05$) better than similar patients managed before eculizumab. Hence, US general population mortality rates (Table 1) [77] informed mortality for patients on eculizumab, and also applied to patients on pegcetacoplan and ravulizumab, as there were no studies suggesting differences.

Utilities

The PRINCE trial did not collect utility data to estimate QALYs; however, data on patient HRQoL were collected using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire [46,78], the most widely used HRQoL instrument used in cancer research [79] and considered to demonstrate adequate reliability and validity in assessing PNH fatigue and HRQoL [80]. To address the lack of EuroQol 5-Dimension (EQ-5D) utility data from PRINCE, we applied an algorithm to map EORTC QLQ-C30 patient scores to EQ-5D utility weights [81]. Assuming that utilities remained constant over time as adjusted for age [81], we calculated utilities as an average value of patient-level utility for each health state (Table 1) and adjustments using general population utilities data (based on Sullivan 2006 [65]) accounted for the potential influence of patient age on the variability of health state utilities. We sourced further utilities for other health states including BTH and MAVE [58], deep venous thrombosis [70], and venous thrombosis [65], from the literature.

Costs

Given the US healthcare payer perspective of the analysis, the CEM only included direct medical costs (adjusted to 2022 price levels), including costs for drugs, administration, and healthcare services for monitoring, transfusions, managing major adverse events, and physician visits (Table 1).

Drug costs

Drugs considered in the CEM comprised complement inhibitors and supportive treatments (such as for MAVE and deep vein thrombosis) [70] with costs based on wholesale acquisition price listings from Merative™ Micromedex® RED BOOK® (April 2022) (Table 1) [82]. Costs of complement inhibitors and the relevant dosing regimens were estimated (Table 1). Because the population in PRINCE consisted mainly (73.6%) of patients from Asia [47], and since the mean weight of individuals from Asia has been found to be lower than that of the US population [83], we deemed it more appropriate to use data from the US CDC Vital statistics [84] for this weight input. The CEM also considered that patients receiving pegcetacoplan and eculizumab may have received increased dosing if they did not respond sufficiently to the labelled dosing [30]. As BTH is most often treated by increasing the dose of drug [38], an additional dose of drug was also included in the cost of managing BTH, where applicable [21].

Vaccinations against *Neisseria meningitidis* types A, C, W, Y, and B are required for all patients receiving complement inhibitors. Furthermore, vaccination against pneumococcal disease is necessary for patients on pegcetacoplan, and so the costs associated with PCV13 and PPSV23 were also included. Therefore, we applied one-off costs of relevant vaccinations and antibiotics in the model during the first cycle, sourcing the data from the CDC Vaccine Price List [68].

Administration costs

In the base-case we assumed that patients had their first pegcetacoplan dose administered in a clinic where they also received outpatient training in subcutaneous self-administration (\$135) followed by self-administered doses at home. We also excluded one-off pump costs for pegcetacoplan (i.e., assumed costs covered by the manufacturer) in the base-case, but subsequently included the cost (\$134.96) [57,85] in a scenario analysis. For pegcetacoplan

administration we applied outpatient costs obtained from the Centers for Medicare & Medicaid Services portal [67], with administration costs for eculizumab and ravulizumab calculated as in-patient intravenous infusions (Table 1).

Blood transfusion costs

Although we calculated the total cost of transfusion based on unit cost and transfusion frequency per cycle, we also considered the cost of treating severe acute reactions of blood transfusion (Table 1). Moreover, real-world evidence suggests large variability in the rate of transfusions within a year, although without transfusions, patients with anemia can steadily worsen [86] which was an assumption validated by clinical experts. Despite the rate of blood transfusion per cycle for patients in the transfusion required health state being based on patient-level data from PRINCE, there was large discrepancy between the mean and maximum number of transfusions in one cycle. Therefore, per confirmation by clinical experts, we assumed that for each cycle in which the patient remained in the transfusion required state, the number of transfusions required would increase by 0.2.

Other resource use costs

Other healthcare costs included fees for consultations with general practitioners, hematologists, and oncologist, and for blood tests (Table 1) [67].

Analysis

The deterministic base-case analysis applied a discount rate of 3.0% for both costs and QALYs following the US CEM guidelines [62]. However, we explored alternative discount rates of 0% and 6% in the deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA) conducted to assess the robustness of the model to parameter uncertainty. The DSA evaluated the one-way precision uncertainty of model parameters (including costs, utilities, discount rates, and the time horizon) based on plausible low and high values for each parameter (Table 1) [87]. The PSA weighed the joint uncertainty in the model parameters based on the inclusion of a stochastic component and considered a cost–effectiveness threshold of \$100,000 [62]. We sampled transition probabilities from Dirichlet or beta distributions, and log-normal distributions to simulate hazard ratios. We evaluated the percentage of patients with Hb normalized based on a Weibull distribution, total costs based on gamma distributions, and assumed beta distributions for utilities values and different proportions (Table 1).

Scenario analyses, considering a range of alternative assumptions and changes to model inputs, investigated the uncertainty from structural parameters and other sources. We first assessed a scenario with Hb stabilization as the model health state. In PNH, besides Hb normalization, Hb stabilization is another key indicator of disease severity and has been used in clinical trials to define categories of response (e.g., optimal or partial response; although based on varying Hb thresholds) to treatment [26,88]. We defined Hb stabilization as the avoidance of a ≥ 1 g/dl decrease in Hb level in the absence of transfusion from baseline through Week 26 [47]. For pegcetacoplan, we used PRINCE patient-level data available to estimate the number of patients with Hb decrease. We included transition probabilities for the threshold of > 1 g/dl in the model but estimated ORs between pegcetacoplan and comparators based on a threshold of > 2 g/dl (Supplementary Tables 1–3 & Supplementary Figure 2B). For eculizumab and ravulizumab, we applied mean Hb and standard deviation from Study 301 to estimate the proportion of the population with *Hb stabilization* [37].

Results

Cost–effectiveness

The base-case analysis indicated that, over a lifetime horizon, pegcetacoplan becomes the economically dominant option (lower costs, enhanced outcomes) compared with eculizumab or ravulizumab in the management of treatment-naïve patients with PNH. The total cost savings for pegcetacoplan were the greatest compared with eculizumab (\$1,176,808); compared with ravulizumab total savings amounted to \$213,062. These substantial cost savings for pegcetacoplan versus both comparators were largely attributed to reduced drug costs (-\$981,242 and -\$86,352, respectively). Moreover, drug administration cost (-\$84,416 and -\$27,203) blood transfusion costs (-\$69,575 and -\$68,000), and adverse event costs (-\$27,052 and -\$17,311) accounted for the other cost differences versus eculizumab and ravulizumab, respectively.

In terms of health outcomes, while all the treatment arms showed equivalent life-years (19.06), pegcetacoplan was associated with improved HRQoL and therefore, additional QALYs of 0.25 and 0.24 relative to eculizumab and ravulizumab, respectively (Table 5).

Table 5. Modeled health outcomes and costs – pegcetacoplan and comparators.

Description	Pegcetacoplan	Eculizumab	Ravulizumab
Health outcomes			
Life years	19.06	19.06	19.06
QALYs	15.40	15.15	15.16
Incremental for pegcetacoplan	–	0.25	0.24
Costs, \$			
Drug cost	8,730,068	9,711,310	8,816,420
Incremental for pegcetacoplan	–	-981,242	-86,352
Supportive treatment	157,734	157,734	157,734
Incremental for pegcetacoplan	–	0	0
Administration cost	135	84,551	27,338
Incremental for pegcetacoplan	–	-84,416	-27,203
Vaccine cost	462	174	174
Incremental for pegcetacoplan	–	288	288
Health state costs	8942	23,752	23,426
Incremental for pegcetacoplan	–	-14,810	-14,484
Blood transfusion costs	14,381	83,956	82,381
Incremental for pegcetacoplan	–	-69,575	-68,000
Adverse events costs	7210	34,262	24,521
Incremental for pegcetacoplan	–	-27,052	-17,311
Total costs	8,918,932	10,095,739	9,131,994
Incremental total costs for pegcetacoplan	–	-1,176,808	-213,062
Bold values indicate the total costs. QALY: Quality-adjusted life year.			

Sensitivity analyses

With DSA run separately on incremental costs and QALYs given the economic dominance of pegcetacoplan versus the comparators, results indicated that against both comparators, the yearly discount rate for cost was the most impactful incremental cost driver, followed by mean patient age (Supplementary Figure 3). Changing health state utility values had the most impact on QALYs – followed in order of impact by Hb normalized, transfusion required, Hb Not normalized, discount rates for health outcomes, OR between comparators and pegcetacoplan for Hb stabilization, mean patient age, and utility decrement and frequency of transfusions.

The PSA indicated that pegcetacoplan remained the economically favorable option compared with eculizumab in 80.2% of simulations. Furthermore, assuming an incremental cost-effectiveness ratio (ICER) threshold of \$100,000 per QALY gained, pegcetacoplan was cost-effective in 100% of simulations (Figure 2). Pegcetacoplan dominated ravulizumab in 79.3% of simulations and was cost-effective in 100% of simulations assuming a threshold of \$100,000 per QALY gained.

Scenario analyses

Pegcetacoplan ICER results remained economically dominant across most scenarios, including Hb stabilization as the model health state. However, when we applied a lower patient mean weight, which was more representative of the PRINCE trial population (i.e., 63.72 kg) we observed that this variable had a large impact on the ravulizumab dose administered. For this scenario, we obtained an ICER for pegcetacoplan of \$94,568 (Table 6). PSA based on the structural alternative resulted in further robust results (Supplementary Figure 4).

Discussion

This study evaluated the cost-effectiveness of pegcetacoplan compared with eculizumab and ravulizumab in treatment-naïve adults with PNH in the USA. The 3-state Markov model employed for the analysis indicated that during the earliest part of the PNH treatment pathway, pegcetacoplan provides added clinical and patient HRQoL benefits, with economic savings, when compared with using either of the two currently available C5i PNH treatments. The substantial cost savings associated with pegcetacoplan use can be attributed to reduced costs of the

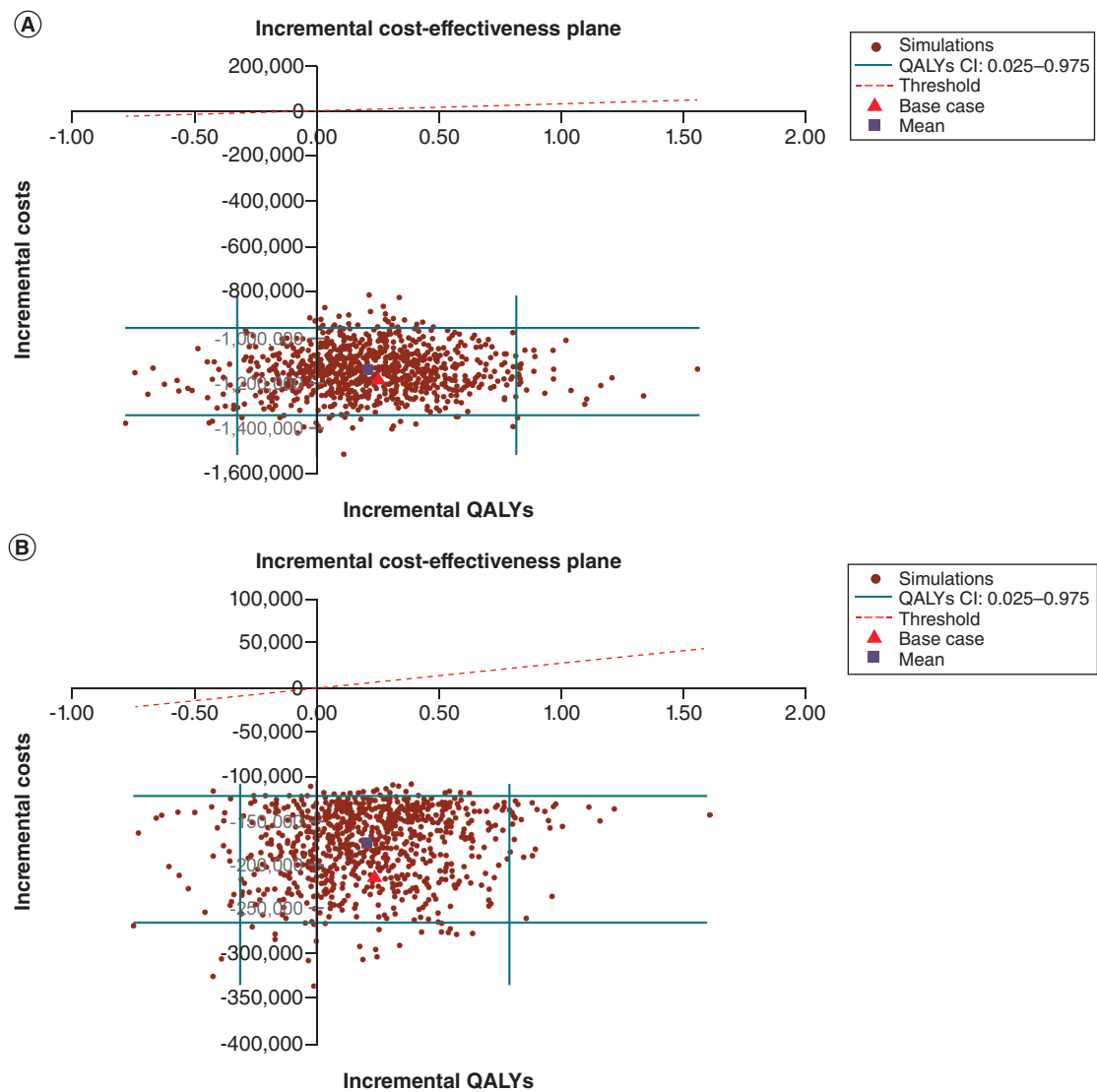


Figure 2. Incremental cost-effectiveness planes. (A) Pegcetacoplan versus eculizumab. (B) Pegcetacoplan versus ravulizumab.
CI: Confidence interval; QALY: Quality-adjusted life year.

Table 6. Scenario analyses.		
Scenario	ICER (Cost/QALY) for Pegcetacoplan vs	
	Eculizumab	Ravulizumab
Mean weight (63.72 kg)	Dominant	\$94,568
Incremental number of transfusions per cycle equal to 0	Dominant	Dominant
Time horizon		
5 years	Dominant	Dominant
10 years	Dominant	Dominant
25 years	Dominant	Dominant
End point definition		
Hemoglobin normalization – proportion estimated with Weibull distribution	Dominant	Dominant
ICER: Incremental cost-effectiveness ratio, QALY: Quality-adjusted life year.		

drug and its administration, a reduction in blood transfusions needed, and due to the reduced number of clinically relevant adverse events relative to either comparator. The significance of drug administration cost is consistent with other published PNH models [21,57–59,89], and when considered in conjunction with the clinical value of treatment, is also consistent with a previous CEM in C5i treatment-experienced patients with PNH [85]. In that evaluation, the clinical superiority of pegcetacoplan, as shown in the head-to-head clinical trial of pegcetacoplan versus continuation with eculizumab [46], led to the economic superiority.

Moreover, in terms of the incrementally greater QALYs for pegcetacoplan versus the C5i comparators found in our evaluation, the gains of more than 3 months in a quality-adjusted lifespan of an individual with PNH demonstrated the long-term implications of some of the remaining clinical shortfalls of C5i treatments in treatment-naïve patients; these include the emergence of EVH and continued transfusion dependency in a large proportion of patients [63]. To otherwise measure the incremental clinical benefits of pegcetacoplan treatment effect, the key input in our analysis was efficacy data from the PRINCE trial which provided evidence associated with treating the PNH population early in their disease course [47]. In the PRINCE trial, pegcetacoplan was associated with improvements across PNH-relevant hematologic parameters, including Hb and LDH levels, in addition to transfusion avoidance and improved HRQoL, and with minimal treatment-associated safety issues [47].

Our modeled outcomes for Hb normalization associated with ravulizumab and eculizumab also approximately align with data from the real-world [90], although producing slightly more conservative estimates favoring the C5i treatments. For example, considering the modeled patients for each health state over the time horizon (i.e., the Markov trace) [91], our CEM indicated that after 6 months to 1 year from baseline (i.e., treatment initiation), approximately 48% and 53–54% of the simulated cohort on the C5i treatments failed to have Hb normalization (Supplementary Figure 5). These estimates roughly compare to a real-world data analysis wherein the proportion of patients who failed to have Hb normalization (Hb levels ≥ 12 g/dl) while treated with C5i: 64.3 to 77.8%, and 50.0 to 82.3% at 6 months and 1 year, respectively [90].

Transfusion need is another a key end point used in PNH efficacy trials [37,47] and validated by clinical experts as the most relevant outcome representing the clinical benefit of PNH treatment, with the majority of nonrespondent patients eventually requiring a transfusion due to PNH disease progression if their complement is uncontrolled [92]. Therefore, our CEM considers the vitality of transfusion independence in PNH clinical assessment [74] and a significant contributor to PNH healthcare costs [21,36–38,41]. Moreover, the further external validity of our model on this outcome is notable. While the proportions of simulated patients on eculizumab were transfusion dependent during the first 10 years in the model (18% to 28%; Supplementary Figure 5); these proportions align with the published data on eculizumab use in the real world, wherein up to 12% to 31% of patients received a blood transfusion over any 24-week period in long-term follow-up [93].

Other aspects of our modeling approach warrant highlighting. As PNH is a disease that directly impacts on Hb, it is one of the most important clinical parameters characterizing response to PNH treatment [39,94]. In addition to clinical relevance, Hb level is a discrete and objectively measurable end point. Previous PNH models in treatment-experienced patients [21,95] have elected to evaluate/model treatment effect based predominantly on LDH, a marker of BTH [21,74]. It is clear that BTH represents loss of disease control, as manifested by classical PNH-related signs and symptoms including anemia, dyspnea, hemoglobinuria, fatigue [38] and associated reductions in overall HRQoL [22–25]. Further, while BTH can be addressed by RBC transfusion or by adjusting the dosing amount and/or frequency of eculizumab administration beyond the approved regimen [36,37], the associated costs of both such therapeutic approaches increase the overall healthcare burden [21,30,96]. However, in terms of such an end point in PNH CEMs, investigators who have previously relied on this parameter caution that BTH episodes are heterogeneous [21], with the end point itself commonly represented by a constellation of symptoms (e.g., fatigue, dyspnea) in tandem with changes in biomarkers (e.g., LDH) [74]. Hemolysis or changes in LDH in PNH could also manifest due to a variety of reasons including a lack of treatment effect and complement-amplifying conditions (e.g., pregnancy, surgery, vaccination) [88]. Hence, consensus is lacking on how to define hemolysis that is associated with or as measured by changes in LDH, making this a difficult biomarker to include as its own health state in an economic model [38]. Keeping these LDH limitations in mind along with that there is currently no universally accepted measure of PNH treatment response available, consensus-based measurement criteria have recently been proposed by the European Society for Blood and Marrow Transplantation (EBMT) [26]. These criteria reflect clinical practice and classify hematologic or clinical response in patients with PNH and are based on several measures, but focus on transfusion needs and Hb improvements after treatment with complement inhibitors [26]. Adding further

evidence on the validity of our modeling structure, the outcomes considered in our CEM reflect the primary end points in more recent PNH clinical trials, wherein LDH is included only as a secondary end point [46,97].

Given the uncertainty associated with a model that relies on BTH as a health state parameter, our CEM has instead considered BTH as an adverse event, which more accurately reflects management of this outcome caused by red blood cell destruction and more directly measured by Hb [74]. Hence, in contrast with previous PNH economic models [21,57–59], our CEM was able to capture the key clinical and patient outcomes, and contextualize more pertinent PNH end points in terms of treatment value, specifically, hemoglobinuria. This end point, after which PNH is named, is experienced by up to 50% of patients [98] and directly correlated with potentially debilitating fatigue [99].

In terms of the structural specificity of our model, we characterized hematological response to PNH treatment in terms of Hb normalization in the base-case, rather than Hb stabilization; in this regard, it is notable that the definition of stabilization has not been consistent between PNH clinical trials [37,47]. Even as transfusion avoidance has been a requirement for stabilization in clinical trials, the definition of Hb stabilization itself differed across the trials. As one of the co-primary efficacy end points in PRINCE, stabilization was defined as Hb that did not decrease by >1 g/dl [47]. Study 301, however, defined stabilization as Hb that did not decrease by >2 g/l [37]. Given this discrepancy, unlike other previously published PNH CEM models [85,100] we considered Hb normalization, as a structural alternative for the present CEM.

Of final consideration of the robustness of our CEM is the consequence of the rarity of PNH and the limited sample size in the PRINCE trial on which clinical inputs were based. Considering that these inherent issues of a rare disease may have placed a risk on the CEM due to the more extreme values of the input parameters, our analysis proved to be reliable after we rigorously explored both parameter uncertainty and model structure uncertainty. Our cost–effectiveness results remained consistent when key inputs such as mean weight of patients, utility values and the drug acquisition costs were varied to their upper and lower bound on sensitivity analysis. The RCT evidence-based clinical efficacy inputs also represent best practice and analytic reliability [101].

Limitations

Hepatotoxicity [102] and the potential for pigment gallstones to form after prolonged use of C5i treatments [63,103] are two clinical concerns that were not included in the model; moreover, our analysis also did not consider the costs of chelation therapy (such as deferasirox and deferoxamine mesilate) to treat iron overload, which is warranted in patients on C5i who need frequent blood transfusions and accumulate iron in the liver and spleen [46]. However, the costs related to both clinical concerns would have only added to the costs of the comparator C5i treatments.

Patients who are treated with pegcetacoplan, which targets both IVH and EVH, see an increase in Hb levels and a return to normalcy, which prevents future iron overload [46]. Before the introduction of pegcetacoplan in transfusion-required patients, however, the build-up of iron from routine transfusions would have required phlebotomy to treat iron overload in pegcetacoplan patients [104]. Despite not including such costs associated with C5i, incremental cost savings for pegcetacoplan were still observed compared with the comparators.

Although our model structure is reflective of the PNH disease pathway and the likely courses of action taken to mitigate/compensate RBC destruction from the disease, interpreting our study also warrants consideration of the PRINCE study design. First, PRINCE permitted patients with severe anemia to enter the treatment arm, hence the data from the trial lacked a reliable number of observations to calculate transitions for the transfusion-avoidant patients who did not achieve normalization. Moreover, unlike prior study designs in patients with PNH who were naive to complement treatment [105], in PRINCE, patients randomized to the control group could transition to pegcetacoplan treatment if their Hb level decreased ≥ 2 g/dL below their baseline measurement or if they had a qualifying thromboembolic event secondary to PNH.

In summary, this lifetime cost–effectiveness analysis, from a US payer perspective and based on a 3-state Markov model, found that pegcetacoplan was the economically dominant treatment strategy compared with ravulizumab and eculizumab for use in treatment-naïve PNH. The findings remained consistent across a variety of scenarios. In terms of future research in ascertaining the value of treatments in PNH, a few considerations are warranted. First, the widespread variation in management of BTH confirms that alternative structures to model PNH are necessary [21]. Investigations of real-world PNH treatment practices and outcomes in patients who are treatment-naïve would also serve to draw further conclusions on effectiveness and healthcare costs associated with PNH treatments.

Conclusion

In treatment-naïve patients with PNH, the base-case cost-effectiveness, scenario analysis, and sensitivity analysis showed both lifetime cost savings and increased QALYs associated with pegcetacoplan compared with eculizumab or ravulizumab, hence potentially offering substantial clinical value within the early PNH treatment paradigm in USA.

Summary points

- Paroxysmal nocturnal hemoglobinuria (PNH) is a rare blood disorder characterized by hemolytic anemia, bone marrow failure, and thrombosis, and is associated with high healthcare burden.
- Pegcetacoplan (Empaveli®) is a treatment for PNH that is approved in the USA based on results from the pivotal phase 3, PEGASUS (NCT03500549) open-label, head-to-head trial.
- Further evidence for pegcetacoplan has more recently been shown in PRINCE (NCT04085601), an open-label trial in C5i-naïve patients randomly assigned 2:1 to treatment with pegcetacoplan (added to best supportive care [BSC]) or BSC (excluding complement-inhibitors).
- PRINCE demonstrated meaningful hematologic and clinical improvements following 26 weeks of treatment with pegcetacoplan versus BSC, with a favorable safety profile.
- In addition to the demonstrated clinical benefits for pegcetacoplan in the PNH treatment-naïve population, the value of pegcetacoplan to US patients and payers is also necessary for informing appropriate treatment funding decisions on the early part of the PNH treatment pathway.
- This study evaluated the cost-effectiveness of pegcetacoplan, a proximal complement-3 inhibitor, compared with the complement-5 inhibitors currently available in the USA, eculizumab and ravulizumab, in complement treatment-naïve adults with PNH, from the US healthcare payer perspective.
- The 3-state Markov model employed for the analysis indicated that during the earliest part of the PNH treatment pathway, pegcetacoplan provides added clinical and patient health-related quality of life benefits, with cost savings, when compared with using either eculizumab or ravulizumab.
- The substantial cost savings associated with pegcetacoplan use can be attributed to reduced costs of the drug and its administration, a reduction in blood transfusions needed, and due to the reduced number of clinically relevant adverse events relative to either comparator.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: <https://bpl-prod.literatumonline.com/doi/10.57264/cer-2023-0055>

Author contributions

All authors were responsible for the conceptualization and interpretation of data and findings of the study. A Drzewiecka and M Pochopień were also responsible for data acquisition and analysis.

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Data sharing statement

The authors certify that this manuscript reports the secondary analysis of clinical trial data that have been shared with them, and that the use of this shared data is in accordance with the terms (if any) agreed upon their receipt. The source of this data is: PRINCE (NCT04085601).

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