NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pegcetacoplan for treating paroxysmal nocturnal haemoglobinuria [ID3746]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pegcetacoplan for treating paroxysmal nocturnal haemoglobinuria [ID3746]

Contents:

The following documents are made available to consultees and commentators:

The **final scope and final stakeholder list** are available on the NICE website.

1. **Technical briefing slides**

2. **Company submission** from Swedish Orphan Biovitrum

3. **Clarification questions and company responses**
   a. Main response
   b. Revised base case results

4. **Patient group, professional group, and NHS organisation submission** from:
   a. PNH Support
      i. Main submission
      ii. Submission appendix
   b. NHS England

5. **Expert personal perspectives** from:
   a. Dr Richard Kelly, Consultant Haematologist – clinical expert, nominated by the Aplastic Anaemia Trust and PNH Support
   b. Louise Pottinger – patient expert, nominated by PNH Support
   c. Nelson Ekwedike – patient expert, nominated by PNH Support

6. **Evidence Review Group report** prepared by Liverpool Reviews and Implementation Group:

7. **Evidence Review Group report – factual accuracy check**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NICE National Institute for Health and Care Excellence

Pegcetacoplan for treating paroxysmal nocturnal haemoglobinuria

Technical briefing

This slide set is the technical briefing for this appraisal. It has been prepared by the technical team and it is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the appraisal committee meeting and is expected reading for committee members. The submissions made by the company, consultees and nominated experts as well as the ERG report are available for committee members, and are optional reading.

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Fast track appraisals: low ICER appraisal

This topic is proposed as an low ICER FTA

- FTAs are appraisals in which less-detailed discussion is sufficient.
- Low ICER FTA considered if:
  - the company's deterministic and probabilistic base-case ICER are less than £10,000 per QALY gained
  - it is likely that the most plausible ICER for a technology is less than £20,000 per QALY gained, and it is highly unlikely that it is greater than £30,000 per QALY gained.

Possible recommendations in a low ICER FTA include:

✓ The committee will recommended the technology as an option.

✓ The ICER is higher than £20,000 but the technology can be recommended.

X The ICER is higher than £30,000 or uncertain so the technology cannot be recommended.

? Request for further exploratory analyses from the company and a critique of these from the ERG, to be discussed at a subsequent committee meeting.

Key considerations

- The assumption of equal efficacy between ravulizumab and eculizumab in the PEGASUS trial population is reasonable.
- The ERG considers that the company's model is well built and satisfactorily reflects the treatment pathway for paroxysmal nocturnal haemoglobinuria.
- All the scenario and sensitivity analyses carried out by the company and ERG show that pegcetacoplan dominates both eculizumab and ravulizumab.
- Company and ERG consider that the most plausible ICERs for pegcetacoplan versus eculizumab and ravulizumab are below £20,000 per QALY gained.
- Risk to NHS is low: small eligible population and high comparator costs.
- Based on the above, there are no critical issues for consideration by the committee.

⊙ ***Is it likely that the most plausible ICER is below £20,000 per QALY gained?***
⊙ ***Is it highly unlikely to be above £30,000 per QALY gained?***

Disease background

- Paroxysmal nocturnal haemoglobinuria (PNH) is a rare blood condition in which red blood cells are attacked by the body's immune system.
- It is characterised by intravascular haemolysis (rupturing of red blood cells) with resultant anaemia often leading to transfusion dependence, severe disabling symptoms of haemolysis and, frequently, thrombosis (blood clotting).
- PNH can also lead to extravascular haemolysis (haemolysis taking place in the liver, spleen, bone marrow, and lymph nodes).
- It is a chronic condition that is associated with complications that can be severely debilitating and life threatening.
- In England, people with paroxysmal nocturnal haemoglobinuria (PNH) are managed by the PNH National Service, consisting of 2 centres and 8 outreach clinics, and their local haematologist through a shared care agreement.
- The severity of symptoms varies between people and over time, which means that not everyone with paroxysmal nocturnal haemoglobinuria needs treatment.
- Current treatments include complement C5 inhibitors: eculizumab and ravulizumab. Supportive care includes blood transfusions, steroids, anticoagulants and supplements.

✓ It is estimated that there are about 650 to 900 people in England with PNH

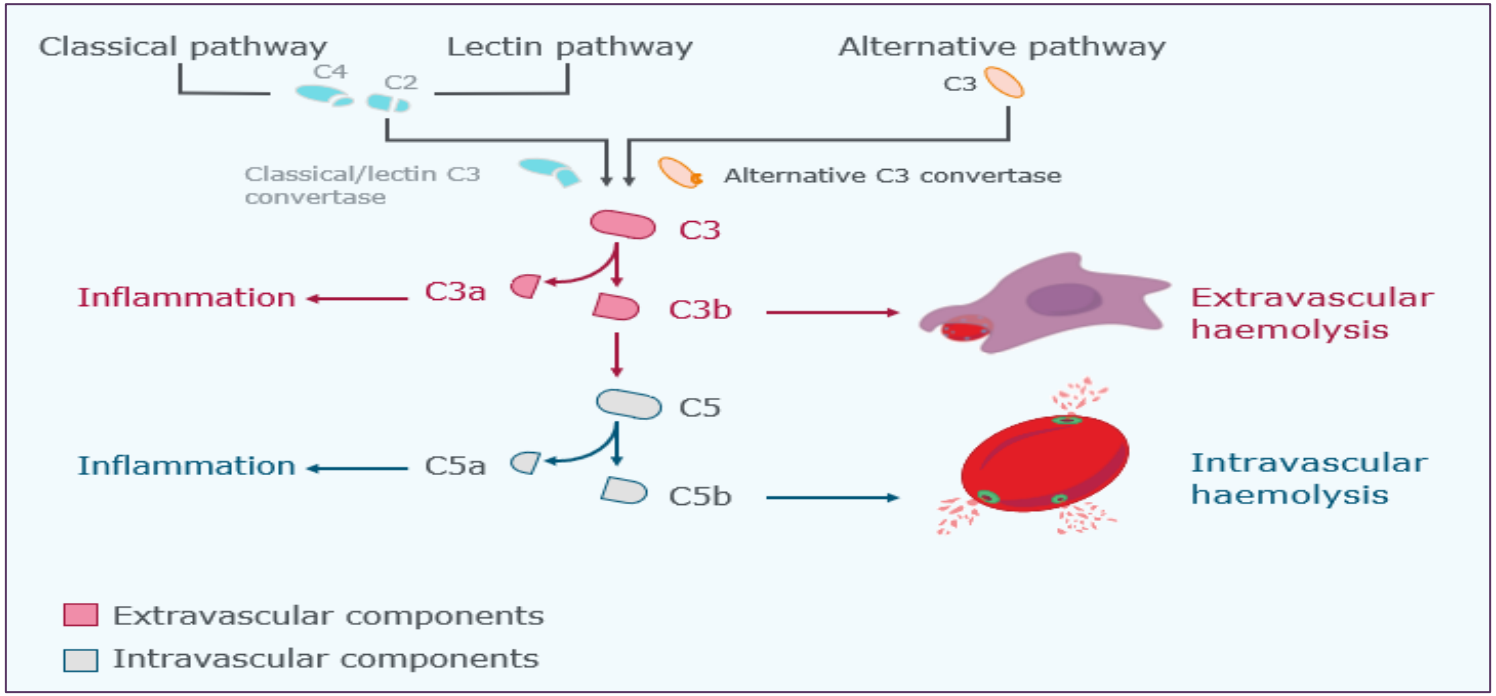
✓ PNH is most frequently diagnosed between the ages of 30-40 years old

Sources: Pegcetacoplan NICE scope, company submission and NICE TA698

PNH complement cascade

Company submission highlights:

- C5 inhibitors target underlying intravascular haemolysis (IVH), but do not address extravascular haemolysis (EVH).
- This may result in suboptimal control of disease and remaining symptoms.
- EVH is the result of unregulated complement protein C3, which due to the complement cascade, activates complement protein C5, in turn causing IVH.
- Pegcetacoplan is a complement C3 inhibitor which prevents both IVH and EVH by targeting the complement cascade earlier than C5 inhibitors.



Source: company submission

Patient, carer and clinician perspectives

Pegcetacoplan offers benefits to people with PNH

- C5 inhibitors have significantly reduced the burden of PNH, however some people still experience EVH and anaemia requiring blood transfusions whilst on treatment. This population has the potential to benefit significantly from pegcetacoplan.
- Current treatment can be inconvenient for some people because a healthcare professional is needed to administer the intravenous infusion at a person's home and frequent canulation can be difficult if venous access is poor.
- Pegcetacoplan is self-administered via the subcutaneous route which is more convenient. However, it is administered more frequently than existing treatments and this may increase the likelihood of injection-site reactions.
- Pegcetacoplan offers many benefits including:
  - improvement of symptoms including fatigue and energy levels
  - reduced need for blood transfusions as a result of anaemia, which together with self-administration results in a decreased burden on the NHS
  - improved quality of life, including a positive impact on a person's mental health, social and family life and ability to work.

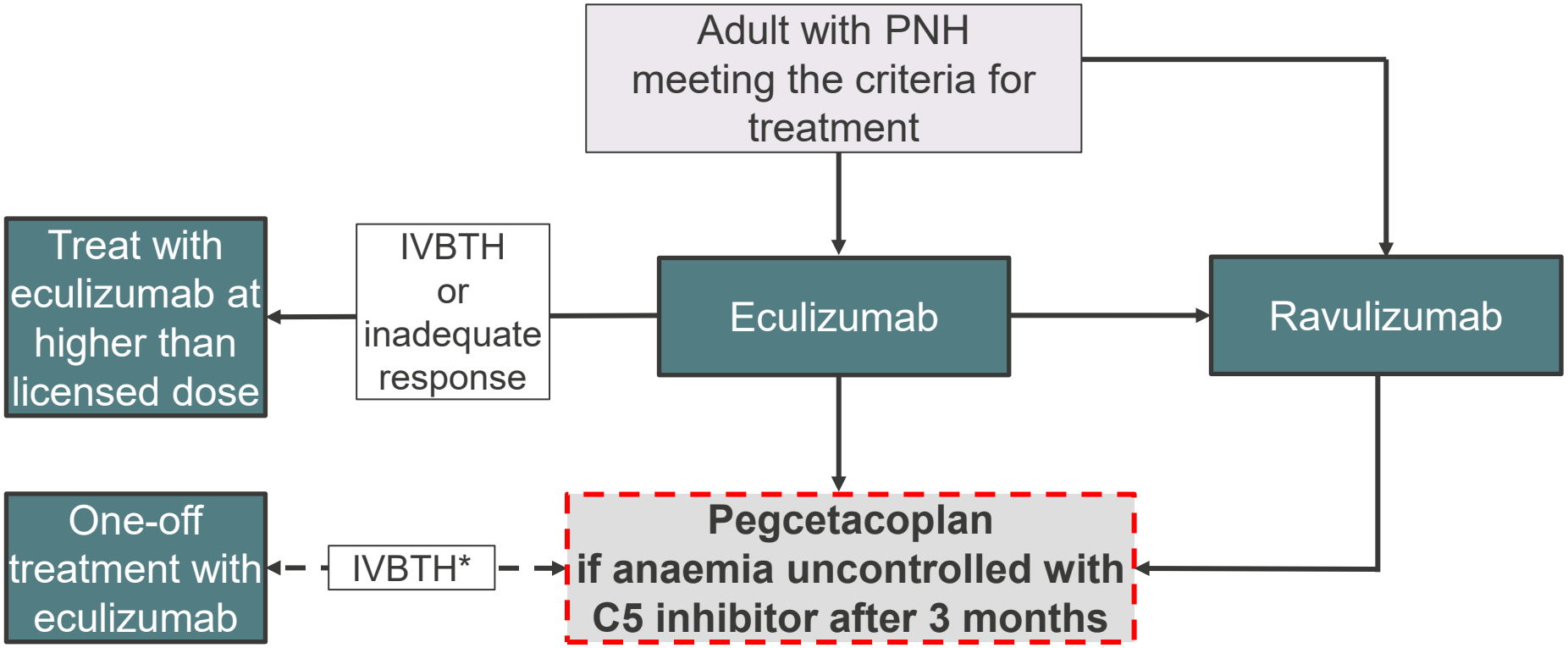
Submissions from 2 patient experts, 1 patient organisation (PNH support) and 1 clinical expert

The technologies

	Pegcetacoplan	Eculizumab	Ravulizumab
Mode of action	Complement C3 inhibitor	Complement C5 inhibitor	
Marketing authorisation (MA)	[redacted]	Treatment of adults and children with PNH.	Treatment of adult patients with PNH: • with haemolysis with clinical symptom(s) indicative of high disease activity, or • who are clinically stable after having been treated with eculizumab for at least the past 6 months.
Posology and method of administration	• Self-administered twice weekly as a 1,080 mg subcutaneous infusion. • For the first 4 weeks pegcetacoplan should be administered in addition to current dose of C5 inhibitor treatment (to minimise risk of haemolysis).	• Administered by intravenous infusion • Dosage by weight. • Initial loading phase (weekly infusion for first 4 weeks), followed by a maintenance phase (infusion every 2 weeks – 900 mg in adults).	• Administered by intravenous infusion • Dosage by weight. • Initial loading dose, followed by maintenance dosing (3,000 to 3,600 mg every 8 weeks), starting 2 weeks after the loading dose
NICE appraisal	In progress	• Not been appraised by NICE, but available through highly specialised service*	• TA698

* Criteria for treatment includes thrombosis related to PNH, complications associated with haemolysis (renal failure, pulmonary hypertension), pregnancy, haemolytic symptomatic PNH.

Company's positioning of pegcetacoplan



IVBTH = intravascular breakthrough haemolysis

* Clinical advice to the company is that IVBTH would be treated in people having pegcetacoplan with a one-off 900 mg dose of eculizumab.

NICE

Source: Pegcetacoplan company submission

Related NICE technology appraisals

Technical team judgement: Medium to low risk

- **NICE experience in appraising technologies for the treatment of PNH is limited to ravulizumab (TA698).**
- The guidance was recently published (May 2021), so it is unlikely that there have been any substantial changes to the treatment pathway since publication.
- The population in this appraisal includes adult anaemic patients with PNH whose disease is not sufficiently controlled by treatment with a C5 inhibitor for at least 3 months (in line with the clinical trial population), which is narrower than that considered in TA698.
- Pegcetacoplan would also be considered as a subsequent treatment following first-line treatment with either ravulizumab or eculizumab in adults with PNH who have anaemia that is uncontrolled after 3 months.
- ERG clinical experts consider that eculizumab and ravulizumab are the most appropriate comparators for this population. People currently treated with eculizumab are likely to switch to treatment with ravulizumab due to the reduced infusion frequency.

Company's decision problem

Technical team judgement: Low risk

- **The decision problem is consistent with the scope and represents the expected marketing authorisation for pegcetacoplan.**
- Clinical evidence is only presented for pegcetacoplan following treatment with eculizumab, based on the key clinical trial (PEGASUS).
- No robust clinical evidence is presented to support the use of pegcetacoplan following treatment with ravulizumab.
- The PEGASUS trial reported outcomes as per the final scope, except for overall survival.
- The company and ERG both consider that for patients receiving treatment, PNH does not affect overall survival (mortality hazards are that same as those for the general population).

Clinical effectiveness

- Direct evidence from the PEGASUS trial allows comparison of pegcetacoplan versus eculizumab
- Company has also presented indirect evidence for the comparison of pegcetacoplan versus ravulizumab

PEGASUS trial: pegcetacoplan and eculizumab

Design	• Phase 3 multicentre, open-label, active-comparator randomised controlled trial • 44 sites across 11 countries in the Asia-Pacific region, North America, and Europe including the UK
Population	Adults with PNH who continued to have Hb levels <10.5 g/dL despite treatment with eculizumab.
Intervention	Pegcetacoplan 1,080 mg self-administered subcutaneously twice weekly or every 3 days (n=41)
Comparator	Eculizumab, at a current dosage that had been stable for at least 3 months prior to screening, administered by infusion (n=39).
Primary outcome	**Change from baseline (CFB) to week 16 Hb level**
Key secondary outcomes	• Transfusion avoidance, CFB to week 16 ARC, LDH level (tested for non-inferiority according to pre-specified margins) • CFB to week 16 in FACIT-Fatigue Scale score version 4

Abbreviations: ARC=absolute reticulocyte count; CFB=change from baseline; FACIT-Fatigue= Functional Assessment of Chronic Illness Therapy; Hb=haemoglobin; LDH=lactate dehydrogenase.

The treatment period of the study consisted of 3 stages:

1) 4-week run-in period where all participants received pegcetacoplan in addition to eculizumab at their current dose
2) 16-week randomised controlled period (RCP) where participants were randomised to either pegcetacoplan or eculizumab
3) 32-week open-label pegcetacoplan-only period (people who received eculizumab in the RCP received pegcetacoplan in addition for 4 weeks, before pegcetacoplan alone for 28 weeks).

PEGASUS trial results: CFB in Hb level at week 16

- The company considers that it would be inappropriate to use data collected after transfusion since this would be expected to improve Hb level, confounding the treatment effect of either intervention.
- For any participant who received a transfusion, all subsequent values were set to missing for the Hb level (censored for transfusion).
- The between treatment group comparisons were performed using a mixed-effect model for repeated measures (MMRM).
- The company provided the observed values and CFB without censoring for transfusion for the primary and other secondary outcomes in response to clarification.
- The ERG considers that the uncensored values are consistent with the censored values.

	Pegcetacoplan (N=41)	Eculizumab (N=39)
MMRM model, censored for transfusion, ITT population		
Least squares mean (standard error) g/dL	2.37 (0.363)	-1.47 (0.666)
Least squares mean difference (95% CI)	**3.84 (2.33 to 5.34)**	
P-value	<0.0001	

CFB in Hb level at week 16 was statistically significantly higher in the pegcetacoplan arm compared to the eculizumab arm.

PEGASUS trial results: key secondary outcomes (1)

Transfusion avoidance at week 16

Transfusion avoidance, ITT population	Pegcetacoplan (N=41)	Eculizumab (N=39)
Yes (patient did not receive a transfusion)		
n (%)	35 (85.4)	6 (15.4)
Difference in percentage		
Risk difference (95% CI)	**0.6253 (0.4830 to 0.7677)**	
P-value	<0.0001	

Transfusion avoidance during the RCP was statistically significantly higher in the pegcetacoplan arm compared to the eculizumab arm. Non-inferiority was demonstrated for pegcetacoplan.

CFB in absolute reticulocyte count (ARC) at week 16

Reduced ARC indicates reduced extravascular haemolysis.

	Pegcetacoplan (N=41)	Eculizumab (N=39)
MMRM model, censored for transfusion, ITT population		
Least squares mean (standard error) 10^9 cells/L	−135.82 (6.54)	27.79 (11.86)
Least squares mean difference (95% CI) 10^9 cells/L	**-163.61 (−189.91 to −137.30)**	
P-value	<0.0001	

CFB in ARC at week 16 was statistically significantly reduced in the pegcetacoplan arm compared to the eculizumab arm. Non-inferiority was demonstrated for pegcetacoplan.

PEGASUS trial results: key secondary outcomes (2)

CFB in lactate dehydrogenase level (LDH) at week 16

Reduced LDH indicates reduced intravascular haemolysis.

	Pegcetacoplan (N=41)	Eculizumab (N=39)
MMRM model, censored for transfusion, ITT population		
Least squares mean (standard error) U/L	−14.76 (42.71)	−10.12 (71.03)
Least squares difference (95% CI) U/L	**−4.63 (−181.30 to 172.04)**	
P-value	0.9557	

LDH levels were well controlled at baseline, as expected with treatment with a C5 complement inhibitor, and remained well controlled at week 16 in both treatment groups. Non-inferiority was not demonstrated for pegcetacoplan.

FACIT-Fatigue Scale

- Baseline scores for FACIT-Fatigue were similar in both arms of the trial.
- CFB results to week 16 in FACIT-Fatigue (censored for transfusion): pegcetacoplan improved quality of life compared to eculizumab in the ITT population (difference was statistically significant and considered clinically meaningful).
- From week 2 onwards, the observed mean score for FACIT-Fatigue of patients in the pegcetacoplan arm was comparable to scores derived from the general population.

Technical team judgement: Low risk

Indirect evidence: pegcetacoplan and ravulizumab (1)

Matching adjusted indirect comparison (MAIC)

- There is no direct evidence comparing the clinical effectiveness of:
  - pegcetacoplan versus ravulizumab or
  - ravulizumab versus eculizumab in the PEGASUS trial population (i.e. people who had anaemia following treatment with eculizumab).
- The company conducted an anchored MAIC using individual patient data from the PEGASUS trial for pegcetacoplan and eculizumab and adjusted the trial population to match the baseline characteristics reported in Study 302.
- Study 302 was a randomised, open-label, multicentre phase 3 non-inferiority study considered in TA698 which compared ravulizumab versus eculizumab in adult patients with PNH who had previously been treated with eculizumab.
- The indirect comparison was anchored by the eculizumab control arm in both studies.
- Statistically significant advantages for pegcetacoplan over ravulizumab were shown for all outcomes considered in the anchored MAIC (intravascular haemolysis, transfusion avoidance, number of packs of red blood cells transfused, haemoglobin stabilisation and HRQoL).

Technical team judgement: Low risk

Indirect evidence: pegcetacoplan and ravulizumab (2)

Limitations of the MAIC

- The company identified key differences in the designs of the two trials which could not be adjusted to make them comparable including:
  - treatment phases
  - lengths of treatment periods
  - routes of administration
  - treatment administration schedules of pegcetacoplan and ravulizumab
  - dose of eculizumab.
- The company also identified important differences in eligibility criteria:
  - The PEGASUS trial population enrolled adults with PNH who had Hb levels lower than 10.5 g/dL despite treatment with eculizumab
  - Study 302 enrolled adults with PNH who were clinically stable after having been treated with eculizumab for at least 6 months (all patients were eligible regardless of Hb levels)
  - Therefore, the company considered that it was not possible to accurately match the Hb levels of patients between trials.

Technical team judgement: Low risk

Indirect evidence: pegcetacoplan and ravulizumab (3)

Conclusions of the MAIC

- The company and ERG consider that the results of the MAIC may be subject to bias due to these differences and because the impact of key effect modifiers (Hb level and history of transfusions) could not be considered in the matching process.
- Therefore, the company did not use the MAIC results in the model.
- The ERG considers that the MAIC results comparing pegcetacoplan with ravulizumab are not robust for decision-making.

Instead of using the MAIC results, the company assumed equal efficacy between eculizumab and ravulizumab (see slide 20).

Safety

Breakthrough haemolysis (BTH)

- Clinical advice to the ERG is that BTH is an important outcome.
- During the RCP, [redacted]/39 patients ([redacted]%) in the eculizumab arm experienced haemolytic events compared to 4/41 patients (9.8%) in the pegcetacoplan arm.
- A post-hoc analysis showed that 4/41 patients (9.8%) in the pegcetacoplan arm and 9/39 patients (23.1%) in the eculizumab arm were considered to have experienced BTH.
- In the pegcetacoplan arm, 3/41 patients discontinued treatment due to BTH; of these, [redacted] withdrew from the study and [redacted] were able to re-enter the study during the follow-up period

Safety summary

- Company considers that pegcetacoplan is well-tolerated and has an acceptable safety profile.
- The most common treatment-emergent adverse events with pegcetacoplan were injection site reactions, but none were severe or led to treatment discontinuation during the RCP.
- No thromboembolic events or deaths were reported in the trial.

Technical team judgement: Medium risk

Assumed equal efficacy – eculizumab and ravulizumab

- Ravulizumab is a re-engineered form of eculizumab (over 99% homologous) with an extended half-life.
- The results from Study 302 showed that ravulizumab was non-inferior to eculizumab, with point estimates favouring ravulizumab for all primary and secondary endpoints however these were not statistically significant.
- The committee concluded in TA698 that ravulizumab and eculizumab were similarly effective and had a similar safety profile.
- In the current appraisal, the company has therefore assumed equal efficacy between eculizumab and ravulizumab in their base case validated through their clinical expert.

ERG comments

- There is no direct evidence (and only biased indirect evidence) to demonstrate the effectiveness of pegcetacoplan versus ravulizumab in the PEGASUS trial population.
- PEGASUS population is a subset of Study 302 population and the trial designs were different.
- Therefore, it is not possible to be certain from the available evidence that the efficacy of ravulizumab is the same as the efficacy of eculizumab in the PEGASUS trial population
- However, clinical advice to the ERG is that eculizumab and ravulizumab are biologically very similar and the efficacy of the 2 treatments is likely to be equal in any population.

Technical team judgement: Low risk

Clinical effectiveness – robustness of PEGASUS trial

ERG comments

- The ERG considers that the PEGASUS trial was well-designed and well-conducted and that appropriate statistical techniques were used to analyse the data.
- The primary efficacy endpoint results, change from baseline to week 16 Hb levels, were consistent across pre-specified subgroup analyses with pegcetacoplan demonstrating superiority over eculizumab.
- The ERG is satisfied that the methods used to account for confounding of treatment effect, handling missing data and that sensitivity and supportive analyses of the primary outcome were appropriate and pre-specified.

Company comments on bias

- The company consider that because all patients were treated with pegcetacoplan up until the RCP, this means that the beneficial effects of pegcetacoplan were likely to continue in the short term for patients having eculizumab.
- Therefore, this is likely to result in a positive bias for eculizumab rather than pegcetacoplan.

Technical team judgement: Low risk

Clinical effectiveness – maturity of trial evidence

NICE technical team comments

- PEGASUS trial included a small population and limited follow-up period (48 weeks for pegcetacoplan and 16 weeks for eculizumab).
- There is uncertainty in the trial results which are used to inform the transition probabilities in the model for a lifetime time horizon (51 years).
- It should be noted that PNH is a rare condition, and therefore recruitment of large numbers of patients to clinical trials in this disease area may be difficult.
- However, it is unclear whether the trial results are likely to reflect the long-term benefit (including the effect on HRQoL) with treatment with pegcetacoplan.

ERG comments

- Clinical advice to the ERG is that the PEGASUS trial 16-week RCP is sufficient to demonstrate most of the benefit that patients would accrue from treatment with eculizumab or pegcetacoplan. However, a longer term follow-up period would be needed to fully assess clinical effectiveness and long-term safety.
- The ERG explored the impact of assuming that after 1 year, the efficacy of pegcetacoplan was equal to the efficacy of eculizumab (and therefore also ravulizumab) which did not impact the cost-effectiveness conclusions.

Technical team judgement: Low risk

Clinical effectiveness – generalisability of trial results

NICE technical team comments

- PEGASUS trial consisted of 44 sites including the UK (1 of the 2 PNH centres), increasing the likelihood that the trial population is generalisable to the population that would likely receive pegcetacoplan in the NHS.
- This assumption was supported by the company's advisory board with multiple UK clinicians experienced in the treatment of PNH.

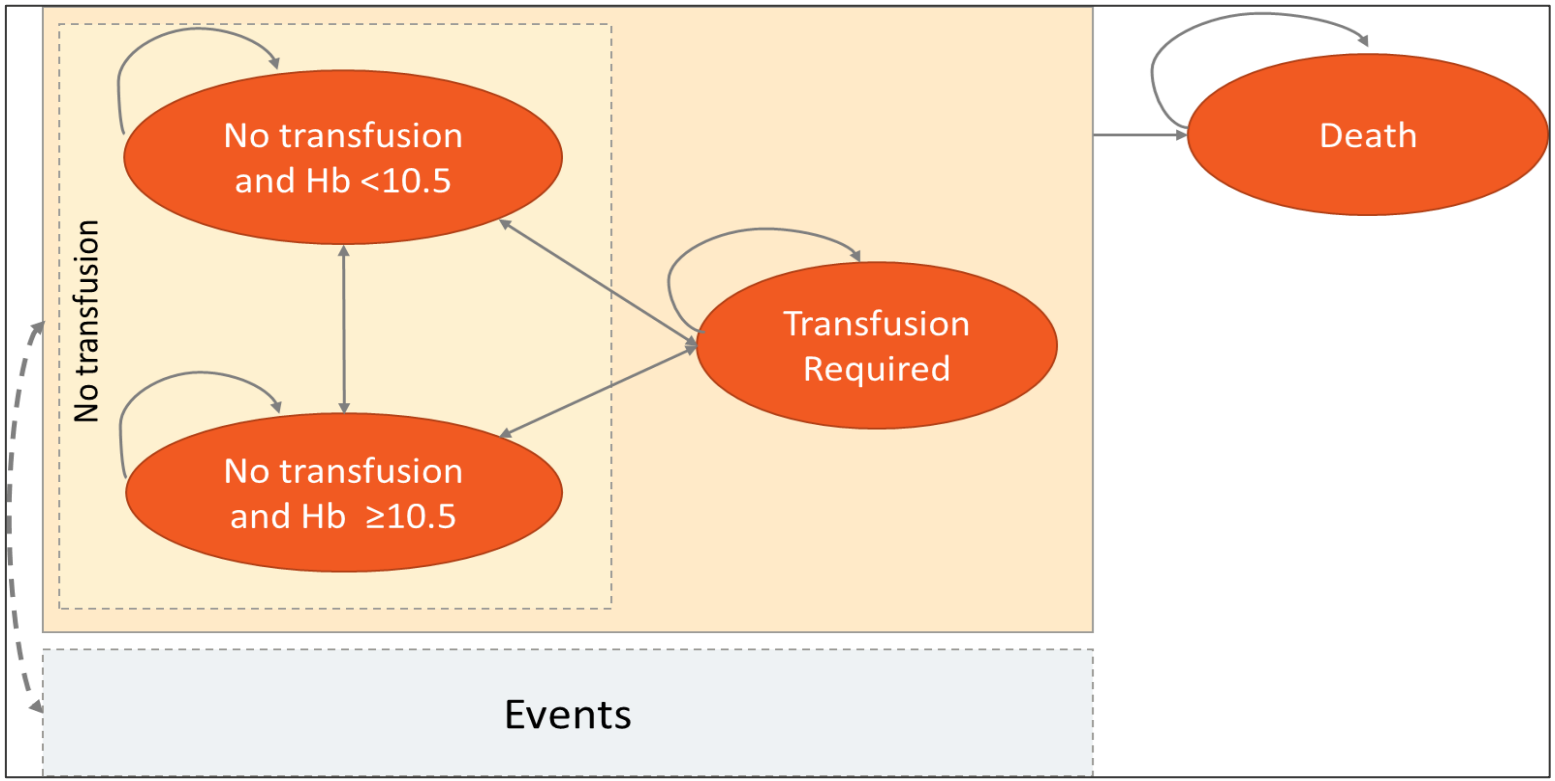
ERG comments

- Clinical advice to the ERG is that the results from the PEGASUS trial are generalisable to patients treated in NHS clinical practice who have uncontrolled anaemia after treatment with a C5 inhibitor for a period of at least 3 months.
- The ERG noted that the trial population included people with PNH with baseline Hb levels <10.5g/dL despite treatment with a stable dose of eculizumab for ≥3 months.
- ERG clinical experts consider that Hb levels greater than 10.5g/dL may also be considered as uncontrolled anaemia in people with PNH. Therefore, the generalisability of this cut-off level to NHS clinical practice is unclear.

Cost effectiveness

Company's cost-effectiveness model

- Cohort-based Markov model.
- All patients begin in the 'no transfusion and Hb <10.5g/dL' health state
- Spontaneous remission was not modelled as this would not be expected to vary by treatment (in line with clinical advice to the company)
- 4-week cycle length with half-cycle correction
- Lifetime time horizon (51 years)



Source: Company submission

Technical team judgement: Medium to low risk

Cost effectiveness – model structure

- The company presented a new model for this appraisal (structure different to TA698) which was designed based on clinical expert opinion and an advisory board.
- The company noted that previous models did not consider EVH, or improvements in fatigue, and so they did not consider these models to be appropriate for capturing the clinical benefits associated with pegcetacoplan.
- The company's clinical experts consider that EVH results in a drop in Hb level and blood transfusions, both of which are captured in the model health states. Therefore EVH is not explicitly modelled, but is captured.
- A haemoglobin cut-off at 10.5g/dL was chosen as it is consistent with inclusion criteria in the PEGASUS clinical trial and was validated by the company's clinical experts as appropriate for capturing differences in HRQoL between health states.
- The company's model uses a cycle length of 4 weeks to align with the PEGASUS trial data and applies a half cycle correction. In TA698, a model cycle length of 2 weeks was used to align with the trial data, however no half-cycle correction was applied.

Technical team judgement: Medium to low risk

Cost effectiveness – quality and validity of model

The ERG considers that the company's model is well built and the model structure reflects the PNH treatment pathway with 2 minor exceptions:

1. Proportion of patients treated with a C5 inhibitor who were receiving chelation therapies at baseline in the model - the ERG has used the proportion reported from the clinical study report ([redacted]) in its base case rather than the value ([redacted]) used by the company based on the PEGASUS trial run-in period, which it considers to be incorrect.

2. Half cycle corrections – the ERG considers the application of half cycle corrections should start from cycle 1 rather than cycle 0 as in the company's model. However, it considers that this would have made a negligible difference to cost effectiveness results.

- Ravulizumab is likely to displace eculizumab over time, and so people who have BTH and discontinue treatment with pegcetacoplan will likely return to their original ravulizumab treatment rather than eculizumab (as in the model).
  - NICE technical team considers that this is not likely to have a large impact on the cost-effectiveness results. This is because BTH requiring discontinuation of treatment occurred in only [redacted] receiving pegcetacoplan at week 16 in the trial and ravulizumab is available to the NHS at a confidential discounted PAS price.

Technical team judgement: Low risk

Cost effectiveness – modelling assumptions from previous appraisals (1)

In TA698, the committee concluded that the proportion of people who get a higher eculizumab dose in the model after IVBTH or an inadequate disease response should be similar to that seen in clinical practice in England.

- In this appraisal, the company has modelled IVBTH only for people receiving treatment with pegcetacoplan who either receive a one-off licensed dose of eculizumab or discontinue treatment with pegcetacoplan (and switch to eculizumab) depending on the severity of the event, in line with their clinical expert opinion.
- The proportion of patients who receive this one-off eculizumab dose is [redacted] per model cycle in line with the PEGASUS trial data, which the company consider to be generalisable to UK clinical practice.
- The model assumes that people having ravulizumab or eculizumab do not experience IVBTH, which the company considers to be a conservative assumption. Expert opinion to the company is that IVBTH with eculizumab is managed in clinical practice by dose adjustments (further dose increases are not included in the model).

Technical team judgement: Low risk

Cost effectiveness – modelling assumptions from previous appraisals (2)

In TA698 the committee concluded that utility values in the base-case should be based on EQ-5D data without an additional utility increment for ravulizumab which captures the benefit of lower infusion frequency compared with eculizumab.

- In this appraisal, the company has used a similar approach to derive utility values as in TA698 by mapping EORTC-QLQ-C30 data collected in the PEGASUS trial to EQ-5D-3L scores to generate health state utility values. The ERG has no concerns relating to this approach.
- The company applied a utility decrement for eculizumab because it is administered more frequently (compared to ravulizumab or pegcetacoplan).
- Removal of this disutility was explored in the company's scenario analysis which did not impact the cost-effectiveness conclusions.

Cost effectiveness results – company base case

ICERs include PAS for pegcetacoplan

Pegcetacoplan versus eculizumab

Deterministic ICER

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Pegcetacoplan	[redacted]	19.706	[redacted]	[redacted]	0.000	[redacted]	**Pegcetacoplan dominates**
Eculizumab	[redacted]	19.706	[redacted]				

ICER = incremental cost-effectiveness ratio; Inc = incremental; LYG = life years gained; QALYs = quality-adjusted life years

Probabilistic ICER

Technologies	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Pegcetacoplan	[redacted]	[redacted]	**Pegcetacoplan dominates**
Eculizumab			

Cost effectiveness results – ERG base case

ICERs include PAS for pegcetacoplan

Pegcetacoplan versus eculizumab

Deterministic ICERs

Assumption	ICER (£/QALY)
Company base case	Pegcetacoplan dominates
1. Chelation therapy proportions from PEGASUS clinical study report	Pegcetacoplan dominates
2. Adverse event costs included (not included in company base case)	Pegcetacoplan dominates
ERG base case (1 + 2)	Pegcetacoplan dominates

Probabilistic ICER

Technologies	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Pegcetacoplan	[redacted]	[redacted]	Pegcetacoplan dominates
Eculizumab			

NICE

Cost effectiveness results – company base case

ICERs include PAS for pegcetacoplan and cPAS for ravulizumab

Pegcetacoplan versus ravulizumab

Deterministic ICER

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Pegcetacoplan	[redacted]	19.706	[redacted]	[redacted]	0.000	[redacted]	**Pegcetacoplan dominates**
Ravulizumab	[redacted]	19.706	[redacted]				

ICER = incremental cost-effectiveness ratio; Inc = incremental; LYG = life years gained; QALYs = quality-adjusted life years

Probabilistic ICER

Technologies	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Pegcetacoplan	[redacted]	[redacted]	**Pegcetacoplan dominates**
Ravulizumab			

Cost effectiveness results – ERG base case

ICERs include PAS for pegcetacoplan and cPAS for ravulizumab

Pegcetacoplan versus ravulizumab

Deterministic ICERs

Assumption	ICER (£/QALY)
Company base case	Pegcetacoplan dominates
1. Chelation therapy proportions from PEGASUS clinical study report at baseline	Pegcetacoplan dominates
2. Adverse event costs included (not included in company base case)	Pegcetacoplan dominates
ERG base case (1 + 2)	Pegcetacoplan dominates

Probabilistic ICER

Technologies	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Pegcetacoplan	[redacted]	[redacted]	Pegcetacoplan dominates
Ravulizumab			

NICE

Technical team judgement: Low risk

Cost effectiveness – sensitivity and scenario analyses

- The company carried out extensive sensitive and scenario analyses, which the ERG considers to be robust for comparisons of pegcetacoplan versus both eculizumab and ravulizumab.
- **The company highlighted that 100% of the probabilistic results fell below the £10,000 per QALY threshold for pegcetacoplan versus both eculizumab and ravulizumab and that pegcetacoplan is 100% cost-effective at all willingness to pay thresholds.**

- The ERG conducted further sensitivity and scenario analyses:
  - using extreme values for key model parameters
  - including adverse event costs (not included in company base case)
  - increasing the discontinuation rate with pegcetacoplan in year 1
  - exploring the impact of assuming that after 1 year, the efficacy of pegcetacoplan was equal to the efficacy of eculizumab (and therefore also ravulizumab).
- **Results from all the scenario and sensitivity analyses carried out by the company and ERG shows that pegcetacoplan dominates both eculizumab and ravulizumab and the ICERs remain under £20,000 per QALY gained.**

Technical team judgement: Low risk

Cost effectiveness – most plausible ICER

ERG comments

- **The most plausible ICERs for comparisons of pegcetacoplan compared with both eculizumab and ravulizumab are likely to be below £20,000 per QALY gained**.
- This is underpinned on the company's base case assumption that the efficacy of ravulizumab is equal to that of eculizumab which is not known for the population who would be expected to receive pegcetacoplan in the NHS.
- If this assumption does not hold, the ICER for pegcetacoplan compared with ravulizumab could be higher than £20,000 per QALY gained.
- The ERG was unable to test the consequence of varying this assumption in the company's model because there is no summary clinical effectiveness measure that can be varied.
- However, the ERG's clinical experts indicated that eculizumab and ravulizumab are likely to be equally efficacious in any population.
- Furthermore, results from PEGASUS indicate that pegcetacoplan is superior to eculizumab in terms of change from baseline in Hb level in the population of interest for this appraisal.

Technical team judgement: Low risk

Cost effectiveness – risk of decision error

- The company estimates that there are about 650 to 900 people in England with PNH.
- Based on 239 people being treated with eculizumab for PNH in the UK in December 2018, the ERG clinical experts consider that approximately 20% of these patients will have a suboptimal response, or their PNH will not be sufficiently controlled. Therefore, it estimates that approximately 50 patients with PNH could be eligible for treatment with pegcetacoplan.
- Company considers that [redacted] people would be eligible to receive pegcetacoplan in NHS in year 1, rising to [redacted] by year 5.
- **NICE technical team considers the risk to the NHS to be low because the eligible population is small and costs for comparators are high (note eculizumab is only available through a highly specialised service).**

Innovation

Comments raised by company, clinical/patient experts, patient organisation:

- Pegcetacoplan will be the first and only C3 inhibitor that can effectively control PNH by preventing both intravascular and extravascular haemolysis.
- Pegcetacoplan is the first self-administered subcutaneous infusion therapy in PNH.

Equality

Potential issues raised during scoping:

- Because pegcetacoplan is given by subcutaneous injection and can be self-administered at home, this may have implications for people who have physical or learning disabilities as they may struggle with the self-administration, especially if they have manual dexterity issues.
- Age and pregnancy were highlighted as protected characteristics. Inequalities may arise if different recommendations are made for children and pregnant women.

- **Children and pregnant women were excluded from the PEGASUS trial. Clinical expert submission to NICE states that pegcetacoplan should not be used in pregnancy.**
- **The committee can only make recommendations within a technology's marketing authorisation.**

Key considerations

- The assumption of equal efficacy between ravulizumab and eculizumab in the PEGASUS trial population is reasonable.
- The ERG considers that the company's model is well built and satisfactorily reflects the treatment pathway for paroxysmal nocturnal haemoglobinuria.
- All the scenario and sensitivity analyses carried out by the company and ERG show that pegcetacoplan dominates both eculizumab and ravulizumab.
- Company and ERG consider that the most plausible ICERs for pegcetacoplan versus eculizumab and ravulizumab are below £20,000 per QALY gained.
- Risk to NHS is low: small eligible population and high comparator costs.
- Based on the above, there are no critical issues for consideration by the committee.

⊙ ***Is it likely that the most plausible ICER is below £20,000 per QALY gained?***
⊙ ***Is it highly unlikely to be above £30,000 per QALY gained?***

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Pegcetacoplan for treating paroxysmal nocturnal haemoglobinuria [ID3746]

Document B

Company evidence submission

May 2021

File name	Version	Contains confidential information	Date
Document B_AiC_CiC	**v1.0**	**Yes**	**20/05/21**

Contents

Tables and figures

B.1 Decision problem, description of the technology and clinical care pathway

- Paroxysmal nocturnal haemoglobinuria (PNH) is a rare blood condition in which red blood cells are attacked by the body's immune system (1). The incidence of PNH in Great Britain has been estimated as approximately 1 in 770,000 each year, with a predicted prevalence of approximately 1 in 62,500 (2). [Link]
- PNH is an acquired condition, meaning it is not inherited so cannot be passed on from parent to child (1). PNH is a chronic condition that is associated with complications that can be severely debilitating and life threatening including abdominal pain, kidney problems, fatigue, shortness of breath, bleeding and blood clots, dysphagia, organ damage, and premature mortality (3). [Link]
- It takes close to two years, on average, though sometimes more than five years, and often multiple clinicians to correctly diagnose PNH due to its rarity and the nature of its diverse symptoms (4,5). The length of time to diagnosis is often be a source of distress affecting the patient's emotional well-being. [Link]
- The current treatment strategy in the UK is focused on managing disease symptoms with C5 inhibitors: eculizumab and ravulizumab. Supportive care includes blood transfusions, steroids, anticoagulants and supplements (6). [Link]
- There is an unmet need to control both forms of haemolysis as C5 inhibitors only target underlying intravascular haemolysis (IVH) but do not address extravascular haemolysis (EVH), resulting in suboptimal control of the disease and remaining symptoms (7). Up to 89% of patients treated with a eculizumab have an incomplete response and continue to experience uncontrolled haemolysis, persistent chronic anaemia, and/or have continued blood transfusions (8). [Link]
- Pegcetacoplan is a novel C3 inhibitor and will be the first and only therapeutic option approved that can effectively control PNH by preventing both IVH and EVH which cause anaemia. By targeting the complement cascade earlier than

C5 inhibitors, improvements in haematological parameters, such as haemoglobin, bilirubin, reticulocytes, and lactase dehydrogenase (LDH), can be achieved (6). [Link]

- PEGASUS, the pivotal randomised controlled trial (RCT) for pegcetacoplan, demonstrated head-to-head superiority in adjusted (least squares [LS]) mean change in haemoglobin (Hb) levels (3.84 g/dL difference; 95% confidence interval: 2.33; 5.34. P value: <0.0001[1]) versus eculizumab, resulting in transfusion avoidance (pegcetacoplan: 85.4%; eculizumab: 15.4%). These benefits were observed regardless of baseline transfusion requirement. Pegcetacoplan also demonstrated clinically meaningful improvements in health-related quality of life (HRQoL) (Functional Assessment of Chronic Illness Therapy [FACIT] Fatigue, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 [EORTC QLQ-C30] and Linear Analog Assessment Scale [LASA]). Pegcetacoplan was well tolerated and had an acceptable safety profile (10). [Link]

B.1.1 Decision problem

This submission covers the full marketing authorisation planned for pegcetacoplan as a treatment of adult anaemic patients with PNH who are not sufficiently controlled by treatment with a C5 inhibitor for at least 3 months.

The decision problem that is addressed in this submission is presented in Table 1.

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[1] Information regarding the PEGASUS trial has been taken from the published article by Hillmen et al. (2020) identified in the SLR, supplemented with information from the clinical study report (CSR) (9,10). Please note the New England Journal of Medicine recommends P values to be reported to no more than three decimal places. Throughout the submission, P values are presented in full from the CSR where possible. (11)

Table 1 The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with paroxysmal nocturnal haemoglobinuria whose anaemia is not controlled after treatment with a C5 complement inhibitor	As per NICE scope	N/A
Intervention	Pegcetacoplan	As per NICE scope	N/A
Comparator(s)	• Eculizumab • Ravulizumab [subject to NICE appraisal]	• As per NICE scope	N/A
Outcomes	The outcome measures to be considered include: • Overall survival • Intravascular haemolysis • Extravascular haemolysis • Breakthrough haemolysis • Transfusion avoidance • Hb • Thrombotic events • Adverse effects of treatment • Health-related quality of life	The outcome measures included are: • IVH (largely measured by LDH level) • EVH (largely measured by bilirubin) • Transfusion avoidance • Hb, including normalisation and response • Thrombotic events • Adverse effects of treatment • Health-related quality of life	Breakthrough haemolysis and overall survival are not included as these were not endpoints in the PEGASUS study. Post-hoc analyses of breakthrough haemolysis are considered where possible. In addition, aligned with the population pegcetacoplan is indicated for, Hb normalisation and response are included.
Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	There are no special considerations relating to issues of equity or equality.	N/A

Abbreviations: EVH, extravascular haemolysis; Hb, haemoglobin; IVH, intravascular haemolysis; LDH, lactate dehydrogenase; N/A, not applicable; NICE, National Institute for Health and Care Excellence; NHS, National Health Service; SoC, standard of care

B.1.2 Description of the technology being appraised

Table 2 presents a description of pegcetacoplan as a treatment for patients with PNH whose anaemia is not sufficiently controlled after treatment with a C5 complement inhibitor. The draft Summary of Product Characteristics (SmPC) can be found in Appendix C.

Table 2 Technology being appraised

UK approved name and brand name	Pegcetacoplan (brand name to be confirmed)
Mechanism of action	Pegcetacoplan inhibits complement proteins C3 and C3b. EVH is the result of unregulated C3, which due to the complement cascade, activates complement protein C5, in turn causing IVH. Pegcetacoplan prevents both IVH and EVH, by targeting the complement cascade earlier than C5 inhibitors, as demonstrated by results in PEGASUS. In PEGASUS, pegcetacoplan demonstrated improvements in Hb levels from baseline, reduction in absolute reticulocyte count (ARC) (improvement in EVH) and decreased LDH levels (improvement in IVH) and other haematological parameters (6)
Marketing authorisation/CE mark status	An application was submitted to the European Medicines Agency in September 2020. [redacted]. No conditional UK marketing authorisation is anticipated.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	In line with the proposed label from the EMA, pegcetacoplan is indicated in the treatment of [redacted]

	[redacted]
Method of administration and dosage	Pegcetacoplan is self-administered twice weekly as a 1,080 mg subcutaneous infusion with a commercially available syringe system infusion pump that can deliver volumes up to 20 ml. The twice weekly dose will be administered on day 1 and day 4 of each treatment week. According to the draft SmPC, for the first 4 weeks, pegcetacoplan is administered as twice weekly subcutaneous doses of 1,080 mg in addition to the patient's current dose of C5 inhibitor treatment to minimise the risk of haemolysis with abrupt treatment discontinuation. After 4 weeks, the patient will discontinue C5 inhibitor before continuing on monotherapy with pegcetacoplan. Clinical advice to date suggests that this period of simultaneous administration may not happen in clinical practice, relying on the ongoing effect of C5 inhibition while initiating pegcetacoplan (13). [redacted] In the event of a dose increase, monitor LDH twice weekly for at least 4 weeks. Clinical advice to date suggests that in clinical practice clinicians would use a single dose of eculizumab at 900 mg to block IVH indicated by an increased LDH level (13). PNH is a chronic disease and treatment with pegcetacoplan is recommended to continue for the patient's lifetime unless the discontinuation of pegcetacoplan is clinically indicated.
Additional tests or investigations	Before receiving treatment with pegcetacoplan, in patients with a known history of vaccination, ensure that patients have received vaccines against encapsulated bacteria including *Streptococcus pneumoniae*, *Neisseria meningitidis* types A, C, W, Y, and B, and Hib within two years prior to starting pegcetacoplan. For patients without known history of vaccination, administer the required vaccines at least 2 weeks prior to receiving the first dose of pegcetacoplan.

	If immediate therapy with pegcetacoplan is indicated, administer required vaccine as soon as possible and provide patients with two weeks of antibacterial drug prophylaxis.
List price and average cost of a course of treatment	The anticipated list price of pegcetacoplan is [redacted] for one dose of a 1,080mg vial. At the recommended dose of 1,080mg twice weekly, this equates to an annual treatment cost of [redacted]
Patient access scheme (if applicable)	A confidential PAS has been approved by the PASLU. This arrangement is in the form of a [redacted]

Abbreviations: EVH, extravascular haemolysis; Hb, haemoglobin; Hib, Haemophilus influenzae Type B; IVH, intravascular haemolysis; LDH, lactate dehydrogenase; PAS, patient access scheme; PASLU, Patient Access Scheme Liaison Unit

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B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease overview

PNH is an extremely rare, chronic, life threatening blood disease that affects younger adults (14). The incidence of PNH in Great Britain has been estimated as approximately 1 in 770,000 each year, with a predicted prevalence of approximately 1 in 62,500 (2). It is estimated that there are about 650 to 900 people in England with PNH (15,16). PNH can occur at any age but is most frequently diagnosed between the ages of 30-40 years old (17).

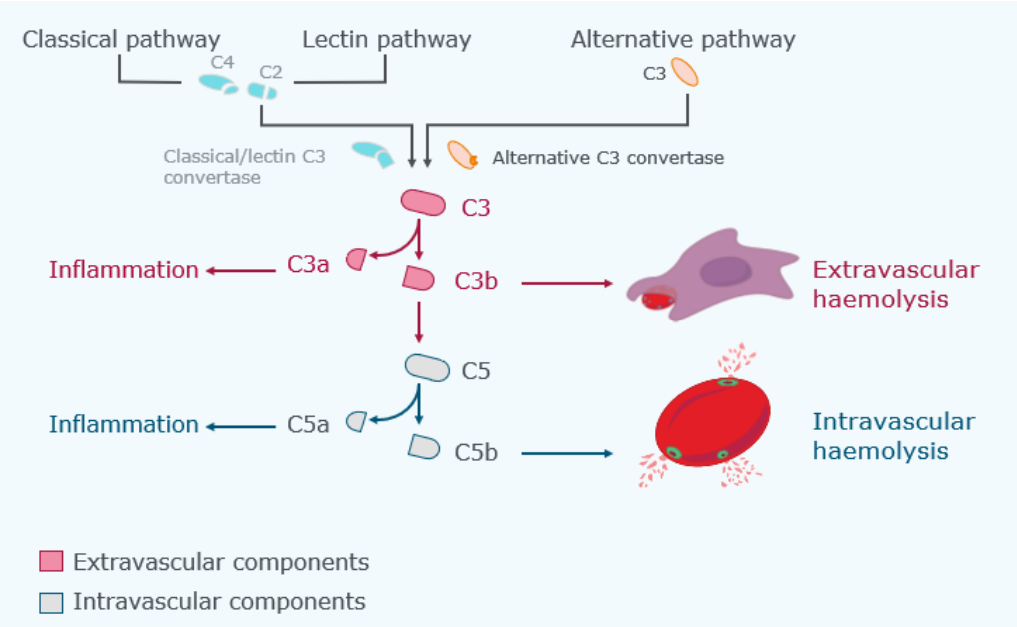
PNH is an acquired blood disorder in which stem cells acquire a gene mutation resulting in the production of abnormal blood cells. Defective red blood cells, white blood cells and platelets lack the connector (known as glycosylphosphatidylinositol [GPI]) for two important surface proteins (CD55 and CD59) that regulate complement activity. Lack of these surface proteins make the red blood cells susceptible to destruction by the body's own complement system. The complement system (complement cascade) is a group of more than 30 proteins that support

(complement) the work of antibodies and phagocytic cells to clear microbes and damaged cells, promote inflammation, and attack the pathogen's cell membrane (14,18,19). The PNH complement cascade is displayed in Figure 1.

The lack of GPI results in the complement protein C3 becoming unregulated, which triggers all downstream effectors that ultimately cause destruction of blood cells (haemolysis) and formation of life-threatening blood clots (thrombosis) (9). PNH is characterised by intravascular haemolysis (IVH), the lysis of red blood cells (RBCs) within circulation, and extravascular haemolysis (EVH), when RBCs are destroyed by phagocytosis in areas outside of circulation, typically in the spleen or liver (14,18,19).

IVH with resultant anaemia often leads to transfusion dependence, severe disabling symptoms of haemolysis and, frequently, thrombosis (blood clotting). The risk of thrombosis is increased in people with PNH and increased further for those with PNH and who are pregnant. PNH also leads to EVH, which is often inconspicuous in the untreated PNH patient because signs and symptoms of IVH dominate. However, EVH can become the primary mechanism of haemolysis in patients treated with C5 inhibitors (7).

Figure 1 PNH complement cascade



Source: Adapted from Merle (2015) (20)

PNH is associated with a high burden of disease, as shown by the proportion of patients who have high disease activity (51.6%), history of major adverse vascular events (18.8%), thrombotic events (13.3%), red blood cell transfusions (61.3%), and impaired renal function (42.8%), if untreated (21). Anaemia can cause multi-organ failure and fatal disease complications if untreated with a 10-year mortality rate of 24-29% (22–24). This can include high output heart failure, angina, arrhythmias, cognitive impairment, and renal failure, among others (25). Despite current treatment, C5 inhibition, the majority of patients with PNH continue to experience uncontrolled haemolysis leading to severe anaemia, blood transfusion dependence, fatigue, and reduced quality of life (8).

B.1.3.2 Clinical manifestations

Haemolysis

Haemolysis is the rupturing of RBCs resulting in the release of their cellular content into the surrounding environment. Upon rupture, indirect bilirubin levels, a yellowish substance in your blood that forms after the breakdown of RBCs, are elevated. The rupture of RBC that occurs within circulation and outside circulation; IVH and EVH, respectively(7), can manifest as persistent anaemia despite C5 inhibitor treatment and may contribute to the need for continued blood transfusions (9).

Haemolysis is directly correlated with fatigue that can be debilitating and is associated with substantial pain. Combined, these significantly impair patients quality of life if the disease is left untreated (26).

Anaemia and Haematological Parameters

As a result of IVH and EVH, patients often present with anaemia and have elevated levels of LDH and haemoglobinuria (27). Chronic anaemia can be life threatening as it results in a decreased oxygen-carrying capacity of the blood. In the short term, the body is able to counteract with an increase in heart rate and respiratory rate; left untreated, anaemia can cause multi-organ failure. This can include high output heart failure, enlarged heart, myocardial infarction, angina, arrhythmias, cognitive

impairment, and renal failure, among others (25). In pregnant women, untreated anaemia can cause premature birth and low birth weight (25)

Because LDH is present in RBCs, the release upon cell destruction correlates with the extent of RBC damage and bilirubin levels. Released Hb is eventually excreted via urine, and the level of serum Hb is a direct marker of the severity of the haemolysis and a predictor of therapy outcome. It also correlates with the risk of death (28).

Fatigue and Haemoglobinuria

Fatigue is the leading symptom among patients with PNH and is most pronounced during a haemolytic episode. The majority of patients (over 80%) report experiencing fatigue, which may result in loss of independence, decreased physical activity, and functional decline, if untreated (29,30). Haemoglobinuria, after which PNH is named, is experienced by almost 50% of patients (14). Haemolysis, the breakdown of RBC, is directly correlated with fatigue that can be debilitating (7).

Smooth Muscle Dystonia

Depending on the severity of PNH, patients may experience chronic IVH. The breakdown of RBC releases free Hb which causes the depletion of nitric oxide (NO), which is important for smooth muscle cell regulation. Absence or lower amounts of NO can have, consequently, gastrointestinal spasms, abdominal pain, difficulty swallowing, vasoconstriction, pulmonary and systemic hypertension, and erectile dysfunction (27). Depletion of NO can also precipitate thrombosis as it can activate platelets, causing them to aggregate (27).

Thrombosis

Occurrence of thrombosis is a significant source of morbidity and mortality. In untreated patients with PNH, thrombosis accounts for up to 50% of mortality (14). Thrombosis occurs in about 40% of patients with PNH. Most common are venous thrombosis of the liver (Budd-Chiari syndrome), abdomen (portal, mesenteric, splenic) and the brain (sagittal and cavernous sinus). In addition, deep vein

thrombosis, pulmonary emboli, and dermal thrombosis are common. The risk of developing thrombosis is correlated with the size of the PNH clone and the severity of IVH that causes the release of haemoglobin and depletion of NO, which in turn activates platelets (27,31).

B.1.2.3 Diagnosis

Patients should be screened for PNH who present with a Coombs-negative haemolytic anaemia, aplastic anaemia, refractory anaemia, or unexplained thrombosis, especially in atypical locations (Budd-Chiari syndrome, cerebral, dermal and intra-abdominal vein thrombosis) co-occurring with cytopenia or haemolysis (18).

Guidelines for the diagnosis, treatment, and management of PNH have been described by several PNH organisations. The PNH Education Study Group (PESG), established in 2013, outlines a treatment algorithm for PNH that groups treatments into three categories: supportive/immunosuppressive treatments, treatments changing the course of disease, and potential curative treatment (32). To date, no clinical guidelines have been published by NICE.

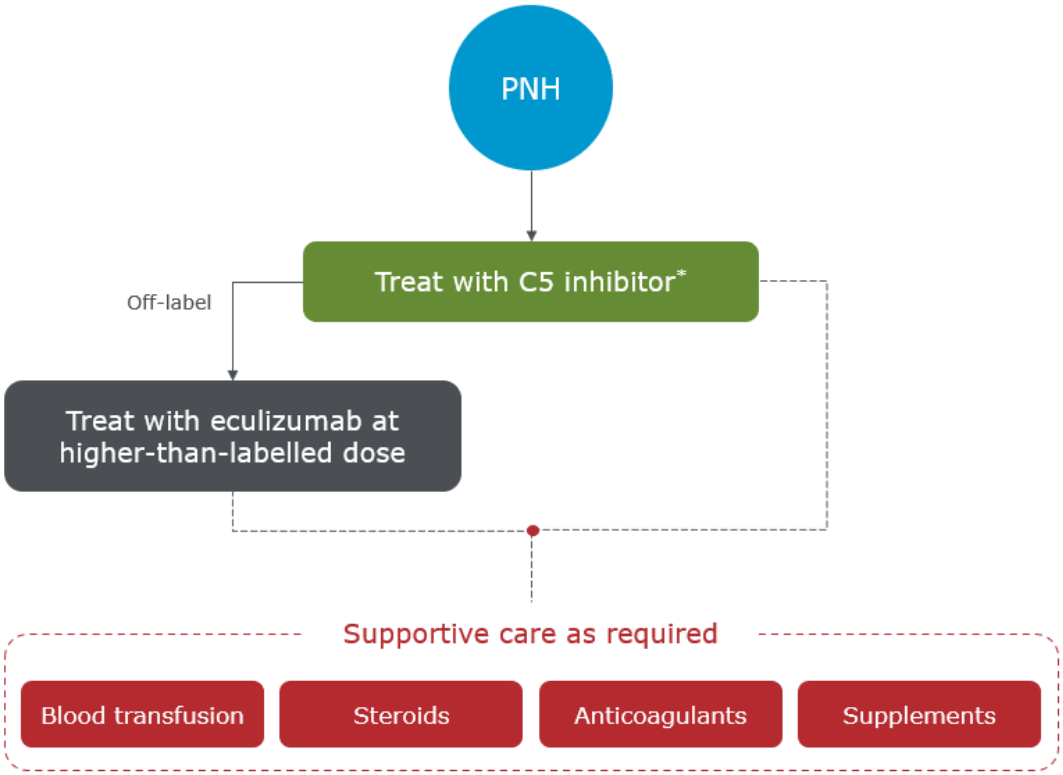
It takes close to two years, on average, though sometimes more than five years, and often multiple clinicians to correctly diagnose PNH due to its rarity and the nature of its diverse symptoms (5). More than one-third of patients reported to have received a diagnosis more than two years after onset of symptoms; in some cases, it took more than five years (4,5). The length of time to diagnosis can be a source of distress affecting the patient's emotional well-being.

B.1.3.3 Overview of treatment landscape

Guidelines on therapeutic treatment for PNH have also been outlined by the International PNH Interest Group (33,34). The current treatment pathway is focused on managing disease symptoms with a C5 inhibitor, eculizumab, currently used in routine clinical practice in England (Figure 2). Ravulizumab has recently been licensed for treatment for patients with PNH (35). In addition, as of April 2021,

ravulizumab was recommended by NICE as an option for treating PNH (36), suggesting that it may shortly become SoC.

Figure 2 Management of PNH



*Eculizumab or ravulizumab
Source: Adapted from Parker (2016) (33)
Abbreviations: PNH, paroxysmal nocturnal haemoglobinuria

Curative treatment

Currently, the only cure for PNH is an allogeneic bone marrow transplant (5). Because of the considerable challenges and risks involved, a bone marrow transplant is not a therapeutic option for most patients and is typically recommended for patients with severe bone marrow failure, reoccurring life threatening thromboembolic incidences, and refractory transfusion-dependent haemolytic anaemia (31,32). In a retrospective study of 26 patients with PNH who received haematopoietic stem cell transplants between 1988 and 2006, the transplant-related mortality rate was 42% (37).

Non-curative treatment

The current treatment strategy is mostly focused on managing disease symptoms and HRQoL.

C5 complement inhibitors

Eculizumab and ravulizumab are, to date, the only US Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved therapies for PNH. NHS England commissions the treatment as a highly specialised service (3,36).

Eculizumab was granted FDA approval in March 2007 and EMA approval in June 2007 and is indicated for use in adults and children with PNH (38,39).

Ravulizumab was approved by the FDA for adult patients with PNH in December 2018 (40). The EMA approved ravulizumab in July 2019 and it is indicated for use in adult patients with PNH with haemolysis with clinical symptoms indicative of high disease activity and also for adult patients who are clinically stable after having been treated with eculizumab for at least the past 6 months (41). Ravulizumab was recommended by NICE in April 2021 for use in adult PNH patients with haemolysis with clinical symptoms suggesting high disease activity, or whose disease is clinically stable after having eculizumab for at least 6 months (36).

Eculizumab is an intravenous infusion that is administered every two weeks. Eculizumab blocks the activation of complement protein C5 and therefore protects the PNH cells from destruction or stimulation. Patients on eculizumab have, therefore, improved haemoglobin levels, thus requiring less frequent blood transfusion. Patients with PNH and kidney disease have also shown sustained improvements on renal functions, likely due to reduced IVH, normalised NO levels, and vascular tone (42). The decreased IVH has been associated with reduced fatigue and improved overall quality of life measurements (31). Eculizumab has been shown to improve survival to a similar level to that of the general population (43). As soon as eculizumab therapy is stopped, complement C5 will become active and the PNH cells that were previously protected will be vulnerable to complement attack again, therefore eculizumab is a chronic treatment (1).

Ravulizumab, an eculizumab-like monoclonal antibody, provides the same benefits as eculizumab (based on results of noninferiority studies), but it has a four-times longer half-life. It is administered via intravenous infusion and, depending on patient's weight, it may take several hours of infusion time (44). Eculizumab is administered intravenously every 2 weeks, whereas ravulizumab is administered every 8 weeks (45).

Even on eculizumab, up to 89% of patients have an incomplete response and continue to experience uncontrolled haemolysis, persistent chronic anaemia, and/or have continued blood transfusions (8). As eculizumab and ravulizumab are C5 inhibitors, they only target underlying IVH but do not address EVH, resulting in the majority of patients with PNH still experiencing uncontrolled haemolysis, leading to severe anaemia, blood transfusion dependence, fatigue, and reduced quality of life (7,8,14).

Supportive care

Blood transfusion: Depending on the symptoms of anaemia, patients may receive supportive treatments, such as blood/erythrocyte transfusion, despite treatment with C5 inhibitors. Transfusions temporarily improve haemolysis and elevate Hb levels. Chronic transfusions can lead to iron overload, which is associated with an elevated risk of morbidity and mortality. Transfusion dependence has a negative impact on a patient's HRQoL and also requires substantial resources, including hospital admissions (46). By offering improvements in Hb levels and other haemolysis measures, pegcetacoplan offsets the health care resource utilisation in PNH, including blood transfusions.

Steroids: The use of corticosteroids to improve haemolytic anaemia is varied, and has not been supported by strong efficacy and safety data. It has been recommended only for short-term use in symptomatic EVH because of its considerable side effects (32,47). The underlying mechanism of action in preventing haemolysis is not yet well understood. Pegcetacoplan has been shown to target EVH (9), and its recommendation would remove the need to prescribe steroids, which have inconsistent response rates and unfavourable toxicity profiles.

Anticoagulants: To reduce the risk of thrombosis, prophylactic anticoagulant therapy with cumarin derivatives and heparin may be an important option. In the event of acute thrombosis, anticoagulant therapy with heparin is used (32). Even with preventive anticoagulant therapy, thrombohaemolytic risk remains high (30). Treatment with pegcetacoplan successfully prevents thrombosis, the main life threatening complication of PNH, by targeting the complement activation destruction of PNH cells (9).

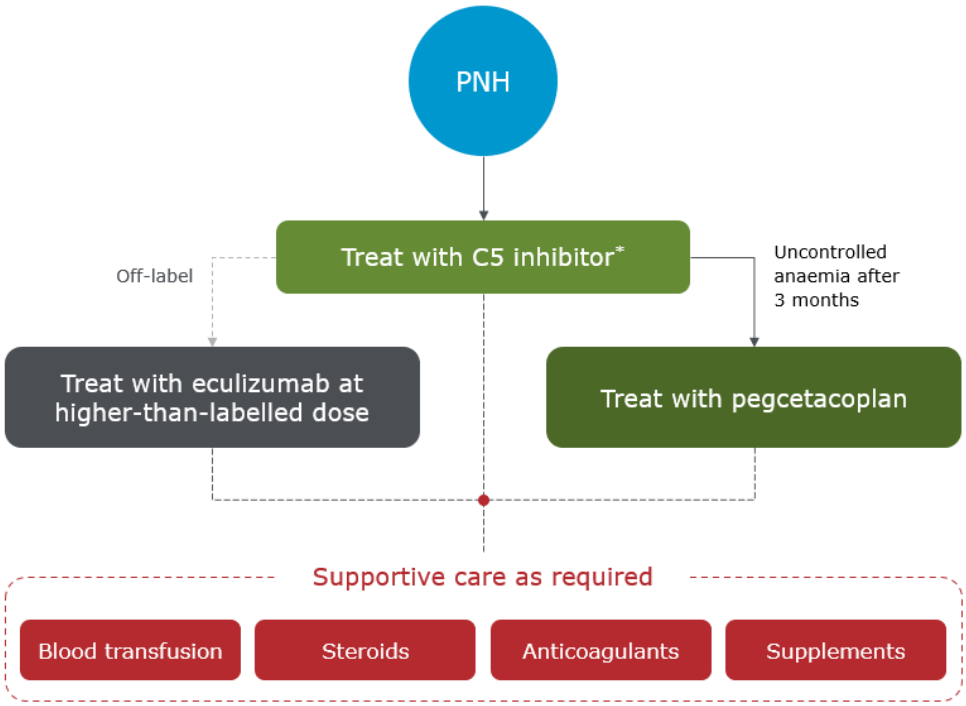
Supplements: Folate and vitamin B12 supplements can be used in order to support increased erythropoiesis (red blood cell formation) in the bone marrow but is not used to treat the underlying condition (32,34). As such, it is evident that there remains a large unmet need for a safe and effective therapy which increases erythropoiesis and consequently the development of reticulocytes.

B.1.3.4 Place of pegcetacoplan in the treatment pathway

Pegcetacoplan is a novel C3 inhibitor and will be the first and only therapeutic option approved that can effectively control PNH by preventing both the IVH and EVH that cause anaemia. By targeting the complement cascade earlier than C5 inhibitors, improvements in haematological parameters, such as Hb, bilirubin, reticulocytes, and LDH, can be achieved (6).

The proposed place in the treatment pathway for pegcetacoplan is as treatment of adult anaemic patients with PNH who are not sufficiently controlled by treatment with a C5 inhibitor for at least three months, as shown in Figure 3.

Figure 3 Proposed future management of PNH



*Eculizumab or ravulizumab
Source: Adapted from Parker (2016) (33)
Abbreviations: PNH, paroxysmal nocturnal haemoglobinuria

Pegcetacoplan has demonstrated head-to-head superiority in adjusted (LS) mean change in Hb levels (3.84 g/dL increase; 95% confidence interval 2.33-5.34) versus eculizumab, resulting in transfusion avoidance (pegcetacoplan: 85.4%; eculizumab: 15.4%). These benefits were observed regardless of baseline transfusion requirement. Pegcetacoplan also demonstrated clinically meaningful improvements in HRQoL (FACIT-Fatigue, EORTC QLQ-C30 and LASA) (9). Pegcetacoplan was also well tolerated and has an acceptable safety profile (10). Pegcetacoplan is the first self-administrated subcutaneous infusion therapy in PNH, enhancing patient control in disease management and delivering savings by reducing the cost and burden of administration in a clinical setting.

The recommendation of pegcetacoplan, which addresses both IVH and EVH, would present an opportunity to provide control to patients whose symptoms are currently not sufficiently controlled by C5 inhibitors (7).

B.1.4 Equality considerations

There are no known equality issues relating to the use of pegcetacoplan in patients with PNH whose anaemia is not sufficiently controlled after treatment with a C5 complement inhibitor.

Pegcetacoplan is the first at home, self-administrated subcutaneous infusion therapy in PNH. Eculizumab, the current SoC, requires twice-monthly dosing by IV infusion for 3-4 hours, which is a major inconvenience for these patients receiving lifelong therapy. Self-administration of pegcetacoplan will enable improved patient satisfaction as disruptions to day-to-day routines are minimised. There is also potential for considerable savings as the burden of administration is reduced. These benefits can be linked to the NHS Long Term Plan and the need to provide a treatment that can be delivered at home, to avoid unnecessary hospital attendance, transfusion risks and hospital-acquired infections.

Self-administration also benefits equity of care through accessible treatment at home by avoiding potential accessibility barriers such as travel, and the substantial time commitments required from patients and their caregivers for the intravenous (IV) administration of C5 inhibitors. Sobi aim to ensure equity of care by providing ongoing home nurse support for patients treated with pegcetacoplan.

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B.2 Clinical effectiveness

Summary of clinical effectiveness

- The clinical effectiveness for pegcetacoplan is based on the PEGASUS trial. PEGASUS was a phase III, prospective, randomised, multicentre, open-label, active-comparator controlled study in patients with PNH who continued to have Hb levels <10.5g/dL despite treatment with eculizumab. Patients were randomised 1:1 to receive either pegcetacoplan (N=41) at a dose of 1,080 mg self-administered subcutaneously (SC) twice weekly, or eculizumab (N=39) administered by IV infusion at a current prescribed dosage that had been stable for at least 3 months prior to screening (9). [Link]

- Baseline demographics and disease characteristics were generally well balanced across treatment groups and representative of the United Kingdom (UK) PNH patient population(13) . Hb levels were aligned across both arms (pegcetacoplan: 8.69 g/dL; eculizumab: 8.68 g/dL) and more than half of patients in each group reported they had ≥4 transfusions in the preceding 12 months (pegcetacoplan: 51.2%; eculizumab: 59%). The outlier to this was lactase dehydrogenase (LDH), which was slightly higher, with greater variability, in the eculizumab group than in the pegcetacoplan group (308.64 [SD: 284.84] versus [SD: 97.65], respectively). [Link]

- Pegcetacoplan demonstrated improvements in Hb levels from baseline and controlled the haematologic manifestations of PNH. Pegcetacoplan met the primary efficacy endpoint, demonstrating head-to-head superiority in Hb levels versus eculizumab. The difference in least-squares (LS) mean change from baseline (CFB) in Hb between the two groups of 3.84 g/dL was highly statistically significant (95% CI: 2.33; 5.34. P value: <0.0001). The clinical benefit of pegcetacoplan was rapid and sustained over time (10). [Link]

- Extensive supportive and sensitivity analyses robustly demonstrated that pegcetacoplan improves Hb levels from baseline, with superiority over

eculizumab. The results of the primary efficacy endpoint of CFB in Hb at Week 16 were reproduced consistently across all additional prespecified analyses, and were retained regardless of subgroups, baseline transfusion status, or baseline platelet count, demonstrating the robust nature of the results. [Link]

- Secondary endpoint analyses demonstrated that pegcetacoplan was noninferior to eculizumab in transfusion avoidance. Pegcetacoplan enabled 85.4% of patients to be transfusion-free compared to 15.4% of patients treated with eculizumab. [Link]

- Pegcetacoplan was shown to improve both extravascular haemolysis (EVH), through improvements (reduction) in absolute reticulocyte count (ARC), and intravascular haemolysis (IVH), through LDH normalisation. The LS mean CFB of ARC at 16 weeks was -135.82× 10^9cells/L for pegcetacoplan and 27.29× 10^9cells/L for eculizumab. Furthermore, a total of 70.7% of patients treated with pegcetacoplan achieved LDH normalisation versus 15.4% of patients treated with eculizumab. In the pegcetacoplan group, [redacted] of patients met the definition for Hb response at Week 16, compared to [redacted] patients in the eculizumab group. Similarly, 34.1% of patients treated with pegcetacoplan achieved Hb normalisation at Week 16, compared to 0% of patients treated with eculizumab. Reticulocyte normalisation occurred for the majority of patients in the pegcetacoplan group (78%), in comparison to only 1 patient (2.6%) in the eculizumab group. Patients in the pegcetacoplan group also had greater mean decreases from baseline in indirect bilirubin than patients in the eculizumab group, at all time points. [Link 1] [Link 2]

- Pegcetacoplan improved HRQoL compared to eculizumab. There was a considerable and clinically meaningful improvement in FACIT-Fatigue scores at Week 16 with pegcetacoplan as compared with eculizumab (9.22 compared to. -2.65 points; P value: 0.0005). Results demonstrate that patients taking pegcetacoplan report similar levels of quality of life as the general population. At just Week 2, the pegcetacoplan group FACIT-Fatigue

score of 43.38 is aligned to the general population score of 43.6 (21,48). Improved HRQoL with pegcetacoplan compared to eculizumab was also demonstrated when measured by LASA and EORTC-QLQ-C30. [Link 1] [Link 2]

- Treatment with pegcetacoplan was well tolerated and had an acceptable safety profile. General disorders and administration site conditions were the most frequently reported system organ class (SOC) of treatment-emergent adverse events (TEAEs), occurring in [redacted] in the pegcetacoplan group and [redacted] in the eculizumab group. The difference in TEAEs was mostly accounted by the greater number of patients who reported injection site reactions (ISRs) in the pegcetacoplan group compared with the eculizumab group. This was expected as pegcetacoplan is administered subcutaneously whereas eculizumab is administered intravenously and patients entering the study were already known to tolerate eculizumab as all patients were receiving eculizumab prior to entering the study. Haemolytic TEAEs were reported more frequently in the eculizumab group as compared with the pegcetacoplan group. Specifically, there were 11 patients (28.2%) in the eculizumab group, compared with 4 patients (9.8%) in the pegcetacoplan group, who had haemolytic TEAEs. [Link]

- Current treatment with C5 inhibitors that is the current standard of care (SoC), only targets IVH, leaving EVH untreated, resulting in suboptimal control of the disease, ongoing anaemia and transfusion dependence. Pegcetacoplan controls both IVH and EVH, reducing the need for dose increases to control ongoing haemolytic episodes, with [redacted] of pegcetacoplan patients increasing their dosing frequency. [Link]

- By improving Hb levels and reducing transfusion requirements, pegcetacoplan will reduce resource utilisation and direct costs and has the potential to create societal benefit from increased productivity and reduced carer burden. [Link]

- Pegcetacoplan is a novel C3 inhibitor and will be the first and only therapeutic option that can fully control PNH by preventing both IVH and EVH. Pegcetacoplan offers an innovative, effective self-administered subcutaneous therapy option for patients with PNH, reducing anaemia, fatigue and transfusion dependence and improving patient HRQoL. [Link]

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B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify relevant literature regarding the efficacy and safety of treatments for PNH. Full details of the methodology and results of the SLR are detailed in Appendix D.

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B.2.2 List of relevant clinical effectiveness evidence

The SLR identified one randomised controlled trial (RCT) that evaluated the efficacy and safety of pegcetacoplan in adult anaemic patients with PNH who are not sufficiently controlled by treatment with a C5 inhibitor. PEGASUS (APL2-302) was a phase III, prospective, randomised, multicentre, open-label, active-comparator controlled study in patients with PNH who continued to have Hb levels <10.5 g/dL despite treatment with eculizumab. The clinical data and cost-effectiveness analyses presented in this submission are therefore based on this study. Table 3 details the clinical effectiveness evidence from PEGASUS that is relevant to this submission.

Table 3 Clinical effectiveness evidence

Study	PEGASUS (APL2-302) ClinicalTrials.gov registration: NCT03500549, extension study: NCT03531255 Hillmen et al. (2020)				
Study design	Phase III, prospective, randomised, multicentre, open-label, active-comparator controlled trial				
Population	Patients, at least 18 years of age, with PNH who continued to have Hb levels <10.5 g/dL despite treatment with eculizumab.				
Intervention(s)	Pegcetacoplan at a dosage of 1,080 mg self-administered SC twice weekly or every 3 days (N=41).				
Comparator(s)	Eculizumab, at a current prescribed dosage that had been stable for at least 3 months prior to screening, administered by infusion (N=39).				
Indicate if trial supports application for marketing authorisation	Yes	X	**Indicate if trial used in the economic model**	Yes	X
	No			No	
Rationale for use/non-use in the model	PEGASUS provides efficacy and safety data concerning the use of pegcetacoplan as a treatment of PNH in adult anaemic patients with PNH who are not sufficiently controlled by treatment with a C5 inhibitor for at least 3 months.				
Reported outcomes specified in the decision problem	• IVH (largely measured by CFB to Week 16 LDH level) • EVH (largely measured by CFB to Week 16 indirect bilirubin level) • **Transfusion avoidance** • **Hb,** normalisation and response (including CFB to Week 16 Hb level) • Thrombotic events • **Adverse effects of treatment** • **Health-related quality of life** (CFB to Week 16 in the FACIT-Fatigue Scale score version 4, **CFB to Week 16 in EORTC-QLQ-C30 scores***, CFB to Week 16 in LASA scores)				
All other reported outcomes	• CFB to Week 16 ARC • Reticulocyte normalisation				

Abbreviations: CFB, change from baseline; EORTC-QLQ, The European Organization for Research and Treatment of Cancer quality of life questionnaire; EVH, extravascular haemolysis; FACIT, The Functional Assessment of Chronic Illness Therapy; Hb, haemoglobin; IVH, intravascular haemolysis; LASA, Linear Analog Assessment Scale; LDH, lactate dehydrogenase, PNH, paroxysmal nocturnal haemoglobinuria; SC, subcutaneous
Note: outcomes in **bold** are incorporated into the economic model
*Utility values mapped from EORTC-QLQ-C30 to EQ-5D-3L are used in the economic model

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B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 Trial design

PEGASUS was a prospective, randomised, multicentre, open-label, active-comparator controlled study to establish the efficacy and safety of pegcetacoplan compared with eculizumab in patients with PNH who continued to have Hb levels <10.5 g/dL despite treatment with eculizumab. The study was conducted in 44 sites across 11 countries in the Asia-Pacific region, North America, and Europe including the UK.

The primary efficacy endpoint was the CFB to Week 16 Hb level. Information regarding the PEGASUS trial has been taken from the published article by Hillmen et al. (2020) identified in the SLR, supplemented with information from the CSR (9,10).

The treatment period of the study consisted of three parts:

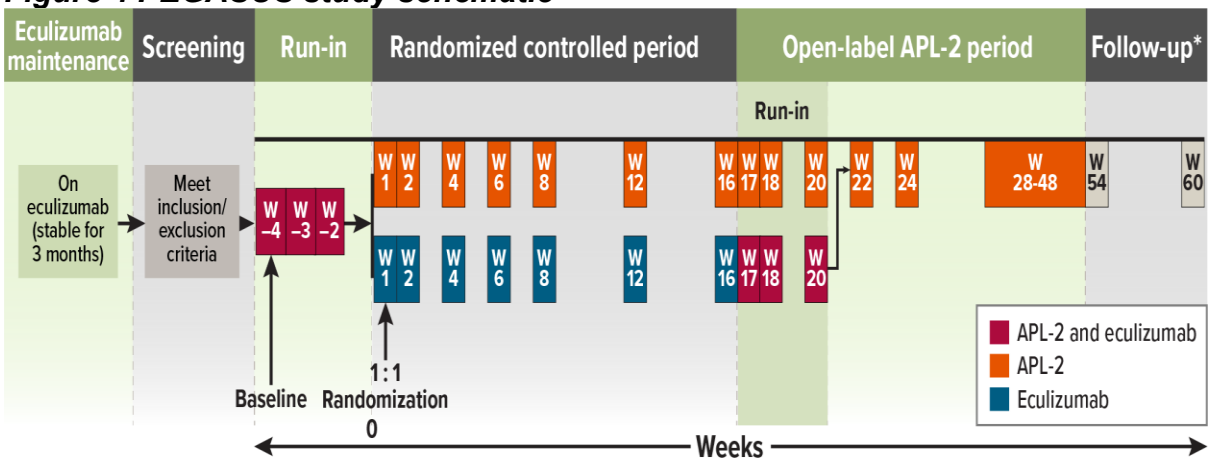
(1) A 4-week run-in period wherein all patients received pegcetacoplan in addition to their current eculizumab treatment,

(2) A 16-week randomised controlled period (RCP) where patients were randomised to either pegcetacoplan or eculizumab treatment, and

(3) A 32-week open-label pegcetacoplan-only period (note: patients who received eculizumab in the RCP received pegcetacoplan in addition for 4 weeks, before pegcetacoplan alone for 28 weeks).

The study schematic of PEGASUS can be found in Figure 4.

Figure 4 PEGASUS study schematic



Source: Apellis Pharmaceuticals, data on file (2020).(6)
*Open-label extension offered to all participants if clinical benefit is evident.
Abbreviations: W, week

Run-in period

During the 4-week run-in period (Week 4 to Day 1), patients received self-administered twice weekly SC doses of pegcetacoplan (1,080 mg) in addition to the current prescribed dose of eculizumab.

Randomised controlled period (RCP)

On Day 1, patients were randomised (1:1) to receive either pegcetacoplan monotherapy (N=41) or eculizumab (N=39) for the 16-week RCP using interactive response technology. Stratification was conducted according to:

- Number of transfusions with packed red blood cells (PRBC) (i.e., number of transfusion events regardless of the number of PRBC units transfused) within the 12 months prior to Day 28 (<4 transfusion events compared with ≥4)
- Platelet count at screening (<100,000 compared with ≥100,000)

During the 16-week RCP, patients had clinical site visits at Weeks 1, 2, 4, 6, 8, 12 and 16 for efficacy and safety assessments.

Open-label period

After completion of the RCP (end of Week 16), patients continued into a 32-week open-label period as follows:

- Patients randomised to pegcetacoplan continued to receive twice weekly doses of pegcetacoplan (1,080 mg). During the 32-week period, patients had clinical site visits at Weeks 17, 18, 20, 22, 24 and every 4 weeks after until Week 48 for efficacy and safety assessment.
- Patients who received eculizumab in the RCP could subsequently receive pegcetacoplan monotherapy. Similar to the initial 4-week run-in period, patients received twice weekly doses of pegcetacoplan (1,080 mg) in addition to eculizumab for 4 weeks as a run-in period (Weeks 16-20). After the run-in period, patients could continue receiving pegcetacoplan monotherapy until Week 48.
- After completion of the entire 52-week treatment period at Week 48 (4-week run-in period + 16-week RCP + 32-week open-label pegcetacoplan period), patients were offered entry into an open-label extension study. If the patient elected not to continue in the long-term safety extension study, they returned to the site for two additional safety visits 6 weeks apart (Weeks 54, 60) and completed their exit visit at Week 60.

Eligibility criteria

The study included adults, at least 18 years of age, with PNH who continued to have Hb levels <10.5 g/dL despite treatment with eculizumab at a current prescribed dosage that had been stable for at least 3 months prior to screening. Additional details regarding the inclusion and exclusion criteria of patients entering the PEGASUS trial are presented in Table 4.

Table 4 PEGASUS inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria

• At least 18 years of age.
• Primary diagnosis of PNH confirmed by high-sensitivity flow cytometry.
• On treatment with eculizumab. Dosage of eculizumab must have been stable for at least 3 months prior to the screening visit.
• Hb <10.5 g/dL at the screening visit.
• ARC >1.0 times the ULN at the screening visit.
• Platelet count of >50,000/mm^3 at the screening visit.
• Absolute neutrophil count >500/mm^3 at the screening visit.
• Vaccination against *N. meningitidis* types A, C, W, Y, and B; *S. pneumoniae*; and *Hib.* either within 2 years prior to Day 1 dosing, or within 14 days after starting treatment with pegcetacoplan. Unless documented evidence exists that patients are nonresponders to vaccination as evidenced by titres or display titre levels within acceptable local limits.
• Women of child-bearing potential must have had a negative pregnancy test at the screening and Day -28 visit (run-in period) and had to agree to use protocol-defined methods of contraception for the duration of the study and 90 days after their last dose of study drug.
• Men had to agree to use protocol-defined methods of contraception and agree to refrain from donating sperm for the duration of the study and 90 days after their last dose of study drug.
• Willing and able to give informed consent.
	• Active bacterial infection that had not resolved within 1 week of Day -28 (first dose of pegcetacoplan).
	• Receiving iron, folic acid, vitamin B12, and erythropoietin, unless the dosage was stable, in the 4 weeks prior to screening.
	• Hereditary complement deficiency.
	• History of bone marrow transplantation.
	• History or presence of hypersensitivity or idiosyncratic reaction to compounds related to the investigational product of SC administration.
	• Participation in any other investigational drug trial or exposure to other investigational agent within 30 days or 5 half-lives (whichever is longer).
	• Women who are currently breastfeeding.
	• Inability to cooperate or any condition that, in the opinion of the investigator, could increase the patient's risk of participating in the study or confound the outcome of the study.
	• This study included cardiac safety evaluations. The following cardiac eligibility criteria were necessary to avoid confounding the cardiac safety outcomes:
	  ○ History or family history of Long QT Syndrome or torsade de pointes, unexplained syncope, syncope from an uncorrected cardiac aetiology, or family history of sudden death.
	  ○ Myocardial infarction, coronary artery bypass grafting, coronary or cerebral artery stenting and/or angioplasty, stroke, cardiac surgery, or hospitalization for

Inclusion criteria	Exclusion criteria
• Willing and able to self-administer pegcetacoplan (administration by caregiver was allowed). • Had a BMI <35.0 kg/m^2.	congestive heart failure within 3 months or > Class 2 Angina Pectoris or New York Heart Association Heart Failure Class >2. ○ QTcF >470 ms, PR interval >280 ms. ○ Mobitz II 2nd degree AV block, 2:1 AV block, High Grade AV block, or complete heart block unless the patient had an implanted pacemaker or implantable cardiac defibrillator with backup pacing capabilities. ○ Receiving Class 1 or Class 3 antiarrhythmic agents, or arsenic, methadone, ondansetron, or pentamidine at screening. ○ Receiving any other QTc – prolonging drugs, at a stable dosage for less than 3 weeks prior to dosing. ○ Receiving prophylactic ciprofloxacin, erythromycin, or azithromycin for less than 1 week prior to the first dose of study medication (must have a repeat screening ECG after one week of prophylactic antibiotics with QTcF <470 ms).

Source: PEGASUS CSR (10)
Abbreviations: ARC, absolute reticulocyte; AV, atrioventricular; BMI, body mass index; ECG, electrocardiogram; Hb, haemoglobin; Hib, H. influenzae Type B; PNH, paroxysmal nocturnal haemoglobinuria; QTc, corrected QT interval; QTcF, Fridericia's corrected QT; SC, subcutaneous; ULN, upper limit of normal

Setting and location

Patients were enrolled from 44 sites across 11 countries in the Asia-Pacific region, North America, and Europe (Australia, Belgium, Canada, France, Germany, Japan, Russia, South Korea, Spain, UK, and US).

Interventions

During the 4-week run-in period (Week 4 to Day 1), patients self-administered twice weekly SC doses of 1,080 mg pegcetacoplan in addition to their current dosage of

eculizumab until Day 1. Patients maintained their eculizumab dose and administration schedule as prescribed, regardless of study visit scheduling or the pegcetacoplan administration schedule. On Day 1, patients received their dose of pegcetacoplan and could receive eculizumab depending on their dosing schedule. Patients were then randomly assigned to either Group 1 (monotherapy pegcetacoplan, n=41) or Group 2 (monotherapy eculizumab, n=39) for the 16-week RCP.

Patients in Group 1 stopped their eculizumab treatment and continued to receive pegcetacoplan (1,080 mg twice a week) on Day 1 and Day 4 of each treatment week until the end of the RCP at Week 16. Patients in Group 2 stopped receiving pegcetacoplan and continued to receive their pre-screening stable dosage of eculizumab until the end of Week 20. Following their Week 16 visit, patients entered the open-label period where they received pegcetacoplan (1,080 mg twice a week) on Day 1 and Day 4 of the treatment week until the end of Week 48.

Starting dose and dose adjustments

The planned dosage of pegcetacoplan monotherapy was 1,080 mg SC twice weekly (equivalent to 308 mg/day). The protocol required dose escalation to 1,080 mg every third day (equivalent to 360 mg/day) if a patient had elevated lactate dehydrogenase (LDH) levels (2 times the upper limit or normal [ULN]).

To have been eligible for study entry, patients had to have received treatment with eculizumab at a stable dosage for at least 3 months prior to screening. Treatment with eculizumab remained at this stable dosage throughout the study except where eculizumab was discontinued on Day 1 for those randomly assigned to pegcetacoplan.

Concomitant medications

All medications and procedures administered to patients from the time of informed consent through the end-of-study visit were regarded as concomitant and were documented.

The [redacted] of patients [redacted] received at least one vaccine during the run-in period (Week 4 to Day 1). Apart from vaccines, analgesics were the [redacted] prescribed concomitant medication ([redacted] of patients), followed by antibacterials for

systemic use (some of which were prophylactic) in [redacted], and antithrombotic agents in [redacted] of patients.

[redacted] received a concomitant medication during the RCP. [redacted] of patients received 1 or more vaccinations during the RCP. [redacted] received systemic antibiotics, some of which were prophylactic. Of these [redacted] were in the pegcetacoplan group, and [redacted] were in the eculizumab group. Analgesics were used in [redacted] during the RCP ([redacted] in the pegcetacoplan group and [redacted] in the eculizumab group). Systemic corticosteroids were used in [redacted] patients ([redacted] patients in the pegcetacoplan group and [redacted] patients in the eculizumab group). During the RCP, [redacted] of patients ([redacted] pegcetacoplan patients and [redacted] eculizumab patients) were on antithrombotic agents. No other classes of medication were used in 10% or more of patients in the RCP.

Outcomes

The primary efficacy endpoint was the CFB from Day 1 to Week 16 Hb level, excluding data before the RCP.

The following key secondary endpoints were assessed:

- Transfusion avoidance (yes/no), defined as the proportion of patients who do not require a transfusion during the 16-week RCP.
- CFB to Week 16 ARC, excluding data before the RCP.
- CFB to Week 16 LDH level, excluding data before the RCP.
- CFB to Week 16 in the FACIT-Fatigue Scale score version 4, excluding data before the RCP.

Additional secondary endpoints included:

- Hb response in the absence of transfusions (yes/no); defined as an increase of at least ≥1 g/dL in Hb from baseline at Week 16, excluding data before the RCP.
- Hb normalisation in the absence of transfusions (yes/no); defined as the Hb level being above the lower limit of the normal range at Week 16[2].

[2] Subjects who received a transfusion between Day 1 and Week 16 or withdrew without providing efficacy data at Week 16 are classified as nonnormalisation

- ARC normalisation in the absence of transfusions (yes/no); defined as the reticulocyte count being below the upper limit of the normal range at Week 16[2].
- CFB to Week 16 in indirect bilirubin level, excluding data before the RCP.
- CFB to Week 16 in LASA scores, excluding data before the RCP.
- CFB to Week 16 in EORTC-QLQ-C30 scores, excluding data before the RCP.

Safety outcomes were evaluated throughout the study, including during the run-in period, the RCP, the open-label period and during follow-up. Safety outcomes included the following:

- Incidence and severity of TEAEs, defined as any adverse event (AE) which occurred after dosing on Day -28 or worsened in severity.
- Incidence of thromboembolic events.
- CFB in laboratory parameters (Hb, neutrophil levels and platelet levels).
- CFB in ECG parameters (heart rate, PR interval, QT interval, QRS interval, QT interval corrected for heart rate using Bazett's formula [QTcB] and Fridericia's corrected QT [QTcF], and QT, QTcF increase from baseline).

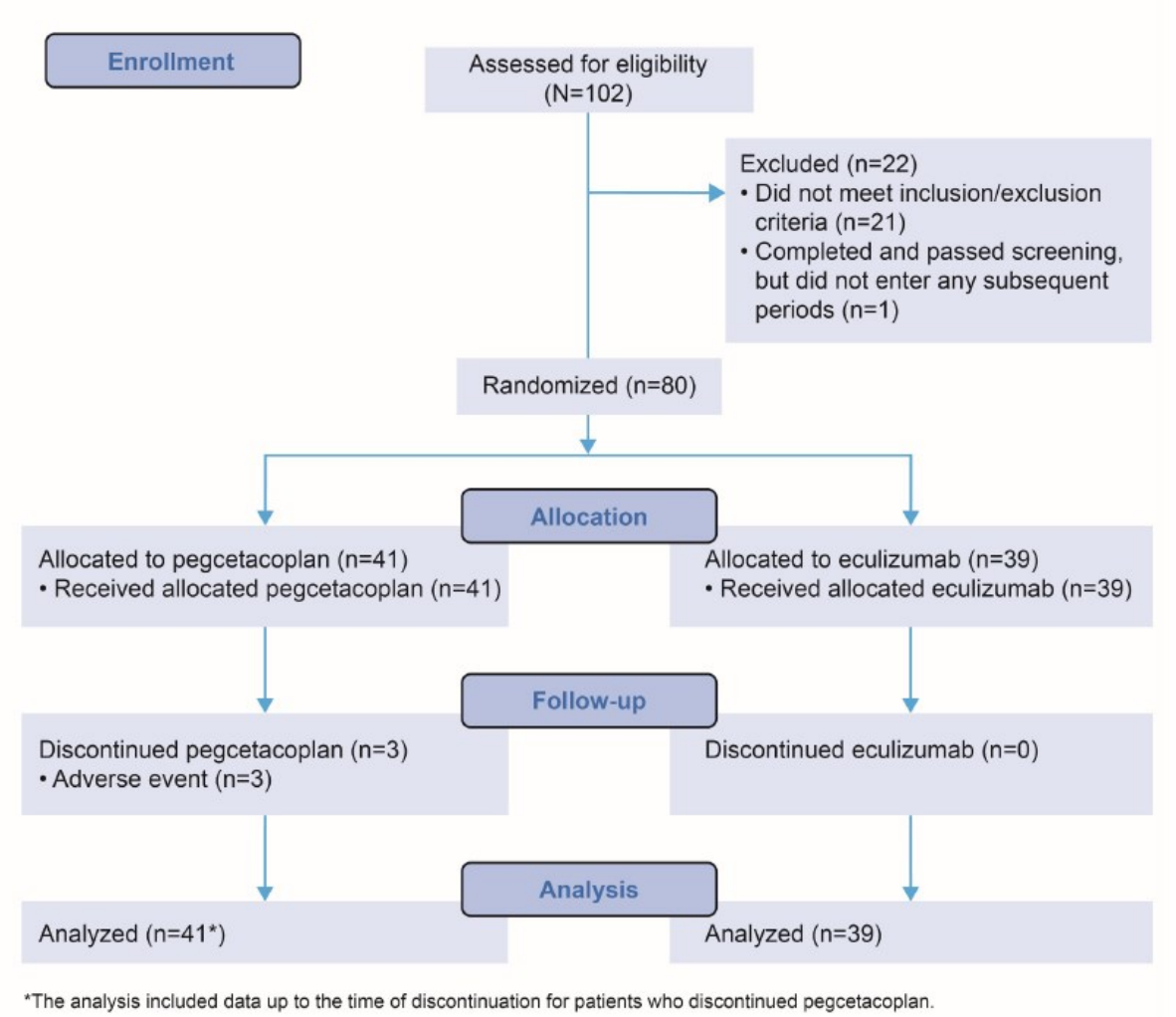
B.2.3.2. Trial population

Patient disposition

Eighty patients were in the safety and intent-to-treat (ITT) populations (defined as having received at least 1 dose of study drug), of which 41 patients were in the pegcetacoplan group, and 39 patients were in the eculizumab group, consistent with the 1:1 randomisation. Three patients in the pegcetacoplan group were withdrawn from treatment during the RCP because of an AE. [redacted]. At Week 16 of the RCP, 38 patients in the pegcetacoplan group and 39 patients in the eculizumab group remained on study drug.

The disposition of patients within the trial is shown in Figure 5.

Figure 5 PEGASUS study disposition



Source: Hillmen *et al.* 2021 (49)

Baseline characteristics

Table 5 displays the distribution of demographic and baseline characteristics for the ITT population, by treatment group. The pegcetacoplan and eculizumab arms were well balanced with regard to age, sex, height, weight, ethnicity, and race. Mean age was similar across the two treatment arms (50.2 years compared with 47.3 years) and in both arms over half of patients were female (61.3%). Mean body mass index (BMI) was similar between the two treatment arms, and [redacted] of patients had BMI <30 kg/m^2.

The mean time since PNH diagnosis to Day –28 was [redacted] years overall and was longer in the eculizumab arm than in the pegcetacoplan arm ([redacted] years compared with [redacted] years). The duration of prior eculizumab treatment was similar between

the two treatment arms ([redacted] days compared with [redacted] days). Although 70% of patients on eculizumab were treated according to the approved product label (900 mg every 2 weeks), the remaining patients were receiving a higher or more frequent dose at enrolment and therefore continued to during the trial. Specifically, 21 patients (26.3%) were receiving 1,200 mg every 2 weeks, 2 patients (2.5%) were receiving 1,500 mg every 2 weeks, and [redacted] patient [redacted] was receiving 900 mg once every 11 days. Baseline mean Hb, platelet, ARC, haptoglobin, total bilirubin, indirect bilirubin, and FACIT-Fatigue score were generally similar between groups. LDH was slightly higher in the eculizumab group than in the pegcetacoplan group (308.64 U/L compared with 257.48 U/L). The mean number of transfusions in the previous 12 months prior to Day –28 was similar between the treatment groups, however slightly more patients in the eculizumab group (59%) reported ≥4 PRBC transfusions than in the pegcetacoplan group (51.2%).

Table 5 Baseline characteristics of the ITT population in the PEGASUS trial

Characteristics	Statistics	Pegcetacoplan (N=41)	Eculizumab (N=39)	Total (N=80)
Age (years)				
	Mean (SD)	50.2 (16.29)	47.3 (15.81)	48.8 (16.02)
≤65 years	n (%)	31 (75.6)	32 (82.1)	63 (78.8)
>65 years	n (%)	10 (24.4)	7 (17.9)	17 (21.3)
Sex				
Female	n (%)	27 (65.9)	22 (56.4)	49 (61.3)
Male	n (%)	14 (34.1)	17 (43.6)	31 (38.8)
Race				
Asian	n (%)	5 (12.2)	7 (17.9)	12 (15.0)
Black or African American	n (%)	2 (4.9)	0	2 (2.5)
White	n (%)	24 (58.5)	25 (64.1)	49 (61.3)
Other	n (%)	0	1 (2.6)	1 (1.3)
Not Reported	n (%)	10 (24.4)	6 (15.4)	16 (20.0)
Ethnicity				
Hispanic or Latino	n (%)	[redacted]	[redacted]	[redacted]
Not Hispanic or Latino	n (%)	[redacted]	[redacted]	[redacted]
Not Reported	n (%)	[redacted]	[redacted]	[redacted]
Region				
APAC	n (%)	[redacted]	[redacted]	[redacted]

Characteristics	Statistics	Pegcetacoplan (N=41)	Eculizumab (N=39)	Total (N=80)
EU	n (%)	[redacted]	[redacted]	[redacted]
North America	n (%)	[redacted]	[redacted]	[redacted]
Weight (kg)				
	Mean (SD)	[redacted]	[redacted]	[redacted]
Height (cm)				
	Mean (SD)	[redacted]	[redacted]	[redacted]
BMI (kg/m^2)				
	Mean (SD)	26.731 (4.3259)	25.898 (4.2683)	26.325 (4.2911)
< 8.5	n (%)	[redacted]	[redacted]	[redacted]
≥18.5 to <25	n (%)	[redacted]	[redacted]	[redacted]
≥25 to <30	n (%)	[redacted]	[redacted]	[redacted]
≥30 to <35	n (%)	[redacted]	[redacted]	[redacted]
≥35	n (%)	[redacted]	[redacted]	[redacted]
Time since diagnosis of PNH (years) to Day 28				
	Mean (SD)	[redacted]	[redacted]	[redacted]
Duration (days) of treatment with eculizumab prior to Day 28				
	Mean (SD)	[redacted]	[redacted]	[redacted]
Current eculizumab dosing level and dosing regimen				
Every 2 weeks IV 900 mg	n (%)	26 (63.4)	30 (76.9)	56 (70.0)
IV 900 mg[a]	n (%)	[redacted]	[redacted]	[redacted]
Every 2 weeks IV 1,200 mg	n (%)	12 (29.3)	9 (23.1)	21 (26.3)
Every 2 weeks IV 1,500 mg	n (%)	2 (4.9)	0	2 (2.5)
Number of transfusions in the last 12 months prior to Day 28				
	Mean (SD)	6.1 (7.26)	6.9 (7.72)	6.5 (7.45)
<4	n (%)	20 (48.8)	16 (41.0)	36 (45.0)
≥4	n (%)	21 (51.2)	23 (59.0)	44 (55.0)
Platelet count at screening (/mm^3)				
	Mean (SD)	166.6 (98.28)	146.9 (68.81)	157.0 (85.24)
<100,000 (count/mm^3)	n (%)	12 (29.3)	9 (23.1)	21 (26.3)
≥100,000 (count/mm^3)	n (%)	29 (70.7)	30 (76.9)	59 (73.8)
Time (days) since last transfusion prior to Day 28	N	31	28	59
	Mean (SD)	[redacted]	[redacted]	[redacted]
Hb level (g/dL)				

Characteristics	Statistics	Pegcetacoplan (N=41)	Eculizumab (N=39)	Total (N=80)
	Mean (SD)	8.69 (1.075)	8.68 (0.886)	8.69 (0.982)
ARC (10^9 cells/mL)				
	Mean (SD)	217.52 (74.964)	216.15 (69.136)	216.85 (71.729)
LDH level (U/L)				
	Mean (SD)	257.48 (97.648)	308.64 (284.842)	282.42 (210.991)
Haptoglobin level (g/L)				
	Mean (SD)	[redacted]	[redacted]	[redacted]
Total bilirubin level (µmol/L)				
	Mean (SD)	42.52 (31.465)	40.51 (26.639)	41.54 (29.045)
Indirect bilirubin level (µmol/L)				
	Mean (SD)	34.65 (28.492)	32.89 (22.967)	33.80 (25.798)
Total FACIT-Fatigue score	N	41	38	79
	Mean (SD)	32.16 (11.380)	31.55 (12.513)	31.87 (11.865)

Source: PEGASUS CSR (10)
[a] Dose once every 11 days.
Abbreviations: APAC, Asia-Pacific; ARC, absolute reticulocyte; EU, European Union; Hb, haemoglobin; ITT, intent-to-treat; IV, intravenous; LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal haemoglobinuria; SD, standard deviation
Notes: Age (years) collected on CRF is used. Because some countries do not allow the collection of race and ethnicity, there is a category of not reported for race and ethnicity. Australia, Japan, Russia, and South Korea are included in APAC; Belgium, France, Germany, United Kingdom, and Spain are included in EU; United States of America and Canada are included in North America.
All baseline laboratory values except Hb are the mean of values recorded prior to dosing with pegcetacoplan at Day −28 using central Lab. The mean baseline value for Hb includes local and central laboratory values assessed prior to first dose of pegcetacoplan at Day −28.
Baseline of FACIT-Fatigue score is the last available, nonmissing observation prior to first pegcetacoplan administration.
If the laboratory results were collected as ≤ or ≥ a numeric value, 0.0000000001 was subtracted or added, respectively, to the value.
Day −28 is the first date of pegcetacoplan during the run-in period for the study.

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B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

The following populations for analysis were defined in the PEGASUS trial, wherein the ITT population was the primary population for all efficacy analyses and the safety population was the primary population for all safety analyses:

- Run-in Population: all patients who received at least one dose of pegcetacoplan.

- ITT Population: all patients who were randomised. The analyses using this population were based on the randomised treatment group allocated. This population was the primary population used for all efficacy analyses.
- Safety Population: all patients who were randomly assigned to treatment and received at least 1 dose of monotherapy study drug. This population was the primary population for all safety analyses. The analyses using this population were based on the actual treatment received.

PEGASUS efficacy and safety analyses were performed in accordance with a comprehensive statistical analysis plan (SAP), which is summarised in

Table ***6***.

Table 6 PEGASUS summary of statistical analyses

Hypothesis objective	The primary objective of the study was to establish the efficacy and safety of pegcetacoplan compared to eculizumab in patients with PNH who continued to have Hb levels <10.5 g/dL despite treatment with eculizumab.
Primary efficacy analysis	The primary efficacy endpoint was the CFB in Hb level at Week 16 of the RCP, censored for transfusion. It would be inappropriate to use data collected after transfusion since a transfusion is required when patients do not have their haemolysis suitably controlled and transfusion would be expected to improve Hb level, confounding treatment effect of either intervention. Consequently, for any subject who received a transfusion, all subsequent values were set to missing for the Hb level. The between treatment group comparison for the primary efficacy endpoint was performed using a MMRM (50). The difference between pegcetacoplan and eculizumab LS mean Hb changes from baseline at Week 16 was calculated along with its 2-sided 95% CI and associated P value from the MMRM model for the ITT population, censored for transfusions. **Sensitivity analyses** Sensitivity analyses were performed to assess the lack of treatment benefits following a patient's discontinuation from study treatment. The following methods were used:

	1. Control-based pattern imputation method using the data up to ICE. 2. Imputation based on the delta-adjusted stress testing (Tipping Point) method using the data up to ICE. **Supportive analyses** Supportive analyses of the primary efficacy endpoint included the following: • An MMRM analysis using data uncensored for transfusion from the ITT population, regardless of whether the Hb measurement was following a transfusion. • Nonparametric randomisation-based ANCOVA using the ITT population.
Key secondary efficacy analysis	Key secondary endpoints were tested in a hierarchical manner after statistical significance was reached for the primary endpoint. The analyses of key secondary efficacy endpoints were based on noninferiority tests in the ITT population. Noninferiority was concluded if the appropriate limit of the 95% 2-sided CI indicated pegcetacoplan was not inferior to eculizumab by the defined NIM for each key secondary efficacy endpoint. Once noninferiority was established for the key secondary endpoints, then superiority was to be assessed for transfusion avoidance, CFB to Week 16 ARC, CFB to Week 16 LDH level, and CFB to Week 16 FACIT-Fatigue score. The proportion of patients with each transfusion avoidance was tabulated by treatment group for the ITT population. The 95% CI for difference in percentage between treatments was constructed using the stratified (Miettinen-Nurminen) method (51). The CFB at Week 16 in ARC, LDH level, and FACIT-Fatigue Scale score was analysed, censored for transfusion, using the same MMRM analysis methods described for the primary analysis of the primary efficacy endpoint, except using their own baseline as a covariate, for the ITT population. • For transfusion avoidance, if the LB of the 95% CI for the difference between pegcetacoplan and eculizumab treatment groups was greater than the NIM of -20%, then pegcetacoplan was considered noninferior to eculizumab.

	• For ARC, if the UB of the 95% CI for the treatment difference was less than the NIM of 10, pegcetacoplan was considered noninferior to eculizumab. • For LDH, if the UB of the 95% CI for the treatment difference was less than the NIM of 20, then pegcetacoplan was considered noninferior to eculizumab. • For FACIT-Fatigue score, if the LB of the 95% CI for the treatment difference was greater than the NIM of -3, then pegcetacoplan was considered noninferior to eculizumab. All statistical superiority tests were to be presented using 2-sided hypothesis tests performed at the 5% level of significance for main effects. Due to the prespecified hierarchical structure of the analyses, noninferiority was not assessed for FACIT-Fatigue and superiority was not strictly assessed for transfusion avoidance, CFB to Week 16 ARC, CFB to Week 16 LDH level, and CFB to Week 16 FACIT-Fatigue score. However, an assessment of the clinically relevant, observed and CFB scores and nominal P values are presented for informational use in Section B.2.6.3 Key secondary efficacy endpoints. LDH normalisation using data censored for transfusion was assessed as an additional analysis for the ITT set using the category for normalisation of ≤ULN.
Subgroup analyses	The primary and key secondary endpoints were summarised and analysed by subgroups based on number of PRBC transfusions within the 12 months prior to Day –28 and platelet count at screening. Summary statistics of the primary and key secondary endpoints were provided for subgroups based on sex, race, and age.
Additional secondary endpoints	**Categorical additional secondary endpoints** Additional categorical secondary endpoints included Hb response, Hb normalisation, and reticulocyte normalisation. For each endpoint the proportion of responders for each of the endpoints for each treatment group was summarised, for the Week 16 ITT population, censored for transfusion. The 95% CI for difference in percentage between treatments was constructed using the stratified (Miettinen-Nurminen) method.

	The odds ratio of being a responder on each of the endpoints for the pegcetacoplan versus eculizumab and associated 95% CI was calculated. **Continuous additional secondary endpoints** Continuous secondary efficacy endpoints included indirect bilirubin level, LASA scores, and EORTC-QLQ-C30. For continuous endpoints superiority was assessed for the CFB to Week 16. The CFB at Week 16 was analysed using the same MMRM analysis methods described for the primary analysis of the primary efficacy endpoint, except using their own baseline as a covariate, for the ITT population, censored for transfusion. The indirect bilirubin was not reported in the database and was derived from the total and direct bilirubin as follows: indirect bilirubin = total bilirubin – direct bilirubin.
Safety analysis	The safety analysis was performed using the run-in and safety analysis populations. For each safety variable, the last value collected before the first dose of investigational product was used as baseline for all analyses of that safety variable. Last observed value on treatment was defined as the last valid assessment obtained after baseline while on investigational product. Last observed value was defined as the last valid assessment obtained after baseline. All safety data available at the time of database lock for Week 16 were provided. Safety analyses were conducted according to the treatment the patient received. Adverse events were coded using MedDRA version 20.0 (52). An AE that occurred during the study was considered a TEAE if it had a start date on or after the first dose of investigational product or if it had a start date before the date of the first dose but increased in severity on or after the date of the first dose. If more than 1 AE with the same preferred term was reported before the date of the first dose, then the AE with the greatest severity was presented in summaries. An AE that occurred more than 30 days after the date of the last dose was not counted as a TEAE.

Sample size, power calculation	A sample size of 64 randomly assigned patients (32 in each group) provides 90% power (using a 2-sided test at the 5% level of significance) of obtaining a statistically significant difference between the groups with the primary endpoint, Week 16 CFB in Hb level. This assumed a treatment difference between pegcetacoplan and eculizumab of 1 g/dL and a standard deviation for the CFB of 1.2 g/dL (effect size = 0.833). To account for loss of power due to discontinuations, the study attempted to randomise 70 patients. It was anticipated that more than 70 patients would need to enter the run-in period to achieve 70 randomly assigned patients.
Data management, patient withdrawals	If a patient discontinued study treatment, any values collected after discontinuation continued to be used in analyses. Data from patients who withdrew from the study were handled in the same manner as for patients who received transfusions.

Source: PEGASUS CSR (10)
Abbreviations: AE, adverse event; ANCOVA, analysis of covariance; ARC, absolute reticulocyte; CFB, change from baseline; CI, Confidence Interval; Hb, haemoglobin; ICE, incurrent event; ITT, intent-to-treat; LB, lower bound; LDH, lactate dehydrogenase; LS, least-square; MMRM, mixed-effect model for repeated measures; PNH, paroxysmal nocturnal haemoglobinuria; RCP, randomised controlled period; UB, upper bound; TEAE, treatment-emergent adverse event.

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B.2.5 Quality assessment of the relevant clinical effectiveness evidence

A complete quality assessment for PEGASUS is provided in Appendix D.

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B.2.6 Clinical effectiveness results of the relevant trials

B.2.6.1 Primary efficacy endpoint: change from baseline to Week 16 haemoglobin level

Pegcetacoplan demonstrated head-to-head superiority in Hb levels versus eculizumab. The difference in LS mean CFB in Hb between the two groups of 3.84 g/dL was highly statistically significant (95% CI: 2.33; 5.34. P value: <0.0001). Table 7 shows the results from PEGASUS that demonstrate pegcetacoplan met the primary efficacy endpoint of CFB to Week 16 Hb level compared to eculizumab in

the ITT population. The LS mean CFB at Week 16 in the pegcetacoplan and eculizumab groups was 2.37 g/dL and -1.47 g/dL, respectively.

Pegcetacoplan demonstrated a rapid and sustained improvement in Hb levels. A plot of LS mean CFB in Hb over time is shown in

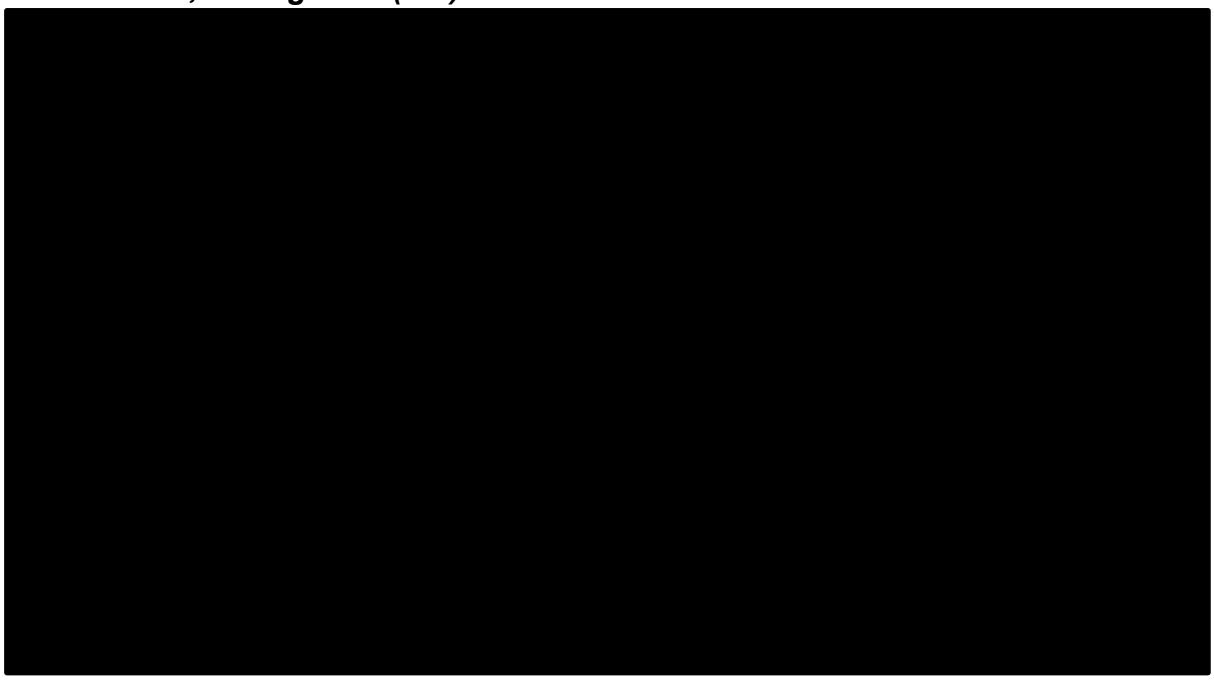
Figure **6**. Pegcetacoplan was superior to eculizumab with regard to CFB in Hb at all time points over the 16-week RCP. The difference in LS mean CFB in Hb between the two groups was statistically significant at all time points. Given the pre-treatment with pegcetacoplan during the run-in period, the beneficial effects of pegcetacoplan are likely to continue in the short term for the eculizumab group. This is seen at Week 2 in the eculizumab arm, where a positive CFB was initially reported, followed by a rapid decline to negative CFB scores between Weeks 4 to 16.

Table 7 MMRM Model: CFB in Hb, censored for transfusion, during RCP (ITT)

	Pegcetacoplan (N=41) LS Mean (SE) g/dL	**Eculizumab (N=39) LS Mean (SE) g/dL**	**Difference (95% CI)**	**P Value**
Week 2	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]
Week 6	[redacted]	[redacted]	[redacted]	[redacted]
Week 8	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	2.37 (0.363)	-1.47 (0.666)	3.84 (2.33; 5.34)	<0.0001 [a]

Source: PEGASUS CSR (10)
[a]Significant at the 0.05 α level
Abbreviations: CI, confidence interval; Hb, haemoglobin; ITT, intend-to-treat; LS, least-square; MMRM, mixed-effect model for repeated measures; RCP, randomised controlled period; SE, standard error

Figure 6 LS mean (± SE) CFB in Hb using MMRM over time, censored for transfusion, during RCP (ITT)



Source: Apellis Pharmaceuticals data on file (2019a).
Abbreviations: Hb, haemoglobin; ITT, intent-to-treat; LS, least-square; MMRM, mixed-effect model for repeated measures; RCP, randomised controlled period; SE, standard error

The observed and CFB Hb data, censored for transfusion, is displayed in Table 8. Comparing this table to the primary mixed-effect model for repeated measures (MMRM) analysis, the results are consistent with increased mean Hb levels in the pegcetacoplan group by Week 2, and through Week 16. At the Week 16 timepoint, mean CFB in Hb was [redacted] for the pegcetacoplan arm, compared to [redacted] for the eculizumab arm.

Table 8 Observed values and CFB in Hb, censored for transfusion, during RCP (ITT)

	Pegcetacoplan (N=41)			**Eculizumab (N=39)**		
	n	**Mean (SD) g/dL**	**CFB g/dL**	**n**	**Mean (SD) g/dL**	**CFB g/dL**
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: PEGASUS CSR (10)
Abbreviations: CFB, change from baseline; Hb, haemoglobin; ITT, intent-to-treat; N/A, not applicable; RCP, randomised controlled period; SD, standard deviation

B.2.6.2 Additional prespecified analyses

Extensive supportive and sensitivity analyses robustly demonstrate that pegcetacoplan improves Hb levels from baseline, with superiority over eculizumab.

Sensitivity analyses

Sensitivity analyses consistently reproduced the results of the primary efficacy endpoint analysis. Sensitivity analyses of the primary efficacy endpoint were conducted using additional analyses that reflected possible lack of treatment benefits following a patient's discontinuation from study treatment using the following methods:

- Control-based pattern imputation method (CBPI), censored for transfusion – this analysis considered a certain type of Missingness Not At Random (MNAR) mechanism for missing data within a pattern-mixture framework, where it was assumed that subjects who discontinue early from the pegcetacoplan group will follow the trajectory of outcomes similar to the one in the eculizumab group after their discontinuation, taking into account the observed values prior to discontinuation.
- Imputation based on the delta-adjusted stress testing (Tipping Point) method, censored for transfusion - this method assumed that subjects who discontinue from the pegcetacoplan group experience worsening defined by a pre-specified adjustment in the primary efficacy endpoint.

The CBPI sensitivity analysis confirmed that the mean CFB in Hb was statistically significantly different for pegcetacoplan and eculizumab (**Error! Not a valid bookmark self-reference.**). Statistical significance was shown at the 0.05 α level (P value: <0.0001), at all time points from Week 2 to Week 16.

Table 9 Sensitivity analysis: CFB in Hb between treatment-group comparison – CFBI, censored for transfusion, during RCP (ITT)

Visit	Estimate of LS mean difference (pegcetacoplan – eculizumab)	95% CI	P value
Week 2	[redacted]	[redacted]	[redacted]

Week 4	[redacted]	[redacted]	[redacted]
Week 6	[redacted]	[redacted]	[redacted]
Week 8	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]

Source: PEGASUS CSR (10)
[a] Significant at the α 0.05 level
Abbreviations: CFB, change from baseline; CFBI, control-based pattern imputation; CI, confidence interval; Hb, haemoglobin; ITT, intent-to-treat; LS, least-sqaure; RCP, randomised controlled period

The tipping point analysis identified the mean difference in Hb CFB required to "tip" the finding from non-statistically significant to statistical significance (at an α level of 0.05). The sensitivity analysis determined that an LS mean difference of [redacted] in Hb CFB would not meet statistical significance, while an LS mean difference of [redacted] would still meet statistical significance. Therefore, the true tipping point is between [redacted] (Table 10). The LS mean difference in Hb CFB in the pegcetacoplan group from the primary efficacy endpoint analysis was 3.84 (95% CI: 2.33; 5.34. P value: <0.0001) at Week 16, which is [redacted]

Table 10 Sensitivity analysis: CFB in Hb between treatment group comparison - tipping point imputation, during RCP (ITT)

Visit	Estimate of LS mean difference (pegcetacoplan – eculizumab)	95% CI	P value
Week 16	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]

Source: PEGASUS CSR (10)
[a] Significant at the α 0.05 level
Abbreviations: CFB, change from baseline; CI, confidence interval; Hb, haemoglobin; ITT, intent-to-treat; LS, least-square; RCP, randomised controlled period

Supportive analyses

Pegcetacoplan was found to be superior to eculizumab in mean CFB in Hb at Week 16 in supportive analyses, confirming the results of the primary analysis.

The analyses included:

1. An MMRM analysis using data uncensored for transfusion based on the ITT population, regardless of whether the Hb measurement was following a transfusion

2. Nonparametric Randomisation-Based analysis of covariance (ANCOVA) based on the ITT population

Supportive analysis 1 differed from the primary efficacy endpoint analysis only in that it evaluated all available data (uncensored for transfusion), rather than only data censored for transfusion. Table 11 demonstrates that the LS mean difference between pegcetacoplan and eculizumab from Week 2 to Week 16 ranged from [redacted] (Week 2) to [redacted] (Week 4) and was [redacted]) at all time points, including Week 16 when the difference was 2.69 (95% CI: 1.99; 3.38). Therefore, these results support the finding, based on the primary efficacy endpoint analysis, that pegcetacoplan is superior to eculizumab in mean CFB in Hb over 16 weeks.

Table 11 Supportive analysis 1 - CFB in Hb, during RCP (ITT)

Visit	**Pegcetacoplan (N=41) LS Mean (SE) g/dL**	**Eculizumab (N=39) LS Mean (SE) g/dL**	**Difference (95% CI)**	***P* Value**
Week 2	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]
Week 6	[redacted]	[redacted]	[redacted]	[redacted]
Week 8	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	2.66 (0.253)	−0.03 (0.261)	2.69 (1.99; 3.38)	<0.0001 [a]

Source: PEGASUS CSR (10)
[a] Significant at the α 0.05 level
Abbreviations: CFB, change from baseline; CI, confidence interval; Hb, haemoglobin; LS, least-square; RCP, randomised controlled period; SA, sensitivity analysis; SE, standard error

The endpoint of supportive analysis 2 was the rank of the CFB in Hb level. The Hb level was defined as follows:

- Last Hb level before intercurrent event (ICE) for patients with ICE
- Last available Hb level for patients without ICE

The results in Table 12 showed a [redacted] in Hb between pegcetacoplan and eculizumab treatment ([redacted]).

Table 12 Supportive analysis 2 - Nonparametric test for treatment difference of Hb CFB, during RCP (ITT)

Treatment difference estimate	Standard error treatment estimate	95% CI	P value
[redacted]	[redacted]	[redacted]	[redacted]

Source: PEGASUS CSR (10)
[a] Significant at the α 0.05 level
Abbreviations: CFB, change from baseline; CI, confidence interval; Hb, haemoglobin; RCP, randomised controlled period

B.2.6.3 Key secondary efficacy endpoints

The analyses of key secondary endpoints were based on noninferiority tests. Key secondary endpoints were tested in a hierarchical manner after statistical significance was reached for the primary endpoint.

Transfusion avoidance

During the 16-week RCP, a larger proportion of pegcetacoplan patients avoided transfusions than eculizumab patients. Transfusion avoidance was defined as the proportion of patients in the ITT population who do not require a transfusion during the 16-week RCP. Table 13 shows the proportion of patients who did not have a transfusion during the RCP.

Pegcetacoplan was noninferior to eculizumab for transfusion avoidance. Pegcetacoplan enabled 85.4% of patients to be transfusion-free compared to 15.4% of patients treated with eculizumab (Table 13). Furthermore, five patients in the pegcetacoplan group received at least 1 transfusion, and 1 patient withdrew from the study without having had a transfusion but was included as having a transfusion in the analysis. In the eculizumab group, 33 patients (84.6%) required at least 1 transfusion. Therefore, a much greater proportion of patients in the eculizumab group required transfusion than in the pegcetacoplan group. The risk difference for transfusion avoidance was 0.6253 (95% CI: 0.4830; 0.7677) between the pegcetacoplan and eculizumab groups (nominal P value: <0.0001).

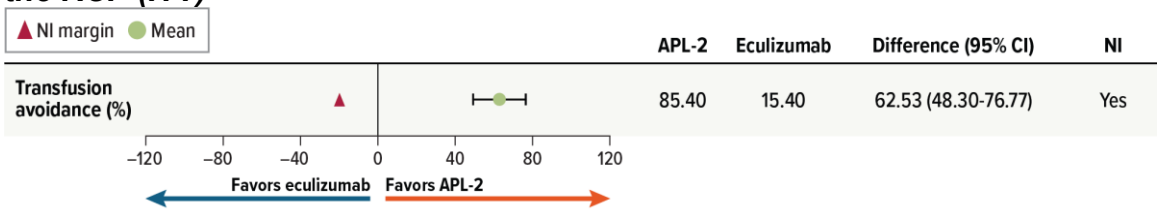
Table 13 Summary of the number of patients with transfusion avoidance, during the RCP (ITT)

Transfusion avoidance	Statistics	Pegcetacoplan (N=41)	Eculizumab (N=39)
Yes (no transfusion)	n (%)	35 (85.4)	6 (15.4)
No	n (%)	6 (14.6)	33 (84.6)
Received at least one transfusion[a]	n (%)	[redacted]	[redacted]
Withdrew from the study without having had a transfusion[a]	n (%)	[redacted]	[redacted]
Difference in percentage (pegcetacoplan - eculizumab)	Risk difference 95% CI Nominal *P* value	0.6253 0.4830; 0.7677 <0.0001	

Source: PEGASUS CSR (10)
[a] Percentages are based on the number of patients in No category for each column.
Abbreviations: CI, confidence interval; ITT, intent-to-treat; RCP, randomised controlled period
Notes: Transfusion avoidance is the proportion of patients who did not require a transfusion during the RCP.
Patients who experienced more than 1 transfusion during RCP are only counted once.
Patients who did not have a transfusion but withdrew before Week 16 were considered as having a transfusion in the analysis of transfusion avoidance.
The 95% CI for difference in percentage between treatments is constructed using the stratified (Miettinen-Nurminen) method.

As the lower bound of the confidence interval exceeded the noninferiority margin (NIM) (48.3>-20), noninferiority was demonstrated for pegcetacoplan versus eculizumab in transfusion avoidance (Figure 7).

Figure 7 Plot of noninferiority margin and statistic for transfusion avoidance in the RCP (ITT)



Source: Apellis Pharmaceuticals, data on file (6)
Abbreviations: CI, confidence interval; ITT, intent-to-treat; NI, noninferiority

After noninferiority was established for transfusion avoidance, noninferiority was assessed for CFB to Week 16 ARC for the ITT population.

Change from baseline to Week 16 in absolute reticulocyte count

During the 16-week RCP, patients in the pegcetacoplan group demonstrated a rapid and sustained reduction in ARC. Reticulocyte count has been identified as a strong indicator of EVH and associated also with IVH (53). Figure 8 shows the CFB in ARC

during the RCP using the MMRM model censored for transfusion for the ITT population.

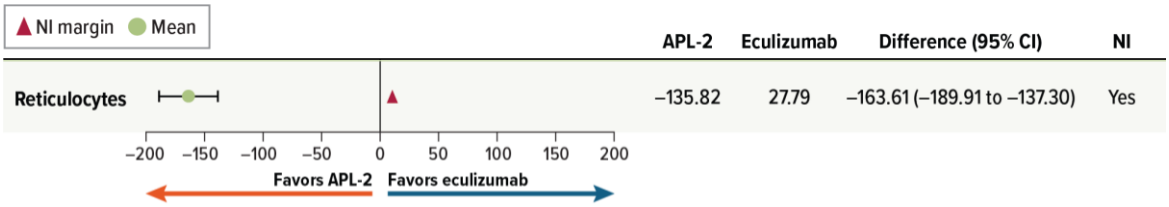
Pegcetacoplan was noninferior to eculizumab in improving the mean CFB of the ARC. The LS mean CFB at 16 weeks was -135.82× 10^9 cells/L for pegcetacoplan and 27.29× 10^9 cells/L for eculizumab. The difference in LS mean at Week 16 was -163.61× 10^9 cells/L (95% CI: -189.91; -137.30. nominal P value: <0.0001) indicating that pegcetacoplan was noninferior to eculizumab for CFB in ARC. Figure 8 is a plot of CFB in ARC censored for transfusion using the MMRM model. As demonstrated, ARC in the pegcetacoplan group decreased from baseline and stayed below baseline through Week 16. In the eculizumab group, the initial decrease from baseline seen during the run-in period was reversed by Week 4 of the RCP, and the ARC generally remained above baseline. This initial decrease in ARC for the eculizumab group was expected as patients are receiving both treatments up until Day 1. However, after Day 1, when patients transitioned to only receive eculizumab, the ARC quickly exceeds the ULN.

Figure 8 LS mean (± SE) CFB in ARC using MMRM over time, censored for transfusion, during RCP (ITT)

Source: Apellis Pharmaceuticals, data on file (6)
Abbreviations: ARC, absolute reticulocyte count; CFB, change from baseline; ITT, intent-to-treat; LLN, lower limit of normal; LS, least-squares; MMRM, mixed-effect model for repeated measures; RCP, randomised controlled period; SE, standard error; ULN, upper limit of normal

As the upper bound of the confidence interval was less than the NIM (-137.30<10), noninferiority was demonstrated for pegcetacoplan versus eculizumab in CFB to Week 16 in ARC (Figure 9).

Figure 9 Plot of noninferiority margin and statistic for ARC in the RCP (ITT)



Source: Apellis Pharmaceuticals, data on file (6)
Abbreviations: ARC, absolute reticulocyte count; CI, confidence interval; ITT, intent-to-treat; NI, noninferiority

After noninferiority was established for ARC, noninferiority was assessed for CFB to Week 16 in LDH in the ITT population.

Change from baseline to Week 16 lactate dehydrogenase level

Over the 16 week period, pegcetacoplan exhibits a decreasing pattern in LDH levels, censored for transfusion. Elevated levels of LDH are indicative of IVH (27). LDH levels were well controlled at baseline, as expected with treatment with a C5 complement inhibitor, and remained well controlled at Week 16 in both treatment groups. These results show that inhibition of complement C3 was adequate to maintain control of IVH as well as preventing EVH. As demonstrated in Table 14, at Week 16, the LS mean CFB for LDH was -14.76 U/L in the pegcetacoplan group and -10.12 U/L in the eculizumab group, for a difference in LS mean of -4.63 U/L (95% CI: -181.30; 172.04. nominal P value: 0.9557).

Figure 10 is a plot of CFB in LDH level using the MMRM model, censored for transfusion for the ITT population. LDH was higher in the eculizumab group in comparison to the pegcetacoplan group through to Week 6. By Week 16, the LDH level-was similar in the two treatment groups. Of note, reduction of mean LDH level to within the normal range was seen at baseline after the run-in period and was maintained in patients receiving pegcetacoplan throughout the RCP (9).

Table 14 MMRM Model: CFB in LDH Level, censored for transfusion, during RCP (ITT)

Visit	Pegcetacoplan (N = 41) LS mean (SE) U/L	Eculizumab (N = 39) LS mean (SE) U/L	Difference (95% CI) in LS mean (vs eculizumab) U/L	Nominal P Value
Week 2	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]
Week 6	[redacted]	[redacted]	[redacted]	[redacted]
Week 8	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	−14.76 (42.708)	−10.12 (71.025)	−4.63 (−181.30; 172.04)	0.9557

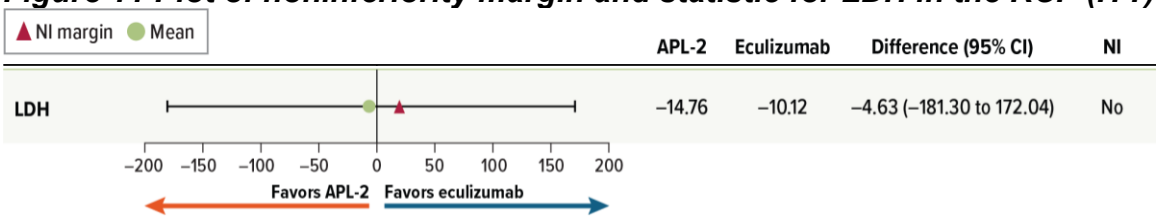
Source: PEGASUS CSR (10)
Abbreviations: CFB, change from baseline; ITT, intent-to-treat; LDH, lactate dehydrogenase; LLN, lower limit of normal; LS, least-squares; MMRM, mixed-effect model for repeated measures; RCP, randomised controlled period; SE, standard error; ULN, upper limit of normal
Notes: Baseline is the mean of available measurements recorded from central laboratory prior to taking the first dose of investigational product pegcetacoplan.
Model includes treatment + baseline value + analysis visit + strata + analysis visit × treatment, where strata is the combination of stratification factors number of transfusions and platelet count at screening.
Data excluded from the model: All values after intercurrent events were set to missing.

Figure 10 LS mean (± SE) CFB in LDH level using MMRM over time, censored for transfusion, during RCP (ITT)

Source: Apellis Pharmaceuticals, data on file *(6)*
Abbreviations: CFB, change from baseline; ITT, intent-to-treat; LDH, lactate dehydrogenase; MMRM, mixed-effect model for repeated measures; RCP, randomised controlled period

As the upper bound of the confidence interval was not less than the NIM (172.04<20), noninferiority was not demonstrated for pegcetacoplan versus eculizumab for CFB to Week 16 in LDH (Figure 11).

Figure 11 Plot of noninferiority margin and statistic for LDH in the RCP (ITT)



Source: Apellis Pharmaceuticals, data on file (6)
Abbreviations: ITT, intent-to-treat; LDH, lactate dehydrogenase; RCP, randomised controlled period

It is important to note that eculizumab is a compound that targets the treatment of IVH, hence LDH levels were relatively well controlled at baseline and remained well controlled at Week 16 in both treatment groups. Additionally, mean LDH levels will be impacted by breakthrough haemolytic events, where a patient may experience LDH levels in the thousands, skewing an entire treatment arm. As such, the median LDH levels are presented in Figure 12.

Figure 12 Median CFB in LDH level using MMRM over time, censored for transfusion, during RCP (ITT)

Source: Apellis Pharmaceuticals, data on file *(6)*

Abbreviations: CFB, change from baseline; ITT, intent-to-treat; LDH, lactate dehydrogenase; MMRM, mixed-effect model for repeated measures; RCP, randomised controlled period

However, when considering all observed data, mean LDH was still consistently lower in the pegcetacoplan group, reaching mean LDH within the normal range (113 to 226 U/L) while in the eculizumab group LDH stayed above the ULN at multiple time points (Table 15). LDH levels were higher at most time points among patients in the eculizumab group. Table 15 shows the LDH level censored for transfusion during the RCP for the observed values (unadjusted data). By Week 16 LDH levels are similar for patients on both treatments.

Table 15 Observed values and CFB in LDH level, censored for transfusion, during RCP (ITT)

Visit	Pegcetacoplan (N=41)			Eculizumab (N=39)		
	n	Mean (SD) U/L	CFB U/L	n	Mean (SD) U/L	CFB U/L
Baseline	[redacted]			[redacted]		
Week 2						
Week 4						
Week 6						
Week 8						
Week 12						
Week 16						

Source: PEGASUS CSR (10)
Abbreviations: CFB, change from baseline; ITT, intent-to-treat; LDH, lactate dehydrogenase; RCP, randomised controlled; SD, standard deviation

LDH normalisation using data censored for transfusion was assessed as an additional analysis for the ITT set using the category for normalisation of ≤ULN. Results in Table 16 demonstrate that a total of 70.7% of patients treated with pegcetacoplan achieved LDH normalisation compared to 15.4% of patients treated with eculizumab.

Table 16 Number and percentage of subjects with LDH normalisation at Week 16, censored for transfusion (ITT)

LDH normalisation	Pegcetacoplan (N = 41)	Eculizumab (N = 39)
Yes, n (%)	29 (70.7)	6 (15.4)

No, n (%)	12 (29.3)	33 (84.6)
Difference in percentage (pegcetacoplan vs. eculizumab), 95% CI	0.4879 (0.3228; 0.6530)	
Odds ratio (pegcetacoplan vs. eculizumab), 95% CI	[redacted]	

Source: PEGASUS CSR (10)
Abbreviations: CI, confidence interval; ITT, intent-to-treat
LDH normalisation is a lactate dehydrogenase level at or below the upper limit of the gender-specific normal range at Week 16. Subjects who received a transfusion between Day 1 and Week 16 or withdraw without providing efficacy data at Week 16 will be classified as non-normalisation.
95% CI for difference in percentage is constructed using the stratified Miettinen-Nurminen method. Both P value and 95% CI for Odds Ratio are obtained using the stratified Cochran-Mantel-Haenszel χ-square test.

Change from baseline to Week 16 in the Functional Assessment of Chronic Illness Therapy Fatigue Scale version 4

Pegcetacoplan improved quality of life compared to eculizumab in the ITT population as demonstrated in Figure 13. The FACIT-Fatigue scale is a HRQoL measure that assesses self-reported fatigue and its impact upon daily activities and function (54). The FACIT-Fatigue scale can generate a score between 0 and 52, where the higher the score, the better the HRQoL. Table 17 shows the CFB in FACIT-Fatigue score during the RCP using the MMRM model censored for transfusion.

Results demonstrate that an LS mean numerical difference of 11.87 (95% CI: 5.49; 18.25) was observed at Week 16 in the pegcetacoplan vs eculizumab groups in the ITT population which was statistically significant at the 0.05α level (nominal P value: 0.0005). A 3-point increase in FACIT-Fatigue score is generally accepted as clinically meaningful (54). This difference of 11.87 is nearly four times the threshold for what is deemed to be clinically meaningful on the FACIT-Fatigue Scale.

Table 17 MMRM model: CFB in FACIT-Fatigue score, censored for transfusion, during RCP (ITT)

Visit	Pegcetacoplan (N = 41) LS mean (SE)	Eculizumab (N = 39) LS mean (SE)	Difference (95% CI) in LS mean (vs eculizumab)	Nominal P Value
Week 2	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]
Week 6	[redacted]	[redacted]	[redacted]	[redacted]
Week 8	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]

Week 16	9.22 (1.607)	−2.65 (2.821)	11.87 (5.49; 18.25)	0.0005

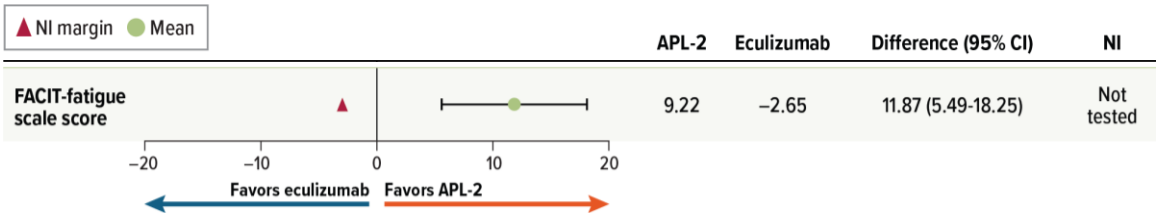
Source: PEGASUS CSR (10)
Abbreviations: CFB, change from baseline; CI, confidence interval; FACIT, Functional Assessment of Chronic Illness Therapy; ITT, intent-to-treat; LS, least-square; MMRM = mixed-effect model for repeated measures; NA, not available; RCP, randomised controlled period; SE, standard error
Notes: Baseline is the last available, nonmissing observation before taking the first dose of pegcetacoplan.
Model includes treatment + baseline value + analysis visit + strata + analysis visit × treatment, where strata is the combination of stratification factors number of transfusions and platelet count at screening.
Data excluded from the model: All values after intercurrent events were set to missing.

Figure 13 LS mean (± SE) CFB in FACIT-fatigue scale score using MMRM over time, censored for transfusion, during RCP (ITT)

Source: PEGASUS CSR (10)
Abbreviations: CFB, change from baseline; FACIT, Functional Assessment of Chronic Illness Therapy; ITT, intent-to-treat; LS, least-square; MMRM, mixed-effect model for repeated measures; NA, not available; RCP, randomised controlled period; SE, standard error
Notes: Baseline is the last available, nonmissing observation prior to first study drug administration. For PRBC transfusion and withdrawal from the study: all measurements after the ICE events were set to missing.

Although noninferiority for FACIT-Fatigue score was not assessed because of the prespecified hierarchical testing, the lower bound of the 95% CI of the adjusted treatment difference was greater than the prespecified NIM of -3 as seen in Figure 14 indicating that pegcetacoplan would demonstrate noninferiority versus eculizumab for FACIT-Fatigue.

Figure 14 Plot of noninferiority margin and statistic for FACIT-Fatigue in the RCP (ITT)



Source: Pegcetacoplan Global Value Dossier
Abbreviations: CI, confidence interval; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy Fatigue Scale; ITT, intent-to-treat; NI, noninferiority

Table 18 demonstrates that patients taking pegcetacoplan report similar levels of quality of life as the general population. At just Week 2, the pegcetacoplan group FACIT-Fatigue score of 43.38 is aligned to the general population score of 43.6 (21,48). From Day 1 to Week 16, the FACIT-Fatigue score in the pegcetacoplan group had increased 11.41 points, and scores in the eculizumab group had decreased 5.83 points.

Table 18 Observed values and CFB in FACIT-Fatigue score, censored for transfusion, during RCP (ITT)

Visit	Pegcetacoplan (N = 41), Mean (SD)			Eculizumab (N = 39), Mean (SD)		
	n	Observed	CFB	n	Observed	CFB
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: PEGASUS CSR (10)
Abbreviations: CFB, change from baseline; FACIT, Functional Assessment of Chronic Illness Therapy; ITT, intent-to-treat; RCP, randomised controlled period; SD, standard deviation
Higher scores denote better HRQoL (54)

B.2.6.4 Additional secondary endpoints

Haemoglobin response

The [redacted] of patients in the pegcetacoplan arm achieved Hb response, compared to [redacted] in the eculizumab arm. Hb response was defined as at least a 1 g/dL increase in Hb. This increase of 1g/dL is the increment which physicians expect following transfusion. Table 19 presents the number and percentage of patients with

Hb response, censored for transfusion, at Week 16 for the ITT population. In the pegcetacoplan group, [redacted] of patients met the definition for Hb response at Week 16, censored for transfusion, compared to [redacted] patients in the eculizumab group.

Table 19 Number and percentage of patients with Hb response at Week 16, censored for transfusion (ITT)

Hb response	Pegcetacoplan (N = 41)	Eculizumab (N = 39)
Yes, n (%)	[redacted]	[redacted]
No, n (%)	[redacted]	[redacted]
Difference in percentage (pegcetacoplan vs. eculizumab)	[redacted]	
95% CI	[redacted]	

Source: PEGASUS CSR (10)
Abbreviations: CI, confidence interval; Hb, haemoglobin; ITT, intent-to-treat
Notes: Haemoglobin response is an increase of at least ≥1 g/dL in haemoglobin from baseline at Week 16, excluding data before the RCP. Patients who received a transfusion between Day 1 and Week 16 or withdraw without providing efficacy data at Week 16 were classified as nonresponders; 95% CI for difference in percentage is constructed using the stratified Miettinen-Nurminen method. Odds ratios could not be calculated as the eculizumab group reports zero events.

Haemoglobin normalisation

Table 20 shows that a higher proportion of pegcetacoplan patients achieved Hb normalisation, censored for transfusion, than eculizumab patients at Week 16 for the ITT population. Hb normalisation was defined as a Hb level at or above the lower limit of the gender-specific normal range. Results demonstrate that 14/41 (34.1%) of patients treated with pegcetacoplan achieved Hb normalisation without a transfusion at week 16, compared to 0 of patients treated with eculizumab.

Table 20 Number and percentage of patients with Hb normalisation at week 16, censored for transfusion (ITT)

Hb normalisation	Pegcetacoplan (N = 41)	Eculizumab (N = 39)
Yes, n (%)	14 (34.1)	0
No, n (%)	27 (65.9)	39 (100.0)
Difference in percentage (pegcetacoplan vs. eculizumab)	0.3043	
95% CI	0.1493; 0.4593	

Source: PEGASUS CSR (10)
Abbreviations: CI, confidence interval; Hb, haemoglobin; ITT, intent-to-treat
Haemoglobin normalisation is a haemoglobin level at or above the lower limit of the gender-specific normal range at Week 16.
Notes: patients who received a transfusion between Day 1 and Week 16 or withdrew without providing efficacy data at Week 16 are classified as non-normalisation.
95% CI for difference in percentage is constructed using the stratified Miettinen-Nurminen method. Odds ratios could not be calculated as the eculizumab group reports zero events.

Absolute reticulocyte count normalisation

ARC normalisation occurred for the majority of patients in the pegcetacoplan group (78%). In the eculizumab group, only 1 patient (2.6%) achieved reticulocyte normalisation. ARC normalisation is defined as the ARC being below the upper limit of the gender-specific normal range at Week 16. Pegcetacoplan is associated with higher odds of reticulocyte normalisation at Week 16 compared to eculizumab (odds ratio [OR]: 135.5938, 95% CI: 15.19; 1210.25). The effect of pegcetacoplan on ARC normalisation is statistically significantly different from the effect of eculizumab. ARC normalisation, censored for transfusion, in the ITT population is shown in Table 21.

Table 21 Number and percentage of patients with ARC normalisation at Week 16, censored for transfusion (ITT)

ARC normalisation censored for transfusion	Pegcetacoplan (N = 41)	Eculizumab (N = 39)
Yes, n (%)	32 (78.0)	1 (2.6)
No, n (%)	9 (22.0)	38 (97.4)
Difference in percentage for pegcetacoplan vs. eculizumab (95% CI)	0.6639 (0.53; 0.80)	
Odds ratio for pegcetacoplan vs eculizumab (95% CI)	[redacted]	

Source: PEGASUS CSR (10)
Abbreviations: ARC, absolute reticulocyte count; CI, confidence interval; ITT, intent-to-treat
Notes: ARC normalisation is a reticulocyte level below the upper limit of the gender-specific normal range at Week 16.
Patients who received a transfusion between Day 1 and Week 16 or withdraw without providing efficacy data at Week 16 will be classified as nonresponders.
95% CI for difference in percentage is constructed using the stratified Miettinen-Nurminen method. Both P value and 95% CI for Odds Ratio are obtained using the stratified Cochran-Mantel-Haenszel χ-square test.

Change from baseline to Week 16 in indirect bilirubin level

Patients in the pegcetacoplan group had [redacted] from baseline in indirect bilirubin at all time points than patients in the eculizumab group (Table 22). Indirect bilirubin is defined as total bilirubin minus direct bilirubin and indicates EVH, and to a lesser extent, IVH (28). Indirect bilirubin increased at all time points except Week 12 in the eculizumab group. At Week 16, the LS mean CFB was [redacted] µmol/L in the pegcetacoplan group and [redacted] µmol/L in the eculizumab group, with a difference in LS mean of [redacted] µmol/L ([redacted]). This result, combined with ARC and LDH normalisation, reflects the additional impact of pegcetacoplan in preventing EVH as well as IVH.

Figure **15** is a plot of LS mean (± SE) CFB in indirect bilirubin censored for transfusion over time during the RCP for the ITT population. After patients were randomly assigned to pegcetacoplan or eculizumab, indirect bilirubin levels increased in patients who received eculizumab, except for week 12. In the pegcetacoplan group, the decrease in indirect bilirubin levels was maintained from baseline through Week 16.

Table 22 MMRM Model: CFB in indirect bilirubin level, censored for transfusion, during RCP (ITT)

Visit	Pegcetacoplan (N = 41) LS mean (SE) µmol/L	Eculizumab (N = 39) LS mean (SE) µmol/L	Difference (95% CI) µmol/L
Week 2	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]
Week 6	[redacted]	[redacted]	[redacted]
Week 8	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]

Source: PEGASUS CSR (10)
Abbreviations: CFB, change from baseline; CI, confidence interval; Hb, haemoglobin; ITT, intent-to-treat; LS, least-square; MMRM, mixed model for repeated measures; RCP, randomised controlled period; SE, standard error
Notes: Baseline is the mean of available measurements recorded from central laboratory prior to taking the first dose of investigational product pegcetacoplan.
Model includes treatment + baseline value + analysis visit + strata + analysis visit × treatment, where strata is the combination of stratification factors number of transfusions and platelet count at screening.
Data excluded from the model: All values after intercurrent events were set to missing.

Figure 15 LS mean (± SE) of CFB in indirect bilirubin level using MMRM over time, censored for transfusion, during RCP (ITT)

Source: PEGASUS CSR (10)
Abbreviations: ITT, intent-to-treat; RCP, randomised controlled period; SE, standard error
Notes: Baseline is the mean of available measurements records from central labs prior to taking the first dose of pegcetacoplan. For PRBC transfusion and withdrawal from the study, all measurements after the ICE events were set to missing.

Change from baseline to Week 16 in Linear Analog Assessment Scale scores

The LASA consists of 3 items asking respondents to rate their perceived level of functioning. Each item produces scores from 0 to 100 where higher scores indicate better HRQoL, and a difference of 10-20 points is considered minimally clinically important (55). In this analysis, items are combined where scores can range from 0 to 300, with a minimally clinically important difference (MCID) of 30-60 points. Across all timepoints, Table 23 shows significantly [redacted] CFB LS mean scores in the pegcetacoplan than the eculizumab group. The difference in the LS mean for LASA scores using data censored for transfusion in the ITT set was [redacted] at Week 16 for the comparison of the pegcetacoplan group with the eculizumab group.

Table 23 MMRM Model: CFB in LASA scores, censored for transfusion, during RCP (ITT)

Visit	Pegcetacoplan (N = 41)	Eculizumab (N = 39)	Difference (95% CI) in LS mean

	LS mean (SE)	LS mean (SE)	(vs eculizumab)
Week 2	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]
Week 6	[redacted]	[redacted]	[redacted]
Week 8	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]

Source: PEGASUS CSR (10)
Abbreviations: CFB, change from baseline; CI, confidence interval; ITT, intent-to-treat; LASA, Linear Analog Assessment Scale; LS, least-square; MMRM, mixed-effect model for repeated measures; RCP, randomised controlled period; SE, standard error
Notes: Baseline is the last available, nonmissing observation before taking the first dose of pegcetacoplan.
Model includes treatment + baseline value + analysis visit + strata + analysis visit × treatment, where strata is the combination of stratification factors number of transfusions and platelet count at screening. Data excluded from the model: All values after intercurrent events were set to missing.
Higher scores denote better HRQoL (54)

Observed values in LASA scores were [redacted]

The observed values and CFB (unadjusted data) through Week 16 align with the MMRM results, [redacted] in the pegcetacoplan group than in the eculizumab group (

Table **24**).

A plot of LS mean (± SE) CFB LASA scores using data censored for transfusion over time during the RCP for the ITT population is shown in Figure 16. In the pegcetacoplan group, LASA scores for patients [redacted]

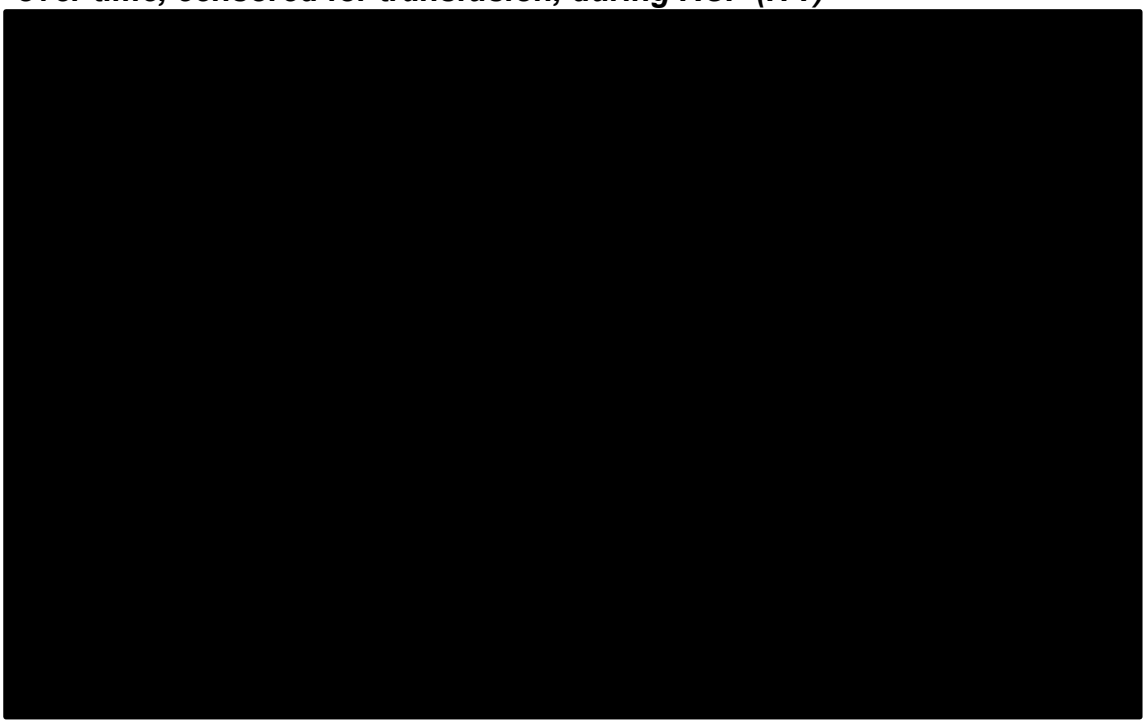
Table 24 Observed values and CFB in LASA score, censored for transfusion, during RCP (ITT)

Visit	Pegcetacoplan N = 41 Mean (SD)			Eculizumab N = 39 Mean (SD)		
	n	Observed	CFB	n	Observed	CFB
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: PEGASUS CSR (10)

Abbreviations: CFB, change from baseline; CI, confidence interval; ITT, intent-to-treat; LASA, Linear Analog Assessment Scale; LS, least-square; NA, not applicable; RCP, randomised controlled period; SD, standard deviation
Notes: Baseline is the last available, nonmissing observation before taking the first dose of pegcetacoplan.
All values after the intercurrent events during RCP were set to missing. This table summarises data as observed with no imputation of missing data.

Figure 16 LS Mean (± SE) plot of CFB in LASA scores over time using MMRM over time, censored for transfusion, during RCP (ITT)



Source: PEGASUS CSR (10)
Abbreviations: ITT, intent-to-treat; LASA, Linear Analog Assessment Scale; RCP, randomised controlled period; SE, standard error

Change from baseline to Week 16 in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 scores

The EORTC-QLQ-C30 consists of 30 questions composed of both multi-item scales and single-item measures to assess overall HRQoL in patients. Higher scores for the functioning scales and global health status indicate a better level of functioning (i.e. an improved state of the patient), while higher scores on the symptom and single-item scales indicate a higher level of symptoms (i.e. a worse state of the patient). (56). Global Health Status(GHS)/QoL and all Functional Scales showed an [redacted] in the pegcetacoplan group at Week 16. In the pegcetacoplan group, the GHS/QoL score [redacted] by Week 16. Conventionally, an increase of 10 points is considered clinically meaningful (57).

The results for GHS/QLQ scores at Week 16 using data censored for transfusion in the ITT population are presented in Table 25.

Table 25 MMRM Model: CFB in GHS/QoL scores, censored for transfusion, during RCP (ITT)

	Pegcetacoplan N = 41 LS Mean (SE)	Eculizumab N = 39 LS Mean (SE)	Difference (95% CI)
Global Health Status/QoL	[redacted]	[redacted]	[redacted]
Functional scales			
Physical functioning	[redacted]	[redacted]	[redacted]
Role functioning	[redacted]	[redacted]	[redacted]
Emotional functioning	[redacted]	[redacted]	[redacted]
Cognitive functioning	[redacted]	[redacted]	[redacted]
Social functioning	[redacted]	[redacted]	[redacted]
Symptom Scales			
Fatigue	[redacted]	[redacted]	[redacted]
Nausea and vomiting	[redacted]	[redacted]	[redacted]
Pain	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]
Appetite loss	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]
Financial difficulties	[redacted]	[redacted]	[redacted]

Source: PEGASUS CSR (10)
Abbreviations: CFB, change from baseline; CI, confidence interval; GHS, Global Health Status; ITT, intent-to-treat; LS, least-square; MMRM, mixed model for repeated measures; QoL, quality of life; RCP, randomised controlled period; SE, standard error.
Notes: Baseline is the last available, nonmissing observation before taking the first dose of pegcetacoplan.
Model includes treatment + baseline value + analysis visit + strata + analysis visit × treatment, where strata is the combination of stratification factors number of transfusions and platelet count at screening. Data excluded from the model: All values after intercurrent events were set to missing.

A plot of LS mean (± SE) CFB EORTC-QLQ-C30 scores using data censored for transfusion over time during the RCP for the ITT population is shown in. In the pegcetacoplan group, GHS/QoL scores [redacted] through Week 16. Scores [redacted] in the eculizumab group through Week 6. After Week 6, scores in the eculizumab group [redacted]

Figure 17 LS Mean (± SE) plot of CFB in GHS/QoL scores over time using MMRM over time, censored for transfusion, during RCP (ITT)

As seen in the MMRM analysis, observed values and CFB in GHS/QoL scores (unadjusted data) also showed an overall mean [redacted] from baseline to Week 16 in the pegcetacoplan group for GHS/QoL of [redacted] and all functional scales. The eculizumab group had a mean [redacted] from baseline in the GHS/QoL of [redacted] (Table 26).

Table 26 Mean CFB in GHS/QoL at week 16, censored for transfusion, during RCP (ITT)

	Pegcetacoplan		Eculizumab	
	n	**Mean (SD)**	**n**	**Mean (SD)**
Global Health Status/QoL	[redacted]	[redacted]	[redacted]	[redacted]
Functional scales				
Physical functioning	[redacted]	[redacted]	[redacted]	[redacted]
Role functioning	[redacted]	[redacted]	[redacted]	[redacted]
Emotional functioning	[redacted]	[redacted]	[redacted]	[redacted]
Cognitive functioning	[redacted]	[redacted]	[redacted]	[redacted]
Social functioning	[redacted]	[redacted]	[redacted]	[redacted]
Symptom scales				
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Nausea and vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Pain	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]

Insomnia	[redacted]	[redacted]	[redacted]	[redacted]
Appetite loss	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Financial difficulties	[redacted]	[redacted]	[redacted]	[redacted]

Source: PEGASUS CSR (10)
Abbreviations: CFB, change from baseline; CI, confidence interval; GHS, Global Health Status; ITT, intent-to-treat; LS, least-square; MMRM, mixed model for repeated measures; QoL, quality of life; RCP, randomised controlled period; SE, standard error.
Notes: Baseline is the last available, nonmissing observation before taking the first dose of pegcetacoplan.
All values after the intercurrent events during RCP were set to missing. This table summarises data as observed with no imputation of missing data.
Higher score for the functioning scales and global health status denote a better level of functioning (i.e. a better state of the patient), while higher scores on the symptom and single-item scales indicate a higher level of symptoms (i.e. a worse state of the patient) (56)

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B.2.7 Subgroup analysis

Prespecified subgroup analyses of the primary and key secondary efficacy endpoints were performed for the following subgroups:

- Number of PRBC transfusions within the 12 months prior to Day -28 (<4; ≥4); (i.e., number of transfusion events regardless of PRBC units transfused)
- Platelet count at screening (<100,000/mm^3; ≥100,000/mm^3).

In addition, summary statistics of the primary and key secondary endpoints are provided for subgroups based on sex, race, and age (≤65 years and >65 years). The primary efficacy endpoint results, CFB to Week 16 Hb levels, were consistent across subgroup analyses. Secondary endpoint treatment effects were retained regardless of subgroups. For detailed results, please see Appendix E.

Change from baseline to Week 16 haemoglobin level: packed red blood cell transfusions

Pegcetacoplan provided consistent improvement in efficacy measures regardless of baseline transfusion dependence in the ITT population, see Table 27. The results demonstrate that improvements in Hb levels with pegcetacoplan versus eculizumab are observed irrespective of baseline transfusion status. LS mean for CFB in Hb in those with ≥4 transfusions was 2.11 g/dL and –4.02 g/dL for the pegcetacoplan and

eculizumab groups, respectively, with a statistically significant difference of 6.13 g/dL (95% CI: 0.79; 11.48. P value: 0.0278). For those in the <4 transfusion stratum, at Week 16 the LS mean for CFB in Hb was 2.97 g/dL and -0.01 g/dL for the pegcetacoplan and eculizumab groups, respectively, with a statistically significant difference of 2.98 g/dL (95% CI: 1.73; 4.23. P value: <0.0001).

Table 27 Subgroup analysis: MMRM model: CFB in Hb (g/dl) using by PRBC transfusion, censored for transfusion, during RCP (ITT)

	Pegcetacoplan LS mean (SE) g/dL	Eculizumab LS mean (SE) g/dL	Difference (95% CI) g/dL	P value
Number of PRBC transfusions <4				
n	20	16	N/A	N/A
Week 16	2.97 (0.364)	−0.01 (0.493)	2.98 (1.73; 4.23)	<0.0001[a]
Number of PRBC transfusions ≥4				
n	21	23	NA	NA
Week 16	2.11 (0.598)	−4.02 (2.395)	6.13 (0.79; 11.48)	0.0278[a]

Source: PEGASUS CSR (10)
Abbreviations: CFB, change from baseline; CI, confidence interval; ITT, intent-to-treat; LS, least-square; N/A, not applicable; PRBC, packed red blood cells; SE, standard error.
[a] significant at the 0.05 α level.

Regardless of transfusion strata, the mean Hb increased by at least [redacted] in the pegcetacoplan group at all time points from Week 4 to Week 16, while in the eculizumab group the mean CFB Hb remained consistently below [redacted] at these same time points (
Table **28**). Therefore, at least a 2 g/dL increase in Hb was observed with pegcetacoplan, even among patients requiring frequent transfusions prior to study entry.

Table 28 Subgroup analysis: observed values and CFB in Hb by number of PRBC transfusions, censored for transfusion, during RCP (ITT)

Visit	Pegcetacoplan (N = 20)			Eculizumab (N = 16)		
	n	Mean (SD) g/dL	CFB g/dL	n	Mean (SD) g/dL	CFB g/dL
Stratification: Number of PRBC transfusions < 4						
Baseline	[redacted]					
Week 2	[redacted]					
Week 4	[redacted]					
Week 6	[redacted]					

Week 8	[redacted]			[redacted]		
Week 12	[redacted]			[redacted]		
Week 16	[redacted]			[redacted]		
	Pegcetacoplan (N = 21)			**Eculizumab (N = 23)**		
Stratification: Number of PRBC transfusions ≥ 4						
Baseline	[redacted]			[redacted]		
Week 2	[redacted]			[redacted]		
Week 4	[redacted]			[redacted]		
Week 6	[redacted]			[redacted]		
Week 8	[redacted]			[redacted]		
Week 12	[redacted]			[redacted]		
Week 16	[redacted]			[redacted]		

Source: PEGASUS CSR (10)
Abbreviations: CFB, change from baseline; CI, confidence interval; ITT, intent-to-treat; LS, least-square; N/A, not applicable; PRBC, packed red blood cells; SD, standard deviation

Change from baseline to Week 16 haemoglobin level: platelet count

Pegcetacoplan provided consistent improvement in efficacy measures in the ITT population regardless of baseline or platelet severity. At least a [redacted] in Hb was observed with pegcetacoplan, even among patients in the low platelet count stratum (<100,000/mm^3). Primary efficacy results by platelet count at screening are presented in Table 29. The LS mean for CFB in Hb in those with <100,000/mm^3 platelets at Week 12 was [redacted] and [redacted] for the pegcetacoplan and eculizumab groups, respectively, with a statistically significant mean difference of 5.08 (95% CI: 2.39; 7.77. P value: 0.0007). Week 12 data are presented as there were no patients in <100,000/mm^3 stratum of the eculizumab group who did not receive transfusions by Week 16. For those with platelets >100,000/mm^3, at Week 16 the LS mean for CFB in Hb was 2.18 and –0.92 for the pegcetacoplan and eculizumab groups, respectively, with a statistically significant mean difference of 3.10 (95% CI: 1.37; 4.82. P value: 0.0009).

Table 29 Subgroup analysis: MMRM model: CFB in Hb (g/dL) by platelet count at screening, censored for transfusion, during RCP (ITT)

	Pegcetacoplan LS mean (SE) g/dL	**Eculizumab LS mean (SE) g/dL**	**Difference (95% CI) g/dL**	**P value**
Number of platelets <100,000/mm^3				
n	12	9	N/A	N/A
Week 12	3.23 (0.673)	−1.84 (1.088)	5.08 (2.39; 7.77)	0.0007[a]

Number of platelets ≥100,000/mm^3				
n	29	30	N/A	N/A
Week 16	2.18 (0.400)	−0.92 (0.743)	3.10 (1.37; 4.82)	0.0009[a]

Source: PEGASUS CSR (10)
Abbreviation: CFB, change from baseline; ITT, intent-to-treat; LS, least-square; MMRM, mixed model for repeated measures; N/A, not applicable; RCP, randomised controlled period.
[a] significant at the 0.05 α level.

Mean Hb [redacted] by at least [redacted] in the pegcetacoplan group at all time points from Week 4 to Week 16, while in the eculizumab group the mean CFB Hb remained consistently [redacted] at these same time points. Table 30 displays the observed and CFB Hb values according to platelet strata from baseline through to Week 16.

Table 30 Subgroup analysis: observed values and CFB Hb by number of platelets, censored for transfusion, during RCP (ITT)

Visit	**Pegcetacoplan**			**Eculizumab**		
	n	**Mean (SD) g/dL**	**CFB**	**N**	**Mean (SD) g/dL**	**CFB**
Stratification: Number of platelets <100,000/mm^3						
Baseline	[redacted]					
Week 2						
Week 4						
Week 6						
Week 8						
Week 12						
Week 16						
Stratification: Number of platelets ≥100,000/mm^3						
Baseline						
Week 2						
Week 4						
Week 6						
Week 8						
Week 12						
Week 16						

Source: PEGASUS CSR (10)
Abbreviations: CFB, change from baseline; ITT, intent-to-treat; N/A, not applicable; RCP, randomised controlled period; SD, standard deviation.

Analyses by subgroup

Subgroup analyses by sex, race and age for key secondary efficacy endpoints can be found in Appendix E.

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B.2.8 Meta-analysis

All efficacy and safety data relevant to this appraisal are provided from one relevant Phase III head-to-head RCT, PEGASUS, therefore, it was not necessary to conduct a meta-analysis.

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B.2.9 Indirect and mixed treatment comparisons

To date, there are no published head-to-head RCTs comparing the efficacy and safety of pegcetacoplan and ravulizumab. In the absence of head-to-head data, an anchored matching-adjusted indirect comparison (MAIC) was performed to assess the comparative effectiveness of pegcetacoplan and ravulizumab among patients who were previously treated with eculizumab in line with NICE DSU Technical Support Document 18 guidance (58).

The MAIC approach used individual patient-level data (IPD) from the PEGASUS trial for pegcetacoplan and eculizumab and adjusted the trial population to match average aggregate baseline characteristics reported in the ALXN1210-PNH-302 (Study 302) trial for patients receiving ravulizumab and eculizumab. This comparison was anchored by the eculizumab control arm in both studies.

B.2.9.1 Feasibility assessment

An assessment of the feasibility of the MAIC between PEGASUS and Study 302 has been performed based on key assumptions outlined in the NICE DSU Technical Support Document (TSD) 18 (58). The Cochrane Handbook for Systematic Reviews of Interventions was used to assess the level of heterogeneity across studies by comparing study designs, baseline characteristics, treatment arms and outcomes (59).

Key differences were identified in the trial designs of the studies. The treatment period in PEGASUS was 16 weeks compared to 26 weeks in Study 302, which may result in over- or under-estimation of endpoints. There were also differences in terms

of route of administration (i.e., pegcetacoplan was self-administered via subcutaneous infusion; ravulizumab was administered by caregivers via intravenous infusion); treatment administration schedule (i.e., pegcetacoplan was administered twice-weekly; ravulizumab was administered every 8 weeks); and treatment modifications (e.g., pegcetacoplan could be administered every 3 days; ravulizumab could be administered prior to every eight weeks, if required). Additionally, the dosing of eculizumab differed between the two trials. In Study 302, patients were given 900mg every two weeks, whereas in PEGASUS patients were only required to be on a stable dose of eculizumab with 30.1% of patients reporting a higher than labelled dosage or dose frequency. PEGASUS also had a 4-week run-in period prior to randomisation during which time patients received both pegcetacoplan and eculizumab, a treatment phase that was not present in Study 302 (i.e., following the screening phase, patients were randomised to receive either ravulizumab or continue stable treatment with eculizumab). The above differences cannot be adjusted for and are potential sources of bias in the comparison.

Differences in the inclusion criteria were also identified. The PEGASUS population included adults with PNH and Hb levels lower than 10.5 g/dL despite eculizumab therapy. The Study 302 population included adults with PNH who were clinically stable after having been treated with eculizumab for at least 6 months; all patients were eligible regardless of Hb levels. Hb is a treatment effect modifier for both clinical and QoL endpoints; it is an important indicator of disease severity and is impacted by underlying IVH, EVH and bone marrow function in patients with PNH (28,60). Given this, the ‘conditional constancy of relative effects’ assumption is violated since the inclusion criteria for the Study 302 trial was wider than that of PEGASUS, therefore it is not possible to match the patients in PEGASUS to the patients in Study 302 due to this lack of overlap in Hb levels. This assumption must be met in order to perform an anchored MAIC, such that overlap in the studies is required for matching (58). In addition, the primary endpoint of the PEGASUS trial was change from baseline in Hb level at week 16, which was impossible to examine in Study 302 as this was not reported.

Despite this, the MAIC analysis was performed, upon which the clinical effect modifiers including Hb level and history of transfusions could not be matched due to

reduced effective sample size (ESS) and the presence of extreme patient weights. These extreme weights and reduction in ESS confirms the issues with overlap in the inclusion criteria between the studies. This means that factors that are not well balanced were excluded from matching in the analysis and only factors that are already well balanced were considered. Transfusion requirements are an effect modifier since they represent an important measure of disease and haemolytic activity both before and during treatment with complement inhibitors (61). The NICE DSU TSD 18 requires the weighting model to include all effect modifiers and states that “failure to include relevant variables will result in a biased estimate”.

Based on not including all effect modifiers and evidence to suggest heterogeneity between the trials, the results of the MAIC may be subject to bias.

B.2.9.2 Methodology

Patient selection

The patients included in the MAIC were ≥18 years of age, previously treated with eculizumab (PEGASUS: ≥3 months; Study 302: ≥6 months), received meningococcal vaccination, had absolute neutrophil count >500/mm^3 at screening, had adequate platelet count at screening (PEGASUS: >50,000/mm^3; Study 302: 30,000/mm^3), and did not have a previous history of bone marrow transplantation. In addition, IPD from PEGASUS were re-analysed and patients with LDH level ≤1.5x ULN at screening and without major adverse vascular events (MAVE) in 6 months prior to treatment were selected to align more closely with the patients enrolled in Study 302.

After applying additional inclusion criteria to patients enrolled in PEGASUS, a total of 36 patients from the pegcetacoplan arm and 32 patients from the eculizumab arm were included in this analysis, see Table 31. Because LDH was >1.5x ULN at screening, 12 patients (5 pegcetacoplan; 7 eculizumab) were excluded from the analysis. No patients in PEGASUS had MAVE in the 6-month period prior to treatment. Overall, 195 patients were included from Study 302: 97 ravulizumab patients, and 98 eculizumab patients.

Table 31 Sample selection for patients enrolled in PEGASUS

Criteria	Pegcetacoplan		Eculizumab	
	N	Percentage from previous step	N	Percentage from previous step
Step 0. PEGASUS study sample size	41	100.0%	39	100.0%
Step 1. LDH level ≤1.5x ULN at screening	[redacted]	[redacted]	[redacted]	[redacted]
Step 2. No MAVE in six months prior to treatment[1]	[redacted]	[redacted]	[redacted]	[redacted]
Total	**36**	---	**32**	---

Abbreviations: LDH, lactate dehydrogenase; MAVE, major adverse vascular event; ULN, upper limit of normal

[1] Per Study 302 protocol, MAVEs include the following: thrombophlebitis/deep vein thrombosis; pulmonary embolus; myocardial infarction; transient ischemic attack; unstable angina; renal vein thrombosis; acute peripheral vascular occlusion; mesenteric/visceral vein thrombosis or infarction; mesenteric/visceral arterial thrombosis or infarction; hepatic/portal vein thrombosis (Budd-Chiari syndrome); cerebral arterial occlusion/cerebrovascular accident; cerebral venous occlusion; renal arterial thrombosis; gangrene (non-traumatic; nondiabetic); amputation (non-traumatic; nondiabetic); and dermal thrombosis.

Baseline characteristics

Based on the information published in Study 302 and available as IPD from the PEGASUS study, the following patient demographic and clinical characteristics were described and compared:

- Age
- Sex
- Race
- Weight
- Height
- Number of years from diagnosis to consent
- Number of years on eculizumab before first study infusion
- History of aplastic anaemia
- Received PRBCs or whole blood transfusions within 1 year of first study infusion (i.e., transfusion history)
- LDH value (U/L)
- Haemoglobin (g/dL)

Statistical analysis

A propensity score model using logistic regression was used to estimate the likelihood of enrolment in Study 302 versus the PEGASUS study. Weights were

assigned such that the weighted mean baseline characteristics in the PEGASUS study matched the means and proportions of the baseline characteristics reported Study 302, where possible. These weights were used to calculate the ESS, and then to recalculate clinical outcomes from PEGASUS. Due to the ESS, it was not possible to adjust for all effect modifiers. The choice of matching parameters is found in Table 32.

Table 32 Baseline characteristics matched in the MAICs

Baseline characteristic	PEGASUS vs Study 302 (Clinical and haematological endpoints)	PEGASUS vs Study 302 (Fatigue and HRQoL endpoints)
Age	✓	✓
Sex	✓	
Race		
White	✓	
Asian	✓	
African American		
Other/multiple races		
NR		
Weight		✓
Height		
Received PRBCs or whole blood transfusions within one year of first study infusion		
History of aplastic anemia	✓	✓
LDH value (U/L)	✓	✓
Hemoglobin (g/dL)		
Number of years on eculizumab before first study infusion		
Number of years from diagnosis to consent		

Note: All items not marked with a tick were not included in matching procedures.
Source: Bhak *et al.* 2020 (62)
Abbreviations: HRQoL, health-related quality of life LDH, lactase dehydrogenase; NR, not reported

Before matching, Wald tests and 95% confidence intervals (CIs) were used to compare categorical and continuous outcomes. After matching, outcomes were compared between balanced treatment groups using statistical tests that incorporated weights generated during matching. Weighted Wald tests with 95% CIs were used for comparisons of categorical and continuous outcomes. Definitions for clinical, haematological, fatigue, and HRQoL outcomes were similar across both the PEGASUS and Study 302 (see Table 33).

Table 33 Comparison of endpoint definitions

Endpoint	PEGASUS Study	Study 302
Clinical and Haematological		
Transfusion avoidance	Proportion of patients with transfusion avoidance through Week 16	Proportion of participants who remained transfusion free and did not require a transfusion per protocol-specified guidelines through Week 26
Transfusion requirements	Total number of units of PRBCs transfused from baseline to Week 16	Total number of units of PRBCs transfused from baseline to Week 26
Haemoglobin stabilisation	Proportion of patients with avoidance of a ≥2 g/dL decrease in Hb level in the absence of transfusion from baseline through Week 16	Proportion of patients with avoidance of a ≥2 g/dL decrease in Hb level in the absence of transfusion from baseline through Week 26
LDH level	Week 16 change from baseline in LDH level	Week 16 change from baseline in LDH level[1]
LDH normalisation	Proportion of patients with LDH level ≤1x ULN (226 U/L) in the absence of transfusions from baseline through Week 16[2]	Proportion of patients with LDH level ≤1x ULN (246 U/L) from baseline through Week 16[3]
Fatigue and Quality of Life		
Fatigue	Week 16 change from baseline in FACIT-Fatigue score	Week 26 change from baseline in FACIT-Fatigue score
General health status	Week 16 change from baseline in general health status EORTC QLQ-C30 score	Week 26 change from baseline in general health status EORTC QLQ-C30 score
Physical functioning	Week 16 change from baseline in physical functioning EORTC QLQ-C30 score	Week 26 change from baseline in physical functioning EORTC QLQ-C30 score
Fatigue symptoms	Week 16 change from baseline in fatigue symptoms EORTC QLQ-C30 score	Week 26 change from baseline in fatigue symptoms EORTC QLQ-C30 score

Abbreviations: EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; FACIT, Functional Assessment of Chronic Illness Therapy; Hb, haemoglobin; LDH, lactate dehydrogenase; PRBC, packed red blood cells; ULN, upper limit of normal

[1] Change from baseline in LDH level was examined for Week 16 (Day 113) for Study 302. Baseline mean and SD for LDH level were reported in Table 1 of the Kulasekararaj et al. (2019) publication. Week 16 (Day 113) mean and 95% CI for LDH level were extracted from Supplemental Figure S3 of the Kulasekararaj et al. (2019) publication. The SD for LDH level at Week 16 (Day 113) was calculated using the following equation: $\sqrt{(N)}$*(upper limit of CI - lower limit of CI)/3.92.

[2] LDH normalization is defined as the proportion of patients who achieved LDH level ≤1x ULN (226 U/L) in the absence of transfusions from baseline through the end of follow-up.

[3] LDH normalization is defined as the proportion of patients who achieved LDH level ≤1x ULN (246 U/L), with or without transfusions (i.e., patients were not excluded if they experienced transfusions during follow-up). Week 16 (Day 113) mean and 95% CI for the proportion of patients with LDH normalization in Study 302 were extracted from Figure 2 of the Kulasekararaj et al. (2019) publication.

B.2.9.3 Results

The comparison of baseline characteristics before and after matching between pegcetacoplan and ravulizumab-treated patients is presented in Table 34 and Table 35.

Prior to matching, the distribution of effect modifiers including patient age, race, weight, history of aplastic anaemia, and LDH level were similar for patients randomised to receive pegcetacoplan in PEGASUS study versus ravulizumab in Study 302. Compared with patients who received ravulizumab, a greater proportion of pegcetacoplan patients were female (69.4% versus. 48.5%) and had a history of transfusions during the year before the study (72.2% versus. 13.4%). Mean haemoglobin was also lower for patients who received pegcetacoplan versus. ravulizumab (8.7 g/dL versus. 11.1 g/dL, respectively).

After matching, all baseline characteristics where matching was possible were balanced (i.e. statistically equivalent) between the trials. However, based on not including all effect modifiers, and evidence to suggest heterogeneity between the trials, the results of the MAIC may be subject to bias. The most notable effect modifiers which could not be matched were Hb level and history of transfusions.

Table 34 Baseline characteristics before and after matching – clinical and haematological endpoints

Characteristic	PEGASUS Study (Before Matching)		PEGASUS Study (After Matching)		302 Study (As Reported)	
	Pegcetacoplan (N=36)	Eculizumab (N=32)	Pegcetacoplan (N=36)	Eculizumab (N=32)	Ravulizumab (N=97)	Eculizumab (N=98)
Effective sample size, n	-	-	[redacted]	[redacted]	-	-
Sex, %						
Male	30.6	40.6	[redacted]	[redacted]	51.5	49.0
Female*	69.4	59.4	[redacted]	[redacted]	48.5	51.0
Age at first infusion of study drug*, mean (SD), y	49.0 (16.8)	48.8 (14.0)	[redacted]	[redacted]	46.4 (14.4)	48.8 (14.0)
Race, %						
White*	58.3	65.6	[redacted]	[redacted]	51.5	62.2
Asian*	13.9	15.6	[redacted]	[redacted]	23.7	19.4
African American	5.6	0.0	[redacted]	[redacted]	5.2	3.1
Other/multiple races	0.0	3.1	[redacted]	[redacted]	3.1	1.0
Not reported/unknown	22.2	15.6	[redacted]	[redacted]	16.5	14.3
Weight, mean (SD), kg	75.2 (19.6)	73.2 (14.2)	[redacted]	[redacted]	72.4 (16.8)	73.4 (14.6)
Height, mean (SD), cm	167.1 (9.7)	168.8 (7.4)	[redacted]	[redacted]	168.3 (10.1)	168.8 (9.9)
Time on eculizumab before 1st study infusion, mean (SD), y	5.4 (4.4)	5.1 (3.8)	[redacted]	[redacted]	6.0 (3.5)	5.6 (3.5)
History of transfusions within 1 y before first dose, %	72.2	71.9	[redacted]	[redacted]	13.4	12.2
Age at PNH diagnosis, mean (SD), y	40.5 (17.0)	35.7 (13.4)	[redacted]	[redacted]	34.1 (14.4)	36.8 (14.1)
Time from PNH diagnosis to consent, mean (SD), y	8.5 (7.1)	13.0 (9.8)	[redacted]	[redacted]	12.4 (8.4)	11.9 (9.4)
LDH*, mean (SD), U/L	229.0 (57.2)	203.5 (35.5)	[redacted]	[redacted]	228.0 (48.7)	235.2 (49.7)
Hemoglobin, mean (SD), g/dL	8.7 (1.1)	8.7 (0.8)	[redacted]	[redacted]	11.1 (1.8)	10.9 (1.8)
History of major adverse vascular events, %	25.0	18.8	[redacted]	[redacted]	28.9	22.4
History of aplastic anaemia*, %	27.8	18.8	[redacted]	[redacted]	35.1	39.8
* Indicates variable included in matching procedures.						

Source: Bhak *et al*. 2020 (62)

Abbreviations: cm, centimetre; kg, kilogram; LDH, lactase dehydrogenase; PNH, paroxysmal nocturnal haemoglobinuria; SD, standard deviation

Table 35 Baseline characteristics before and after matching – fatigue and HRQoL endpoints

Characteristic	PEGASUS Study (Before Matching)		PEGASUS Study (After Matching)		302 Study (As Reported)	
	Pegcetacoplan (N=36)	Eculizumab (N=32)	Pegcetacoplan (N=36)	Eculizumab (N=32)	Ravulizumab (N=97)	Eculizumab (N=98)
Effective sample size, n	-	-	[redacted]	[redacted]	-	-
Sex, %						
Male	30.6	40.6	[redacted]	[redacted]	51.5	49.0
Female	69.4	59.4	[redacted]	[redacted]	48.5	51.0
Age at first infusion of study drug*, mean (SD), y	49.0 (16.8)	48.8 (14.0)	[redacted]	[redacted]	46.4 (14.4)	48.8 (14.0)
Race, %						
White	58.3	65.6	[redacted]	[redacted]	51.5	62.2
Asian	13.9	15.6	[redacted]	[redacted]	23.7	19.4
African American	5.6	0.0	[redacted]	[redacted]	5.2	3.1
Other/multiple races	0.0	3.1	[redacted]	[redacted]	3.1	1.0
Not reported/unknown	22.2	15.6	[redacted]	[redacted]	16.5	14.3
Weight*, mean (SD), kg	75.2 (19.6)	73.2 (14.2)	[redacted]	[redacted]	72.4 (16.8)	73.4 (14.6)
Height, mean (SD), cm	167.1 (9.7)	168.8 (7.4)	[redacted]	[redacted]	168.3 (10.1)	168.8 (9.9)
Time on eculizumab before 1st study infusion, mean (SD), y	5.4 (4.4)	5.1 (3.8)	[redacted]	[redacted]	6.0 (3.5)	5.6 (3.5)
History of transfusions within 1 y before first dose, %	72.2	71.9	[redacted]	[redacted]	13.4	12.2
Age at PNH diagnosis, mean (SD), y	40.5 (17.0)	35.7 (13.4)	[redacted]	[redacted]	34.1 (14.4)	36.8 (14.1)
Time from PNH diagnosis to consent, mean (SD), y	8.5 (7.1)	13.0 (9.8)	[redacted]	[redacted]	12.4 (8.4)	11.9 (9.4)
LDH*, mean (SD), U/L	229.0 (57.2)	203.5 (35.5)	[redacted]	[redacted]	228.0 (48.7)	235.2 (49.7)
Hemoglobin, mean (SD), g/dL	8.7 (1.1)	8.7 (0.8)	[redacted]	[redacted]	11.1 (1.8)	10.9 (1.8)
History of major adverse vascular events, %	25.0	18.8	[redacted]	[redacted]	28.9	22.4
History of aplastic anaemia*, %	27.8	18.8	[redacted]	[redacted]	35.1	39.8
* Indicates variable included in matching procedures.						

Source: Bhak *et al.* 2020 (62)

Abbreviations: cm, centimetre; kg, kilogram; HRQoL, health-related quality of life; LDH, lactase dehydrogenase; PNH, paroxysmal nocturnal haemoglobinuria; SD, standard deviation

Clinical and haematological endpoints

After anchoring on eculizumab, treatment with pegcetacoplan was associated with statistically significant improvements on numerous clinical and haematological endpoints when compared with ravulizumab. Pegcetacoplan was associated with 71.4% more transfusion avoidance (95% CI: 53.5%, 89.3%; p<0.0001), 5.7 fewer units of PRBCs transfused during treatment (95% CI: -7.2, -4.2; p<0.0001), 75.5% more haemoglobin stabilisation (95% CI: 56.4%, 94.6%; p<0.0001) and [redacted] more LDH normalisation in the absence of transfusions ([redacted]) than ravulizumab. Given the distribution of LDH data, the mean change from baseline in LDH level did not differ for pegcetacoplan versus ravulizumab.

Fatigue and HRQoL endpoints

Outcomes related to fatigue and HRQoL all showed statistically significant adjusted mean differences favouring pegcetacoplan when compared with ravulizumab. The adjusted difference in mean change from baseline in FACIT-Fatigue was [redacted] (63). Thus [redacted] (57). The adjusted difference in mean change from baseline in global health status (EORTC QLQ-C30) was [redacted], physical functioning was [redacted] and fatigue symptoms was [redacted] when compared with ravulizumab.

Sensitivity analyses

Unanchored comparisons that excluded patients randomised to receive eculizumab in both studies were consistent in magnitude and direction of effect as the anchored comparisons.

In the sensitivity analysis, the definition of LDH normalisation was revised to match the Study 302 definition, which was agnostic to transfusions of PRBCs (i.e., patients who received a transfusion during follow-up were not excluded in the measurement of LDH normalisation). Results [redacted] and show that regardless of transfusion status during follow-up, pegcetacoplan was associated with

[redacted] LDH normalisation (adjusted difference = [redacted]).

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B.2.10 Adverse reactions

B.2.10.1 Overview

Pegcetacoplan was well tolerated and has an acceptable safety profile, as demonstrated in PEGASUS. The safety results are presented across all patients in the safety population who were randomly assigned to treatment and received at least 1 dose of monotherapy study drug.

No thromboembolic events were reported in PEGASUS, therefore no results on this safety outcome are reported in this section.

B.2.10.2 Exposure and dosing

Run-in period

The run-in period was 28 days, during which patients received both eculizumab and pegcetacoplan. Eighty patients received both pegcetacoplan and eculizumab during this study period for a mean of [redacted] and [redacted] days, respectively. [redacted] completed all pegcetacoplan infusions without dosing interruption. Pegcetacoplan infusions were interrupted in [redacted] patients a total of [redacted] times, which accounted for [redacted] of pegcetacoplan infusions. The mean number of pegcetacoplan infusions completed per patient was [redacted]. The completion status of infusions for eculizumab was not evaluated.

Randomised controlled period

Forty-one patients received pegcetacoplan for a mean of [redacted] days, and 39 patients received eculizumab for a mean of [redacted] days. [redacted] in the pegcetacoplan group received [redacted] infusions. [redacted] had [redacted] infusions, and [redacted] received [redacted] infusions. Most patients in the eculizumab group [redacted] received [redacted] infusions. [redacted] completed all infusions, with a mean of [redacted] infusions completed. [redacted] patients had interrupted

pegcetacoplan infusions a total of [redacted] times, accounting for [redacted] of all study infusions. Table 36 shows drug exposure for the RCP for the safety population.

All patients started pegcetacoplan at a dosage of 1,080 mg SC twice weekly. The protocol required dose escalation if a patient had elevated LDH levels > 2xULN. Only [redacted] had their dosage increased to every 3 days as per the protocol, reflecting the reduced need for dose increases to control ongoing haemolytic episodes.

Note: During the RCP, patients were to receive only the therapy to which they were randomly assigned (pegcetacoplan or eculizumab). On Day 1, all patients received a dose of pegcetacoplan before being randomly assigned to monotherapy with either pegcetacoplan or eculizumab. Eculizumab dosing continued per the patient's usual dosing schedule prior to randomisation and therefore, most patients (n = 79) continued to have combined exposure to both eculizumab and pegcetacoplan until a few days after randomisation (up to 4 days for pegcetacoplan and 14 days for eculizumab). The term "pegcetacoplan + eculizumab" is used to denote this portion of continued combination exposure at the beginning of the RCP.

Table 36 Study drug exposure, during RCP (safety population)

		Pegcetacoplan + Eculizumab*		Pegcetacoplan	Eculizumab
	Statistics	**Pegcetacoplan exposure (n=2)**	**Eculizumab exposure (n=1)**	**Pegcetacoplan exposure (n=41)**	**Eculizumab exposure (n=39)**
Total dose administered					
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]	[redacted]
Duration of treatment (days)					
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]	[redacted]
Patients received infusion	n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Patients with all infusions completed	n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Patients with any infusions interrupted	n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Number of infusions completed by patient					
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]	[redacted]
Total number of infusions	M	[redacted]	[redacted]	[redacted]	[redacted]
Infusion completed	m (%)	[redacted]	[redacted]	[redacted]	[redacted]
Infusion interrupted	m (%)	[redacted]	[redacted]	[redacted]	[redacted]

Source: PEGASUS CSR (10)
m (%), m/M x100; M, number of total infusions; N, number of patients exposed to the drug; N/A, not applicable (Infusion for eculizumab was not evaluated whether it was completed or not); SD, Standard Deviation.
Notes: Number of infusions means number of infusions in accordance with the schedule and treatment arm allocation.
Duration of Treatment (days) = Date of Last Injection – Date of First Injection + 1.
Infusion completed is defined as infusion without interruption.
*Because some patients might take the combination of pegcetacoplan and eculizumab in RCP, their exposure is summarised in pegcetacoplan + eculizumab Group.

B.2.10.3 Incidence of treatment-emergent adverse events

Run-in period

Co-administration of pegcetacoplan and eculizumab in the run-in period of 28 days was well tolerated with no discontinuations due to TEAEs. There was [redacted] serious adverse event (SAE) during the run-in period ([redacted]) that was considered related to both pegcetacoplan and eculizumab. This SAE resolved during the run-in period by Day -15, despite continued treatment with both pegcetacoplan and eculizumab. The patient was later randomly assigned to pegcetacoplan and had no subsequent TEAEs of infection. No patients experienced any TEAEs leading to study discontinuation, drug discontinuation or death in the run-in period.

Randomised controlled period

During monotherapy in the RCP, a similar percentage of patients in the pegcetacoplan and eculizumab groups experienced at least one TEAE, including 36 (87.8%) of 41 patients who received pegcetacoplan and 34 (87.2%) of 39 patients who received eculizumab (Table 37). There were [redacted] in the pegcetacoplan group and [redacted] in the eculizumab group that had TEAEs deemed related to study treatment, with most of these being (injection site reactions) ISRs. This was expected as pegcetacoplan is administered subcutaneously whereas eculizumab is administered intravenously and patients entering the study were already known to tolerate eculizumab as all patients were receiving eculizumab prior to entering the study. ISRs were experienced by [redacted] in the pegcetacoplan group. However, there were no ISRs that were serious, severe, or led to study drug discontinuation. In addition, the total number of TEAEs and unique events are similar between the pegcetacoplan and eculizumab groups when ISRs are excluded. The pegcetacoplan group experienced a total of [redacted], and the eculizumab group experienced a total of [redacted] unique events. The difference in the two group is largely accounted for by ISR TEAEs ([redacted]). Most subjects experienced TEAEs with a maximum severity of mild or moderate.

There were seven and six patients who experienced serious TEAEs in the pegcetacoplan and eculizumab groups respectively, of which only [redacted] in each

treatment group experienced a TEAE which was deemed related to treatment. No TEAEs leading to death were reported in either study group.

Three patients discontinued because of TEAEs, all in the pegcetacoplan group, and all because of intravascular breakthrough haemolysis (IVBTH). [redacted]. Therefore, these discontinuations do not raise a safety concern with pegcetacoplan. In fact, aAdverse events of haemolysis occurred less frequently in the pegcetacoplan group than in the eculizumab group, [redacted] versus [redacted] of pegcetacoplan and eculizumab patients, respectively, experienced at least one haemolytic event. For more information on haemolytic adverse events see **Error! Reference source not found.**.

Table 37 Overview of treatment-emergent adverse events, during RCP (safety population)

	Pegcetacoplan + Eculizumab[a] (N=79) n (%)	**Pegcetacoplan (N=41) n (%)**	**Eculizumab (N=39) n (%)**
Any TEAEs	12 (15.2)	36 (87.8)	34 (87.2)
Total events	[redacted]	[redacted]	[redacted]
Unique events	[redacted]	[redacted]	[redacted]
Treatment-related TEAEs, related to pegcetacoplan	[redacted]	[redacted]	[redacted]
Treatment-related TEAEs, related to eculizumab	[redacted]	[redacted]	[redacted]
Treatment-related TEAEs, related to infusion	[redacted]	[redacted]	[redacted]
Serious TEAEs	2 (2.5)	7 (17.1)	6 (15.4)
Serious TEAEs, related to pegcetacoplan	[redacted]	[redacted]	[redacted]
Serious TEAEs, related to eculizumab	[redacted]	[redacted]	[redacted]
Serious TEAEs, related to infusion	[redacted]	[redacted]	[redacted]
TEAEs by maximum severity			
Mild	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]
Injection site reaction	[redacted]	[redacted]	[redacted]
TEAEs leading to study drug discontinuation	0	3 (7.3)	0
TEAEs leading to death	0	0	0

Source: PEGASUS CSR (10)
[a] TEAEs that occurred after randomisation date but before the first monotherapy are summarised under the pegcetacoplan + eculizumab group
Abbreviations: AE, adverse event; NA, not applicable; RCP, randomised controlled period; TEAE, treatment-emergent adverse event

Common treatment-emergent adverse events

Run-in period

TEAEs in [redacted] patients were deemed to be related to pegcetacoplan. General disorders and administration site conditions were reported by [redacted] Injection site erythema was the most frequently reported of these events [redacted] followed by injection site pruritus and injection site swelling ([redacted]), ISR [redacted] injection site induration [redacted] and injection site pain ([redacted]). [redacted] reported nervous system disorders, including headache reported by [redacted] No other TEAEs were reported in 5% or more of subjects in this study period.

[redacted] reported six eculizumab-related TEAES. These included [redacted] report each of alanine aminotransferase (ALT) increased, sepsis, platelet count decreased, leukopenia, neutropenia, and pain in jaw.

[redacted] reported at least 1 ISR TEAE. The most frequently reported events (5% or greater) were injection site erythema [redacted] injection site pruritus [redacted] injection site swelling [redacted] ISR [redacted] injection site induration [redacted] and injection site pain [redacted]

Randomised controlled period

Table 38 shows that general disorders and administration site conditions were the most frequently reported SOC of TEAEs, occurring in [redacted] in the pegcetacoplan group and [redacted] in the eculizumab group. The difference in TEAEs was mostly accounted by the greater number of patients who reported ISRs in the pegcetacoplan group as compared with the eculizumab group. Fatigue was more common in the eculizumab group (15.4% compared with 4.9% in the pegcetacoplan group). Pyrexia occurred in 2 patients in each treatment group (5.1% of patients in the eculizumab group and 4.9% in the pegcetacoplan group). TEAEs in the SOC of nervous system disorders were more frequent in the eculizumab group [redacted] when compared with the pegcetacoplan group [redacted] and were attributed to more frequent headache and dizziness TEAEs in the

eculizumab cohort none of which led to drug discontinuation. In the eculizumab group, headache and dizziness were reported by 9 subjects (23.1%) and 4 subjects (10.3%), respectively. In the pegcetacoplan group, headache was reported by 3 subjects (7.3%) and dizziness was reported by 1 subject (2.4%). TEAEs related to diarrhoea, all rated mild, were more frequent in the pegcetacoplan group (22% vs. 2.6%) and did not lead to study drug discontinuation.

Table 38 Treatment-emergent adverse events reported by 5% or more subjects in any monotherapy treatment group in general disorders and administration site conditions, during RCP (safety population)

System Organ Class/ Preferred Term	Pegcetacoplan + Eculizumab[a] (N=79) n (%)	Pegcetacoplan (N=41) n (%)	Eculizumab (N=39) n (%)
Any TEAEs	12 (15.2)	36 (87.8)	34 (87.2)
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]
Injection site erythema	[redacted]	7 (17.1)	0
Injection site reaction	[redacted]	5 (12.2)	0
Injection site swelling	[redacted]	4 (9.8)	0
Asthenia	[redacted]	3 (7.3)	3 (7.7)
Injection site induration	[redacted]	3 (7.3)	0
Fatigue	[redacted]	2 (4.9)	6 (15.4)
Pyrexia	[redacted]	2 (4.9)	2 (5.1)
Vaccination site pain	[redacted]	0	2 (5.1)
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	3 (7.3)	4 (10.3)
Pain in extremity	[redacted]	3 (7.3)	1 (2.6)
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	9 (22.0)	1 (2.6)
Abdominal pain	[redacted]	5 (12.2)	4 (10.3)
Nausea	[redacted]	2 (4.9)	2 (5.1)
Vomiting	[redacted]	0	3 (7.7)
Infections and infestations	[redacted]	[redacted]	[redacted]
Viral upper respiratory tract infection	[redacted]	2 (4.9)	2 (5.1)
Urinary tract infection	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]
Haemolysis	[redacted]	4 (9.8)	9 (23.1)
Anaemia	[redacted]	0	5 (12.8)

Nervous system disorders	[redacted]	[redacted]	[redacted]
Headache	[redacted]	3 (7.3)	9 (23.1)
Dizziness	[redacted]	1 (2.4)	4 (10.3)
Vascular disorders	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	3 (7.3)	1 (2.6)
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	1 (2.4)	2 (5.1)
Oropharyngeal pain	[redacted]	0	2 (5.1)
Hepatobiliary disorders	[redacted]	[redacted]	[redacted]
Hyperbilirubinaemia	[redacted]	0	2 (5.1)
Psychiatric disorders	[redacted]	[redacted]	[redacted]
Anxiety	[redacted]	1 (2.4)	2 (5.1)
Insomnia	[redacted]	0	2 (5.1)
Cardiac disorders	[redacted]	[redacted]	[redacted]
Palpitations	[redacted]	0	2 (5.1)
Renal and urinary disorders	[redacted]	[redacted]	[redacted]
Chromaturia	[redacted]	0	2 (5.1)

Source: PEGASUS CSR (10)
[a] TEAEs that occurred after randomisation date but before the first monotherapy are summarised under the pegcetacoplan + eculizumab group
Abbreviations: AE, adverse event; NA, not applicable; RCP, randomised controlled period; TEAE, treatment-emergent adverse event

Post-hoc analyses of adverse events

Randomised controlled period

Haemolytic TEAEs were evaluated through a post-hoc analysis in which all TEAEs that included the term “haemolysis” or “haemolytic” were counted**Error! Reference source not found.**. By this analysis, haemolytic TEAEs were reported more frequently in the eculizumab group as compared with the pegcetacoplan group. Specifically, there were [redacted] in the eculizumab group, compared with 4 patients (9.8%) in the pegcetacoplan group, who had haemolytic TEAEs. Of these, 9 patients (23.1%) in the eculizumab group and 4 patients (9.8%) in the pegcetacoplan group were considered to have BTH. Two patients in the eculizumab group had LDH levels of >3x ULN during their BTH, while 4 patients in the pegcetacoplan group had LDH levels of >3x ULN during their BTH.

Patient narrative for those with intravascular breakthrough haemolysis events in the pegcetacoplan arm

28-year-old male with low transfusion requirements (two transfusions in prior year), body mass index (BMI) of 38.92 kg/m^2 at baseline (40.08 kg/m2 at time of SAE), and treated with higher-than-labelled dose of eculizumab (1,500 mg every 2 weeks):

- Baseline haemoglobin, 7.4 g/dl; LDH, 249.5 U/l; reticulocyte count, 190 × 10^9/l; indirect bilirubin, 51 µmol/l.
- Randomized to pegcetacoplan group.
- Experienced two adverse events (AEs) of haemolysis prior to withdrawal from treatment:
    - One moderate event of haemolysis on study days 42–47.
    - Second severe SAE of haemolysis on study days 47–53, with LDH of 1,539 U/l 3 days prior to event, which led to treatment withdrawal.
- No precipitating event or concurrent infection reported with either event.
- High BMI (>35 kg/m^2) considered a possible confounder and study inclusion criteria subsequently amended.
- Most recent pegcetacoplan level prior to episode of IVBTH noted to be lower than average value at steady state for adult patients with PNH dosed with pegcetacoplan at 1,080 mg twice weekly subcutaneously.

71-year-old female who was transfusion independent (no transfusions in prior year), had a BMI of 21.7 kg/m^2, and was treated with a higher than label dose of eculizumab (1,200 mg every 2 weeks):

- Baseline haemoglobin, 8.6 g/dl; LDH, 158 U/l; reticulocyte count, 220 × 10^9/l; indirect bilirubin, 31 µmol/l.
- Randomized to pegcetacoplan group.
- Experienced a moderate AE of haemolysis on study days 49–56 with LDH of 1,157 U/l (local laboratory value, range 130–460 U/l).
- No precipitating event or concurrent infection reported.

63-year-old female who was transfusion dependent (five transfusions in prior year), had a BMI of 22.4 kg/m^2, and was treated with eculizumab 900 mg every 2 weeks:

- Baseline haemoglobin, 6.0 g/dl; LDH, 316.5 U/l; reticulocyte count, 365 × 10^9/l; indirect bilirubin, 36 µmol/l.
- Randomized to pegcetacoplan.
- Experienced a moderate AE of haemolysis on study days 36–39 with LDH of 4,147 U/l (local laboratory value, range 130–460 U/l).
- No precipitating event or concurrent infection reported.
- Most recent pegcetacoplan level prior to episode of IVBTH noted to be lower than average value at steady state for adult patients with PNH dosed with pegcetacoplan at 1,080 mg twice weekly subcutaneously.

40-year-old female who was transfusion dependent (30 transfusions in prior year) had a BMI of 28.1 kg/m^2, and was treated with eculizumab 1,200 mg every 2 weeks:

- Baseline haemoglobin, 10.3 g/dl; LDH, 258 U/l; reticulocyte count, 260 × 10^9/l; indirect bilirubin, 25.9 µmol/l.
- Randomized to pegcetacoplan.
- Experienced severe AE of haemolysis on days 106–140 with LDH of 3,300 U/l.
- On day 103 developed an upper respiratory tract infection that likely triggered the IVBTH.
- In response to the event of haemolysis, the pegcetacoplan dose regimen was increased to every 3 days.

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B.2.11 Ongoing studies

There are no ongoing studies that will provide additional evidence in the next 12 months for the indication being appraised in this submission. Data from Part three of PEGASUS (32-week open-label pegcetacoplan-only period) will be available in H2 2021.

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B.2.12 Innovation

Pegcetacoplan is a novel C3 inhibitor and will be the first and only therapeutic option approved that can effectively control PNH by preventing both IVH and EVH. Current treatment with C5 inhibitors targets IVH, leaving EVH untreated, resulting in suboptimal control of the disease (7). The majority of patients still experience persistent anaemia, leading to reduced HRQoL, fatigue, and reduced ability to perform activities of daily living, and also require continued blood transfusions, further reducing HRQoL (14).

Pegcetacoplan is the first self-administrated SC infusion therapy in PNH. Self-administration enhances patient control in disease management and will reduce patient burden of administration compared with bi-weekly, 3-4-hour IV infusions required for eculizumab and 8-weekly 2-3-hour IV infusions required for ravulizumab. There are also benefits to equity of care through accessible treatment at home and not prohibiting PNH patients' ability to access care.

Pegcetacoplan demonstrated head-to-head superiority in adjusted (LS) mean change in Hb levels (3.84 g/dL difference; 95% CI: 2.33;5.34. P value: <0.0001) compared to eculizumab. Furthermore, a total of 34.1% of patients treated with pegcetacoplan achieved Hb normalisation compared to 0% treated with eculizumab. This results in transfusion avoidance (pegcetacoplan: 85.4%; eculizumab: 15.4%) and clinically meaningful improvements in measures of bone marrow function, anaemia, and haemolysis. These benefits were observed regardless of baseline transfusion requirement or baseline platelet count. Pegcetacoplan also demonstrated clinically meaningful improvements in HRQoL. Pegcetacoplan demonstrated a substantial improvement in patient fatigue compared to a eculizumab, as measured by an 11.9-point increase that is nearly four times the threshold for what is deemed to be clinically meaningful on the FACIT-Fatigue Scale. Pegcetacoplan also [redacted] patients' overall HRQoL as shown on the EORTC-QLQ-C30 scale. In the pegcetacoplan group, the GHS/QoL score [redacted] by Week 16. Conventionally, an increase of 10 points is considered clinically meaningful (57).

Pegcetacoplan reduced the need for dose increases to control ongoing haemolytic episodes, with fewer than [redacted] of pegcetacoplan patients increasing their dosing frequency. By improving Hb levels and reducing transfusion requirements, pegcetacoplan will reduce resource utilisation and direct costs and has the potential to create societal benefit from increased productivity and reduced carer burden (64).

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B.2.13 Interpretation of clinical effectiveness and safety evidence

Clinical effectiveness

PEGASUS is the pivotal study for the use of pegcetacoplan in adult anaemic patients with PNH who are not sufficiently controlled by treatment with a C5 inhibitor. Pegcetacoplan will be the first and only C3 inhibitor for patients with PNH previously treated with a C5 inhibitor, which prevents both IVH and EVH. The phase III randomised, multicentre, open-label, active-comparator controlled trial met its primary efficacy endpoint, demonstrating rapid and sustained efficacy over the RCP. The resulting data showed that pegcetacoplan was superior over eculizumab for controlling anaemia and controlling haematologic symptoms of PNH.

Pegcetacoplan demonstrated head-to-head superiority in Hb levels which was statistically significant compared to eculizumab. Pegcetacoplan demonstrated improvements in Hb levels from baseline and controlled the haematologic manifestations of PNH. The difference in LS mean CFB in Hb between the two groups of 3.84 g/dL was highly statistically significant (95% CI: 2.33; 5.34. P value: <0.0001). The results of the primary efficacy endpoint of CFB in Hb at Week 16 were reproduced consistently across multiple sensitivity analyses and supportive analyses, and were retained regardless of subgroups, baseline transfusion status, or baseline platelet count, supporting the robust nature of the results.

Secondary endpoint analyses demonstrated that pegcetacoplan was noninferior to eculizumab in transfusion avoidance. Consequently, the number of transfusions required by PNH patients will be reduced upon approval, leading to a decreased burden on the NHS. This reduction was demonstrated in PEGASUS, when compared with eculizumab, more patients in the pegcetacoplan group avoided transfusions (85% and 15%, respectively; P value: <0.0001).

Pegcetacoplan improved HRQoL compared to eculizumab. There was a considerable and clinically meaningful improvement in FACIT-Fatigue scores at Week 16 with pegcetacoplan as compared with eculizumab (9.22 vs. -2.65 points; P value: 0.0005). Results demonstrate that patients taking pegcetacoplan report similar levels of quality of life as the general population. At just Week 2, the pegcetacoplan group FACIT-Fatigue score of 43.38 is aligned to the general population score of 43.6 (21,48).

The results of this study support the use of pegcetacoplan at a dose of 1,080 mg self-administered SC twice weekly or every 3 days for adult anaemic patients with PNH who are not sufficiently controlled by treatment with a C5 inhibitor.

Safety

Pegcetacoplan was well tolerated and has an acceptable safety profile, as demonstrated in PEGASUS. In the safety population, most patients in both treatment arms groups experienced at least one TEAE, including 87.8% of pegcetacoplan patients and 87.2% of eculizumab patients. During the RCP, [redacted] of patients in the pegcetacoplan group and [redacted] in the eculizumab group had TEAES deemed related to study treatment, with most of these being ISRs. This was expected as patients entering the study were already known to tolerate eculizumab as all patients were receiving eculizumab prior to entering the study. ISRs were experienced by [redacted] in the pegcetacoplan group. The total number of TEAEs and unique events are similar between the pegcetacoplan and eculizumab groups when ISRs are excluded. There were no injection-related TEAEs that were serious, severe, or led to study drug discontinuation. No patients died in PEGASUS.

Strengths of the clinical evidence

PEGASUS demonstrates that the clinical benefit of pegcetacoplan was sustained over time. No evidence of treatment waning was observed.

The robustness of these results was supported by extensive sensitivity and supportive analyses. The additional prespecified analyses demonstrate that pegcetacoplan improves Hb levels from baseline, with superiority over eculizumab regardless of baseline transfusion status, or baseline platelet count. The consistency of these results provides strength and validity to the findings of primary endpoint analysis.

An advisory board including six UK clinicians with experience in the treatment of PNH, including clinicians from the only two nationally commissioned centres for the treatment of PNH in England discussed the generalisability of the trial evidence. These clinicians agreed that the patients enrolled in PEGASUS would be representative of those likely to receive treatment with pegcetacoplan in the UK (13).

Limitations of the clinical evidence

One limitation is that all patients were treated with pegcetacoplan up to and including Day 1 of the RCP. As such, the beneficial effects of pegcetacoplan are likely to continue in the short term for the eculizumab group, creating a positive bias for eculizumab as seen in Section B.2.6.1 Primary efficacy endpoint: change from baseline to Week 16 haemoglobin level.

Secondly, the prespecified hierarchical testing of the key secondary endpoints led to FACIT-Fatigue score not being tested statistically, despite this being a key benefit of pegcetacoplan administration as described by clinicians and pegcetacoplan demonstrating a substantial improvement in fatigue that is nearly four times the threshold for what is deemed to be clinically meaningful on the FACIT-Fatigue Scale (13,65).

End of life criteria

Pegcetacoplan does not meet the criteria for ‘life-extending treatment at the end of life’.

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B.3 Cost effectiveness

Summary of cost-effectiveness analysis

- A three-state Markov model was developed to evaluate the cost-effectiveness of pegcetacoplan in comparison to eculizumab and ravulizumab in adults with PNH whose anaemia is not sufficiently controlled after treatment with a C5 complement inhibitor.

- The model structure consists of three states: no transfusion and Hb <10.5g/DL, no transfusion and Hb ≥10.5g/dL, and transfusion required. In addition, iron overload and discontinuation due to BTH is modelled between treatment arms.

- Clinical data to inform transition probabilities, HRQoL, drug utilisation and baseline patient characteristic was sourced from the PEGASUS trial comparing pegcetacoplan, ravulizumab and eculizumab in patients with insufficiently controlled PNH. The clinical efficacy of ravulizumab and eculizumab were assumed to be equal.

- EQ-5D-3L utilities were mapped from EORTC QLQ-C30 values collected in the PEGASUS trial. The mapping method used was from Longworth et al. (66)

- Costs associated with PNH treatment, breakthrough haemolysis, iron overload, blood transfusions and healthcare resource use are considered in the economic analysis for all treatments. All costs are from relevant national UK sources. Resource use associated with health states was derived by clinical opinion. The key cost drivers in the economic model are drug costs and the cost of iron overload.

- The base case results show [redacted] incremental QALYs over a lifetime horizon for pegcetacoplan compared to ravulizumab and ravulizumab compared to eculizumab, and [redacted] and [redacted] and incremental costs over a lifetime horizon for pegcetacoplan compared to

ravulizumab and ravulizumab compared to eculizumab respectively, with pegcetacoplan dominating both eculizumab and ravulizumab.

- Sensitivity analysis in the form of PSA and OWSA show that 100% of 1,000 simulations remained below the £10,000 per QALY cost effectiveness threshold compared to both eculizumab and ravulizumab. Given this, pegcetacoplan is eligible for the fast-track appraisal process.
- The cost-effectiveness results remained consistent when key inputs such as mean weight of patients, utility values and the drug acquisition costs associated with iron chelation were varied to their upper and lower bound on OWSA. This demonstrates the robustness of the economic analysis.
- Scenario analysis results demonstrate that pegcetacoplan dominates ravulizumab and eculizumab in all scenarios.
- All key model inputs and modelling assumptions have been validated by UK clinicians and independent health economics experts (13), with internal, external and cross-validation steps taking place also.

B.3.1 Published cost-effectiveness studies

A cost-effectiveness systematic literature review (SLR) was conducted on July 30th 2020, and updated on March 11th 2021, in medical literature databases (MEDLINE, MEDLINE In-Process, Embase, BioScience Information Service of Biological Abstracts, EconLit and Cochrane Library). A single combined search was performed to identify existing cost-effectiveness, HRQoL and cost and resource use studies in PNH. Full details of the economic SLR can be found in Appendix G.

In total, the review identified 12 publications for economic evaluations of therapies used in the treatment of PNH, of which 10 were unique. Among them, 5 health technology assessment (HTA) reports for eculizumab and one HTA report for ravulizumab was identified which are summarised in Table 39. In addition, there were 4 further cost-effectiveness evaluations (also summarised in Table 39): preliminary economic evaluations from Connock et al. (67) for the UK, a comparison

of the cost-effectiveness of eculizumab plus SoC vs SoC from Coyle et al. (68), a comparison of the cost-effectiveness of eculizumab vs ravulizumab from O'Connell et al. (69) from a US perspective and a further analysis from O'Connell et al using the same model structure, from a German perspective (70)

Table 39 Summary list of published cost-effectiveness studies

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (currency) (per QALY gained)
SMC (71)	2021	The study consisted of both a cost minimisation analysis (CMA) and a cost-utility (CUA) analysis. The cost-minimisation analysis assumed no difference in clinical effectiveness between ravulizumab and eculizumab and was a simple comparison of acquisition and administration costs. The CUA was a state transition model covering 10 health states, representing different categories of breakthrough haemolysis (Complement-amplifying-condition associated and incomplete C5 inhibition-related), as well as modelling history of previous breakthrough haemolysis (BTH) events. Two states were applied which assumed patients required an increased dose of eculizumab for the remainder of the time horizon, following two incomplete C5 inhibition-related BTH events. Background mortality was assumed constant with the	Patients with PNH	(Incremental QALYs in CUA, ravulizumab vs eculizumab) 0.97	(Incremental costs, CMA, ravulizumab vs eculizumab) £1,470,7784	Dominant

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (currency) (per QALY gained)
		general population, and spontaneous remission and PNH-specific mortality were only modelled in scenario analyses.				
O'Connell et al. (69)	2020	This study was a cost-utility, Markov state-transition model comparing ravulizumab and eculizmab, with a US payer perspective, lifetime horizon and two-week cycle length. Three cohorts of adult patients with PNH were considered (see patient population column). 11 health states: • 8 related to BTH events (with distinction between BTH events related to suboptimal free C5 inhibition vs related to complement-amplifying condition) • 2 related to mortality (natural/background and PNH-related) • 1 related to spontaneous remission	Cohort 1 (PNH patients naive to eculizumab) Mean age: 45.5 Cohort 2 (PNH patients clinically stable on the maintenance dose of eculizumab) Mean age: 47.7 Cohort 3 (PNH patients clinically stable on off-label use of a higher maintenance dose) Mean age: 47.7	Eculizumab vs ravulizmab Base-case 17.25,18.93 Cohort 1 16.87, 18.07 Cohort 2 17.29, 19.00 Cohort 3 17.29, 19.00	(USD; eculizumab vs ravulizmab) Base-case 9,363,868, 7,690,403 Cohort 1 9,702,919, 7,898,350 Cohort 2 9,333,678, 7,671,887 Cohort 3 11,566,315, 7,671,887	(USD) Base-case -1,000,818 Cohort 1 -1,512,000 Cohort 2 -909,137 Cohort 3 -2,272,060
O'Connell et al (70)	2019	Cost utility analyses from a German payer perspective, with a lifetime horizon. Outcomes modelled included: • Current/historical/no BTH	Adult outpatients with PNH: • Cohort 1: eculizumab naive	Eculizumab vs ravulizumab (incremental) 0.53	(EUR, eculizumab vs ravulizumab, incremental) -1,906,440	(EUR) Dominant

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (currency) (per QALY gained)
		• Dosage • Administration frequency • Remission • Blood transfusion	• Cohort 2: stable on eculizumab (labelled dosage) • Cohort 3: stable on eculizumab (higher dosage)			
SMC (72)	2016	Cost consequence Markov model from an NHS Scotland perspective and a lifetime horizon. Health states included: • PNH and no thrombosis • PNH with previous thrombosis • PNH and initial thrombosis • PNH and subsequent thrombosis • PNH and end-stage renal failure • PNH, thrombosis and end end-stage renal failure • Death	Adult patients with PNH	Eculizumab vs best supportive care 11.96, 9.23	NR	NR
Coyle et al. (68)	2014	This study was a cost-utility, Markov model comparing eculizumab in addition to standard of care to standard of care alone, with a Canadian health care system perspective. Health states were based on 6 consequences of PNH:	Patients with classic PNH. Analysis was stratified based on 2 characteristics of patients with PNH: 1. PNH clone size	Eculizumab and standard of care (SoC) vs SoC 9.01; 6.56	(CAD) Eculizumab and SoC vs SoC 5,237,742; 185,956	(CAD) 2,134,156

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (currency) (per QALY gained)
		1. thrombotic events 2. marrow related problems 3. kidney related problems 4. iron overload 5. meningococcal infections, 6. spontaneous resolution Modelled containing 47 health states, 42 of which were hybrid health states (combinations of states related to thrombosis [3 levels], marrow complications [2 levels], transfusions and related renal problems [3 levels], and iron overload [3 levels]), 3 related to the most severe complications related to PNH (myelodysplastic syndrome, acute myeloid leukemia and requiring renal replacement therapy), 1 related to spontaneous resolution of symptoms, and the final absorbing state was death	2. Blood transfusion requirements Age: NR			
AETSA (73)	2011	HTA report, Andalusian Public Health System perspective comparing eculizumab to best supportive care	NR	NR	NR	(EUR) Per thrombotic event: 6,034,912 Per QoL improvement: 1,508,728

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (currency) (per QALY gained)
						Per PRBC unit avoided in 6 months: 19,669.00 Per PRBC unit avoided in 1 year: 47,147.75 Per transfusion independence for 6 months: 754,364
CADTH (74)	2010	CADTH Common Drug Review: CEDAC Final Recommendation; Canadian perspective. Cost-effectiveness analysis from Canadian health care system perspective with 26 week cycle length	NR	NR	NR	(CAD, eculizumab plus supportive care vs supportive care alone) 2,400,000
PBAC (75,75,75)	2008, 2009, 2010	Australian HTA report; cost-effectiveness analysis from Australian payer perspective with 2 year horizon (original) and 3 year horizon (cycle length)	PNH patients	NR	NR	(AUD, eculizumab vs supportive care) >200,000 per death avoided
AWMSG (76)	2009	AWMSG final appraisal report. Discussion of the analyses reported by Connock, 2008 (67)	PNH patients	As reported in Connock, 2008 (67)		
Connock et al. (67)	2008	Comparison of eculizumab and standard of care. Three	All PNH patients who are eligible to	Analysis 1:	(GBP) Analysis 1:	(GBP) Analysis 1:

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (currency) (per QALY gained)
		preliminary economic evaluations were carried out. Analysis 1: • Cost-effectiveness • UK NHS perspective • 26 week time horizon • ICER calculated per stabilisation of haemoglobin and stabilisation of LDH Analysis 2: • Cost-effectiveness for standard of care costs, savings and survival • UK NHS perspective • 25-year time horizon Analysis 3: • Cost-effectiveness for averted thrombosis-related mortality • UK NHS perspective • Decision tree following patients with PNH who can develop thrombosis, some of whom will die • 10-15 year time horizon	the treatment, as per clinical expert opinion.	Cost-effectiveness per stabilisation of haemoglobin • 0.49 Cost-effectiveness per stabilisation of range of LDH • 0.37 Analysis 2: NR Analysis 3: 10-year time horizon • NR 15-year time horizon • NR	Cost-effectiveness per stabilisation of haemoglobin • 126,000 Cost-effectiveness per stabilisation range of LDH • 126,000 Analysis 2: • NR Analysis 3: 10-year time horizon • 2,248,000 15-year time horizon • 3,044,000	Cost-effectiveness per stabilisation of haemoglobin • 257,142 Cost-effectiveness per normal range of LDH • 340,541 Analysis 2 (estimated): • 0.6-1 million Analysis 3: 10-year time horizon • 3,211,000 15-year time horizon • £2,768,000

Abbreviations: BTH, breakthrough haemolysis; CAD, Canadian dollars; GBP, Great British Pound; ICER, incremental cost-effectiveness ratio; LDH, lactate dehydrogenase; LY, life year; NHS, National Health Service; PNH, paroxysmal nocturnal haemoglobinuria, QALY, quality-adjusted life-year, USD, US dollar; UK, United Kingdom

B.3.2 Economic analysis

The aforementioned economic SLR identified three unique variations of CEMs for treatment in PNH (1,4,5) however none of these models were deemed appropriate to capture the economic impact of the introduction of pegcetacoplan in the patient population in question. Analyses from Connock et al. (67) were preliminary analyses comparing eculizumab with SoC and focused on improvements in mortality given treatment paradigm at the time (2008). The model from Coyle et al. (68) was particularly complicated, modelling six different consequences from PNH or from treatment (thrombotic problems, marrow related problems, kidney related problems, iron overload, meningococcal infection, and spontaneous resolution). Conditions were modelled simultaneously such that patients could be in composite states—that is, they may have more than 1 complication at a time resulting in a total of 47 health states. This structure has substantial data requirements introducing unnecessary uncertainty around outcomes. Furthermore, many of the modelled outcomes are not relevant due to non-inferiority in a C5 versus C3 inhibitor comparison.

O'Connell et al. (69) compared the cost-effectiveness of ravulizumab and eculizumab, both of which are C5 inhibitors with the same mode of action. The model focused on health states defined by breakthrough haemolysis (BTH) with 8 BTH related health states and 3 BTH free health states. While it is referred to generally as BTH, the definition of BTH used in these analyses is intravascular BTH (IVBTH), which is generally defined as:

"at least 1 new or worsening symptom or sign of intravascular haemolysis (fatigue; haemoglobinuria; abdominal pain; shortness of breath [dyspnoea]; anaemia [Hb <10 g/dL]; major adverse vascular events, including thrombosis; dysphagia; or erectile dysfunction) in the presence of elevated LDH ≥2 × ULN, after prior LDH reduction to <1.5 × ULN on therapy".

IVBTH is caused by the formation of the membrane attack complex (MAC) creating holes in red blood cells causing them to rupture inside blood vessels. C5 inhibitors such as eculizumab and ravulizumab prevent IVBTH however they do not act on C3

related EVH. Given this, previous models for ravulizumab (C5 inhibitor) centre around IVBTH and do not consider EVH.

As pegcetacoplan is a C3 inhibitor, it works further up the complement cascade, working to overcome both IVH and EVH (9). As the model from O'Connell et al. (69) did not consider EVH, or improvements in fatigue, it was not considered appropriate for capturing the clinical benefits associated with pegcetacoplan.

According to clinical experts, if patients who continue to experience EVH despite treatment with a C5 inhibitor (eculizumab or ravulizumab) are better managed by pegcetacoplan, they will have a better clinical outcome in terms of anaemia (less fatigue), blood transfusion requirement, ability to work (better productivity), and some disease-related complications such as jaundice and gallstone disease (77).

A de novo Markov CEM was developed in Microsoft Excel to estimate the long-term cost-effectiveness of the introduction of pegcetacoplan. The model has three mutually exclusive health states defined based on Hb levels (indication of anemia) and transfusion status as well as an absorbing death health state. Spontaneous remission was not modelled in line with clinical opinion as any remission would not be expected to vary by treatment arm. This was validated as appropriate by clinical opinion at the April 2021 advisory board (13). The model estimates the long-term costs and outcomes (e.g., quality-adjusted life-year [QALY]) incurred in the target population (adults with PNH whose anaemia is not sufficiently controlled after treatment with a C5 complement inhibitor). The final model structure was designed based on opinions from clinical experts through interviews held in 2020 (77) as well as an advisory board held in April 2021 (13).

Patient population

The modelled patient population is the intended MRHA-licensed population for pegcetacoplan in the treatment of PNH: adults with paroxysmal nocturnal haemoglobinuria whose anaemia is not sufficiently controlled after treatment with a C5 complement inhibitor for at least 3 months (referred to as treatment switch patients hereafter). This patient population is aligned with the pivotal pegcetacoplan trial, PEGASUS, the NICE scope and decision problem. The patient characteristics (e.g., baseline age, percentage of patients who were female, mean weight, and time

since diagnosis) were based on the treatment-switch patients included in the PEGASUS trial (9).

Time horizon

The time horizon considered was a lifetime (51 years), in line with the NICE reference case (78). The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect all important differences in costs or outcomes between the technologies being compared. Therefore, a lifetime horizon was chosen since patients accumulate differential costs and QALYs until death.

Discounting

Costs and utilities were discounted at 3.5% per annum, in line with the NICE reference case (78).

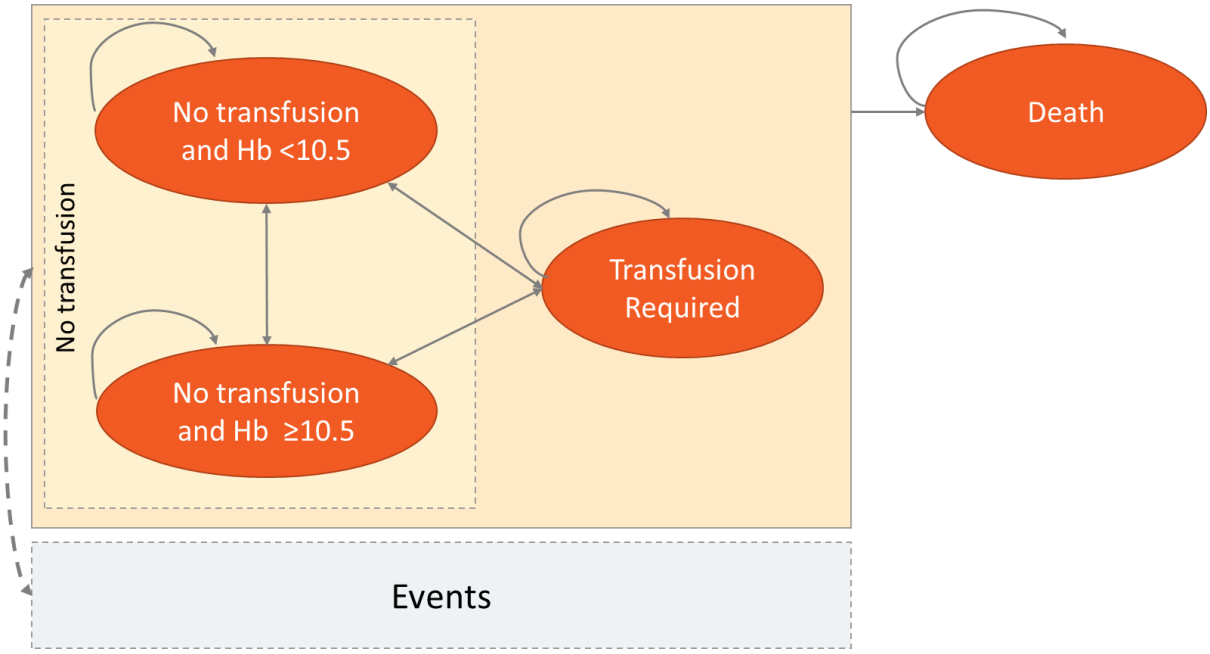
Perspective

An NHS and personal social services (PSS) perspective was chosen, in line with the NICE reference case (78).

Model structure

A de novo Markov CEM was developed with health states defined on Hb levels and transfusion status and is outlined in Figure 18. A combination of Hb level and blood transfusion requirements was chosen to define health states as together, they represent different levels of disease status.

Figure 18 Model structure



The model consists of three transfusion-related health states as defined below, spontaneous remission and death.

- No transfusion and Hb <10.5g/dL: no transfusion in previous 4 weeks and Hb <10.5g/dL at time of assessment.
- No transfusion and Hb ≥10.5g/dL: no transfusion in previous 4 weeks and Hb <10.5g/dL at time of assessment.
- Transfusion Required: transfusion required in previous 4 weeks

A haemoglobin cut-off at 10.5g/dL was chosen as it is consistent with inclusion criteria in the PEGASUS clinical trial and was validated by clinical opinion as appropriate for capturing differences in HRQoL between health states. According to clinicians, although anaemia is generally defined as Hb <13.5g/dL in men and Hb < 12g/dL in women, patients with PNH may have a Hb lower than the general population and feel 'normal'. Given this, a lower threshold of Hb level of 10.5g/dL was seen as appropriate to categorise patients as having 'controlled' and 'uncontrolled' anaemia (13). Further stratifications of Hb levels was not possible due to low patient numbers.

In the base case, the distribution of patients at baseline is taken from the pre-trial distribution of patients. In each 4-week model cycle, patients can remain in their

current health state, move to a different health state, or move to death, which is an absorbing state.

IVBTH and iron overload are modelled based on clinical opinion using data from the PEGASUS trial and are discussed further in Section B.3.3.

For each cycle, total costs and QALYs are calculated based on the distribution of patients across the health states. These are accumulated over the model time horizon to calculate total costs and QALYs per treatment arm from which incremental results and the cost per QALY are determined.

A half-cycle correction was applied to both costs and health benefits in the Markov model in accordance with conventional modelling standards. This accounts for the fact that transitions may occur at any point during a cycle rather than exclusively at end/beginning of each cycle (79).

The key features of the economic analysis with justification are presented in Table 40. A comparison against the ravulizumab NICE TA is also provided (35).

Table 40 Features of the economic analysis

	Previous appraisal (TA10690)	**Current appraisal**	
Factor	**Chosen values**		**Justification**
Patient population	Adults with PNH, who have haemolysis with clinical symptom(s) indicative of high disease activity or whose disease is clinically stable after having eculizumab for at least 6 months	Adults with PNH whose anaemia is not sufficiently controlled after treatment with a C5 complement inhibitor	Aligned with population defined in the NICE scope and decision problem and the anticipated licence for pegcetacoplan (Table 1).
Analytical method	Markov model	Markov model	Patients can fluctuate between discrete no transfusion and Hb <10.5g/dL, no

			transfusion and Hb≥10.5g/dL, and transfusion required health states each cycle. This simple structure accurately captures the course of PNH and has been validated by expert health economists (13).
Model structure	10 health states: Specifically, there are eight BTH health states, one mortality-related health state, and a spontaneous remission health state (included in scenario analysis only).	Three health states: no transfusion and Hb <10.5g/DL, no transfusion and Hb ≥ 10.5g/dL and transfusion required	Capture HRQoL and resource use associated with continued EVH in the patient population under consideration and impact of treatment with pegcetacoplan versus C5 inhibitors. Validated by clinical opinion (13).
Time horizon	Lifetime	Lifetime (51 years)	In line with NICE reference case (78). The time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect all important differences in costs or outcomes between the technologies being compared. Therefore, a lifetime horizon was chosen since patients accumulate differential costs and QALYs until death.
Cycle length	2 weeks	4 weeks	The chosen cycle period allows all

			relevant costs and health benefits to be captured and is consistent with published cost-effectiveness studies identified from the economic SLR for treatment in PNH. In addition, the cycle period is aligned with the data available from the PEGASUS trial. Shorter cycle lengths are likely to overcomplicate the model calculation given the use of a lifetime horizon of 51 years and to not meaningfully impact on cost or QALY estimates, while longer cycle lengths increase the risk of over or under predicting costs or QALYs when averaging across cycle times. A half cycle correction was applied.
Treatment waning effect?	Not applied	None	Not considered appropriate in line with clinical opinion (13).
Discounting per year of costs and utilities	3.5% per annum	3.5% per annum	In line with NICE reference case (78).
Perspective	NHS and PSS	NHS and PSS	In line with NICE reference case (78).
Health effects	QALYs and life years	QALYs and life years	In line with NICE reference case (78).

Clinical efficacy and safety	ALXN1210-PNH-301 (NCT02946463) and ALXN1210-PNH-302 (NCT03056040)	Data were sourced from: • PEGASUS trial (9,10) • Published clinical evidence	The PEGASUS trial is the primary source of evidence of the efficacy and safety of pegcetacoplan as a treatment of adults with PNH whose anaemia is not controlled after treatment with a C5 complement inhibitor.
Costs and resource use	Standard UK sources including eMIT and MIMS for drug costs, and NHS reference costs.	Data were sourced from: • BNF for drug costs • NHS reference costs for disease management unit costs • Clinical expert opinion	In line with NICE reference case (78) and previous appraisals.
Health state utilities	EORTC QLQ-C30 data from the ALXN1210-PNH301 and ALXN1210-PNH302 studies mapped to EQ-5D-3L utility estimates, using the Longworth et al. (66) mapping algorithm.	Apellis data on file (10); EQ-5D utilities mapped from EORTC QLQ-C30 HRQoL data collected from the PEGASUS trial and mapped using Longworth et al. (66)	In line with NICE reference case (78) and previous appraisals (35,71).
Disutility associated with frequent regular IV infusion for eculizumab (versus pegcetacoplan and ravulizumab)	0.025	-0.025 taken from ravulizumab TA10690 (35).	In line with NICE reference case (78), supporting a positive utility difference observed with reduced administration burden.

Abbreviations: EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D, EuroQol Five-Dimension; FACT, Functional assessment of Cancer Therapy; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PNH, paroxysmal nocturnal haemoglobinuria; PSS, Personal social services; QALY, Quality-adjusted life-years; QoL, quality of life.

Intervention technology and comparators

The model compares the use of pegcetacoplan against comparators for the target population in the UK; treatment switch patients.

Eculizumab was licensed by the European Medicines Agency (EMA) in 2007 for the treatment of PNH (38). In the UK, it has been used to treat patients with PNH for more than a decade. The EMA approved ravulizumab in July 2019 and it is indicated for use in adult patients with PNH with haemolysis with clinical symptoms indicative of high disease activity and also for adult patients who are clinically stable after having been treated with eculizumab for at least the past 6 months (41). Ravulizumab was recommended by NICE in April 2021 for use in adult PNH patients with haemolysis with clinical symptoms suggesting high disease activity, or whose disease is clinically stable after having eculizumab for at least 6 months (36), suggesting that it may shortly become SoC.

Hence, eculizumab and ravulizumab were selected as the base-case comparator in treatment-switch patients. This aligns with comparators defined in the NICE scope and decision problem. Further detail on this is given in Section B.2 Clinical effectiveness. When comparing against eculizumab, data from the PEGASUS clinical trial was used to inform the baseline clinical demographics, subsequent transitions between health states and health state utilities. The PEGASUS trial was identified from a clinical SLR as the only relevant clinical trial, and is a phase III, prospective, randomised, multicentre, open-label, active-comparator controlled study in patients with PNH who continued to have Hb levels <10.5g/dL despite treatment with eculizumab. Clinical data inputs were validated by health economic and clinical experts during an advisory board carried out in April 2021 (13).

A MAIC analysis was performed to assess the comparative effectiveness of pegcetacoplan and ravulizumab, however results of the MAIC are not used in the economic model as there is some evidence to suggest results of the MAIC may be subject to bias due to heterogeneity between the trial patient populations. Furthermore, outcomes from the MAIC are not directly applicable to the CEM structure and would introduce considerable and unnecessary uncertainty to the modelling.

However, results of clinical trials ALXN1210-PNH-301 (Study 301) and Study 302 demonstrated ravulizumab met non-inferiority versus eculizumab across all disease markers mortality (e.g., LDH, terminal complement inhibition and BTH events) (61). Based on the non-inferiority observed in the pivotal trials, and the fact that ravulizumab was derived from eculizumab with the technologies sharing over 99% homology (35) an economic comparison with ravulizumab is presented using the PEGASUS data and assuming equal efficacy between eculizumab and ravulizumab. This assumption is based on equal efficacy assumption presented in TA10690 (36) and the cost minimisation model presented in the SMC submission for ravulizumab (72).

Clinical experts at the technical engagement call for the ravulizumab NICE TA noted that eculizumab and ravulizumab are essentially the ‘same’ drug and the difference seen with regard to BTH is not so much driven by difference in efficacy, but reflects the extended bioavailability of ravulizumab, due to the modifications in its structure that allow for ‘recycling’ of the active compound that leads to a longer half-life, as well as the weight-based dosing, to provide complete and sustained inhibition of C5 (35).

The approach of equal efficacy between eculizumab and ravulizumab is deemed to be conservative for the following reasons:

- The patient population under consideration here is patients who are not sufficiently controlled despite treatment with a C5 inhibitor in line with the population studied in PEGASUS. Study 302 studied patients treated with eculizumab according to the labelled dosing recommendation for PNH for at least 6 months however these patients were not necessarily deemed ‘uncontrolled’ since they were eligible regardless of Hb levels, with mean Hb levels at baseline of 11.1 and 10.9 g/dL for ravulizumab and eculizumab, respectively, compared with 8.7 g/dL in both the pegcetacoplan and eculizumab treatment arms in PEGASUS. In addition, history of transfusions within one year before receipt of first dose was 13.4% and 12.2% for ravulizumab and eculizumab in Study 302, respectively, with much higher proportions in PEGASUS with 72.2% and 71.9% in the pegcetacoplan and

eculizumab treatment arms, respectively. Given this, there is limited data on the effectiveness of ravulizumab in this patient population.

- Both Study 301 and Study 302 provided comparative efficacy of ravulizumab versus eculizumab 900 mg every 2 weeks with no up dosing of eculizumab permitted throughout the trial (up dosing occurs in clinical practice when patients are not sufficiently controlled on eculizumab leading to IVBTH). In PEGASUS, patients remained on their pre-trial dose with 30% of patients on a dose higher than 900 mg every 2 weeks. By using the PEGASUS data for ravulizumab, it is generously assumed ravulizumab is equally efficacious to higher doses of eculizumab in this patient population.

- In clinical practice, patients on eculizumab who experience BTH may have their dose increased (up dosing) or their dose brought forward. However, as both Study 301 and Study 302 did not allow for dose adjustments the trial may bias against eculizumab as it is not reflective of clinical practice.

B.3.3 Clinical parameters and variables

Baseline demographics

Patient demographics at baseline were based on the PEGASUS trial, and are detailed in Table 41.

Table 41 PEGASUS baseline patient demographics

Baseline demographics	Base-case values
Mean age (years)	48.8
Female (%)	61.3
Mean weight (kg)	[redacted]
Time since diagnosis (years)	[redacted]

The baseline distribution of patients across health states is given in Table 42. In the base-case, 100% of patients were assumed to be in the no transfusion and HB <10.5 g/dL health state. In a scenario analysis, the pre-run-in distribution of patients in the PEGASUS trial was used.

Table 42 Baseline distribution of patients across health states

Health state	Distribution of patients (base case)	Distribution of patients (scenario analysis based on PEGASUS pre-run in)
No transfusion and Hb <10.5 g/dL	100%	61.8%
No transfusion and Hb ≥10.5 g/dL	0%	3.9%
Transfusion required	0%	34.2%

Abbreviations: Hb, haemoglobin

Transition probabilities applied in the analysis

Transition probabilities for patients receiving pegcetacoplan and eculizumab were estimated from the patient level data of PEGASUS trial based on the following approach:

- Patients were classified into appropriate health states depending on their medical characterisation on the planned visits during PEGASUS clinical trial period.
- Transition probabilities between health states were estimated using a multinomial logistic regression model (Equation 1), estimated using SAS software, with:
    - The current health state as outcome variable,
    - Health state 4 weeks earlier, treatment (Tx), visit category (Visit) and age as covariates,
    - Random intercept at patient level (i) (u_i),
    - Interaction between treatments and visit category.

Equation 1. Multinomial logistic regression model used to estimate transition probabilities

$$Health\ state_{current} \sim Health\ state_{previous} + T_X + Visit + T_X * T_X * Visit + Age + U_i$$

In the PEGASUS study, there was a 4-week run in period where patients received both pegcetacoplan and eculizumab. However, based on clinical opinion (12), it is unlikely that this run in period will happen in clinical practice and thus costs associated with the run-in period are not modelled. In order to mitigate the impact of the run-in period, the base case analyses uses transition probability calculated using data from week 4 to week 16. Four weeks was deemed to be an appropriate length

of time to mitigate for the 'hangover' effect of the run in period by key opinion leaders, it was agreed that a 4 week washout period was sufficient (13), and is in line with the efficacy data illustrating that after 4 weeks, haemoglobin stabilises for both pegcetacoplan and eculizumab (10). While it is appreciated that ravulizumab has a longer half-life than eculizumab (32 days), the impact of a 'hangover' effect for patients switched from ravulizumab to pegcetacoplan is somewhat unknown, given this a conservative approach was taken and data from weeks 4-16 was used in line with eculizumab. Starting from week 4 also helps to start the analysis from a theoretically "washed out" patient, helping to apply the same transition probabilities for ravulizumab and eculizumab in line with the assumptions that were also made in TA10690 (35) (discussed in Section B.3.2). A scenario is provided using the 0-4-week data for cycle 1 and 4-16 week data for subsequent cycles. Base-case transition probabilities are presented in Table 43 with the scenario analysis in

Table ***44***.

The transition probabilities show that over time, patients on eculizumab return to their pre-trial state with low Hb levels and transfusion dependence. This was in line with expectations for this patient population, with clinical data demonstrating that patients receiving eculizumab ultimately return to their pre-trial state in terms of Hb levels and transfusion requirements (53,60,80). Patients enrolling in PEGASUS had been on eculizumab treatment for ~4-5 years and had reached their 'steady state' (as described by clinicians). For pegcetacoplan, the transition probabilities show that over time a high proportion of patients achieved Hb levels greater than or equal to 10.5g/dL. The following statements were validated with clinicians (13) as representative of their experiences in this patient population and expectations for the impact of pegcetacoplan:

- A much higher percentage of patients will require transfusions and remain transfusion dependent on eculizumab than on pegcetacoplan
- A small percentage of patients will have controlled anaemia (Hb <10.5g/dL) on eculizumab compared with pegcetacoplan
    - In particular, if patients achieve 'controlled anaemia' (Hb ≥10.5g/dL) they are very likely to remain 'controlled'

- If patients have not achieved ‘control’ (Hb ≥10.5g/dL) in the first 4 weeks, the probability of achieving ‘control’ reduces to 50-60%

Of note, once patients have had a transfusion, the transition probabilities based on data from PEGASUS show that patients receiving pegcetacoplan have a small probability of requiring a transfusion in the next 4 weeks (pegcetacoplan: 4.84% versus eculizumab: 60.13%) and a much higher chance of then returning to a ‘controlled anaemia’ (Hb >10.5g/dL) state (pegcetacoplan: 71.23% versus eculizumab: 0.09%). This was validated by clinical opinion (13) as key opinion leaders noted that for eculizumab, the patients entering PEGASUS were highly selected, and would have been receiving transfusions regularly, in the region of every 2-6 weeks (see Table 5 for baseline patient characteristics). In contrast, patients receiving pegcetacoplan who responded in the first 4 weeks were highly likely to remain on pegcetacoplan.

Transition probabilities derived from the trial were validated by clinical opinion alongside model projections at 1,2,5 and 10 years (see Table 45) (13). The Markov trace for pegcetacoplan is provided in Figure 19 and for eculizumab and ravulizumab in Figure 20.

Table 43 Transition probabilities applied in base case (Week 4 to Week 16)

From	To		
	No transfusion and Hb <10.5g/dL	**No transfusion and Hb ≥10.5g/dL**	**Transfusion required**
Transition probabilities for patients receiving pegcetacoplan			
No transfusion and Hb <10.5g/dL	[redacted]	[redacted]	[redacted]
No transfusion and Hb ≥10.5g/dL	[redacted]	[redacted]	[redacted]
Transfusion required	[redacted]	[redacted]	[redacted]
Transition probabilities for patients receiving eculizumab/ravulizumab			
No transfusion Hb and <10.5g/dL	[redacted]	[redacted]	[redacted]
No transfusion and Hb ≥10.5g/dL	[redacted]	[redacted]	[redacted]
Transfusion required	[redacted]	[redacted]	[redacted]

Abbreviations: Hb, haemoglobin

Table 44 Transition probabilities applied in the first cycle (0-4 week data for cycle 1 and 4-16 week data for subsequent cycles) (scenario analysis)

From	To		
	No transfusion and Hb <10.5g/dL	**No transfusion and Hb ≥10.5g/dL**	**Transfusion required**
Transition probabilities for patients receiving pegcetacoplan			
No transfusion and Hb <10.5g/dL	[redacted]	[redacted]	[redacted]
No transfusion and Hb ≥10.5g/dL	[redacted]	[redacted]	[redacted]
Transfusion required	[redacted]	[redacted]	[redacted]
Transition probabilities for patients receiving eculizumab/ravulizumab			
No transfusion and Hb <10.5g/dL	[redacted]	[redacted]	[redacted]
No transfusion and Hb ≥10.5g/dL	[redacted]	[redacted]	[redacted]
Transfusion required	[redacted]	[redacted]	[redacted]

Abbreviations: Hb, haemoglobin

Table 45 Base case projections: % of patients in each health state over time

From	To		
	No transfusion and Hb <10.5g/dL	**No transfusion and Hb ≥10.5g/dL**	**Transfusion required**
Patients receiving pegcetacoplan			
1 month	[redacted]	[redacted]	[redacted]
1 year	[redacted]	[redacted]	[redacted]
2 years	[redacted]	[redacted]	[redacted]
5 years	[redacted]	[redacted]	[redacted]
10 years	[redacted]	[redacted]	[redacted]
20 years	[redacted]	[redacted]	[redacted]
40 years	[redacted]	[redacted]	[redacted]
Patients receiving eculizumab/ravulizumab			
1 month	[redacted]	[redacted]	[redacted]
1 year	[redacted]	[redacted]	[redacted]
2 years	[redacted]	[redacted]	[redacted]
5 years	[redacted]	[redacted]	[redacted]
10 years	[redacted]	[redacted]	[redacted]
20 years	[redacted]	[redacted]	[redacted]
40 years	[redacted]	[redacted]	[redacted]

Abbreviations: Hb, haemoglobin

Figure 19 Markov trace for patients treated with pegcetacoplan (base case)

Figure 20 Markov trace for patients treated with ravulizumab and eculizumab (base case)

Breakthrough haemolysis and discontinuation

Based on clinical opinion the following approach has been taken.

Extravascular breakthrough haemolysis (EVBTH)

According to clinical opinion, EVBTH haemolysis results in a drop in Hb level and blood transfusions, both of which are captured in the model health states and thus EVBTH is not explicitly modelled.

Intravascular breakthrough haemolysis (IVBTH)

Patients receiving treatment with ravulizumab or eculizumab are conservatively assumed to not experience IVBTH. Clinicians noted that the current practise with eculizumab is to adjust doses either by increasing doses or bringing doses closer together where there is evidence of IVBTH (further dose increases conservatively not modelled in CEM).

IVBTH is modelled for pegcetacoplan. Four patients receiving pegcetacoplan had IVBTH (49):

- One patient remained on treatment,
- Three patients discontinued treatment with pegcetacoplan during the RCP.

However, of these three patients, [redacted] At the time of the PEGASUS trial there was no established way of treating IVBTH for patients on pegcetacoplan and as such the safest treatment decision was for patients to switch back to eculizumab. Clinicians confirmed that they would treat IVBTH for patients on pegcetacoplan with a one-off 900 mg dose of eculizumab. Clinicians noted that eculizumab is preferred over ravulizumab for this one-off off label dose due to the shorter half-life (13). Clinical opinion (13) is that:

- A small proportion of patients will discontinue pegcetacoplan after a 'settle in period' when clinicians can identify the select number of patients for whom pegcetacoplan is unsuitable. This is estimated in the model by the 'one-off' discontinuation at Week 16 in PEGASUS, calculated as [redacted] out of 41 [redacted] on the pegcetacoplan arm. These patients discontinue pegcetacoplan and switch onto eculizumab treatment in line with clinical opinion.

- Other patients who have IVBTH will receive 900 mg dose of eculizumab. A per cycle rate is used in the model based on three patients out of 41 with an event in the 16-week period ([redacted]%) of PEGASUS, which was converted from a probability. These patients do not discontinue in the model and instead continue on pegcetacoplan.

- Discontinuation is not considered for eculizumab or ravulizumab in line with results from PEGASUS trial and clinical opinion.

Table 46 Treatment discontinuation and BTH

	Data Input	Sources
Discontinuation		
Pegcetacoplan	[redacted] at week 16	Apellis data on file (10); one patient (out of 41) discontinued pegcetacoplan.
Eculizumab	0.00%	Apellis data on file (10)
Ravulizumab	0.00%	Assumed to be the same as eculizumab
BTH requiring dose of eculizumab		
Pegcetacoplan	[redacted] per cycle	Apellis data on file (10) (3 events out of 41 patients over 16 weeks)

Abbreviations: AE, adverse event; CSR, clinical study report; RCT, randomised controlled trial.

Iron overload

Frequent transfusions in severely anaemic, transfusion-dependent patients may cause the development of iron overload in PNH patients (81–83). According to clinical opinion, the majority of transfusion dependent patients with EVH will be on life-long chelation therapy for iron overload (13), which was thought to be a key differentiator between pegcetacoplan and C5 inhibitors. In the PEGASUS trial, [redacted] % of patients were reported to be on deferoxamine mesilate and [redacted]% of patients were receiving deferasirox at baseline, resulting in a total of [redacted]% of patients experiencing iron overload. However, according to clinicians, patients on pegcetacoplan do not require chelation therapy, as patients have sufficient increases in Hb levels such that clinicians can remove iron by removing blood in this cohort, which is much cheaper and safer for patients (13).

Modelling mortality

The leading cause of death in PNH patients before eculizumab became available was thrombosis, which has now been proven to be well managed by eculizumab.

Published long-term overall survival (OS) data suggest patients receiving eculizumab have comparable OS to the age-adjusted general population (43).

Pegcetacoplan reduces both IVH and EVH therefore, in principle, this means it can reduce the risk of kidney damage and mortality risks associated with complications of blood transfusions. However, due to:

- the rarity of complications from blood transfusion;
- rarity of PNH patients developing life threatening kidney disease;
- and unavailability of long-term data on pegcetacoplan,

mortality is assumed equal between all treatments. The probability of death was estimated based on age- and sex-matched general population mortality (84) .

B.3.4 Measurement and valuation of health effects

Health-related quality-of-life data from clinical trials

In the PEGASUS trial, patient HRQoL was measured weekly based on the EORTC QLQ-C30. A 30-item questionnaire composed of both multi-item scales and single-item measures to assess overall HRQoL. HRQoL measures were reported directly by patients, in line with the NICE reference case (78). The EORTC QLQ-C30 questionnaire has been validated for use in PNH patients due to the fatigue and impaired quality of life associated with the illness (14). EORTC-QLQ-C30 score results collected during the PEGASUS trial are reported in Table 25 based on the change from baseline to Week 16.

Results from the PEGASUS clinical trial showed EORTC-QLQ-C30 Global Health Status(GHS)/QoL and all Functional Scales improved in the pegcetacoplan arm at week 16 compared with eculizumab. In the pegcetacoplan arm, the GHS/QoL score increased by 15.91 (SE: 3.635) which is clinically meaningful (an increase of 10 points is considered clinically meaningful (57)).

As EQ-5D data were not collected in the PEGASUS clinical study, and the SLR identified no published data reporting EQ-5D responses in PNH patients, the EORTC QLQ-C30 data collected in the trial were mapped to EQ-5D-3L utility weights (in line with the NICE reference case (78)). Utility values were age adjusted using Ara and Brazier 2011 (85).

Mapping

A targeted literature review identified two studies, Longworth et al. 2014 (66) and McKenzie and van der Pol et al. 2009 (86). Longworth et al. 2014 (66) was used in TA10690 (35) in PNH patients and was published under the HTA programme, as part of the National Institute for Health Research (NIHR) (87). A validation exercise of Longworth et al. 2014 (66) has shown that the algorithm performed well on several validation criteria and that response mapping performed well in new samples (88). While McKenzie and van der Pol et al. 2009 (86) was identified it was not considered in scenario analyses as, upon investigation, the linear model predicted utility values greater than one, lacking internal and external validity.

Longworth et al. 2014 (66) was validated by expert opinion (13) and accepted by the committee in TA10690 for patients with PNH. Longworth et al. 2014 (66) was based on the following data sets:

- Patients newly diagnosed with multiple myeloma from a randomised open-label trial (Velcade as Initial Standard Therapy [VISTA])
- Patients diagnosed with breast cancer and attending an outpatient clinic in Vancouver Cancer Clinic
- Patients diagnosed with lung cancer attending an outpatient clinic in Vancouver Cancer Clinic

The coefficients from the Longworth et al. (2014) regression were used to calculate the probabilities of being in different states of each domain of the EQ-5D-3L questionnaire. The EQ-5D-3L utilities were then calculated for each patient, at each visit, by substituting the probability of being in each response level using Equation *2*.

Equation 2. Derivation of EQ-5D-3L utilities

$$\begin{aligned} Expected\ EQ5D \\ &= 1 - \left(P_{mobility2} * 0.069\right) - \left(P_{mobility3} * 0.314\right) - \left(P_{self-care2} * 0.214\right) \\ &- \left(P_{self-care3} * 0.036\right) - \left(P_{usualactivities3} * 0.094\right) - \left(P_{pain2} * 0.123\right) \\ &- \left(P_{pain3} * 0.386\right) - \left(P_{anxiety2} * 0.071\right) - \left(P_{anxiety3} * 0.236\right) \\ &- \left(1 - P_{perfecthealth}\right) * 0.081 - P_{alllevels3} * 0.269 \end{aligned}$$

Next, health-related utilities for health states considered in the cost-effectiveness model were calculated using regression analysis (A Tobit model was used since it accounts for the censored distribution of EQ-5D data, which is truncated at 1.

Equation 3). A Tobit model was used since it accounts for the censored distribution of EQ-5D data, which is truncated at 1.

Equation 3. Health-related utilities for health states regression

$$Utility \sim Health\ state_{current} + Age + Visit + u^i$$

The current health state, age and visit category were considered as fixed-effects and the random intercept at patient level (u_i) as random. The following independent variables were selected and several models were tested with (1) health state, (2) treatment, (3) Age, (4) visit and (5) Id and the interaction between (1) health state and (2) treatment. A significant interaction suggested that pegcetacoplan is associated with increased utility compared with eculizumab, however treatment was conservatively removed from the model as an independent variable.

Visits were organised into the run-in period, RCT period, open-label and follow-up. This categorisation was considered since descriptive analyses suggested that utilities vary between visits, and health states are expected to vary between visits. Therefore, visit was a potential confounder when looking at the association between health state and utility. The average age of patients (48.8 years) was also considered within the model. Results of the regression model is given in Table 47 and the resulting utility weights by health state is given in Table 48.

Table 47 Regression analysis, Tobit model, using Longworth et al. 2014 (66)

Covariate	Coefficient	SE	t	P>|t|	95% CI
intercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No transfusion <10.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No transfusion ≥10.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Run-in	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RCP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Open-label	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Follow-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 48 EQ-5D-3L health state utility weights mapped from EORTC QLQ-C30 HRQoL data using Longworth et al. 2014 (66)

	Mean (SD)
No transfusion and Hb ≥10.5	[redacted]
No transfusion and Hb <10.5	[redacted]
Transfusion required	[redacted]

Abbreviations: EORTC QLQ-C30, EORTC Quality of Life Questionnaire - Core Questionnaire; Hb, haemoglobin; SD, standard deviation

Health-related quality-of-life studies

A HRQoL SLR was performed to identify published evidence of the impact of relevant comparators on the HRQoL of patients with PNH, and to identify relevant utility values. The SLR was conducted on July 30th 2020, with an update on Match 11th 2021, within medical literature databases (MEDLINE, MEDLINE In-Process, Embase, BioScience Information Service of Biological Abstracts, EconLit and Cochrane Library). A single combined search was performed to identify existing cost-effectiveness, HRQoL and cost and resource use studies in PNH. Please see Appendix G for the methods used to identify relevant studies. A description of identified HRQoL studies is given in Appendix H. The systematic review identified 2 studies evaluating public preferences for PNH treatment attributes and estimating disutilities for use in cost-effectiveness analyses (89,90). These studies are summarised in Table 49.

Both were stated-preference discrete-choice experiment surveys. Lloyd et al. (89) evaluated the UK general public's preferences for several treatment attributes for PNH, including overall survival, treatment administration, burden of haemolysis, risk of meningitis, and need for blood transfusions. The study suggested that participants preferred an infusion frequency of every 8 weeks (ravulizumab dosing frequency) compared with every 2 weeks (eculizumab dosing frequency). The disutility of 0.057 was reported for intravenous infusion every 2 weeks compared with every 8 weeks. Analysis of the choice data indicated that maximising life expectancy was the most important attribute. Lloyd et al. (90) evaluated public preferences for the same

attributes in Australia, Canada, the Netherlands, Sweden, and the UK. The disutility for intravenous infusion every 2 weeks compared with every 8 weeks ranged between 0.044 in Canada and 0.070 in the Netherlands (90).

Table 49 Health related quality-of-life studies

Author	Year	Country	Study population	Method of elicitation and valuation	Health state description	Utility estimate
Lloyd et al. (90)	2020	Australia, Canada, Netherlands, Sweden, UK	N = 1,764 Public participants aged ≥ 18 years	A stated-preference discrete-choice experiment survey The mixed logit model estimated preference strength and disutilities for each treatment attribute (overall survival, administration, risk of haemolysis and meningitis, and the need for blood transfusions).	Infusions every 8 weeks versus every 2 weeks	Disutility: −0.058 (Australia) −0.044 (Canada) −0.070 (Netherlands) −0.069 (Sweden) −0.057 (UK)
					Risk of developing meningitis infection	Disutility: −0.034 (Australia) −0.036 (Canada) −0.046 (Netherlands) −0.047 (Sweden) −0.040 (UK)
					Risk of developing severe haemolysis	Disutility: −0.140 (Australia) −0.132 (Canada) −0.155 (Netherlands)

						−0.153 (Sweden) −0.158 (UK)
					Need for annual blood transfusions	Disutility: −0.071 (Australia) −0.016 (Canada) −0.053 (Netherlands) −0.084 (Sweden) −0.073 (UK)
Lloyd et al. (89)	2019	UK	N = 385 UK general public participants aged ≥ 18 years	A stated-preference discrete-choice experiment survey The mixed logit model estimated strength of preference for the attributes and disutilities for each attribute. Marginal rates of substitution were estimated between survival and other attributes in order to estimate disutilities, weighted against average life expectancy.	Infusions every 8 weeks vs every 2 weeks	-0.057
					Risk of developing meningitis infection	-0.040
					Risk of developing severe haemolysis	-0.158
					Need for annual blood transfusions	-0.073

Since so few health-state utility studies in PNH were identified, the included economic evaluations of treatments in PNH (given in Appendix G) were also used to extract the relevant utility estimates. The review identified 4 published economic evaluations, of which 3 were full-text publications, 2 of these were cost-utility analyses (68,69). In addition, an SMC submission for ravulizumab was identified in the SLR update (71). The utility estimates are summarised in Table 50.

In the O'Connell et al. analysis (69), health utilities were estimated by mapping the HRQoL measure collected in the trials (EORTC QLQ-C30) to the EQ-5D-3L. Mapping was performed using the methodology reported in McKenzie and van der Pol et al. (86). Health-utility benefit of reduced visit frequency was taken from the discrete-choice experiment by Lloyd et al. (89), which isolated the HRQoL impact of visit frequency from other aspects of treatment.

The Coyle et al. analysis (68) used utility weights from a study that assessed the impact of transfusion dependency in patients with myelodysplasia (transfusion independent, reduced transfusion requirements, and transfusion dependent) (91). Utility weights for the various complications of PNH (thrombotic event, iron overload, iron overload–related cardiac disease, renal disease, dialysis, and cytopenia) were obtained from the literature (92–95). Utility values for all potential health states were calculated as a product of the utility value for the relevant transfusion-dependence state and the utility weight for the various complications of PNH. In addition, utility values for myelodysplastic syndrome/acute myeloid leukemia and spontaneous resolution, which do not require consideration of additional complications, were included (96).

The SMC and NICE submission for ravulizumab (36,71) reported utilities associated with eculizumab, ravulizumab and the utility increment associated with decreased administration frequency within IV infusion.

The utility estimates extracted from the following studies were not relevant to the health states utilised in the current cost-effectiveness analysis, making a comparison between the utility values used in the model and the ones throughout the literature difficult. As a result of this, it was necessary to derive utilities from the PEGASUS trial.

Table 50 Utilities from cost-utility studies

Author	Year	Country	Study population	Method of elicitation and valuation	Health state description	Utility estimate
O'Connell et al. (69)	2020	US	**Cohort 1:** PNH patients naive to eculizumab **Cohort 2:** PNH patients clinically stable on the maintenance dose of eculizumab **Cohort 3:** PNH patients clinically stable on off-label use of a higher maintenance dose	Health utility estimated by mapping the HRQoL measure collected in the 301 and 302 studies (QLQ-C30 to EQ-5D-3L). Mapping was performed using the methodology reported in McKenzie and van der Pol (86).	No BTH state: eculizumab	0.79, 0.83, 0.83
					No BTH state: ravulizumab	0.80, 0.87, 0.87
					Decrease in health utility for BTH event: eculizumab or ravulizumab	−0.11, −0.40, −0.40
					Decrease in health utility for transmission: eculizumab or ravulizumab	−0.11, −0.10, −0.10
					Increase in health utility associated with reduced health care provider visit frequency: ravulizumab	+0.057
Coyle et al. (68)	2014	Canada	Patients with MDS	Analysis used utility weights from a study that assessed the impact of transfusion dependency in patients with myelodysplasia.	Transfusion independent	0.84
					Reduced transfusion requirements	0.77
					Transfusion dependent	0.60
			Depending on the complication, different patient populations were used	Utility values for complications were derived from the literature.	Iron overload	0.85
					Iron overload–related cardiac disease	0.80
					Thrombotic event	0.94
					Advanced renal disease	0.88
					Renal dialysis	0.81
					Cytopenia	0.997
					MDS/AML	0.26
					Spontaneous resolution	0.925

SMC Ravulizumab (71)	2021	UK	Patients with PNH	Mapping algorithm to translate EORTC-QLQ-C30 data into EQ-5D as well as discrete choice experiment	Baseline eculizumab utility	0.79
					Baseline ravulizumab utility	0.85
					Utility increment associated with reduced frequency of IV administration	0.057

Abbreviations: BTH, breakthrough haemolysis; EQ-5D, EuroQol-5 Dimension; HRQoL, health-related quality of life; MDS, myelodysplastic syndrome; PNH, paroxysmal nocturnal haemoglobinuria; QLQ, quality of life questionnaire

Adverse reactions

AEs included in the model were derived from the PEGASUS trial: serious treatment-emergent AEs for which the incidence differed by 2% or more between the pegcetacoplan arm and eculizumab arm.

Costs associated with adverse events are not included in the base case. Disutility associated with AEs was assumed to be accounted for within the EQ-5D-3L utility weights from mapped EORTC QLQ-C30 HRQoL data collected during the PEGASUS trial therefore, no additional disutility was included to avoid double counting. In a scenario analysis, AE costs and additional disutility associated with AEs are modelled.

Disutilities are estimated based on probability of developing AEs per cycle, the corresponding disutility per event, and the duration per event. Disutilities were sourced from targeted literature searches. The probability of developing AEs per cycle are presented in

Table **51** alongside disutilities and corresponding durations sourced from the PEGASUS trial (10). Data inputs for pegcetacoplan and eculizumab were estimated based on the PEGASUS trial.

Table 51 Probability of developing adverse events per cycle (10)

	Pegcetacoplan	Eculizumab	Duration	Disutility	Source
Bacterial infection	0.006	0.000	23.0	-0.016	Maruszczak et al., 2015 (97)
Gastroenteritis	0.006	0.000	3.0	-0.071	NICE, 2013
Atrial fibrillation	0.006	0.000	1.0	-0.048	Paix et al., 2018 (98)
Hyperthermia	0.000	0.006	4.0	0.000	TA215 (99)
Facial paralysis	0.006	0.000	27.0	-0.063	Wilson et al., 2003 (100)
Dyspnoea	0.006	0.000	2.0	-0.290	Grutters et al., 2010 (101)
Abdominal pain	0.000	0.006	44.0	0.000	NICE, 2013
Biliary colic	0.000	0.006	0.0	-0.050	Weinstein et al., 1990 (102)

Hepatocellular injury	0.000	0.006	6.0	0.000	Assumption
Hyperbilirubinemia	0.000	0.006	6.0	0.000	Assumption
Jaundice	0.000	0.006	6.0	-0.060	Arguedas et al., 2002 (103)

Disutility associated with iron overload

Targeted literature searches were used to identify a disutility associated with chelation therapy, which was estimated to be -0.03 (104). This was applied to the proportion of patients estimated to be receiving chelation therapy in the eculizumab arm based on PEGASUS, with ravulizumab assumed to the same ([redacted] % of patients, a sum of the [redacted]% of patients receiving deferoxamine mesilate and [redacted]% of patients receiving deferasirox at baseline), resulting in per cycle disutilities. A summary of this is given in Table 52.

Table 52 Iron overload disutility

Drug arm	Probability of developing iron overload	Per cycle disutility	Source
Pegcetacoplan	0	0	Clinical opinion (13)
Eculizumab	[redacted]	[redacted]	Baseline proportion of patients with iron overload in PEGASUS
Ravulizumab	[redacted]	[redacted]	Assumption - equal to eculizumab

Disutility associated with IV infusion

A summary of administration for each treatment is given below:

- Eculizumab is administered via intravenous infusion every two weeks, with some patients having more frequent transfusions (every 11 days).
- Ravulizumab is also given by infusion, however ravulizumab is only required every 8 weeks, reducing the burden of administration when compared with eculizumab.
- Pegcetacoplan is administered by subcutaneous injection twice weekly also reducing the burden of administration when compared with eculizumab.

Targeted searches were used to identify an SLR by Stoner and colleagues showing that patients prefer subcutaneous over IV delivery (105). In addition, a discrete choice experiment reported in the ravulizumab SMC (72) and NICE (35) submission reported a utility increment of 0.057 associated with the reduced administration frequency of IV administration (71). Patients have also been shown to have a preference for a reduction in the number of IV infusions required as described in TA10690 (-0.025 accepted base case value) (35). Given this, the following approach has been taken in the base case:

- Eculizumab has a disutility of -0.025 associated with frequent regular IV infusion versus ravulizumab.
- There is no comparative difference in utility associated with ravulizumab and pegcetacoplan as each treatment improves on the administration burden of eculizumab.

Scenario analyses are presented assuming no utility decrement for eculizumab and a utility decrement of -0.057 as proposed in the manufacturers base case in TA10690 (35) as well as the SMC submission for ravulizumab (72).

Health-related quality-of-life data used in the cost-effectiveness analysis

HRQoL is expected to differ according to respective health states. A transfusion related health state is likely to be associated with the biggest decrement in HRQoL as suggested in the literature (46) due to the fatigue, resource burden and potential complications associated with transfusion. In addition, a Hb <10.5mg/dl, is likely to be associated with HRQoL impairments for a multitude of reasons – including but not limited to cardiovascular complication, functional impairment and mobility impairment (55).

The base-case analysis used the mapping algorithm based on Longworth et al. 2014 (66) as described in Section B.3.4. Table 53 provides a summary of the utility values used in the base-case analysis. Health state utilities are assumed to be constant over the lifetime time horizon and are adjusted for age using Ara and Brazier 2011 (85). These utilities were validated for clinical plausibility through UK clinical experts during an advisory board carried out in April 2021 (13).

Table 53 Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Health state utility				
No transfusion and Hb ≥ 10.5	[redacted]	NA	Mapping, Table 48	The base-case analysis used the mapping algorithm from Longworth et al. 2014(66). EORTC QLQ-C30 values were mapped to EQ-5D-3L values, in line with the NICE reference case (78)
No transfusion and Hb < 10.5	[redacted]			
Transfusion required	[redacted]			
Adverse events				
Adverse events	**Base-case:** Excluded			AE disutility is already accounted for within the mapped EQ-5D-3L utility
	Sensitivity analysis: Various, Adverse reactions			
Iron overload				
Iron overload	−0.03		Iron overload, Table 52	Cherry et al. (36), not accounted for within the mapped EQ-5D-3L utility
IV disutility				
Disutility due to eculizumab IV infusion	**Base-case:** -0.025	NA	Adverse reactions	Assumption based on ravulizumab TA (35)
	Sensitivity analysis: -0.057	NA		Ravulizumab SMC submission (72)

Abbreviations: EQ-5D, EuroQol-5 dimension; GP, general population; Hb, haemoglobin; IV, intravenous; PNH, paroxysmal nocturnal haemoglobinuria; QoL, quality of life

B.3.5 Cost and healthcare resource use identification, measurement and valuation

A cost and resource use SLR was performed to identify published evidence for relevant therapies in the treatment of PNH in July 30th 2020 with an update performed in March 11th 2021. A single combined search was performed to identify existing cost-effectiveness, HRQoL and cost and resource use studies in PNH. Please see Appendix G for the methods used to identify relevant studies. A description of identified cost and resource use studies are given in Appendix I.

A brief summary of the studies identified that reported cost and resource use data globally is reported in Table 54. In addition, the cost estimates used in the key published economic evaluations previously identified (O'Connell et al. 2020 (69); Coyle et al. 2014 (68); Connock et al. 2008 (67)) is given in Table 55. No data found in the SLR was deemed appropriate for the current cost-effectiveness analysis.

Table 54 Cost and resource studies identified from the SLR

Study and year	Country	Cost year	Applicability to clinical practice in England	Cost or healthcare resource reported in study	Costs or healthcare resource use reported in economic analyses
Simabuku et al. 2018 (106)	Brazil	2017	Estimates may not be relevant for the UK because the analysis was conducted in Brazil.	Price per one 30-ml vial of eculizumab	R$17,060
				Annual per patient cost of eculizumab for the treatment of PNH	R$1.8 million
Evers and Jansen 2018 (107)	Netherlands	NR	Estimates may not be relevant for the UK because the analysis was conducted in the Netherlands.	Annual per-patient cost of eculizumab for the treatment of PNH	€360,000
Kanters et al. 2013 (108)		2008-2010		Annual per-patient cost of eculizumab for the treatment of PNH	€358,000
Schey et al. 2017 (109)		2014	Estimate may be relevant to the UK because the	Annual per-patient drug cost for the treatment of PNH	€322,000

			analysis was conducted using UK list prices.		
Korubo et al. 2018 (110)	Nigeria	2017	Estimates are not relevant for the UK because the analysis was conducted in Nigeria.	Total	$269.73
				Investigations	$203.98
				Treatments	$65.75
Hyde and Dobrobolny 2010 (111)	US	NR	Estimates may not be relevant for the UK because the analysis was conducted in the US.	Annual per-patient cost of eculizumab for the treatment of PNH	$486,000-$508,000
Hernandez et al. 2018 (112)		2017		US average wholesale price per milligram	$25.65
				Annual per-patient cost of eculizumab for the treatment of PNH (based on a standard patient: a 70-kg/1.80-m adult)	$592,654
Jalbert et al 2019 (113)		NR		**N (%)**	
				At diagnosis, past-year RBC transfusion	35 (14%)
				At diagnosis, past-year hospitalization	81 (31.5%)
				RBC transfusions at 6 months	37 (14.6%)
				RBC transfusions at 1 year	45 (17.4%)
				Eculizumab initiation over a mean follow-up period of 385.6 days	27 (10.3%)
Levy et al. 2019 (114)		NR		**Eculizumab**	
				Clinic setting total time for travel, administration, and recovery	25,920 hours
				Clinic setting lost productivity	$518,400
				Home setting lost productivity	$320,100
				Ravulizumab	
				Clinic setting lost productivity	$184,800
				Home setting lost productivity	$154,000
Tomazos et al 2019 (115)		NR		Treatment cost due to complement-amplifying conditions	$51,716
				Treatment cost due to insufficient C5 inhibition	$152,895
				Treatment cost due to pregnancy	$186,107

Levy et al 2019 (116)	France, Germany, Italy, Spain, Russia, UK and US	2018	Estimates may be relevant to the UK due to presence of EU countries and UK	Productivity cost associated with eculizumab in-clinic infusion (without caregiver, per 10% increase in caregivers)	
				US	$4,306,790, $414,865
				Germany	$815,264, $79,543
				UK	$575,711, $57,759
				France	$564,088 $58,692
				Italy	$408,217, $41,859
				Spain	$405,431, $42,648
				Russia	$343,969, $31,240
				Productivity cost associated with ravulizumab in-clinic infusion (without caregiver, per 10% increase in caregivers)	
				US	$1,535,099 $147,892
				Germany	$290,627, $29,006
				UK	$205,230, $20,590
				France	$201,087, $20,923
				Italy	$145,522, $14,922
				Spain	$144,529, $15,203
				Russia	$122,619, $11,13
Schrezenmeier et al 2014 (30)	237 centres across 25 countries	NR	Estimates may be relevant for the UK because the analysis was conducted in 25 countries, including the UK.	PNH hospitalisations, n(%)	
				Hospitalization in the 6 months prior to completion of the baseline questionnaire	194 of 856 (22.7%)
				Treatment received prior to enrollment in patients diagnosed with aplastic anemia (n = 701), n (%)	
				Anticoagulation therapy	147 (21.0%)
				Immunosuppressive therapy	270 (38.5%)
				Eculizumab therapy	131 (18.7%)
				Red blood cell transfusion	262 (37.4%)
				Immunosuppressive therapy plus:	
				Anticoagulation	35 (5.0%)
				Eculizumab	37 (5.3%)

				Red blood cells	123 (17.6%)
				Anticoagulation plus:	
				Eculizumab	53 (7.6%)
				Red blood cells	65 (9.0%)
				Eculizumab plus red blood cells	60 (8.6%)
				Anticoagulant use within 12 months prior to enrolment based on history of thrombotic events	
				No (n=1,300)	318 (24.5%); P < 0.01
				Yes (n=250)	176 (70.4%); P < 0.01
				Treatment received at enrolment (n = 1,610), n (%)	
				Anticoagulation therapy	501 (31.1%)
				Immunosuppressive therapy	301 (18.7%)
				Pain medication	133 (8.3%)
				Eculizumab	411 (25.5%)
				Unemployment or part-time work due to PNH	88 of 506 (17.4%)
				Missed work in past 6 months due to PNH	82 of 312 (26.3%) full-time or part-time workers
Schrezenmeier et al (2020) (21)	NR	NR	Estimates may be relevant for the UK because the analysis was conducted in 25 countries, including the UK.	Concomitant medication use at baseline	
				Anticoagulation therapy	849 of 4,206 (20.2%)
				Immunosuppressive therapy	1,642 of 4,232 (38.8%)
				Transfusions	
				RBC transfusions at baseline	2,219 of 3,620 (61.3%)
Kolbin et al. 2020 (117)	Russia		Estimates may not be relevant for the UK because the analysis was conducted in Russia.	Eculizumab therapy	RUB 25.5 million
				Ravulizumab therapy	RUB 26.5 million
				Cost difference when considering increasing dosages per year	RUB 7,431,805 rubles
				Cost differences when considering a reduction in administration interval	RUB 8.627,957
				Cost differences when considering therapy correction	RUB 19,944,588
				Introduction of ravulizumab saving	RUB 616.1 million

Tomazos et al. 2020 (115)	US	2018	Estimates may not be relevant for the UK because the analysis was conducted in US	Multiple costs (associated with episodes of BTH), please see Appendix I

Abbreviations: BTH, breakthrough haemolysis; PNH, paroxysmal nocturnal haemoglobinuria; RBC, red blood cells

Table 55 Cost and resource use identified from relevant economic evaluations

Study and year	Country	Cost year	Applicability to clinical practice in England	Cost or healthcare resource reported in study	Costs or healthcare resource use reported in economic analyses
O'Connell et al. 2020 (69)	US	2018	Estimates may not be relevant for the UK because the analysis was conducted in US.	Eculizumab loading administration costs	$144.72
				Eculizumab maintenance administration costs	$144.72
				Eculizumab other administration costs	$244.60
				Ravulizumab loading administration costs	$176.40
				Ravulizumab maintenance administration costs	$208.08
				Ravulizumab other administration costs	$244.60
				Meningococcal vaccine	$308.80
				Transfusion administration costs	$974.52
				Transfusion packed red blood cell count costs	$213.77
Coyle et al. 2014 (68)	Canada	2012	Estimates may not be relevant for the UK because the analysis was conducted in Canada.	First-year cost of eculizumab	CAD $528,855
				Subsequent-year cost of eculizumab	CAD$506,203
				Annual warfarin monitoring costs	CAD$295.3
				Meningococcal vaccine	CAD$78.50
				Annual cost of iron chelation therapy	CAD$56,665
				Annual cost of myelodysplastic syndrome	CAD$22,674
				Annual cost of acute myeloid leukemia	CAD$57,682
				Annual cost of cytopenia	CAD$962
				Thrombotic event	CAD$2,300
				Cost per transfusion	CAD$464

				Annual cost of advanced renal disease	CAD$2,782
				Annual cost of renal dialysis	CAD$67,352
				Annual cost of iron overload–related cardiac disease	CAD$7,226
				Nonfatal bleeding event	CAD$104
				Fatal bleeding event	CAD$4,392
Connock et al. 2008 (67)	UK	NR	Relevant to the current submission as the study is a UK based analysis, however reported costs are dated and/or estimates where more relevant data is available.	Eculizumab first year of treatment	£252,000
				Eculizumab subsequent year of treatment	£245,700

Abbreviations: BTH, breakthrough haemolysis; CAD, Canadian dollars, NR, not reported; UK, United Kingdom; US, United States

Intervention and comparators' costs and resource use

Technology costs

Technology costs were estimated based on treatment dosing regimens and corresponding drug price. The cost for pegcetacoplan with [redacted] per 1,080 mg.

The drug price for eculizumab was derived from the British National Formulary (BNF) and is £3,150 per 300 mg (118). The drug price for ravulizumab was sourced from the most recent NICE TA (35) and is £4,533 per 300mg (71).

Dosing for eculizumab and pegcetacoplan is taken from the PEGASUS trial from Day 1 to week 16 (excluding run-in) in line with the clinical data used in the CEM and presented in Table 56. Before entering the PEGASUS trial, patients received eculizumab for an average of five years (4.93 years) and a proportion of patients were on higher than label dosing. Patients on the eculizumab arm remained on their pre-trial dose of eculizumab throughout the trial. A protocol amendment was made to allow patients on pegcetacoplan to receive a dose escalation after a single measurement of LDH that was >2 x ULN, rather than requiring 2 consecutive measurements 1 week apart. As previously discussed in Section B.3.3 Clinical parameters and variables, at the time of the PEGASUS trial there was no

established way for treating breakthrough haemolysis and it was thought an increase in the pegcetacoplan dose may be appropriate. However, since then clinicians have established a treatment practice whereby patients who have IVBTH are either treated with a one-off dose of eculizumab or switched back onto eculizumab (13). Both of which are modelled and as such dose escalations for pegcetacoplan are not included in the CEM.

Ravulizumab dosing has weight-based dosage and is assumed as per the label (119). A loading dose given two weeks after the last dose of eculizumab, followed by an IV infusion every eight weeks, starting two weeks after the loading dose. The cost calculations included in the CEM do not include the loading dose given the patient population under consideration are the treatment switch population. This information is summarised in Table 57. Method of moments was used to calculate the distribution of patients' weight from the mean weight reported in the PEGASUS trial to give a weighted average drug cost.

The calculated costs per treatment per cycle is summarised in Table 58. A summary of the costs per dose for ravulizumab are given in

Table **59**. Wastage costs were not included in the model as the required dosage for eculizumab, pegcetacoplan and ravulizumab do not result in any wastage. Patients were assumed to receive treatment across a lifetime horizon.

Table 56 Dosing of pegcetacoplan and eculizumab from PEGASUS trial

Treatment	Dosing Regimen	% split	Source
Pegcetacoplan	Labelled dosing: • 4-week run-in period: 1,080 mg SC administration twice weekly + current dose of eculizumab • Maintenance period: 1,080 mg SC administration twice weekly	100%	Data on file (10)
Eculizumab	Labelled dosing • 900 mg IV infusion every 14 ± 2 days	70%	Data on file (10)
	Dosing escalation • IV 900 mg IV every 11 days	1.3%	
	Dosing escalation • IV 1,200 mg every 11 days	26.3%	
	Dose escalation • IV 1,500 mg every 11 days	2.5%	

Abbreviations: IV, intravenous; SC, subcutaneous

Table 57 Summary of ravulizumab dosage (119)

Ravulizumab	**Weight-based dosing**	**Body weight range (kg)**	**Loading dose (mg)**	**Maintenance dose (mg)**
		≥40 to <60	2,400	3,000
		≥60 to <100	2,700	3,300
		≥100	3,000	3,600
	Maintenance dose	Weight-based IV infusion every 8 weeks starting 2 weeks after the loading dose		

Table 58 Summary of pegcetacoplan and eculizumab costs

Treatment	Dosing Regimen		Cost Per Dose (£)	N. Doses Per Week	Drug Cost Per Week (£)	% Patients
Pegcetacoplan	Labelled dosing	1,080 mg twice weekly	[redacted]	2.00	[redacted]	100%
Weighted average cost per week (£)						[redacted]
Eculizumab	Loading dose	600 mg IV infusion every week	6,300	1	6,300	NA
	Labelled dosing	IV 900 mg every 2 weeks	9,450	0.50	4,725	70%
	Dose escalation	IV 900 mg every 11 days	9,450	0.64	6,014	1.3%
	Dose escalation	IV 1200 mg every 2 weeks	12,600	0.50	6,300	26.3%
	Dose escalation	IV 1500 mg every 2 weeks	15,750	0.50	7,875	2.5%
Weighted average cost per week						£5,233
Weighted average cost per cycle						£20,933

Table 59 Summary of ravulizumab costs

Maintenance dosage				
# of Vials	**Total mg**	**Weight (kg)**	**% distribution**	**Weighted costs (£)**
10	3,000	59	17.47%	7,919
11	3,300	99	72.86%	36,330
12	3,600	100+	9.66%	5,255
Weighted average drug cost per dose				28,361
Weighted average cost per cycle				£24,754

Vaccines and antibiotic costs associated with complement inhibition

Vaccinations against *Neisseria meningitidis* types A, C, W, Y, and B; *Streptococcus pneumoniae*; and *Haemophilus influenzae* type B are required for all patients receiving complement inhibitors. Before receiving treatment with pegcetacoplan, in patients with a known history of vaccination, it is ensured that patients have received vaccines against encapsulated bacteria including Streptococcus pneumoniae, Neisseria meningitidis types A, C, W, Y, and B, and Hib within two years prior to starting pegcetacoplan. If patients have known history of vaccination, the required vaccines are administered at least 2 weeks prior to receiving the first dose of pegcetacoplan. However, costs of vaccines were not applied to the model, as they are only applicable for a treatment naïve population, of which the patients receiving pegcetacoplan are not.

Prophylactic antibiotics, specifically penicillin, are required in all treated patients, while on treatment. The drug cost was derived from the drugs and pharmaceutical electronic market information tool (eMIT) (120). It was assumed that prophylactic penicillin would be given at a dose of 500 mg, twice daily. The cost is applied to all treatment arms. Cost calculations are given in Table 60.

Table 60 Penicillin cost calculations

Drug	Number in packet	Dosage (mg)	Drug cost	Dosage (mg)	Drug cost	Dosage description	Frequency	Cost per four-week cycle	
Penicillin	28	500	£0.52	500	£0.52	*500 mg twice daily*	Once daily	Amount in mg in a packet	14000
								Doses in a packet	14
								Packets in a 4-week cycle	2
								Price per 4-week cycle	**£1.04**

Administration

The base-case analysis assumed patients on pegcetacoplan have their first administration in a clinic and receive training on self-administration. Patients self-administer subsequent doses at home. The unit cost for subcutaneous administration training was estimated to be £49 (assuming 20 minutes of specialist nurse time, band 6) (121). Following this, at home care is assumed for the second and third doses (30 minutes per visit) in order to check that patients were administering correctly (121), at a cost of £29.67. One-off pump costs for pegcetacoplan in-home infusion were excluded in the base case.

Eculizumab and ravulizumab administration costs were excluded in the base-case, as only treatment switch patients (who will have been receiving treatment) are considered in the analyses.

Table 61 Administration resource use

Generic Name	Admin. Method	Unit	Cost per administration	Source
Pegcetacoplan initial dose (applied in cycle 1 only)	SC	First SC administration includes training for self-administration at home (20 minutes nurse specialist band 6 £147 per hour of contact time)	£49.00	PSSRU 2020 (121)
Pegcetacoplan dose 2 and 3 (applied in cycle 1 only)	SC	At home care assumed for doses 2 and 3 to check patients administering correctly (30 minutes community nurse £89 per hour of patient related work)	£29.67	PSSRU 2020 (121)

Abbreviations: SC, subcutaneous; PSSRU, personal social services research unit

Other costs

Iron overload

According to clinical opinion, patients receiving pegcetacoplan do not require chelation therapy. Patients have sufficient increase in Hb levels such that clinicians can remove iron by removing blood (13). According to NHS guidance on haemochromatosis (122), there are 2 main stages to treatment:

- Induction – blood is removed on a frequent basis (usually weekly) until your iron levels are normal; this can sometimes take up to a year or more
- Maintenance – blood is removed less often (usually 2 to 4 times a year) to keep your iron levels under control; this is usually needed for the rest of your life

Patients on pegcetacoplan are assumed to be in the maintenance phase and require an average of 3 phlebotomies per year. Therefore, the cost of phlebotomy, £4 (HRG code: DAPS08 (123)) was multiplied by the number of phlebotomies occurring in a four-week cycle. This was then multiplied by the proportion of patients receiving chelation therapy.

Frequent transfusions in severely anaemic, transfusion-dependent patients may cause the development of iron overload in PNH patients (81). Clinical opinion suggests that since ravulizumab and eculizumab do not control EVH, patients will require lifelong treatment with chelation therapy due to the risks associated with frequent transfusions (13). In the PEGASUS study, [redacted]% of patients were reported to be on deferoxamine mesilate and [redacted] % of patients were receiving deferasirox at baseline (10). As eculizumab and ravulizumab do not control EVH, this percentage is assumed to be constant throughout the model time horizon. According to clinicians, patients on pegcetacoplan do not require chelation therapy, as patients have sufficient increases in Hb levels such that clinicians can remove iron by removing blood in this cohort, which is much cheaper and safer for patients. This was thought to be a key differentiator between pegcetacoplan and C5 inhibitors (13). The cost of chelation has been calculated based on baseline (pre-run in) concomitant medication use as reported in the PEGASUS CSR (10), which is required for patients with iron overload (Table 62). This cost is applied to the eculizumab arm and assumed to also be applicable to patients receiving ravulizumab, and is summarised in Table 63.

Table 62 Baseline proportion of patients on chelation therapy

Baseline concomitant medications	Total	% on chelation therapies
Prior Medication (Run-in Set)		
Deferoxamine mesilate	[redacted]	[redacted]
Deferasirox	[redacted]	[redacted]

Table 63 Ravulizumab and eculizumab iron chelation costs

Drug	N in packet	Dosage (mg)	Drug cost	Dosage (mg/kg)	Frequency	Cost per four-week cycle (£)		Average cost per patient *
Deferasirox *'Initially 7–21 mg/kg once daily, dose adjusted according to serum-ferritin concentration and amount of transfused blood—consult product literature, then adjusted in steps of 3.5–7 mg/kg every 3–6 months, maintenance dose adjusted according to serum-ferritin concentration; maximum 28 mg/kg per day; Usual maximum 21 mg/kg.'* (124) Assume 21 mg/kg	30	360	£504.00	21.00	Once daily	Average weight of an adult multiplied by dosage per kg	1580.25	£594.68
						Amount in mg in a packet	10800	
						Doses in a packet	6.8	
						Packets in a 4-week cycle	4.1	
						Price per 4-week cycle	**£2,064.86**	
Deferoxamine mesilate *'20–50 mg/kg daily.'* (125) Assume 35mg/kg	10	500	£41.97	35.00	Once daily	Average weight of an adult multiplied by dosage per kg	2633.75	£147.31
						Amount in mg in a packet	5000	
						Doses in a packet	1.90	
						Packets in a 4-week cycle	14.7	
						Price per 4-week cycle	**£618.97**	
Total average weighted cost per four-week cycle			£742					
**assuming 28.8% on deferasirox, 23.8% on deferoxamine mesilate*								

Breakthrough haemolysis

As previously mentioned in Section B.3.3 Clinical parameters and variables, IVBTH is not modelled for eculizumab and ravulizumab explicitly. For pegcetacoplan, IVBTH is modelled in two ways in the CEM:

- A proportion of patients that have IVBTH receive a 900mg dose of eculizumab. Clinicians indicated that eculizumab is used in this circumstance since it has a shorter half-life and a better ability to control these acute events (13). A per cycle rate is calculated based on four episodes in the 16-week period from PEGASUS (2.5%). A cost of £9,450 (118) is applied calculated from the list price of eculizumab as described in B.3.5.

- The remaining small proportion of patients discontinue pegcetacoplan after a 'settle in period' when clinicians can identify the select number of patients for whom pegcetacoplan is unsuitable. This is estimated by a 'one-off' discontinuation at Week 16, calculated as [redacted] out of 41 ([redacted]) on the pegcetacoplan arm from PEGASUS. At the point of discontinuation patients are assumed to incur associated costs for the treatment of the BTH event, which is calculated as £392.86 as summarised in Table 64. Patients discontinue onto eculizumab treatment and health state costs are as described for the eculizumab treatment arm.

Table 64 BTH cost for patients who discontinue due to IVBTH

	% patients / n days	**Source/ description**	**Cost used in CEM**
General ward	15% / 1 day	NHS reference costs 2020 Average of non-elective short stay costs for haemolytic anaemia with cc SCORE 3+ & haemolytic anaemia with CC score 0-2 (currency codes SA03G, SA03H)	£1,312.00
Intensive care	1% 1 day	Average cost of £15407.47 reported in TA10690.	£15,747.98

		Uplifted to 2020 prices using PSSRU pricing index	
Dialysis	4% 7 days	£134.82 per day used in TA10690: calculated using all currency descriptions for haemodialysis and peritoneal dialysis in adults (19 years and over) were used to derive the unit costs and number of sessions using NHS reference costs. Cost uplifted to 2020 prices using PSSRU pricing index	£137.80 per day
Total cost per 4-week cycle			£392.86

Abbreviations: CEM, Cost-effectiveness model; NHS, National Health Service; PSSRU, Personal Social Services Research Unit

Costs of blood transfusion

Costs of blood transfusion were incurred by patients in the transfusion required health state. Blood transfusion costs were estimated based on unit cost per transfusion and transfusion frequency per cycle. The unit cost per transfusion was estimated to be £532.46 derived from 2020 NHS reference cost (123).

Monitoring costs

Monitoring costs associated with general practitioner (GP) visits, haematologist visits, and blood tests differ by health state. The monitoring cost for each health state was estimated based on number of visits/tests per cycle (Table 66) multiplied by the respective unit costs for each resource (Table 65) per health state. Monitoring costs were applied as cycle rates.

Table 65 Unit costs of physician visits/tests

	Unit Costs	**Source**
GP visit	£40.09	PSSRU (2019); Outpatient GP consultation lasting 9.22 minutes
Haematologist	£110.61	Ravulizumab TA (35)
Blood test	£32.18	NCGC (2015); NG45

Abbreviations: GP – general practitioner; NCGC – National Clinical Guideline Centre; NHS – National Health Service; PSSRU – Personal Social Services Research Unit.

Table 66 Number of physician visits/tests per cycle

	No transfusion and Hb < 10.5	No transfusion and Hb ≥ 10.5	Transfusion required	Source
GP visit	0.00	0.00	0.00	UK clinical opinion (13)
Haematologist	0.15	0.15	2.00	UK clinical opinion, one visit every 6 months for patients in no transfusion health states and one visit every 2 weeks for patients in transfusion required patients (13)
Blood test	0.31	0.31	2.00	UK clinical opinion, blood test required at least every 3 months for patients in no transfusion health states (13) Transfusion required health states will require blood tests every time going to a haematologist appointment (once every 2 weeks) (13)
Cost per cycle	**£26.92**	**£26.92**	**£285.57**	

Abbreviations: GP, general practitioner; Hb, haemoglobin

Adverse reaction unit costs and resource use

Adverse events were not included in the base case but are considered in scenario analyses. The adverse events detailed in the SmPCs for eculizumab (126), ravulizumab (127) and pegcetacoplan (12) are comparable. Adverse event costs were estimated based on the probability of developing an AE per cycle (

Table **51**) and the corresponding unit cost per AE (Table 67) per treatment arm. A sum product of the probabilities of AEs and their respective unit costs were calculated to obtain total AE costs per treatment. As previously mentioned, AEs included in the model were derived from the PEGASUS trial: serious TEAEs for which the incidence differed by 2% or more between the pegcetacoplan arm and eculizumab arm. Adverse events costs for pegcetacoplan, eculizumab and ravulizumab per cycle were calculated as £48.49, £46.49 and £6.87 respectively.

Table 67 Unit costs of managing adverse events

	Unit Cost	Source
Bacterial infection	£1121.00	NHS (123) (assumption, weighted average total HRG cost of upper respiratory tract infection)
Gastroenteritis	£1255.70	NHS (123) (weighted average total HRG cost of gastrointestinal infections)
Atrial fibrillation	£1364.70	Kassianos et al. (128) (inflated to 2020 UK cost)
Hyperthermia	£40.09	Assumed one GP visit (PSSRU (121); outpatient GP consultation lasting 9.22 minutes)
Facial paralysis	£3438.95	Wilson et al., (100) (converted and inflated to 2020 UK cost)
Dyspnoea	£698.91	Farquhar et al. (129) (inflated to 2020 UK cost)
Abdominal pain	£634.50	NHS (123) (weighted average total HRG cost of abdominal pain)
Biliary colic	£3204.29	Assumed to have a cholecystectomy (NHS (123); weighted average total HRG cost of cholecystectomy)
Hepatocellular injury	£500.00	NHS (123) (assumption, weighted average total HRG cost of liver failure disorders)
Hyperbilirubinemia	£29.50	Foglia et al., (130) (converted and inflated to 2020 UK cost)
Jaundice	£929.60	NHS (123) (weighted average total HRG cost of non-obstructive Jaundice)

Abbreviations: AE, adverse event

Miscellaneous unit costs and resource use

Indirect costs were excluded in the base case as the analysis was conducted from a health care payer's perspective, in line with the NICE reference case (78). There are no other relevant unit and resource use costs.

B.3.6 Summary of base-case analysis inputs and assumptions

Summary of base-case analysis inputs

The base-case variables utilised in the model are summarised in Table 68. Where standard errors were not available, they were assumed to be 10% of the mean value.

Table 68 Base case inputs

Variable	Value	Measurement of uncertainty (distribution)	Reference and corresponding section in this report
Perspective	NHS and PSS	N/A	NICE reference case (78); Perspective
Time horizon	Lifetime (51 years)	N/A	NICE reference case (78); Time horizon
Discount rate: costs	3.5%	Lower bound: 1.5% Upper bound: 5.0%	NICE reference case (78); Discounting
Discount rate: outcomes			
Mean age (years)	48.8	SE = 1.79 (normal)	Data on file (10); Baseline demographics
Percentage female	61.3%	n/N = 49/80 (beta)	
Mean weight (kg)	[redacted]	SE = 1.97 (normal)	
Time since diagnosis (years)	[redacted]	SE = 0.96 (normal)	
Transition probabilities for patients receiving pegcetacoplan	Table 43	Dirichlet	Data on file (10); Transition probabilities applied in the analysis
Transition probabilities for patients receiving eculizumab	Table 43	Dirichlet	Data on file (10); Transition probabilities applied in the analysis
Transition probabilities for trial for patients receiving ravulizumab	Table 43	Dirichlet	Data on file (10); Transition probabilities applied in the analysis
Discontinuation for patients receiving pegcetacoplan (at week 16)	[redacted]	Beta	Data on file (10); Table 46
BTH requiring a dose of eculizumab	[redacted]	Beta	Data on file; Table 46
Percentage of patients receiving chelation therapy (deferoxamine mesilate and deferasirox)	[redacted]	Beta	Data on file; Iron overload
Dosing level for patients on eculizumab	Table 56	Dirichlet Distribution based on the approach from Briggs et al. (132)	Data on file(10); Intervention technology and comparators
Dosing level for patients on pegcetacoplan	Table 56	Dirichlet Distribution based on the approach from	Data on file (10); Intervention technology and comparators

		Briggs et al (132)	
Pegcetacoplan arm HR for death: PNH vs general population	1.0	Fixed	Assumption, patients receiving complement inhibitors have comparable mortality to age- and sex-matched general population
Eculizumab arm HR for death: PNH vs general population	1.0	Fixed	
Ravulizumab arm HR for death: PNH vs general population	1.0	Fixed	
Utility: No transfusion and Hb <10.5	[redacted]	Beta	Data on file (10); Longworth et al. (66); Mapping
Utility: No transfusion and Hb ≥10.5	[redacted]	Beta	
Utility: Transfusion required	[redacted]	Beta	
Probability of developing AEs per cycle	Table 51	Beta	Data on file (10); Adverse reaction unit costs and resource use
Disutility associated with AEs	Excluded		Assumption; AE disutility was already accounted for within the mapped EQ-5D utility
Iron overload disutility	-0.03	Normal	Cherry et al. (104); Health-related quality-of-life data used in the cost-effectiveness analysis
Disutility due to eculizumab IV infusion	−0.025	Normal	Ravulizumab TA10690 (35); Ravulizumab SMC submission (72); Health-related quality-of-life data used in the cost-effectiveness analysis
Pegcetacoplan 1,080 mg PAS price (£)	[redacted]	Fixed	Data on file; Intervention and comparator's costs and resource use
Ravulizumab 300 mg price (£)	4,533	Fixed	NHS Scotland (35); Intervention and comparator's costs and resource use
Eculizumab 300 mg price (£)	3,150	Fixed	BNF (118); Intervention and comparator's costs and resource use
Prophylactic antibiotic cost (£)	0.52	Gamma	Electronic market information tool (eMIT) (120); Table 60
Pegcetacoplan pump cost for in-home infusion	Excluded		Assumption

Administration cost for pegcetacoplan (£)	78.67	Normal	Assumption (20 minutes of specialist nurse time for first injection followed by two visits by a community nurse to ensure correct technique); Table 61
Administration cost for eculizumab (£)	£0	Normal	Assumption - administration cost of eculizumab is paid by the manufacturer in the UK. The first and second doses are calculated in line with TA547; Table 61
Administration cost for ravulizumab (£)	£0	Normal	Assumption - administration cost of ravulizumab is paid by the manufacturer in the UK. The first and second doses are calculated in line with TA547; Table 61
Cost of chelation therapy	£742 per 4-week cycle		BNF (124,125); Table 63
Unit cost of blood transfusion (£)	532.46	SE = 5.325a (Gamma)	NHS (2020); SA44A; total HRG cost; inflated to 2020 cost (123)
Mean number of transfusions per cycle	1	Fixed	Structural assumption
Health care resource use frequency by health state	Table 66	Normal	UK clinical opinion; Other costs
Health care resource use unit costs	Table 65	Normal	Various, Other costs
AE unit costs	Table 67	Gamma	Various, Adverse reaction unit costs and resource use
Indirect costs	Excluded		Assumption

Abbreviations: BNF, British National Formulary; BTH, Breakthrough haemolysis; HR, Hazard ratio; N/A, Not applicable; NHS, National Health Service; PSS, Personal Social Services; PSSRU, Personal Social Services Research Unit; PNH, Paroxysmal nocturnal haemoglobinuria

Assumptions

Table 69 Assumptions in base case analysis

Assumption	Justification
Population and comparators	
The PEGASUS trial was representative of the patient population receiving treatment with pegcetacoplan and eculizumab	Assumption validated through UK clinical opinion (13). In addition, the patient population in the PEGASUS trial (adults with PNH and haemoglobin levels lower than 10.5 g/dL despite eculizumab therapy) is aligned with the population described in the NICE scope (adults with PNH whose anaemia is not

	controlled after treatment with a C5 complement inhibitor).
Eculizumab and ravulizumab are considered the only appropriate comparator for pegcetacoplan	In the UK, eculizumab has been used to treat patients with PNH for more than a decade. As of April 2021, ravulizumab has been approved for use in England and is expected to become standard of care.
Time horizon and cycle length	
A lifetime horizon is assumed	In line with NICE reference case (16). The time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect all important differences in costs or outcomes between the technologies being compared. Therefore, a lifetime horizon was chosen since patients accumulate differential costs and QALYs until death.
The model has a 4-week cycle length.	A 4-week cycle allows all relevant costs and health benefits to be captured and is consistent with published cost-effectiveness studies.
Half-cycle correction is applied	In line with the NICE reference case (78).
Model structure	
The important costs and consequence associated with PNH can be captured by the modelled health states	A combination of Hb level and blood transfusion requirements was chosen to define health states as together, they represent different levels of disease status. No transfusion was further stratified based on patients' Hb level above and below a threshold level of 10.5g/dL in line with the PEGASUS trial inclusion criteria and was validated by clinical opinion as appropriate for capturing differences in HRQoL between health states (14, 21).
Spontaneous remission is not allowed	There is no evidence to indicate spontaneous remission rates will differ by treatment option.
Clinical parameters	
Modelling is long-term, and therefore assumes a sustained treatment effect	Assumption validated through UK clinical opinion (13).
Ravulizumab is assumed to have equal efficacy to eculizumab	Assumption validated through UK clinical opinion (13).
Mortality of patients receiving complement inhibitors were assumed to be the same as age- and sex-adjusted general mortality.	The leading cause of death in PNH patients is thrombosis, which is well managed by current treatment options. This has validated by UK clinical opinion (9).
IVBTH is assumed to be managed in two ways depending on severity: • One off dose of 900mg eculizumab • Discontinue to eculizumab	Clinical opinion on management of IVBTH (13).
HRQoL	
Utilities are considered constant over time with adjustment for age from Ara and Brazier (85)	Assumption validated through UK clinical opinion (13). Age adjusted in line with best practice.

Utility decrement for administration of eculizumab versus ravulizumab and pegcetacoplan.	An SLR literature review by Stoner and colleagues suggesting that patients prefer subcutaneous over IV delivery (105). Analysis presented in TA10690 shows patients also prefer reduced number of infusions (13).This is supported with data from the ravulizumab SMC submission (72) and ravulizumab TA10690 (35).
Disutility of AEs that were observed in the trial were not included in the model	Disutility was already accounted for within mapped utility data from the trial.
A mapping algorithm was used to convert EORTC-QLQ-C30 utilities to EQ-5D-3L utilities.	EQ-5D-3L utilities are the preferred measure of HRQoL by NICE (78). This is in line with previous analyses (35).
Costs	
Administration costs of C5 inhibitors were not included in the model	Assumed to be borne by the manufacturer.
AE costs are not included in the base-case	Assumed to be captured within health state costs.
Costs for iron overload are captured through the baseline proportion of patients in the PEGASUS trial receiving chelation therapy, where pegcetacoplan patients are assumed to have iron overload treated through venesection (phlebotomy) and ravulizumab and eculizumab patients are assumed to have iron overload treated through chelation therapies	Assumption was validated through UK clinical opinion (13).
Patients received the first dose of pegcetacoplan in the clinic and self-administered the subsequent doses at home, with the second and third doses requiring supervision from a community nurse to ensure correct injection technique.	Standard clinical practice after being given an initial administration and training in a clinic. This assumption was validated through UK clinical opinion (13).
Wastage is not included in the model	No wastage is assumed with pegcetacoplan, eculizumab or ravulizumab as all treatments are given per vial.

Abbreviations: AE, Adverse event; IVBTH, Breakthrough haemolysis; NICE, National Institute for Health and Care Excellence; PNH, Paroxysmal nocturnal haemoglobinuria; SMC, Scottish Medicines Consortium

B.3.7 Base-case results

Base-case incremental cost-effectiveness analysis results

As mentioned in Section B.3.5 Cost and healthcare resource use identification, measurement and valuation, a confidential PAS has been approved by the PASLU. This arrangement is in the form of a simple PAS at [redacted]. This PAS has been applied and the results presented reflect this discount. In the base case analysis, pegcetacoplan results in [redacted] incremental QALYs compared to ravulizumab, and ravulizumab results in [redacted] incremental QALYs compared to eculizumab. In addition, pegcetacoplan is associated with [redacted] incremental costs over a lifetime horizon compared with ravulizumab, and ravulizumab is associated with [redacted] incremental costs over a lifetime horizon compared with eculizumab. Pegcetacoplan dominates both eculizumab and ravulizumab. Disaggregated base case results are presented in Appendix J.

Table 70 Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Eculizumab	[redacted]	19.706	[redacted]	[redacted]	-	[redacted]	-	-
Ravulizumab	[redacted]	19.706	[redacted]	[redacted]	0.000	[redacted]	2,990,271	2,990,271
Pegcetacoplan	[redacted]	19.706	[redacted]	[redacted]	0.000	[redacted]	Dominant	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

B.3.8 Sensitivity analyses

Probabilistic sensitivity analysis

Probabilistic sensitivity analyses (PSA) were conducted to explore the impact of model parameters uncertainty on the results. PSA involves drawing a value at random for each variable from its uncertainty distribution. This is performed for each parameter simultaneously and the resulting incremental results are recorded. This constitutes one 'simulation'. 1,000 simulations were performed, which each gave a distribution of incremental results, and consequently, an assessment of the robustness of the cost-effectiveness results.

For event rates and utilities, a beta distribution was used to restrict draws to between 0 and 1. For costs and resource use estimates, and hazard ratios a gamma distribution was fitted to prevent values less than zero. Treatment costs remained fixed. An incremental cost-effectiveness plane (ICEP) scatter plot and cost-effectiveness acceptability curve (CEAC) were produced to graphically illustrate the level of variability and uncertainty in the results.

The mean values for total costs, LYs, QALYs, and incremental cost per QALY gained for pegcetacoplan versus eculizumab and ravulizumab for the population of interest generated through 1,000 simulations of the PSA are presented in Table 71. The output shows that on average, pegcetacoplan results in [redacted] incremental QALYs compared to ravulizumab, and ravulizumab results in [redacted] incremental QALYs compared to eculizumab. In addition, pegcetacoplan is associated with [redacted] incremental costs over a life-time horizon compared with ravulizumab, and ravulizumab is associated with [redacted] incremental costs over a lifetime horizon compared with eculizumab. Pegcetacoplan dominates both eculizumab and ravulizumab.

The ICEP (Figure 21) shows that 100% of results are in the South East quadrant for both pegcetacoplan versus eculizumab and pegcetacoplan versus ravulizumab, meaning that pegcetacoplan continues to dominate eculizumab and ravulizumab in each simulation. In addition, the CEAC (Figure 22) shows that pegcetacoplan is 100% cost-effective at all willingness to pay thresholds.

Table 71 Mean PSA results

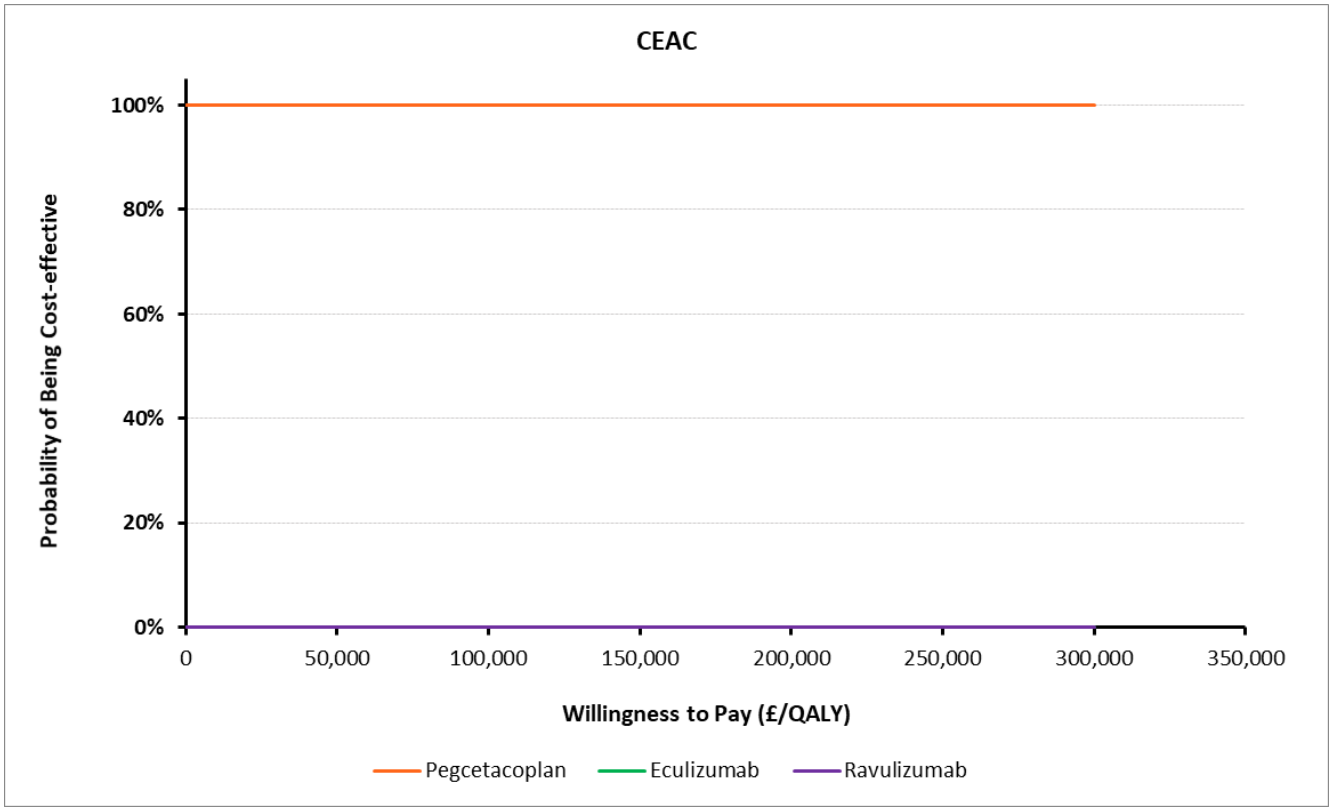
Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Eculizumab	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]	2,959,722	2,959,722
Pegcetacoplan	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Figure 21 Incremental cost-effectiveness plane

Abbreviations: QALY, quality-adjusted life year

Figure 22 Cost-effectiveness acceptability curve



Abbreviations: CEAC, cost-effectiveness acceptability curve; QALY, quality-adjusted life year

Deterministic sensitivity analysis

Deterministic one-way sensitivity analysis (OWSA) was conducted to explore the level of uncertainty in the model results. The OWSA involved varying one parameter at a time and assessing the subsequent impact on the incremental QALYs and incremental costs. By adjusting each parameter individually, the sensitivity of the model results to that parameter can be assessed.

The OWSA was conducted by allocating a 'low' value and a 'high' value to each parameter; the low value is the lower bound of the 95% confidence interval (CI), the high value is the upper bound of the 95% CI. In the absence of CI data, the variable was altered by +/- 20%. A tornado diagram was developed to graphically present the parameters which have the greatest effect on the net monetary benefit (NMB), at a WTP threshold of £10,000 per QALY. The NMB was used as an alternative to the ICER in order to avoid negative ICERs within the OWSA (when pegcetacoplan dominates both eculizumab and ravulizumab). The upper and lower bound utility values have been capped so that they are clinically plausible.

A OWSA tornado diagram presenting the top 10 most sensitive parameters for pegcetacoplan versus ravulizumab is presented in Figure 23. Table 72 presents the OSWA results for these 10 parameters. The model was most sensitive to the mean weight of patients, utility values for no transfusion and Hb ≥10.5mg/dl and the pack cost of deferasirox.

A OWSA tornado diagram presenting the top 10 most sensitive parameters for pegcetacoplan versus eculizumab is presented in Figure 23. Table 73 presents the OSWA results for these 10 parameters. The model was most sensitive to utility values for no transfusion and Hb ≥10.5mg/dl, and the percentage of patients receiving deferasirox.

Figure 23 Tornado diagram for OWSA for pegcetacoplan versus ravulizumab

Figure 24 Tornado diagram for OWSA for pegcetacoplan versus eculizumab

Table 72 OWSA results for the 10 parameters that contribute the largest difference to the NMB for pegcetacoplan versus ravulizumab

Parameter	Base case NMB	Lower bound NMB	Upper bound NMB	Max Difference NMB
Mean weight (kg)	[redacted]	[redacted]	[redacted]	[redacted]
Utility pegcetacoplan: no transfusion and Hb ≥10.5		[redacted]	[redacted]	[redacted]
Pack cost deferasirox		[redacted]	[redacted]	[redacted]
% on deferasirox (Eculizumab arm)		[redacted]	[redacted]	[redacted]
Utility pegcetacoplan: Transfusion Required		[redacted]	[redacted]	[redacted]
Cost of blood transfusion		[redacted]	[redacted]	[redacted]
Mean units of blood per transfusion		[redacted]	[redacted]	[redacted]
Female percentage		[redacted]	[redacted]	[redacted]
Utility pegcetacoplan: no transfusion and Hb<10.5		[redacted]	[redacted]	[redacted]
Pack cost deforoxamine mesilate		[redacted]	[redacted]	[redacted]

Abbreviations: NMB, Net medical benefit; OWSA, One-way sensitivity analysis

Table 73 OWSA results for the 10 parameters that contribute the largest difference to the NMB for pegcetacoplan versus eculizumab

Parameter	Base case NMB	Lower bound NMB	Upper bound NMB	Max Difference NMB
Mean weight (kg)	[redacted]	[redacted]	[redacted]	[redacted]
Utility pegcetacoplan: no transfusion and Hb ≥10.5		[redacted]	[redacted]	[redacted]
Pack cost deferasirox		[redacted]	[redacted]	[redacted]
% on deferasirox (Eculizumab arm)		[redacted]	[redacted]	[redacted]
Utility pegcetacoplan: Transfusion Required		[redacted]	[redacted]	[redacted]
Cost of blood transfusion		[redacted]	[redacted]	[redacted]
Mean units of blood per transfusion		[redacted]	[redacted]	[redacted]
Female percentage		[redacted]	[redacted]	[redacted]
Utility pegcetacoplan: no transfusion and Hb<10.5		[redacted]	[redacted]	[redacted]
Pack cost deforoxamine mesilate		[redacted]	[redacted]	[redacted]

Abbreviations: NMB, Net medical benefit; OWSA, One-way sensitivity analysis

Scenario analysis

Table 74 details scenario analyses results for pegcetacoplan versus eculizumab and pegcetacoplan versus ravulizumab. Pegcetacoplan dominates eculizumab and ravulizumab in all scenarios.

Table 74 Scenario analysis results

Parameter	Base case	Scenario analysis	ICER (£/QALY) pegcetacoplan vs eculizumab	ICER (£/QALY) pegcetacoplan vs ravulizumab
Time horizon	Lifetime	10 years	Dominant	Dominant
		20 years	Dominant	Dominant
Discount rate (costs and QALYS)	3.5%	0%	Dominant	Dominant
		6%	Dominant	Dominant
Utility decrement of eculizumab vs. ravulizumab and pegcetacoplan	0.025	0.000	Dominant	Dominant
		0.057	Dominant	Dominant
Utility: general population age adjustment	Applied	Not applied	Dominant	Dominant
Iron overload disutility	-0.03	0.00	Dominant	Dominant
Transition probabilities	4-16-week data for all cycles	0-4 weeks per first cycle; 4-16-week data for subsequent cycles	Dominant	Dominant
Baseline distribution of patients	100% in no transfusion Hb <10.5	Distribution pre run-in	Dominant	Dominant
% of patients discontinuing pegcetacoplan	[redacted] at week 16	Assume all patients who initially discontinue remain discontinued (3 out of 41, 7.32%)	Dominant	Dominant

Abbreviations: Hb, Haemoglobin; ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year

B.3.9 Subgroup analysis

No subgroup analyses were considered.

B.3.10 Validation

Validation of cost-effectiveness analysis

- The CEM was subject to a PRIMA review and feedback has been implemented in the submitted model.

- Where possible, insights from the recent ravulizumab NICE submission (TA10690) were utilised within the cost-effectiveness model (36).

- An internal validity check was performed by the model developers. This included a quality check of model codes, model inputs including both a comparison to the original source and any intermediate calculations, and a check of model output. The model was developed by two independent health economists and validated externally by health economics experts.

- All key inputs and assumptions were informed by the opinion of six UK clinicians who attended an advisory board (13). During the advisory board clinicians were asked to validate key modeling assumptions and asked to provide estimates for the resource use associated with health states. The mean values of these estimates were used to inform the resource use parameters used within the economic analysis.

- The fundamental modeling assumptions have been validated by independent UK health economics experts who also attended the advisory board (13).

B.3.11 Interpretation and conclusions of economic evidence

Over a lifetime time horizon, patients receiving pegcetacoplan accrued [redacted] QALYs at a cost of [redacted] Over the same time horizon patients receiving ravulizumab accrued [redacted] QALYs at a cost of [redacted], whereas patients receiving eculizumab accrued [redacted] QALYs at a cost of [redacted]. This results in pegcetacoplan dominating both treatments. Therefore, pegcetacoplan is a cost-effective treatment option which should be considered for fast-track appraisal.

100% of the probabilistic results fell below the £10,000 per QALY threshold which demonstrates the substantial robustness of the cost effectiveness of pegcetacoplan despite subjection to variation of key input values. The OWSA results showed that the analysis was most sensitive to the mean weight of patients, utility values for no transfusion and Hb ≥10.5mg/dl and the pack cost of deferasirox for pegcetacoplan versus ravulizumab, and the utility values for no transfusion and Hb ≥10.5mg/dl , pack cost of defasirox and the percentage of patients receiving defasirox for pegcetacoplan versus eculizumab.

A variety of scenario analyses investigating variations in time horizons, discount rates, utilities, and clinical efficacy all resulted in pegcetacoplan dominating both eculizumab and ravulizumab.

Overall, the base case results, results of the probabilistic sensitivity analysis and all scenario analyses results strongly indicate that pegcetacoplan is a cost-effective use of NHS resources. The results show that the introduction of pegcetacoplan into the treatment paradigm will significantly improve the HRQoL for patients with PNH, alongside a cost reduction.

The strengths of the analysis include:

- The clinical data used to inform the analysis was sourced from PEGASUS, which included UK sites.
- All costs are sourced from relevant UK sources. This validates the estimated cost implications in UK clinical practice.
- Inputs of the economic analysis have been validated by UK clinicians. Again, this validifies the estimated cost implications in UK clinical practice (13).
- The key assumptions of the analysis have been validated by independent UK-based health economists (13).
- Cost-effectiveness results at a threshold of £10,000 per QALY are robust with 100% of probabilistic iterations remaining below this threshold and OWSA results showing pegcetacoplan remains the cost-effective treatment option when varying key parameters.

The weaknesses of the analysis include:

- There are small patient numbers informing the clinical observations. The PEGASUS population was small, meaning that variation observed in a few patients drives the clinical measures in the economic analysis which may introduce bias if extreme values are observed.

- Due to the nature of the condition and the structure of the trial, no EQ-5D data could be obtained. HRQoL data was mapped, however this may be associated with uncertainty.

- Comparative efficacy between ravulizumab and eculizumab was assumed, however this assumption is thought to be conservative.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Fast track appraisal

Pegcetacoplan for treating paroxysmal nocturnal haemoglobinuria [ID3746]

Clarification questions

June 2021

File name	Version	Contains confidential information	Date
ID3746 pegcetacoplan clarification letter to PM_RESPONSE_29Jun21_AiC_CiC_Redacted	v1.0	No	29 June 2021

Notes for company

Highlighting in the template

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Section A: Clarification on effectiveness data

PEGASUS trial: trial design

A1. Please clarify the basis for selecting the following non-inferiority margins (NIMs) for the PEGASUS trial secondary efficacy outcomes as outlined in Table 6 of the company submission (CS):

a) Transfusion avoidance: NIM of -20% (i.e., if the lower bound [LB] of the 95% Confidence Interval [CI] for the treatment difference was greater than the NIM of -20%, then pegcetacoplan was considered non-inferior to eculizumab)

b) Absolute Reticulocyte Count (ARC): NIM of 10 (i.e., if the upper bound [UB] of the 95% CI for the treatment difference was less than the NIM of 10, then pegcetacoplan was considered noninferior to eculizumab)

c) Lactate Dehydrogenase (LDH): NIM of 20 (i.e., if the UB of the 95% CI for the treatment difference was less than the NIM of 20, then pegcetacoplan was considered non-inferior to eculizumab)

d) FACIT-Fatigue score: NIM of -3 (i.e., if the LB of the 95% CI for the treatment difference was greater than the NIM of -3, then pegcetacoplan was considered noninferior to eculizumab)

The NIM for FACIT-Fatigue score was based on the threshold (3-point change) considered to be a clinically meaningful change (1). The NIMs for transfusion avoidance and LDH were selected based on those used in the recent non-inferiority study for ravulizumab compared with eculizumab, CHAMPION-301, which were based on an analysis of the Alexion PNH registry (2,3).

ARC often remains elevated because most patients with PNH treated with eculizumab continue to have extravascular haemolysis (EVH) (4). In CHAMPION-301, ARC was not tested for non-inferiority for ravulizumab compared with eculizumab as they have the same mode of action, C5 inhibition, therefore this would not be expected to change.

There is no documented formal analysis to set the NIMs for transfusion avoidance, ARC, LDH or FACIT-Fatigue. The sample size calculation was based on the primary endpoint only and not for considering non-inferiority testing in secondary endpoints. It is important to note that for the two endpoints that met noninferiority, the mean and confidence intervals in the change from baseline were far from zero (favouring pegcetacoplan) and would satisfy superiority claims had these been pre-specified irrespective of chosen NIM. For transfusion avoidance the NIM was -20% and pegcetacoplan demonstrated a difference of 62.53% (95% CI: 48.30–76.77) compared with eculizumab during the 16-week randomised controlled period (RCP) such that pegcetacoplan was considered non-inferior to eculizumab and the outcome would also have supported a superiority claim. For ARC, the NIM was 10 and pegcetacoplan demonstrated a difference in the least-squares (LS) mean change from baseline (CFB) at Week 16 of -163.61x 10^9 cells/L (95% CI: -189.91-137.30) compared with eculizumab such that pegcetacoplan was considered non-inferior to eculizumab and this outcome would also have satisfied a superiority claim.

Due to the prespecified hierarchical nature of the non-inferiority endpoint testing, non-inferiority was not assessed for FACIT-fatigue or LDH. However, for FACIT-Fatigue, results demonstrated an LS mean numerical difference of 11.87 (95% CI: 5.49–18.25) at Week 16 in the pegcetacoplan vs eculizumab groups. The lower bound of the 95% CI of the adjusted treatment difference was greater than the prespecified NIM of -3, indicating that pegcetacoplan would demonstrate noninferiority versus eculizumab for FACIT-Fatigue.

For LDH pegcetacoplan demonstrated a difference in LS mean of -4.63 U/L (95% CI: -181.30; 172.04) compared with eculizumab at Week 16, such that non-inferiority was not demonstrated. It is important to note that eculizumab is a compound that targets the treatment of IVH, in contrast to pegcetacoplan which effectively prevents both IVH and EVH, hence LDH levels were relatively well controlled at baseline (eculizumab: 308.64 U/L; pegcetacoplan: 257.48 U/L) and remained well controlled at Week 16 in both treatment groups (eculizumab: 183.33 U/L; pegcetacoplan: 188.77 U/L). Additionally, mean LDH levels will be impacted by breakthrough haemolytic events, where a patient may experience LDH levels in the thousands, skewing an entire treatment arm. This is evidenced in PEGASUS, where four patients in the pegcetacoplan group experienced breakthrough haemolysis (BTH), who had LDH levels of >3x the upper limit of normal (ULN) during their BTH (range: 1,157 U/L – 4,147 U/L) (5). See Section B.2.10.3 in the CS for further details. Once again, no non-inferiority is claimed.

A2. In the CS, the PEGASUS trial schematic (Figure 4) shows ‘baseline’ as the start of the run-in period but the ‘Outcomes’ section (page 35) states that data from before the randomised controlled period (RCP) were excluded from analyses of primary and secondary efficacy endpoints. Please clarify whether the clinical effectiveness outcomes which are measured as change from baseline (CFB) to Week 16 (haemoglobin [Hb] level, ARC, LDH level, FACIT-Fatigue scale, indirect bilirubin level, Linear Analog Assessment Scale [LASA] scores and EORTC-QLQ-C30 scores) include data from the RCP only, or include data from both the run-in period and the RCP.

Clinical effectiveness outcomes which were measured as CFB to Week 16 include data from baseline and from the RCP only. Baseline was taken as the mean of measurements prior to the start of pegcetacoplan treatment (nominally Day –28, i.e. 28 days prior to start of RCP) for efficacy endpoints. Data from the run-in period were excluded from analyses of primary and secondary efficacy endpoints, as well as the economic model. Clinicians at a recent advisory board generally agreed that it would be unlikely that a run-in period would be required in clinical practice. This would only be necessary for patients where the management of the disease has been difficult, which one clinician deemed to be less than <1% of patients (6). Therefore, no efficacy results are presented for the run-in period in the CS.

A3. Please provide observed values and CFB (where appropriate) without censoring for transfusion (i.e., based on all available data) in an equivalent format to Table 8 of the CS for the following outcomes:

a) CFB to Week 16 Hb level

The observed and CFB Hb data, uncensored for transfusion, is displayed in Table 1. Comparing this table to the observed and CFB Hb data, censored for transfusion, presented in Table 8 of the CS, the results are consistent with increased mean Hb levels in the pegcetacoplan group by Week 2, and through Week 16. At the Week 16 timepoint, uncensored mean CFB in Hb was [redacted] for the pegcetacoplan arm, compared to [redacted] for the eculizumab arm. Therefore, both the censored and uncensored results demonstrate that pegcetacoplan is able to improve Hb levels and hence control anaemia in patients with PNH.

Table 1: Observed values and CFB in Hb, uncensored for transfusion, during RCP (ITT)

	Pegcetacoplan (N=41)			Eculizumab (N=39)		
	n	Mean (SD) g/dL	CFB g/dL	n	Mean (SD) g/dL	CFB g/dL
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: PEGASUS CSR (5)
Abbreviations: CFB, change from baseline; Hb, haemoglobin; ITT, intent-to-treat; N/A, not applicable; RCP, randomised controlled period; SD, standard deviation

b) CFB to Week 16 ARC

The observed and CFB ARC data, uncensored for transfusion, is displayed in Table 2. Comparing this table to the mixed-effect model for repeated measures (MMRM) analysis presented in Figure 8 of the CS, the results are consistent with decreased

mean ARC in the pegcetacoplan from baseline and stayed below baseline through Week 16. At the Week 16 timepoint, uncensored mean [redacted] for the pegcetacoplan arm, compared to [redacted] for the eculizumab arm. In the eculizumab group, the initial decrease from baseline seen during the run-in period was reversed by Week 4 of the RCP, and the ARC remained above baseline at Week 16. This demonstrates an initial benefit from the run-in period, continuing slightly into the RCP, due to the treatment with both eculizumab and pegcetacoplan. Since ARC has been identified as a strong indicator of EVH (7), both the censored and uncensored results show that pegcetacoplan effectively controls EVH.

Table 2: Observed values and CFB in ARC, uncensored for transfusion, during RCP (ITT)

	Pegcetacoplan (N=41)			Eculizumab (N=39)		
	n	Mean (SD) 10^9 cells/L	CFB 10^9 cells/L	n	Mean (SD) 10^9 cells/L	CFB 10^9 cells/L
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: PEGASUS CSR (5)
Abbreviations: ARC, absolute reticulocyte count; CFB, change from baseline; ITT, intent-to-treat; N/A, not applicable; RCP, randomised controlled period; SD, standard deviation

c) CFB to Week 16 LDH level

The observed and CFB LDH data, uncensored for transfusion, is displayed in Table 3. Comparing this table to the observed and CFB LDH data, censored for transfusion, presented in Table 15 of the CS, the results are consistent. Mean LDH levels are lower among patients in the pegcetacoplan group at all time points, reaching mean LDH within the normal range (113 to 226 U/L (5)), while in the eculizumab group mean LDH levels for the eculizumab arm are higher than baseline at all timepoints,

except Week 12. At the Week 16 timepoint, uncensored mean CFB in LDH was [redacted] U/L for the pegcetacoplan arm, compared to [redacted] U/L for the eculizumab arm. As elevated LDH levels are indicative of IVH (8), sustained control of these levels, as shown in the censored and un-censored results, demonstrate that pegcetacoplan effectively controls IVH.

Table 3: Observed values and CFB in LDH, uncensored for transfusion, during RCP (ITT)

	Pegcetacoplan (N=41)			Eculizumab (N=39)		
	n	Mean (SD) U/L	CFB U/L	n	Mean (SD) U/L	CFB U/L
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: PEGASUS CSR (5)
Abbreviations: CFB, change from baseline; ITT, intent-to-treat; LDH, lactate dehydrogenase; N/A, not applicable; RCP, randomised controlled period; SE, standard error

d) CFB to Week 16 in the FACIT-Fatigue Scale score

The observed and CFB FACIT-Fatigue Scale score, uncensored for transfusion, is displayed in Table 4. Comparing this to the observed and CFB FACIT-Fatigue Scale score, censored for transfusion, presented in Table 18 of the CS, the results are similar in that by just Week 2 patients taking pegcetacoplan report similar levels of quality of life as the general population. From day 1 to Week 16, the uncensored FACIT-Fatigue score in the pegcetacoplan group had increased [redacted] points, and scores in the eculizumab group had decreased [redacted] points. Since a higher FACIT-Fatigue score is indicative of improved health-related quality of life (HRQoL), and a 3-point increase is generally accepted as clinically meaningful (1), both the censored and uncensored results show that pegcetacoplan considerably improves HRQoL in patients with PNH.

Table 4: Observed values and CFB in FACIT-Fatigue Scale score, uncensored for transfusion, during RCP (ITT)

	Pegcetacoplan (N=41)			Eculizumab (N=39)		
	n	Mean (SD)	CFB	n	Mean (SD)	CFB
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: PEGASUS CSR (5)
Abbreviations: CFB, change from baseline; FACIT, Functional Assessment of Chronic Illness Therapy; ITT, intent-to-treat; N/A, not applicable; RCP, randomised controlled period; SD, standard deviation

e) Hb response in the absence of transfusions (yes/no)

The Week 16 results for Hb response are provided in Table 19 of the CS. Since these results are analysed in the absence of transfusions, it is not appropriate to provide results which are uncensored for transfusions.

f) Hb normalisation in the absence of transfusions (yes/no)

The Week 16 results for Hb normalisation are provided in Table 20 of the CS. Since these results are analysed in the absence of transfusions, it is not appropriate to provide results which are uncensored for transfusions.

g) ARC normalisation in the absence of transfusions (yes/no)

The number and percentage of patients with ARC normalisation, uncensored for transfusion, is displayed in Table 5. ARC normalisation occurred for the majority of patients in the pegcetacoplan group [redacted], compared to only [redacted] of patients in the eculizumab group. Comparing this to the ARC normalisation data, censored for transfusion, presented in Table 21 of the CS, results are consistent with pegcetacoplan being associated with higher odds of ARC normalisation at Week 16 compared to [redacted]. The normalisation of ARC, as demonstrated by both the censored and uncensored results, indicates that pegcetacoplan effectively controls EVH.

Table 5: Number and percentage of patients with ARC normalisation at Week 16, uncensored for transfusion, during RCP (ITT)

Reticulocyte normalisation in the absence of transfusions	Pegcetacoplan (N = 41)	Eculizumab (N = 39)
Yes, n (%)	[redacted]	[redacted]
No, n (%)	[redacted]	[redacted]
Difference in percentage for pegcetacoplan vs. eculizumab (95% CI)	[redacted]	
Odds ratio for pegcetacoplan vs eculizumab (95% CI)	[redacted]	

Source: PEGASUS CSR (5)
Abbreviations: CI, confidence interval; ITT, intent-to-treat

h) CFB to Week 16 in indirect bilirubin level

The observed and CFB indirect bilirubin level, uncensored for transfusion, is displayed in Table 6. Comparing this table to the MMRM analysis presented in Table 22 of the CS, the results are consistent with the pegcetacoplan group showing [redacted] from baseline in indirect bilirubin at all time points than patients in the eculizumab group. At Week 16, mean CFB was [redacted] µmol/L in the pegcetacoplan group, compared to [redacted] µmol/L in the eculizumab group. As elevated indirect bilirubin levels are an indicator of haemolysis (9), these results further demonstrate the ability of pegcetacoplan to inhibit EVH.

Table 6: Observed values and CFB in indirect bilirubin level, uncensored for transfusion, during RCP (ITT)

	Pegcetacoplan (N=41)			Eculizumab (N=39)		
	n	Mean (SD) µmol/L	CFB µmol/L	n	Mean (SD) µmol/L	CFB µmol/L
Baseline	[redacted]					
Week 2						
Week 4						
Week 6						
Week 8						
Week 12						
Week 16						

Source: PEGASUS CSR (5)
Abbreviations: CFB, change from baseline; CI, confidence interval; ITT, intent-to-treat; N/A, not applicable; RCP, randomised controlled period; SD, standard deviation

i) CFB to Week 16 in LASA scores

The observed and CFB Linear Analog Assessment Scale (LASA) scores, uncensored for transfusion, are displayed in Table 7. Comparing this table to the observed and CFB LASA scores, censored for transfusion, presented in Table 24 of the CS, the results are consistent with the pegcetacoplan group maintaining an increase from baseline through to Week 16. On the other hand, the eculizumab group decreased below baseline from Week 4 to Week 16. At Week 16, the uncensored mean CFB in LASA scores was [redacted] for the pegcetacoplan group, compared to [redacted] for the eculizumab group. Given that a higher LASA score demonstrates improved functioning, and a difference of 10-20 points is considered minimally clinically important (10), this suggests that pegcetacoplan is associated with improved QoL in comparison to eculizumab.

Table 7: Observed values and CFB LASA scores, uncensored for transfusion, during RCP (ITT)

	Pegcetacoplan (N=41)			Eculizumab (N=39)		
	n	Mean (SD)	CFB	n	Mean (SD)	CFB
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: PEGASUS CSR (5)
Abbreviations: CFB, change from baseline; CI, confidence interval; ITT, intent-to-treat; LASA, Linear Analog Assessment Scale; N/A, not applicable; RCP, randomised controlled period; SD, standard deviation

j) CFB to Week 16 in EORTC-QLQ-C30 scores

Mean CFB in EORTC-QLQ-C30 Global Health Status (GHS)/QoL scores at Week 16, uncensored for transfusion, is displayed in Table 8. Comparing this table to the CFB in GHS/QoL data, censored for transfusion, presented in Table 26 of the CS, results are consistent with an overall mean [redacted] from baseline to Week 16 in the pegcetacoplan group for GHS/QoL of [redacted] and all functional scales. The

eculizumab group had a mean [redacted] from baseline in the GHS/QoL of [redacted] Higher scores for the functioning scales and global health status indicate a better level of functioning, and an increase of 10 points is indicative of a moderate-high change which is conventionally considered clinically meaningful (11). These results demonstrate that pegcetacoplan is associated with considerable improvements in QoL.

Table 8: Mean CFB in GHS/QoL at Week 16, uncensored for transfusion, during RCP (ITT)

	Pegcetacoplan		Eculizumab	
	n	Mean (SD)	n	Mean (SD)
Global Health Status/QoL	[redacted]	[redacted]	[redacted]	[redacted]
Functional scales				
Physical functioning	[redacted]	[redacted]	[redacted]	[redacted]
Role functioning	[redacted]	[redacted]	[redacted]	[redacted]
Emotional functioning	[redacted]	[redacted]	[redacted]	[redacted]
Cognitive functioning	[redacted]	[redacted]	[redacted]	[redacted]
Social functioning	[redacted]	[redacted]	[redacted]	[redacted]
Symptom scales				
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Nausea and vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Pain	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]	[redacted]
Appetite loss	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Financial difficulties	[redacted]	[redacted]	[redacted]	[redacted]

Source: PEGASUS CSR (5)
Abbreviations: CFB, change from baseline; CI, confidence interval; GHS, Global Health Status; ITT, intent-to-treat; LS, least-square; MMRM, mixed model for repeated measures; QoL, quality of life; RCP, randomised controlled period; SE, standard error.

A4. Ravulizumab is listed as a comparator in the final scope issued by NICE. Ravulizumab is recommended by NICE for the treatment of treating paroxysmal nocturnal haemoglobinuria in adults:

- with haemolysis with clinical symptoms suggesting high disease activity, **or**
- whose disease is clinically stable after having eculizumab for at least 6 months.

Please explain whether all patients in the PEGASUS trial met these clinical criteria. If not, please provide details of the number of patients who did not meet these criteria and the reasons for not meeting these criteria.

Patients with haemolysis with clinical symptoms suggesting high disease activity

High disease activity is not defined in the label for ravulizumab and the NICE guidance for ravulizumab states that "high disease activity is not clearly defined, and depends on a number of factors" (12). It is therefore challenging to assess an exact proportion of patients in PEGASUS that would be considered to have high disease activity. Despite this, a definition for high disease activity was used in the eligibility criteria for the phase III clinical trial of ravulizumab in complement inhibitor naïve patients (2), which was a key source of evidence for the positive recommendation of ravulizumab in this patient population (12). The definition used was:

> *"LDH level ≥ 1.5 × ULN at screening along with the presence of 1 or more of the following PNH-related signs or symptoms within 3 months of screening: fatigue, haemoglobinuria, abdominal pain, shortness of breath (dyspnoea), anaemia (haemoglobin < 10 g/dL), history of a major adverse vascular event (including thrombosis), dysphagia, or erectile dysfunction; or history of packed red blood cell (pRBC) transfusion due to PNH."*

However, high LDH, used here to define disease activity, is a clinical indicator of IVH (8) that is not necessarily relevant when identifying patients whose continued haemolysis is primarily driven by EVH and would therefore benefit from pegcetacoplan treatment (those in the PEGASUS trial).

As would be expected, only a small proportion of patients in the PEGASUS trial met the criteria of high disease activity above (n=12, 15%) as patients were treated with eculizumab (C5 inhibitor), blocking IVH, resulting in acceptable LDH levels. Patients who did meet the 'high disease activity' definition were those who had high disease activity despite treatment with a C5 inhibitor. Naturally, this was a smaller group of patients than those considered in the CHAMPION-301 ravulizumab trial (2), which only included patients who were complement-inhibitor naïve with high disease activity.

For the PEGASUS population, IVH was adequately controlled, with the associated generally acceptable LDH levels (mean [SD] LDH at enrolment: 282.4 [210.9] U/L). However EVH had become the primary mechanism of haemolysis, which continued to cause severe anaemia (all patients in PEGASUS had Hb< 10.5 g/dL) and transfusion dependency (patients entering PEGASUS had a mean of 6.5 transfusions in the preceding 12 months, with 55% (44 patients) requiring more than four transfusions in the preceding 12 months) (5).

Pegcetacoplan is the only treatment that effectively controls both IVH and EVH in this patient population, targeting complement proximal inhibition by inhibiting C3.

Patients whose disease is clinically stable after having eculizumab for at least 6 months.

Defining clinically stable is challenging and, as with high disease activity, there is no one definition that is clinically meaningful for a cross section of patients. Additionally, the NICE guidance for ravulizumab does not define clinically stable (12). However, to more fully explore this answer the company engaged with an expert with extensive experience in treating PNH, during which they corroborated that there is no real clinical consensus on this within the field (Appendix A, 5)

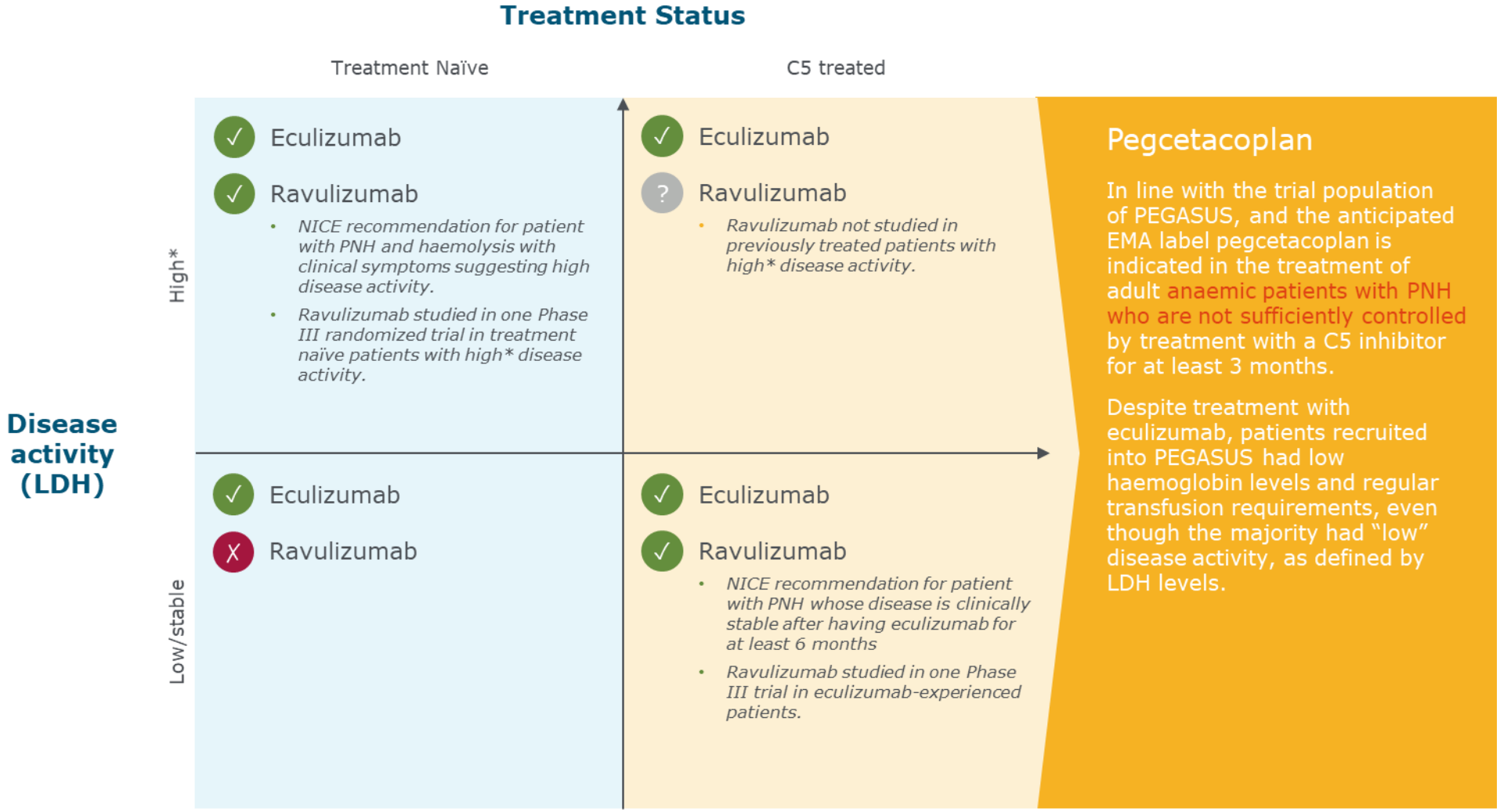
The inclusion criteria for CHAMPION-302 (in C5-inhibitor-experienced patients) and the label for ravulizumab define clinically stable as patients with LDH levels of <1.5 x ULN after treatment with eculizumab for at least six months. 80% of patients in PEGASUS were on a stable dose of eculizumab for at least six months and had LDH levels of <1.5 x ULN. However, it should be noted that 30% of patients enrolled in PEGASUS were treated with a higher-than-labelled dose of eculizumab (5). As previously noted, patients enrolled in PEGASUS also had a mean of 6.5 transfusions in the preceding 12 months, with 55% (44 patients) requiring more than four transfusions in the preceding 12 months despite treatment with eculizumab (5). Although patients enrolled in PEGASUS could be considered to be clinically stable, as defined by the ravulizumab label, they had anaemia, frequent transfusion requirements and reduced quality of life – and could not be considered to have optimised control of their disease (6).

The company understands that, when NICE recommended ravulizumab in patients who are clinically stable on eculizumab for at least six months it was to identify a population where C5 inhibitors work well, and thus those who may benefit from a switch from eculizumab to ravulizumab given the reduced administration burden it offers to patients. This is not the population in which pegcetacoplan is anticipated to be used. Instead, the anticipated pegcetacoplan label is reflective of the patients enrolled in PEGASUS, patients who are not sufficiently controlled, despite treatment with a C5 inhibitor (13).

The NICE recommendation for ravulizumab concluded that it had similar efficacy to eculizumab, which is supported by clinical opinion from the Advisory Board conducted by the company (6,12). Clinical opinion estimates that approximately 15-30% of patients would be expected to remain anaemic with insufficient control of their disease, despite C5 treatment (eculizumab or ravulizumab) (6).

Expert opinion believed that, following NICE guidance on ravulizumab, the majority of patients treated with eculizumab would switch to ravulizumab. As such, we have provided a figure detailing the within-guidance treatment options for patients with PNH that considers eculizumab, ravulizumab and pegcetacoplan (see Figure 1). As detailed above and in the figure, eculizumab and ravulizumab are indicated for the treatment of high-disease activity in treatment naïve patients, and ravulizumab is indicated for the treatment of clinically stable C5-experienced patients. Only pegcetacoplan will offer the new treatment option for patients who have insufficient control, despite C5 inhibitor treatment.

Figure 1: Overview of treatment labelling and anticipated place of pegcetacoplan



**Eligible patients entering CHAMPION-301 had to demonstrate high disease activity, defined as LDH level ≥1.5 × upper limit of normal (ULN) at screening along with the presence of 1 or more of the following PNH-related signs or symptoms within 3 months of screening: fatigue, haemoglobinuria, abdominal pain, shortness of breath (dyspnoea), anaemia (haemoglobin <10 g/dL), history of a major adverse vascular event (including thrombosis), dysphagia, or erectile dysfunction; or history of packed red blood cell (pRBC) transfusion due to PNH.*

A5. Please explain why, in the PEGASUS trial, a haemoglobin level of <10.5g/dL was used to define patients whose anaemia was not controlled after treatment with a C5 complement inhibitor. In the CS (page 109) it is stated, “According to clinicians, although anaemia is generally defined as Hb <13.5g/dL in men and Hb <12g/dL in women, patients with PNH may have a Hb lower than the general population and feel ‘normal’. Given this, a lower threshold of Hb level of 10.5g/dL was seen as appropriate to categorise patients as having ‘controlled’ and ‘uncontrolled’ anaemia”. Please provide the advisory board report that includes this information (reference 13) as this is not included within the reference pack received.

The WHO (2011) anaemia guidelines define anaemia as Hb below 13 g/dL in men and Hb below 12 g/dL in women (14). However, whilst these thresholds are appropriate for the general population, they cannot be generalised to PNH patients who have adjusted to functioning with lower Hb. Additionally, there is limited variation in Hb between men and women with PNH, meaning that a gender-specific threshold in the trial would not be appropriate (6). Clinical experts with experience of treating PNH in the UK estimate that only 10-20% of patients receiving eculizumab treatment will achieve Hb above 12 g/dL (15). Therefore, a Hb threshold of 12 g/dL or higher would have misrepresented the reality of uncontrolled anaemia in patients with PNH.

PNH clinical experts have confirmed that there is no consensus on an exact Hb level which corresponds to anaemia, and that this will vary on a patient-by-patient basis (6). However, in the absence of an accepted threshold, a level of <10.5 g/dL was selected for the PEGASUS trial based on support from publications throughout the PNH literature. Risitano et al. (2019) proposed a system to classify haematological response in PNH patients on eculizumab. Here, 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 (16). Given this classification, a <10.5 g/dL threshold to define uncontrolled anaemia was suitable for the PEGASUS trial, since this trial intended to select those patients who had not responded to eculizumab.

Furthermore, Schrezenmeier et al. (2014) reported that the 1,425 patients enrolled in the international PNH registry had a median Hb of 10.6 g/dL (3). This supports the selection of a <10.5 g/dL threshold to define anaemia in the PEGASUS trial, which

intended to select patients who were likely to have worse than average Hb levels. Similarly, McKinley et al. (2017) 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, further supporting the use of a <10.5 g/dl threshold (7). Finally, a <10.5 g/dL Hb threshold is also consistent with the selection criteria used for previous clinical trials in PNH. The pivotal TRIUMPH study, which investigated eculizumab in comparison to placebo, excluded patients with a mean Hb level prior to transfusion over the previous 12 months of above 10.5 g/dL (17).

Overall the 10.5 g/dL threshold used in the PEGASUS trial has been validated by clinical opinion and is also aligned with previous clinical trials in PNH, the published literature and Hb levels observed in the Alexion PNH registry (3,7,16,17). Please also find the advisory board report alongside this response as an additional attachment (6).

A6. Priority question. Please provide PEGASUS trial data for patients who were initially randomised to the pegcetacoplan arm as follows:

a) **The number of patients who, at 48 weeks, had discontinued treatment with pegcetacoplan and indicate whether patients either had a treatment break and later re-commenced pegcetacoplan treatment, discontinued pegcetacoplan permanently or had a treatment break and later re-commenced treatment with eculizumab or ravulizumab. If treatment discontinuations occurred at different rates over different trial time periods e.g., 0-16 weeks or 16-48 weeks, then please include any variation in a scenario analysis within the cost effectiveness results.**

A summary of discontinuations occurring in the RCP and open label period (OLP) of the PEGASUS trial along with reason for discontinuation and whether patients re-initiated treatment is presented in Figure 2, further detail is given in text in the following sections. Figure 2 also provides details on the rationale for the application of discontinuation rates used in the company submission (CS) base case and scenario analyses along with new scenario analyses based on 48-week data, which was not included in the original CS. Treatment discontinuation does not appear to vary over time, however patient numbers and discontinuation rates are sufficiently low, compounded by implications of trial design (cross-over with run-in period

between RCP and OLP), such that this cannot be further explored in a statistically meaningful way.

During the update to the cost-effectiveness model (CEM) with 48-week data, an error in the application of the one-off 900mg eculizumab dosing was identified, whereby costs for this were not incorporated into the Markov traces. This error has now been resolved, the results from this correction are shown alongside further scenario analyses on discontinuation in Table 9. Transition probabilities and adverse event data have also been updated using 48-week data in the CEM. Full results, sensitivity and scenario analyses are given in Appendix A: Full results with revised base-case.

Table 9: Revised base case and discontinuation scenario analyses

Scenario	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
Revised base case: 1 discontinuation from RCP (2.4% applied at Week 16)	Eculizumab	[redacted]	19.706	[redacted]	[redacted]	-	[redacted]	-	-
	Ravulizumab		19.706			0.000		2,989,356	2,989,540
	Pegcetacoplan		19.706			0.000		Dominant	Dominant
Scenario 1: 3 discontinuations from RCP (7.32% applied at week 16)	Eculizumab	[redacted]	19.706	[redacted]	[redacted]	-	[redacted]	-	-
	Ravulizumab		19.706			0.000		2,989,356	2,989,356
	Pegcetacoplan		19.706			0.000		Dominant	Dominant
Scenario 2: 1 discontinuation from RCP (0.62% applied at cycle rate in year 1)	Eculizumab	[redacted]	19.706	[redacted]	[redacted]	-	[redacted]	-	-
	Ravulizumab		19.706			0.000		2,989,356	2,989,356
	Pegcetacoplan		19.706			0.000		Dominant	Dominant
Scenario 3: 3 discontinuations from RCP + OLP (0.63% applied at cycle rate in year 1)	Eculizumab	[redacted]	19.706	[redacted]	[redacted]	-	[redacted]	-	-
	Ravulizumab		19.706			0.000		2,989,356	2,989,356
	Pegcetacoplan		19.706			0.000		Dominant	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; OLP, open label period; LYG, life years gained; QALY, quality adjusted life year; RCP, randomised controlled period
Note: The model assumes equal efficacy between eculizumab and ravulizumab, however this assumption is thought to be conservative and may underestimate costs associated with ravulizumab.

Figure 2: Overview of discontinuation and application to CEM

Abbreviations: BC, base case; CEM, cost-effectiveness model, CS, company submission; FUP, follow-up period; OLP, open label period, RCP, randomised controlled period, SA, sensitivity analyses* 16 weeks used based on clinical opinion that a small proportion of patients discontinue after 'settle-in' period (see advisory board report p.35 (6)). While exact number of weeks is unclear, 16 weeks was used in line with end of RCP as conservative estimate.

Week 0-48 data (Figure 1)

At 48 weeks, [redacted]
This includes patients who had received pegcetacoplan monotherapy throughout the study (n=41, 5 discontinuations, 1 death) and those who had switched from eculizumab to pegcetacoplan in the OLP (n=39, 7 discontinuations).

Week 0-16 data (RCP) – CS Base Case

During the RCP, [redacted], all of which were due to [redacted]. Only [redacted] had severe IVBTH (entailing very high LDH levels), [redacted] however they did not resume treatment with pegcetacoplan.

Following clinical expert engagement, the company were advised that the trial protocol was not reflective of clinical practise with regards to IVBTH and discontinuation of treatment. Although 3 patients discontinued pegcetacoplan in the RCP period, only the 1 patient who had severe IVBTH was identified as someone who would discontinue treatment in in clinical practise (severe IVBTH and very high LDL levels, (Section 3.3.4, page 35) (6). The remaining 2 patients would instead be treated with 900mg of eculizumab before continuing treatment with pegcetacoplan. One-off eculizumab dosing has become the standard clinical management of IVBTH as discussed at length in the clinical engagement section of TA10690 (12). The manufacturer acknowledges that, in the future, if ravulizumab becomes standard of care, IVBTH may instead be treated with a one-off dose of ravulizumab however there is no clinical use data to assess this at present. When discussing management of IVBTH with clinicians throughout the development of the CEM, it was clear that, wherever possible, clinicians do not want to switch patients back to a C5 inhibitor that was already inadequately managing disease symptoms in these patients (6)

Based on this clinical feedback, [redacted] of patients were assumed to discontinue treatment with pegcetacoplan in the base case This was applied as a one-off discontinuation at Week 16. Based on this clinical feedback, [redacted] of patients were assumed to discontinue treatment with pegcetacoplan in the base case (Section 3.3.4, page 35) (6). This was applied as a one-off discontinuation at Week

16. Week 16 was used based on clinical opinion that, in the real world setting, a small proportion of patients discontinue after 'settle-in' period (6). The number of weeks comprising the 'settle in' period in uncertain however, clinicians agreed around 16 weeks is appropriate and in line with the end of RCP.

Week 17-48 data (Open-label period)

During the OLP, [redacted] additional patients discontinued in total, of which [redacted] discontinuations [redacted] were from the original pegcetacoplan group, [redacted] were from the eculizumab switch group.

Original pegcetacoplan group

Of the patients who originally received pegcetacoplan during the RCP and went on to continue receiving pegcetacoplan, there were [redacted], and [redacted]

Of these [redacted] patients who discontinued pegcetacoplan, [redacted] and therefore has not been modelled as a discontinuation in the base case. The other patient discontinued due to [redacted] and as such is not modelled in the base case.

Scenario analyses are given assuming

- [redacted] discontinuations in RCP [redacted] applied as one-off discontinuation at Week 16 ([redacted] Table 9, Scenario 1)
- [redacted] discontinuation over weeks 0-48 modelled as cycle rate in year one. Comprises [redacted] Table 9, Scenario 2).

- [redacted] over weeks 0-48 modelled as cycle rate in year one. Comprises of one [redacted] Table 9, Scenario 3).

Results of all scenario analyses (Table 9) demonstrate that treatment with pegcetacoplan remains dominant in cost-effectiveness.

While scenario analyses are presented for completeness, it is important to reiterate that the [redacted] in the OLP (diffuse large-B cell lymphoma and pancytopenia) were not thought to be related to pegcetacoplan treatment, and the most likely situation is [redacted]

Original eculizumab group, crossed over to pegcetacoplan

Of the patients who originally received eculizumab during the RCP period and went on to receive eculizumab and pegcetacoplan for a four-week run in period followed by pegcetacoplan only in the OLP, [redacted] discontinued. [redacted] of these patients discontinued due to some form of [redacted] of which [redacted] patients discontinued potentially due to [redacted] however [redacted]

[redacted] Another [redacted] discontinued due [redacted] however [redacted]

Due to the complex treatment history of these patients (a four-week run-in period of receiving pegcetacoplan and eculizumab, 16 weeks of treatment with eculizumab, an additional four-week run in period of pegcetacoplan and eculizumab and finally treatment switch to pegcetacoplan), the company does not believe that the discontinuation experienced in this treatment group is appropriate to model, nor will it be representative of clinical practice or included in the dosage indication of pegcetacoplan in the draft Summary of Product Characteristics (SmPC). This

assumption was validated through a PNH key opinion leader (KOL) during a clinician interview (Appendix A) (5).

b) The number of patients requiring transfusions and the total number of transfusions required in the pegcetacoplan arm in the follow-up period (weeks 16-48).

Across the whole study in the pegcetacoplan arm, [redacted] did not require a transfusion while on pegcetacoplan therapy (48 weeks). Of the remaining [redacted] withdrew from treatment without having had a transfusion. Of the 7 patients requiring transfusion, [redacted] required a transfusion in the RCP period (0-16 weeks) and [redacted] required a transfusion in the OLP (17-48 weeks).

In the OLP, there were [redacted] across the eculizumab switch group and the pegcetacoplan group.

c) The occurrence of breakthrough haemolysis in patients in the pegcetacoplan arm in the follow-up period (weeks 16-48).

During the OLP (Week 17 to Week 48), [redacted]

Of the patients experiencing BTH in the pegcetacoplan arm, none of these were deemed attributable to pegcetacoplan. Two of these patients developed BTH which was likely triggered by an upper respiratory tract infection, and one patient had BTH of an unknown cause.

However, as noted in the CS, BTH was not a pre-defined endpoint of the PEGASUS trial and relies on post-hoc analyses using a definition approximated to that used in ravulizumab trials. Furthermore, for the purposes of modelling it is important to note that these BTH rates are not directly applicable to the model as they contain both IVBTH and extravascular breakthrough haemolysis (EVBTH); which have different clinical consequences.

- IVBTH: C5 inhibitors, such as eculizumab, stop IVH. Pegcetacoplan stops EVH and the vast majority of IVH. However, a small proportion of patients

receiving pegcetacoplan may still experience IVBTH. This will require either discontinuation for very severe events or a one-off dose of eculizumab for mild to moderate events (both of which are modelled in the CEM) (6).

- EVBTH: C5 inhibitors such as eculizumab do not stop EVBTH. Therefore, EVBTH was seen in the eculizumab arm. The consequences of this include drop in Hb levels and blood transfusions, which is already captured in the model (6).

A7. Priority question. The ERG notes that PEGASUS trial outcomes at 48 weeks have been partially reported in a news release. (18) Please provide the latest available results from the PEGASUS trial.

All results presented in this section have come from the 48-Week Pegcetacoplan CSR (19).

Patients who had received eculizumab in the RCP entered a second open-label run-in period (OLRIP) and received open-label pegcetacoplan in addition to eculizumab for 4 weeks (Weeks 17 through 20) before crossing over to pegcetacoplan monotherapy for 28 weeks, through to Week 48. Patients who received pegcetacoplan in the RCP continued with pegcetacoplan monotherapy in the open label period (OLP) (Weeks 17-48) (19). This section presents efficacy and safety findings following the open-label period (Weeks 17 through 48) for those in the pegcetacoplan group, eculizumab/pegcetacoplan group and total OLP pegcetacoplan group (Table 10).

Table 10: Treatment group descriptions

Treatment or study group name	Description
Pegcetacoplan group	Patients who were randomly assigned to pegcetacoplan monotherapy in the RCP (Week 1 through Week 16) and continued with pegcetacoplan monotherapy in the OLP (Week 17 through Week 48)
Eculizumab/pegcetacoplan group	Patients who were randomly assigned to eculizumab monotherapy in the RCP and then received eculizumab + pegcetacoplan for 4 weeks (Week 17 through Week 20; the OLRIP), followed by pegcetacoplan monotherapy until the end of the study

Total OLP pegcetacoplan group	All patients who were treated with pegcetacoplan monotherapy during the OLP. This includes: • Patients switching from eculizumab after OLP run (Weeks 21-48) • Patients continuing on pegcetacoplan monotherapy (Weeks 17-48)

Source: Apellis, data on file (19)
Abbreviations: ITT, intent-to-treat; OLP, open label period; OLRI, open label run-in; RCP, randomised controlled period

Change from baseline to Week 48 haemoglobin level

Across the OLP, pegcetacoplan demonstrated sustained improvements in Hb with a mean CFB of [redacted] at Week 48. A change of [redacted] was observed for the pegcetacoplan group, and [redacted] for the eculizumab/pegcetacoplan group (19). The observed and CFB in Hb across the OLP by treatment group for the ITT population is presented in Table 11.

Mean CFB in Hb levels across the entire study is presented in Figure 3. The improvement in Hb levels observed during the RCP for patients randomised to pegcetacoplan at baseline (Week 16 CFB [redacted]) was sustained at Week 48 (CFB [redacted]) for the pegcetacoplan group (see Section B.2.6.1, Table 8 in the CS for RCP results).

Similarly, for patients treated with eculizumab in the RCP, a marked improvement was observed in Hb levels once patients switched to pegcetacoplan (Week 16 CFB [redacted] compared with Week 48 CFB [redacted]). These patients improved by Week 20 (end of OLP run-in) and this improvement was maintained by pegcetacoplan throughout the open label period.

Table 11: Observed values and CFB in Hb, uncensored for transfusion, during the OLP (ITT)

	Pegcetacoplan (N=41)			Eculizumab/pegcetacoplan (N = 39)*			Total OLP pegcetacoplan (N=77)		
	n	Mean (SD) g/dL	CFB g/dL	n	Mean (SD) g/dL	CFB g/dL	n	Mean (SD) g/dL	CFB g/dL
Week 17	[redacted]								
Week 18									
Week 20									
Week 22									
Week 24									
Week 28									
Week 32									
Week 36									
Week 40									
Week 44									
Week 48									

Source: Apellis, data on file (19)
Abbreviations: CFB, change from baseline; Hb, haemoglobin; ITT, intent-to-treat; RCP, randomised controlled period; OLP, open label period; SD, standard deviation
Note: results are only presented for the OLP, for RCP results see Table 8 of the CS.
*Eculizumab/pegcetacoplan group: Patients who were randomised to the eculizumab group in the randomised controlled period received pegcetacoplan (APL-2) in addition to eculizumab for 4 weeks (Weeks 17-20) during the OLP, and then received APL-2 monotherapy.

Figure 3: Mean (± SE) CFB in Hb, uncensored for transfusion, during the OLP (ITT)

Source: Apellis, data on file (19)
Abbreviations: CFB, change from baseline; ITT, intent-to-treat; OLP, open-label period; SE, standard error

Transfusion Avoidance at Week 48

For the pegcetacoplan group, nearly [redacted] of patients ([redacted] did not require a transfusion at Week 48. [redacted] patients required a transfusion, [redacted] of whom [redacted] received at least one transfusion while [redacted] withdrew from treatment without having had a transfusion (19).

For the eculizumab/pegcetacoplan group, [redacted] did not require a transfusion after switching to pegcetacoplan monotherapy (19). Of the [redacted] patients who required a transfusion, [redacted] received at least one transfusion and one [redacted] withdrew from treatment without having had a transfusion (19).

The number of patients with transfusion avoidance, defined as the proportion of patients who do not require a transfusion over the OLP until Week 48, is presented in Table 12. No data is reported for the total OLP pegcetacoplan group. Week 48 results are consistent with those at Week 16 (85.4% of pegcetacoplan patients not requiring transfusion versus 15.4% for eculizumab patients). See Section B.2.6.3, Table 13 in the CS for RCP results.

Table 12: Summary of the number of patients with transfusion, during the OLP (ITT)

Transfusion avoidance	Statistics	Pegcetacoplan (N=41)	Eculizumab/pegcetacoplan* (N=39)
Yes (no transfusion)	n (%)	[redacted]	[redacted]
No	n (%)	[redacted]	[redacted]
Received at least one transfusion[a]	n (%)	[redacted]	[redacted]
Withdrew from the study without having had a transfusion	n (%)	[redacted]	[redacted]

Source: Apellis, data on file (19)
Transfusions during the run-in period are excluded.
No data is reported for the total OLP pegcetacoplan group.
*Eculizumab/pegcetacoplan group: Patients who were randomised to the eculizumab group in the randomised controlled period received pegcetacoplan (APL-2) in addition to eculizumab for 4 weeks (Weeks 17-20) during the OLP, and then received APL-2 monotherapy.
[a]Percentages are based on the number of patients in No category for each column.

Change from baseline to Week 48 in absolute reticulocyte count

ARC improvement was sustained with pegcetacoplan across the OLP. At Week 48, the mean CFB in ARC were [redacted] for the total OLP pegcetacoplan group, the

pegcetacoplan group and the eculizumab/pegcetacoplan group, respectively (19). Observed values and CFB in ARC across the OLP by treatment group for the ITT population is presented in Table 13.

Mean CFB in ARC across the entire study is presented in Figure 4. The CFB in ARC observed at Week 48 ([redacted]) during the OLP is consistent with the LS mean CFB at 16-weeks (-135.82× 10^9 cells/L) for pegcetacoplan patients (see Section B.2.6.3, Figure 8 in the CS for RCP results). The ARC CFB observed at Week 16 during the RCP on eculizumab/pegcetacoplan achieved comparable decreases during the OLRIP [redacted] which were maintained through Week 48 [redacted]

Table 13: Observed values and CFB in ARC, uncensored for transfusion, during the OLP (ITT)

	Pegcetacoplan (N=41)			Eculizumab/pegcetacoplan (N = 39)*			Total OLP pegcetacoplan (N=77)		
	n	Mean (SD) $\times 10^9$ cells/L	CFB $\times 10^9$ cells/L	n	Mean (SD) $\times 10^9$ cells/L	CFB $\times 10^9$ cells/L	n	Mean (SD) $\times 10^9$ cells/L	CFB $\times 10^9$ cells/L
Week 17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 32	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 44	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Apellis, data on file (19)
Abbreviations: ARC, absolute reticulocyte count; CFB, change from baseline; ITT, intent-to-treat; OLP, open label period; SD, standard deviation
*Eculizumab/pegcetacoplan group: Patients who were randomised to the eculizumab group in the randomised controlled period received pegcetacoplan (APL-2) in addition to eculizumab for 4 weeks (Weeks 17-20) during the OLP, and then received APL-2 monotherapy.

Figure 4: Mean (± SE) CFB in ARC, uncensored for transfusion, during the OLP (ITT)

Source: Apellis, data on file (19)
Abbreviations: ARC, absolute reticulocyte count; CFB, change from baseline; ITT, intent-to-treat; OLP, open-label period

Change from baseline to Week 48 in lactase dehydrogenase level

At Week 48, mean CFB in LDH level were [redacted] for the pegcetacoplan group, [redacted] for the eculizumab/pegcetacoplan group and [redacted] for the total OLP pegcetacoplan group (19). At Week 48, mean LDH levels had decreased from baseline to within the normal range in all groups. Observed values and CFB in LDH levels across the OLP for the ITT population are presented in Table 14.

Mean CFB in LDH levels across the whole study period is presented in Figure 5. LDH decreased from baseline in the pegcetacoplan group and eculizumab/pegcetacoplan group and was maintained across the entire study. This is consistent with the LS mean CFB at 16-weeks for pegcetacoplan, which was [redacted] (see Section B.2.6.3, Table 15 in the CS for RCP results).

Table 14: Observed values and CFB in LDH Level, uncensored for transfusion, during the OLP (ITT)

	Pegcetacoplan (N=41)			Eculizumab/pegcetacoplan (N = 39)*			Total OLP pegcetacoplan (N=77)		
	n	Mean (SD) U/L	CFB U/L	n	Mean (SD) U/L	CFB U/L	n	Mean (SD) U/L	CFB U/L
Week 17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 32	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 44	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Apellis, data on file (19)
Abbreviations: CFB, change from baseline; ITT, intent-to-treat; LDH, lactase dehydrogenase; OLP, open-label period; SD, standard deviation
*Eculizumab/pegcetacoplan group: Patients who were randomised to the eculizumab group in the randomised controlled period received pegcetacoplan (APL-2) in addition to eculizumab for 4 weeks (Weeks 17-20) during the OLP, and then received APL-2 monotherapy.

Figure 5: Mean (± SE) CFB in LDH, uncensored for transfusion, during the OLP (ITT)

Source: Apellis, data on file (19)
Abbreviations: CFB, change from baseline; ITT, intent-to-treat; LDH, lactase dehydrogenase; OLP, open-label period

Lactase dehydrogenase level normalisation at Week 48

Results show that [redacted] of patients in the pegcetacoplan group achieved LDH normalisation at Week 48 (19). In the eculizumab/pegcetacoplan group, [redacted] of patients achieved LDH normalisation (19). The number and percentage of patients with LDH normalisation, defined as an LDH level below the ULN range at Week 48, censored for transfusion, by treatment group for the ITT population is presented in Table 15. Results in the OLP are consistent with the majority of patients in the RCP. At Week 16 in the RCP, a total of [redacted] of patients treated with pegcetacoplan achieved LDH normalisation (see Section has B.2.6.3, Table 16 in the CS for RCP results). No data is reported for the total OLP pegcetacoplan group.

Table 15: Number and percentage of patients with LDH normalisation at Week 48, censored for transfusion, during the OLP (ITT)

LDH normalisation	Pegcetacoplan (N = 41)	Eculizumab/pegcetacoplan (N = 39)*
Yes, n (%)	[redacted]	[redacted]
No, n (%)	[redacted]	[redacted]

Source: Apellis, data on file (19)
Abbreviations: ITT, intent-to-treat; LDH, lactase dehydrogenase; OLP, open-label period
*Eculizumab/pegcetacoplan group: Patients who were randomised to the eculizumab group in the randomised controlled period received pegcetacoplan (APL-2) in addition to eculizumab for 4 weeks (Weeks 17-20) during the OLP, and then received APL-2 monotherapy.
Pegcetacoplan patients who received transfusions in the RCP or OLP or withdrew early were classified as not normalised. Eculizumab patients who received transfusions past Week 20 in OLP or withdrew early were classified as not normalised.

Change from baseline to Week 48 in the Functional Assessment of Chronic Illness Therapy Fatigue Scale version 4

Pegcetacoplan demonstrated clinically meaningful improvement in FACIT-Fatigue Scale score across the OLP. A [redacted] increase in FACIT-Fatigue Scale score was seen in the pegcetacoplan group at Week 48 from baseline (19). For the eculizumab/pegcetacoplan group, a CFB increase of [redacted] points was observed at Week 48, and for the total OLP pegcetacoplan group, a [redacted] increase was observed (19). A 3-point improvement is generally considered to be clinically meaningful (1). These improvements of 10.14 and 9.62 are three times the threshold for what is deemed to be clinically meaningful on the FACIT-Fatigue Scale (1). Observed values and changes from baseline in FACIT-Fatigue Scale score across the OLP per treatment group for the ITT population is presented in Table 16.

Mean CFB values for the entire study period are presented in Figure 6.

OLP results are consistent with those at Week 16 in the RCP where the pegcetacoplan group reported a CFB of 11.41 in FACIT-Fatigue score (see Section B.2.6.3, Table 18 in the CS for RCP results).

Table 16: Observed values and CFB in FACIT-Fatigue Score, uncensored for transfusion, during the OLP (ITT)

	Pegcetacoplan (N=41)			Eculizumab/pegcetacoplan (N = 39)*			Total OLP pegcetacoplan (N=77)		
	n	Mean (SD)	CFB	n	Mean (SD)	CFB	n	Mean (SD)	CFB
Week 17	[redacted]								
Week 18									
Week 20									
Week 22									
Week 24									
Week 28									
Week 32									
Week 36									
Week 40									
Week 44									
Week 48									

Source: Apellis, data on file (19)
Abbreviations: CFB, change from baseline; FACIT, Functional Assessment of Chronic Illness Therapy; ITT, intent-to-treat; OLP, open-label period; SD, standard deviation
*Eculizumab/pegcetacoplan group: Patients who were randomised to the eculizumab group in the randomised controlled period received pegcetacoplan (APL-2) in addition to eculizumab for 4 weeks (Weeks 17-20) during the OLP, and then received APL-2 monotherapy.

Figure 6: Mean (± SE) CFB in FACIT-Fatigue scale score, uncensored for transfusion, during the OLP (ITT)

Source: Apellis, data on file (19)
Abbreviations: CFB, change from baseline; FACIT, Functional Assessment of Chronic Illness Therapy; ITT, intent-to-treat; OLP, open-label period

Haemoglobin response at Week 48

[redacted] of patients on pegcetacoplan achieved the predefined Hb response in the absence of transfusion at Week 48 (19). [redacted] of patients in the eculizumab/pegcetacoplan group achieved the predefined Hb response (19). Hb response was defined as a ≥1 g/dL increase from baseline in the absence of transfusions. The number and percentage of patients with Hb response at Week 48 for the ITT population is presented in Table 17. Similarly, in the RCP at Week 16, the [redacted] of patients in the pegcetacoplan arm achieved Hb response, compared to [redacted] in the eculizumab arm (see Section B.2.6.4, Table 19 in the CS for RCP results).

Table 17: Number and percentage of patients with Hb response, at Week 48, censored for transfusion, during the OLP (ITT)

Hb response	Pegcetacoplan (N = 41)	Eculizumab/pegcetacoplan (N = 39)*
Yes, n (%)	[redacted]	[redacted]
No, n (%)	[redacted]	[redacted]

Source: Apellis, data on file (19)
Abbreviations: Hb, haemoglobin; ITT, intent-to-treat; OLP, open label period
Note: Pegcetacoplan patients who received transfusion in the RCP or OLP or withdrew early were classified as nonresponders. Eculizumab patients who received transfusions past Week 20 in the OLP or withdrew early were classified as nonresponders.
*Eculizumab group/pegcetacoplan: Patients who were randomised to the eculizumab group in the randomised controlled period received pegcetacoplan (APL-2) in addition to eculizumab for 4 weeks (Weeks 17-20) during the OLP, and then received APL-2 monotherapy.

Haemoglobin normalisation at Week 48

Approximately [redacted] of patients in the pegcetacoplan group achieved Hb normalisation in the absence of transfusion at Week 48 (19). In the eculizumab/pegcetacoplan group, [redacted] of patients achieved Hb normalisation. Hb normalisation is defined as the Hb level being above the lower limit of the gender-specific normal range at Week 48 (19).The number and percentage of patients with Hb normalisation in the absence of transfusions at Week 48 for the ITT population is presented in Table 18. Results are consistent with the 16-week RCP, where 34.1% of patients treated with pegcetacoplan achieved Hb normalisation without a transfusion, compared to zero in the eculizumab arm (see Section B.2.6.4, Table 20 in the CS for RCP results).

Table 18: Number and percentage of patients with Hb normalisation, at Week 48, censored for transfusion, during the OLP (ITT)

Hb normalisation	Pegcetacoplan (N = 41)	Eculizumab/pegcetacoplan* (N = 39)
Yes, n (%)	[redacted]	[redacted]
No, n (%)	[redacted]	[redacted]

Source: Apellis, data on file (19)
Abbreviations: Hb – haemoglobin; ITT – intent-to-treat; OLP, open label period
Note: Pegcetacoplan patients who received transfusion in the RCP or OLP or withdrew early were classified as not normalized. Eculizumab patients who received transfusions past Week 20 in the OLP or withdrew early were classified as not normalized.
*Eculizumab/pegcetacoplan group: Patients who were randomised to the eculizumab group in the randomised controlled period received pegcetacoplan (APL-2) in addition to eculizumab for 4 weeks (Weeks 17-20) during the OLP, and then received APL-2 monotherapy.

Absolute reticulocyte count normalisation at Week 48

ARC normalisation occurred for the [redacted] of patients in the pegcetacoplan group [redacted](19). In the eculizumab/pegcetacoplan group, [redacted] achieved reticulocyte normalisation (19). ARC normalisation is defined as the ARC being below the upper limit of the gender-specific normal range at Week 48. ARC normalisation, in the absence of transfusions at Week 48 by treatment group for the ITT population is shown in Table 19. Results are consistent with Week 16 in the RCP, where the majority of pegcetacoplan patients (78%) achieved ARC normalisation (see Section B.2.6.4, Table 21 in the CS for RCP results).

Table 19: Number and percentage of patients with reticulocyte normalisation, at Week 48, censored for transfusion, during the OLP (ITT)

ARC normalisation	Pegcetacoplan (N = 41)	Eculizumab/ pegcetacoplan* (N = 39)
Yes, n (%)	[redacted]	[redacted]
No, n (%)	[redacted]	[redacted]

Source: Apellis, data on file (19)
Abbreviations: ARC, absolute reticulocyte count; ITT, Intent-to-treat; OLP, open-label period
Reticulocyte normalization is defined as the reticulocyte count being below the upper limit of normal range at week 48.
*Eculizumab/pegcetacopan group: Subjects who were randomised to the eculizumab group in the randomised controlled period received pegcetacoplan (APL-2) in addition to eculizumab for 4 weeks (Weeks 17-20) during the OLP, and then received APL-2 monotherapy.

Change from baseline to Week 48 in indirect bilirubin level

At Week 48, CFB for indirect bilirubin for the total OLP pegcetacoplan group was [redacted] for the pegcetacoplan group and [redacted] for the eculizumab/pegcetacoplan group (19). All patients had similar improvement in indirect bilirubin levels at Week 48. Observed values and CFB in indirect bilirubin level, across the OLP for the ITT population are presented in Table 20. Mean (± SE)

observed values and CFB in indirect bilirubin level from baseline to Week 48 is presented in Figure 7. Indirect bilirubin improvements were demonstrated for all patients receiving pegcetacoplan across the entire study period (see Figure 7).

The results in the OLP are aligned with those at Week 16 in the RCP. The LS mean CFB at Week 16 was [redacted] in the pegcetacoplan group (see Section B.2.6.4, Table 22 in the CS for RCP results).

Table 20: Observed values and CFB in Indirect Bilirubin Level, uncensored for transfusion, during the OLP (ITT)

	Pegcetacoplan (N=41)			Eculizumab/pegcetacoplan (N = 39)*			Total OLP pegcetacoplan (N=77)		
	n	Mean (SD) µmol/L	CFB µmol/L	n	Mean (SD) µmol/L	CFB µmol/L	n	Mean (SD) µmol/L	CFB µmol/L
Week 17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 32	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 44	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Apellis, data on file (19)
Abbreviations: CFB, change from baseline; ITT, intent-to-treat; OLP, open-label period; SD, standard deviation
*Eculizumab group: Patients who were randomised to the eculizumab group in the randomised controlled period received pegcetacoplan (APL-2) in addition to eculizumab for 4 weeks (Weeks 17-20) during the OLP, and then received APL-2 monotherapy.

Figure 7: Mean (± SE) CFB in Indirect Bilirubin, uncensored for transfusion, during the OLP (ITT)

Source: Apellis, data on file (19)
Abbreviations: CFB, change from baseline; ITT, intent-to-treat; OLP, open-label period

Change from baseline to Week 48 in Linear Analog Assessment Scale scores

The LASA consists of 3 items asking respondents to rate their perceived level of functioning. Each item produces scores from 0 to 100 where higher scores indicate better HRQoL, and a difference of 10-20 points is considered minimally clinically important (10). In this analysis, items are combined where scores can range from 0 to 300, with a minimally clinically important difference (MCID) of 30-60 points. Observed values in LASA scores were similar at baseline for both treatment groups. At Week 48, both pegcetacoplan and eculizumab/pegcetacoplan patients had similar improvements from baseline in LASA scores. The mean (SD) CFB in LASA score for the pegcetacoplan group was [redacted] eculizumab/pegcetacoplan group was [redacted] and the total OLP pegcetacoplan group was [redacted] at Week 48 (19). Observed values and CFB in LASA score scores across the OLP for the ITT population are presented in Table 21.

Mean (± SE) CFB in LASA score over the entire study period are plotted in Figure 8. The LASA improvement observed during the RCP on pegcetacoplan at Week 16 ([redacted]) was sustained at Week 48 for the pegcetacoplan group (see Section B.2.6.4, Table 24 in the CS for RCP results), and the eculizumab/pegcetacoplan group achieved comparable improvement by Week 20 [redacted] and were maintained through to Week 48 [redacted]

Table 21: Observed values and CFB in LASA Score, uncensored for transfusion, during the OLP (ITT)

	Pegcetacoplan (N=41)			Eculizumab/pegcetacoplan (N = 39)*			Total OLP pegcetacoplan (N=77)		
	n	Mean (SD)	CFB	n	Mean (SD)	CFB	n	Mean (SD)	CFB
Week 17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 32	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 44	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Apellis, data on file (19)
Abbreviations: CFB, change from baseline; ITT, intent-to-treat; LASA; Linear Analog Scale Assessment; OLP, open-label period; SD, standard deviation
*Eculizumab/pegcetacoplan group: Patients who were randomised to the eculizumab group in the randomised controlled period received pegcetacoplan (APL-2) in addition to eculizumab for 4 weeks (Weeks 17-20) during the OLP, and then received APL-2 monotherapy.

Figure 8: Mean (± SE) CFB in LASA score, uncensored for transfusion, during the OLP (ITT)

Source: Apellis, data on file (19)
Abbreviations: CFB, change from baseline; ITT, intent-to-treat; LASA; Linear Analog Scale Assessment; OLP, open label period; SE, standard error

Change from baseline to Week 48 in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 scores

The EORTC-QLQ-C30 consists of 30 questions composed of both multi-item scales and single-item measures to assess overall HRQoL in patients. Higher scores for the functioning scales and GHS indicate a better level of functioning (i.e. an improved state of the patient), while higher scores on the symptom and single-item scales indicate a higher level of symptoms (i.e. a worse state of the patient). (20). Improvement was seen in the GHS/QoL scale and in all functional scales for patients treated with pegcetacoplan at Week 48. The GHS/QoL score increased by [redacted] and [redacted] at Week 48 in the pegcetacoplan group, eculizumab/pegcetacoplan group and total OLP pegcetacoplan group respectively, which is above the clinically meaningful increment of 10 points indicative of a moderate-high change (11,19). Symptom scales were generally improved for all patients through Week 48. At Week 48, the mean (SD) CFB in EORTC-QLQ-C30 GHS/QoL score is presented in Table 22.

Results were consistent with the RCP where the pegcetacoplan group reported a mean CFB of [redacted] at Week 16 (see Section B.2.6.4, Table 26 in the CS for RCP results).

Table 22: Mean (SD) CFB in GHS/QoL at Week 48, uncensored for transfusion, during the OLP (ITT)

	Pegcetacoplan (N = 41)	Eculizumab/ pegcetacoplan (N = 39)	Total OLP pegcetacoplan (N = 77)
Observed at Week 48, n	[redacted]	[redacted]	[redacted]
CFB Global health status/QoL	[redacted]	[redacted]	[redacted]
Functional scales			
Physical functioning	[redacted]	[redacted]	[redacted]
Role functioning	[redacted]	[redacted]	[redacted]
Emotional functioning	[redacted]	[redacted]	[redacted]
Cognitive functioning	[redacted]	[redacted]	[redacted]
Social functioning	[redacted]	[redacted]	[redacted]
Symptom scales			
Fatigue	[redacted]	[redacted]	[redacted]

Nausea and vomiting		[redacted]			[redacted]			[redacted]	
Pain		[redacted]			[redacted]			[redacted]	
Dyspnoea		[redacted]			[redacted]			[redacted]	
Insomnia		[redacted]			[redacted]			[redacted]	
Appetite loss		[redacted]			[redacted]			[redacted]	
Constipation		[redacted]			[redacted]			[redacted]	
Diarrhoea		[redacted]			[redacted]			[redacted]	
Financial difficulties		[redacted]			[redacted]			[redacted]	

Source: Apellis, data on file (19)
Abbreviations: CFB, change from baseline; GHS, global health score; ITT, intent-to-treat; OLP, open-label period; QoL, quality of life.
Notes: Eculizumab/pegcetacoplan group: Subjects who were randomised to the eculizumab group in the randomised controlled period received pegcetacoplan in addition to eculizumab for 4 weeks (Weeks 17-20) during the OLP, and then received pegcetacoplan monotherapy. Baseline is the last available, nonmissing observation before taking the first dose of pegcetacoplan. This table summarises data as observed with no imputation of missing data.

Subgroup analysis

Change from baseline to Week 48 Haemoglobin level: packed red blood cell transfusions

The results demonstrate that improvements in Hb levels with pegcetacoplan are observed irrespective of baseline transfusion status. For those in the <4 PRBC transfusions strata, the mean Hb increased by [redacted] and [redacted] in the pegcetacoplan, eculizumab/pegcetacoplan and total OLP pegcetacoplan groups, respectively (19). In patients who had ≥4 PRBC transfusions, mean Hb increased by [redacted] and [redacted] in the pegcetacoplan, eculizumab/pegcetacoplan and total OLP pegcetacoplan groups, respectively (19). Therefore, significant Hb improvements were observed with pegcetacoplan, even among patients requiring frequent transfusions prior to study entry.

Table 23 presents the mean (SD) observed values at baseline and at Week 48 and the mean (SD) CFB at Week 48 in Hb levels by number of PRBC transfusions for the ITT population. These results are consistent with those reported at Week 16 in the RCP. At Week 16, the pegcetacoplan group reported a CFB in Hb of [redacted] and [redacted] in the <4 and ≥4 PRBC transfusion strata's respectively (see Section B.2.7, Table 28 in the CS for RCP results).

Table 23: Observed values and CFB in Hb at Week 48 by PRBC transfusions (ITT)

Observed/change from baseline	Statistics	Pegcetacoplan (N = 20)	Eculizumab/ pegcetacoplan (N = 16)	Total OLP pegcetacoplan (N = 34)
Number of PRBC transfusions <4				
Baseline	n	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]
Observed at Week 48	n	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]
Change from baseline at Week 48	n	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]
Number of PRBC transfusions ≥4				
Observed/change from baseline	**Statistics**	**Pegcetacoplan (N = 21)**	**Eculizumab/ pegcetacoplan (N = 23)**	**Total OLP pegcetacoplan (N = 43)**
Baseline	n	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]
Observed at Week 48	n	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]
Change from baseline at Week 48	n	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]

Source: Apellis, data on file (19)
Abbreviations: CFB, change from baseline; Hb, haemoglobin; ITT, intent-to-treat; OLP, open-label period; PRBC, packed red blood cell
Notes: Eculizumab/pegcetacoplan group: Patients who were randomised to the eculizumab group in the randomised controlled period received pegcetacoplan in addition to eculizumab for 4 weeks (Weeks 17-20) during the OLP, and then received pegcetacoplan monotherapy. Baseline is the average of measurements recorded before taking the first dose of pegcetacoplan, which will include local and central laboratory test values during the screening period.
This table summarises data as observed with no imputation of missing data.

Change from baseline to Week 48 Haemoglobin level: platelet count

Pegcetacoplan provided consistent improvement in efficacy measures in the ITT population regardless of baseline or platelet severity. Regardless of platelet stratum, Hb level increased from baseline and was sustained at Week 48 in the total OLP pegcetacoplan group. Patients with lower platelet count (<100,000/mm^3) at screening demonstrated substantial improvements in Hb with pegcetacoplan treatment ([redacted]) (19).

Table 24 presents the mean (SD) observed values at baseline and Week 48 and CFB at Week 48 in Hb levels by platelet count at screening for the ITT population.

These results in the OLP (Weeks 17-48) are improvements on those in the RCP (Weeks 1-16) where a [redacted] mean increase in Hb was observed with pegcetacoplan in patients with lower platelet count (see Section B.2.7, Table 30 in the CS for RCP results).

Table 24: Observed values and CFB in Hb at Week 48 by number of platelets (ITT)

Observed/change from baseline	Statistics	Pegcetacoplan (N = 12)	Eculizumab/ pegcetacoplan (N = 9)	Total OLP pegcetacoplan (N = 20)
Number of platelets <100,000/mm^3				
Baseline	n	[redacted]	[redacted]	[redacted]
	Mean (SD) x10^9 cells/L	[redacted]	[redacted]	[redacted]
Observed at Week 48	n	[redacted]	[redacted]	[redacted]
	Mean (SD) x10^9 cells/L	[redacted]	[redacted]	[redacted]
Change from baseline at Week 48	n	[redacted]	[redacted]	[redacted]
	Mean (SD) x10^9 cells/L	[redacted]	[redacted]	[redacted]
Number of platelets ≥100,000/mm^3				
Observed/change from baseline	**Statistics**	**Pegcetacoplan (N = 29)**	**Eculizumab/ pegcetacoplan (N = 30)**	**Total OLP pegcetacoplan (N = 57)**
Baseline	n	[redacted]	[redacted]	[redacted]
	Mean (SD) x10^9 cells/L	[redacted]	[redacted]	[redacted]
Observed at Week 48	n	[redacted]	[redacted]	[redacted]
	Mean (SD) x10^9 cells/L	[redacted]	[redacted]	[redacted]
Change from baseline at Week 48	n	[redacted]	[redacted]	[redacted]
	Mean (SD) x10^9 cells/L	[redacted]	[redacted]	[redacted]

Source: Apellis, data on file (19)
Abbreviations: CFB, change from baseline; Hb, haemoglobin; ITT, intent-to-treat; OLP, open-label period; SD, standard deviation
Notes: Eculizumab/pegcetacoplan group: Patients who were randomised to the eculizumab group in the randomised controlled period received pegcetacoplan in addition to eculizumab for 4 weeks (Weeks 17-20) during the OLP, and then received pegcetacoplan monotherapy. Baseline is the average of measurements recorded before taking the first dose of pegcetacoplan, which will include local and central laboratory test values during the screening period.
This table summarises data as observed with no imputation of missing data.

Safety Analyses

Exposure and dosing

Open-label period

Seventy-seven patients received pegcetacoplan for a mean of duration of [redacted] days during the OLP. [redacted] patients had an interruption in [redacted] pegcetacoplan infusion, accounting for [redacted] % of all infusions during the OLP; the complete volume was administered regardless of interruptions. The mean number of pegcetacoplan infusions completed per patient was [redacted] (19). Table 25 shows drug exposure for the OLP for the safety population.

Whole Study (RCP + OLP + Follow-up)

Eighty patients received pegcetacoplan for a mean of [redacted] days. [redacted] patients had a total of [redacted] interruptions in infusions during pegcetacoplan monotherapy, accounting for [redacted] % of all infusions given during this period. The mean number of pegcetacoplan infusions completed per subject was [redacted]. The most common reasons for infusion interruption included pump malfunction and user error; the action taken in most cases was to restart and complete infusion.

Table 25: Study drug exposure during the OLP (Safety)

		OLP	RCP + OLP + follow-up
	Statistics	**Total OLP pegcetacoplan group**	**Overall pegcetacoplan monotherapy (RCP + OLP)**
		Pegcetacoplan exposure (N=77)	**Pegcetacoplan exposure (N=80)**
Total dose administered			
	Mean (SD)	[redacted]	[redacted]
Duration of treatment (days)			
	Mean (SD)	[redacted]	[redacted]
Patients received infusion	n (%)	[redacted]	[redacted]
Patients with all infusions completed	n (%)	[redacted]	[redacted]
Patients with any infusions interrupted	n (%)	[redacted]	[redacted]
Number of infusions completed by patient			
	Mean (SD)	[redacted]	[redacted]
Total number of infusions	M	[redacted]	[redacted]
Infusion completed	m (%)	[redacted]	[redacted]
Infusion interrupted	m (%)	[redacted]	[redacted]

Source: Apellis, data on file (19)
Abbreviations: OLP, open-label period; RCP, randomised controlled period; SD, standard deviation
Note: Duration of treatment (days) = date of last injection – date of first injection + 1. Infusion completed is defined as infusion without interruption.

Incidence of treatment-emergent adverse events

Across all study periods, the majority of TEAEs were mild or moderate and were considered by the investigator to be unrelated to pegcetacoplan. During the RCP (Weeks 1-16), [redacted] of TEAEs were classed as mild and moderate respectively, in the OLP (Weeks 17-48), this was [redacted] (19). In the RCP, there were [redacted] in the pegcetacoplan group that had TEAEs deemed related to study treatment, with most of these being injection site reactions (see Section B.2.10.3 in the CS for RCP results). Similar findings were reported in the OLP with [redacted] experiencing TEAEs deemed related to pegcetacoplan (19). ISRs were experienced by [redacted], and all ISRs were mild or moderate in severity.

Open-label period

[redacted] in the total OLP pegcetacoplan group had TEAEs. The majority were mild [redacted] or moderate [redacted] in severity. [redacted] patients [redacted] had TEAEs deemed related to pegcetacoplan. [redacted] had serious adverse events (SAEs). [redacted] had SAEs deemed related to pegcetacoplan. [redacted] had TEAEs that led to study discontinuation. During the OLP, in the total OLP pegcetacoplan group, [redacted] had a TEAE of COVID-19 that led to death (19). Detailed results are reported in Table 26.

Whole study (RCP + OLP + Follow-up)

Across the whole study (RCP + OLP + follow-up) in the pegcetacoplan group, [redacted] had TEAEs. The majority were mild [redacted] or [redacted] in severity, and [redacted] had TEAEs deemed related to pegcetacoplan. Twenty-four patients (30.0%) had SAEs. Five patients (6.3%) had SAEs that were deemed related to pegcetacoplan. Twelve patients (15.0%) had TEAEs that led to study discontinuation (19).

Table 26: Overview of TEAEs, during the OLP (Safety)

	OLP	RCP + OLP + follow-up

	Total OLP pegcetacoplan group (N=77)	Overall pegcetacoplan monotherapy (RCP+OLP) (N=80)
Any TEAEs	[redacted]	[redacted]
Total events	[redacted]	[redacted]
TEAEs by closest relationship to pegcetacoplan	[redacted]	[redacted]
TEAEs by closest relationship to eculizumab	[redacted]	[redacted]
Serious TEAEs	[redacted]	24 (30.0)
Serious TEAEs by closest relationship to pegcetacoplan	[redacted]	5 (6.3)
Serious TEAEs by closest relationship to eculizumab	[redacted]	[redacted]
TEAEs by maximum severity		
Mild	[redacted]	[redacted]
Moderate	[redacted]	[redacted]
Severe	[redacted]	[redacted]
Injection site reaction	[redacted]	[redacted]
TEAEs leading to study drug discontinuation	[redacted]	[redacted]
TEAEs leading to death	[redacted]	[redacted]
TEAEs due to COVID-19	[redacted]	1 (1.3)

Source: Apellis, data on file (19)
Abbreviations: COVID-19, coronavirus disease 2019; NA, not applicable; OLP, open-label period; RCP, randomised controlled period; TEAE, treatment-emergent adverse event

Common treatment-emergent adverse events

Table 27 shows that for pegcetacoplan-treated patients, haemolysis, diarrhoea, and injection site erythema remained common TEAEs throughout the study. As the length of the study increased, additional TEAEs became common, and small differences in the frequency of these events were observed between the OLP and the whole study.

Open-label period

In the total OLP pegcetacoplan group, TEAEs that occurred in ≥10% of patients by decreasing frequency were [redacted] (19).

Whole study (RCP + OLP + Follow-up)

In the pegcetacoplan group, TEAEs that occurred in ≥10% of patients by decreasing frequency were haemolysis (23.8%), diarrhoea (21.3%), [redacted] (19).

Table 27: Treatment-emergent adverse events reported by ≥10% patients in any treatment group by system organ, during the OLP

System Organ Class/ Preferred Term	OLP	RCP + OLP + follow-up
	Total OLP pegcetacoplan group (N=77)	Overall pegcetacoplan monotherapy (RCP+OLP) (N=80)
General disorders and administration site conditions	[redacted]	[redacted]
Injection site erythema	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Injection site pruritus	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Injection site reaction	[redacted]	[redacted]
Injection site swelling	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Diarrhoea	[redacted]	17 (21.3)
Abdominal pain	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]
Haemolysis	[redacted]	19 (23.8)
Anaemia	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]
Cough	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]

Source: Apellis, data on file (19)
Abbreviations: OLP, open-label period; RCP, randomised controlled period

Haemolytic TEAEs

Open-label period

In the total OLP pegcetacoplan group, [redacted] had a haemolytic event (10 patients had severe events, [redacted] patients had moderate events, and [redacted] had at least 1 mild event). Of the [redacted] who experienced a haemolytic event, the majority [redacted] were in the eculizumab/pegcetacoplan arm (19). Clinicians in a recent advisory board advised that haemolytic events may occur shortly after initiation of pegcetacoplan due to a 'settling in' phase which could explain why more patients in the eculizumab/pegcetacoplan arm experienced haemolytic TEAEs (6). The events are self-limiting and in clinical practise are resolved by a one-off 900 mg dose of eculizumab, and patients remain on treatment with pegcetacoplan (for more detail, please refer to A6 response).

Haemolysis was the most common TEAE ([redacted]). [redacted] had an event of haemolysis that was determined to be related to study drug, and [redacted] had an SAE of haemolysis. Dose was increased in [redacted] patients, and study drug was withdrawn in [redacted] patients. Patients also had events of haemolytic anaemia (including one SAE and one event determined to be related to study drug), haemoglobinaemia, haemoglobinuria, and intravascular haemolysis. The highest incidence among these events was [redacted](19).

Whole study (RCP + OLP + Follow-up)

In the overall pegcetacoplan monotherapy group, [redacted] had a haemolytic disorder ([redacted] patients had severe events, [redacted]patients had moderate events, and [redacted] had at least 1 mild event). Haemolysis was the most common haemolytic TEAE (occurring in [redacted]). [redacted] patients each had an event of haemolysis that was determined to be related to study drug, and [redacted] patients each had an SAE of haemolysis. As a result of the haemolytic events, the dose of pegcetacoplan was increased to 1,080mg every three days in [redacted] patients after a single measurement of LDH that was>2 × ULN; clinicians in a recent advisory board commented that this would not occur in clinical practise (6). Study drug was withdrawn in [redacted] patients. Patients also had haemolytic anaemia ([redacted] patients [2.5%]; one SAE that was determined to be possibly related to study drug),

haemoglobinaemia, haemoglobinuria, and intravascular haemolysis (all in [redacted] each) (19).

Section B: Clarification on cost-effectiveness data

B1. Please clarify whether the 'censored for transfusion data' or the 'uncensored for transfusion data' were used in the regression model to derive the transition probabilities used in the economic model. Please provide transition probabilities using the alternative approach to censoring and provide the results of a scenario analysis using these alternative values.

Censoring for transfusion could be logical only if we consider transfusion required as permanent state without the possibility for the transition to no transfusion states. This assumption was explored, however this was seen as too restrictive by key opinion leaders, not in line with clinical practice and resulted in implausible results (21). Based on this feedback the model structure allowed for patients to transition between transfusion required and no transfusion health states, a structure that was validated by key clinicians with experience in treating PNH in the UK and independent health economists (6). Therefore, it is not possible to censor for transfusion data.

B2. Please fully explain why chelation therapy is used for patients with iron overload who are treated with C5 inhibitors whereas blood removal is used for patients who are treated with pegcetacoplan, when patient outcomes are the same for each treatment option and the only difference is the treatment cost.

As described in response to question A4, patients in the PEGASUS trial continue to experience EVH despite treatment with a C5 inhibitor. On average, patients required 6.5 transfusions in the preceding 12 months, with 55% (44 patients) requiring more than four transfusions in the preceding 12 months. Blood transfusion therapy results in accumulation of iron, which is a key component of haemoglobin present in the red blood cells. Each unit of blood contains between 200-250 mg iron (22). The human body has no mechanism for removal of the iron. Therefore, patients on C5 inhibitors who are regularly transfused will accumulate iron in the liver and spleen, developing iron overload (23–25). According to clinical opinion, the majority of patients with EVH (those in the PEGASUS trial) who receive transfusions will

experience iron overload and will require chelation therapy (6). At enrolment of PEGASUS, [redacted]% of patients were receiving therapy for iron overload, either deferasirox, which is costly and associated with gastro-intestinal side effects, or deferoxamine mesylate, which requires a nightly 8-hour subcutaneous infusion. As the majority of iron is bound to haemoglobin (26), iron chelation therapy is only able to remove a small percentage of it, meaning that iron chelation is a life-long therapy (27).

When patients in this population (who are inadequately controlled with a C5 inhibitor) switch from a C5 inhibitor (such as eculizumab and ravulizumab) to a C3 proximal complement inhibitor, such as pegcetacoplan), both IVH and EVH is targeted as the complement cascade is inhibited earlier. By targeting EVH, C3 proximal complement inhibitors are able to increase and normalise patient haemoglobin meaning patients do not require blood transfusions, and do not suffer from iron overload (6,13).

However, iron overload takes a substantial amount of time to resolve due to the iron which is built up prior to the initiation of pegcetacoplan in transfusion dependent patients, and the inability of the body to remove iron. This iron overload is dealt with through venesection (blood removal). Clinical experts suggest that venesection is possible for patients treated with pegcetacoplan as their Hb levels have been adequately controlled, as shown in the PEGASUS trial, to make it a viable, safe treatment option. Therefore, alternate ways to treat iron overload, such as chelation therapy, are not required.

This is not the case for patients who continue treatment with a C5 inhibitor. These patients remain inadequately controlled, with associated low Hb levels and transfusion dependency. Venesection is not a viable option for these patients due to their low Hb levels and transfusion dependence and instead their iron overload is treated with chelation therapy. According to clinical opinion, a key benefit of pegcetacoplan is that patients do not require costly life-long chelation therapy (such as deferasirox and deferoxamine mesilate) to treat iron overload as required by patients on C5 inhibitors who continue to require blood transfusions (6). Iron overload takes longer to resolve in these anaemic patients (with low haemoglobin levels) through chelation therapy, since the majority of their iron is bound to

haemoglobin. Therefore, not only is chelation therapy costly, but relatively inadequate in reducing iron levels.

The baseline percentage of patients with iron overload was taken from the baseline proportion of patients who had a treatment history of deferasirox and deferoxamine mesilate (both iron chelation treatments) in the PEGASUS trial, as these are life-long therapies. This was used to estimate the number of patients experiencing iron overload for both treatment arms due to the lack of acute events of iron overload during the PEGASUS trial. While validating this assumption, one clinician acknowledged the PEGASUS data and felt that an alternative scenario should be explored in the model to reflect their clinical experience, though it was noted that clinical experience may vary substantially between each clinician (6). During further clinical engagement to discuss this topic, the clinical expert in PNH offered alternative values for the percentage of patients receiving deferasirox ([redacted]%), and deferoxamine mesilate ([redacted]%) which are presented in scenario analyses. This clinician also believed the current cost and resource utilisation of venesection for the pegcetacoplan arm should be amended, as venesection for PNH was more likely to be a discrete course of events lasting approximately one year until iron overload was resolved (as opposed to a lifetime cost) and would entail approximately 30 minutes of specialist nurse time (6). This has been updated in the base case analyses presented in response to question A6 and in Table 28. Regardless, pegcetacoplan remained dominant.

Table 28: Revised base case and iron overload scenario analysis

Scenario	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
Revised base case: Baseline iron overload from PEGASUS trial data	Eculizumab	[redacted]	19.706	[redacted]	[redacted]	-	[redacted]	-	-
	Ravulizumab		19.706			0.000		2,989,540	2,989,540
	Pegcetacoplan		19.706			0.000		Dominant	Dominant
Scenario 1: Iron overload based on KOL opinion	Eculizumab	[redacted]	19.706	[redacted]	[redacted]	-	[redacted]	-	-
	Ravulizumab		19.706			0.000		2,989,540	2,989,540
	Pegcetacoplan		19.706			0.000		Dominant	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; KOL, key opinion leader; LYG, life years gained; QALY, quality adjusted life year

Section C: Textual clarification and additional points

C1. It is usually possible for the ERG to directly export references from a CS (and appendices) to EndNote from links where references have been inserted. However, in this submission, the CS and appendices do not appear to contain links to a bibliographic database, possibly because these were removed prior to submission to NICE. If possible, please provide access to versions of the CS and appendices with these links or a copy of an EndNote file that includes all the references cited in the CS (and appendices).

Versions of the CS and appendices with links have been provided as an attachment.

Appendix A: Full results with revised base-case

In the base case analysis, pegcetacoplan results in [redacted] incremental QALYs compared to ravulizumab, and ravulizumab results in [redacted] incremental QALYs compared to eculizumab. In addition, pegcetacoplan is associated with [redacted] incremental costs over a lifetime horizon compared with ravulizumab, and ravulizumab is associated with [redacted] incremental costs over a lifetime horizon compared with eculizumab. Pegcetacoplan dominates both eculizumab and ravulizumab.

Table 29 Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Eculizumab	[redacted]	19.706	[redacted]	[redacted]	-	[redacted]	-	-
Ravulizumab	[redacted]	19.706	[redacted]	[redacted]	0.000	[redacted]	2,989,356	2,990,271
Pegcetacoplan	[redacted]	19.706	[redacted]	[redacted]	0.000	[redacted]	Dominant	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Sensitivity analyses

Probabilistic sensitivity analysis

The mean values for total costs, LYs, QALYs, and incremental cost per QALY gained for pegcetacoplan versus eculizumab and ravulizumab for the population of interest generated through 1,000 simulations of the probabilistic sensitivity analysis (PSA) are presented in Table 30. The output shows that on average, pegcetacoplan results in [redacted] incremental QALYs compared to ravulizumab, and ravulizumab results in [redacted] incremental QALYs compared to eculizumab. In addition, pegcetacoplan is associated with [redacted] incremental costs over a life-time horizon compared with ravulizumab, and ravulizumab is associated with [redacted] incremental costs over a lifetime horizon compared with eculizumab. Pegcetacoplan dominates both eculizumab and ravulizumab.

The incremental cost-effectiveness plane (ICEP) (Figure 9) shows that 100% of results are in the southeast quadrant for both pegcetacoplan versus eculizumab and pegcetacoplan versus ravulizumab, meaning that pegcetacoplan continues to dominate eculizumab and ravulizumab in each simulation. In addition, the cost-effectiveness acceptability curve (CEAC) (Figure 10) shows that pegcetacoplan is 100% cost-effective at all willingness to pay thresholds.

Table 30: Mean PSA results

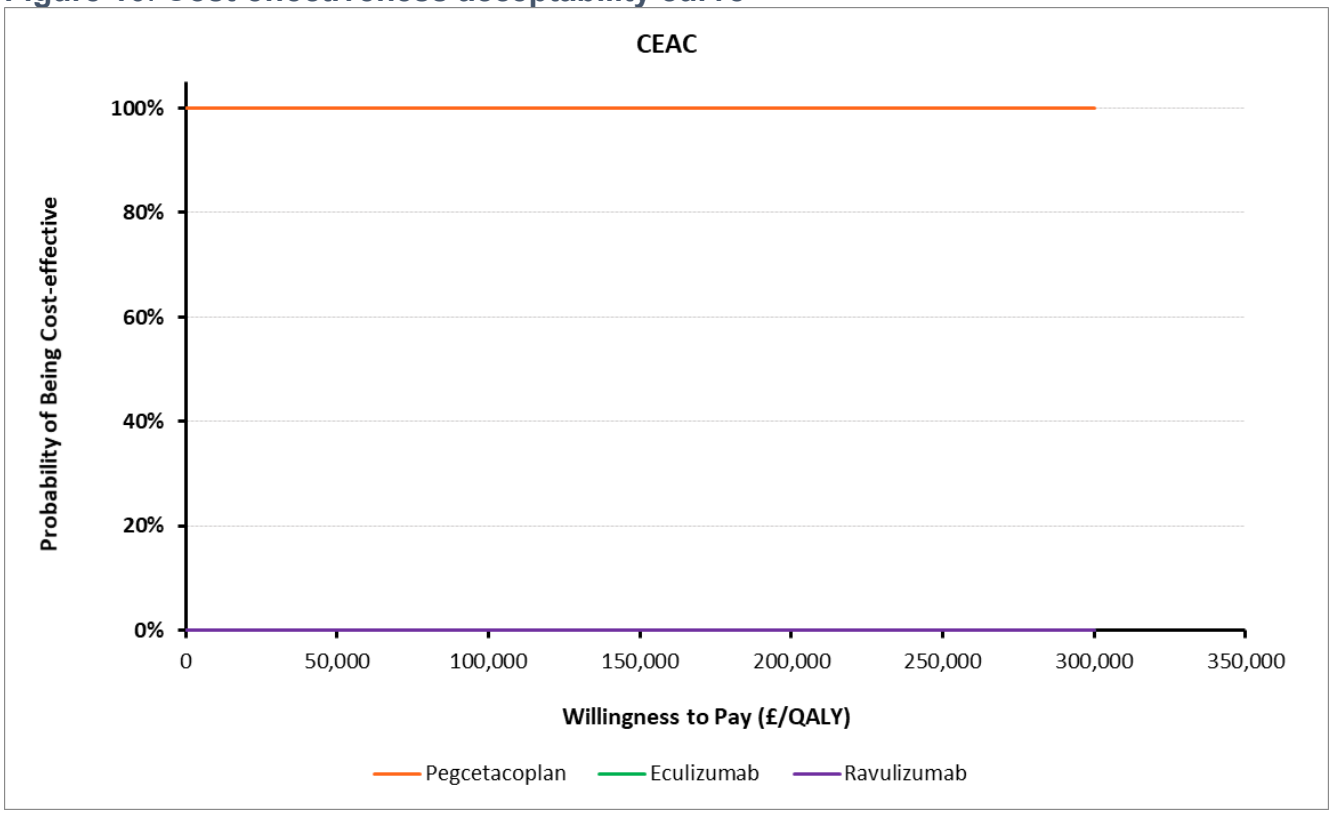
Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Eculizumab	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]	2,924,373	2,924,373
Pegcetacoplan	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Figure 9: Incremental cost-effectiveness plane

Abbreviations: QALY, quality-adjusted life year

Figure 10: Cost-effectiveness acceptability curve



Abbreviations: CEAC, cost-effectiveness acceptability curve; QALY, quality-adjusted life year

Deterministic sensitivity analysis

A OWSA tornado diagram presenting the top 10 most sensitive parameters for pegcetacoplan versus ravulizumab is presented in Figure 11. Table 31 presents the one-way sensitivity analysis (OWSA) results for these 10 parameters. The model was most sensitive to the mean weight of patients, utility values for no transfusion and Hb ≥10.5mg/dl health state and utility values for the transfusion required health state the cost of blood transfusion

A OWSA tornado diagram presenting the top 10 most sensitive parameters for pegcetacoplan versus eculizumab is presented in Figure 11. Table 32 presents the OSWA results for these 10 parameters. The model was most sensitive to utility values for no transfusion and Hb ≥10.5mg/dl, the utility values for the transfusion required health state and the cost of blood transfusion.

Figure 11 Tornado diagram for OWSA for pegcetacoplan versus ravulizumab

Figure 12 Tornado diagram for OWSA for pegcetacoplan versus eculizumab

Table 31: OWSA results for the 10 parameters that contribute the largest difference to the NMB for pegcetacoplan versus ravulizumab

Parameter	Base case NMB	Lower bound NMB	Upper bound NMB	Max Difference NMB
Mean weight (kg)	[redacted]	[redacted]	[redacted]	[redacted]
Utility pegcetacoplan: No transfusion and Hb≥10.5		[redacted]	[redacted]	[redacted]
Utility pegcetacoplan: Transfusion Required		[redacted]	[redacted]	[redacted]
Cost of blood transfusion		[redacted]	[redacted]	[redacted]
Mean units of blood per transfusion		[redacted]	[redacted]	[redacted]
Pack cost deferasirox		[redacted]	[redacted]	[redacted]
% on deferasirox		[redacted]	[redacted]	[redacted]
Female percentage		[redacted]	[redacted]	[redacted]
Cycle rate of patients receiving one-off dose of eculizumab		[redacted]	[redacted]	[redacted]
Utility pegcetacoplan: No transfusion and Hb<10.5		[redacted]	[redacted]	[redacted]

Abbreviations: NMB, net monetary benefit; OWSA, one-way sensitivity analysis

Table 32 OWSA results for the 10 parameters that contribute the largest difference to the NMB for pegcetacoplan versus eculizumab

Parameter	Base case NMB	Lower bound NMB	Upper bound NMB	Max Difference NMB
Utility pegcetacoplan: No transfusion and Hb≥10.5	[redacted]	[redacted]	[redacted]	[redacted]
Utility pegcetacoplan: Transfusion Required		[redacted]	[redacted]	[redacted]
Cost of blood transfusion		[redacted]	[redacted]	[redacted]
Mean units of blood per transfusion		[redacted]	[redacted]	[redacted]
Pack cost deferasirox		[redacted]	[redacted]	[redacted]
% on deferasirox		[redacted]	[redacted]	[redacted]
Mean weight (kg)		[redacted]	[redacted]	[redacted]
Female percentage		[redacted]	[redacted]	[redacted]
Cycle rate of patients receiving one-off dose of eculizumab		[redacted]	[redacted]	[redacted]
Utility pegcetacoplan: No transfusion and Hb<10.5		[redacted]	[redacted]	[redacted]

Abbreviations: NMB, net monetary benefit; OWSA, one-way sensitivity analysis

Scenario analysis

Table 33 details scenario analyses results for pegcetacoplan versus eculizumab and pegcetacoplan versus ravulizumab. Pegcetacoplan dominates eculizumab and ravulizumab in all scenarios.

Table 33: Scenario analysis results

Parameter	Base case	Scenario analysis	ICER (£/QALY) pegcetacoplan vs eculizumab	ICER (£/QALY) pegcetacoplan vs ravulizumab
Time horizon	Lifetime	10 years	Dominant	Dominant
		20 years	Dominant	Dominant
Discount rate (costs and QALYS)	3.5%	0%	Dominant	Dominant
		6%	Dominant	Dominant
Utility decrement of eculizumab vs. ravulizumab and pegcetacoplan	0.025	0.000	Dominant	Dominant
		0.057	Dominant	Dominant
Utility: general population age adjustment	Applied	Not applied	Dominant	Dominant
Iron overload disutility	-0.03	0.00	Dominant	Dominant
Transition probabilities	4-48 week data for all cycles	0-4 weeks per first cycle; 4-16 week data for subsequent cycles	Dominant	Dominant
Baseline distribution of patients	100% in no transfusion Hb <10.5	Distribution pre run-in	Dominant	Dominant
% of patients discontinuing pegcetacoplan	[redacted] at week 16	Assume all patients who initially discontinue remain discontinued (3 out of 41, 7.32%)	Dominant	Dominant

Abbreviations: Hb, Haemoglobin; ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year

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Full results with revised base-case

In the base case analysis, pegcetacoplan results in [redacted] incremental QALYs compared to ravulizumab, and ravulizumab results in [redacted] incremental QALYs compared to eculizumab. In addition, pegcetacoplan is associated with [redacted] incremental costs over a lifetime horizon compared with ravulizumab, and ravulizumab is associated with [redacted] incremental costs over a lifetime horizon compared with eculizumab. Pegcetacoplan dominates both eculizumab and ravulizumab.

Table 1 Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Eculizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2,989,356	2,989,356
Pegcetacoplan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Sensitivity analyses

Probabilistic sensitivity analysis

The mean values for total costs, LYs, QALYs, and incremental cost per QALY gained for pegcetacoplan versus eculizumab and ravulizumab for the population of interest generated through 1,000 simulations of the probabilistic sensitivity analysis (PSA) are presented in Table 2. The output shows that on average, pegcetacoplan results in [redacted] incremental QALYs compared to ravulizumab, and ravulizumab results in [redacted] incremental QALYs compared to eculizumab. In addition, pegcetacoplan is associated with [redacted] incremental costs over a life-time horizon compared with ravulizumab, and ravulizumab is associated with [redacted] incremental costs over a lifetime horizon compared with eculizumab. Pegcetacoplan dominates both eculizumab and ravulizumab.

The incremental cost-effectiveness plane (ICEP) (Figure 1) shows that 100% of results are in the southeast quadrant for both pegcetacoplan versus eculizumab and pegcetacoplan versus ravulizumab, meaning that pegcetacoplan continues to dominate eculizumab and ravulizumab in each simulation. In addition, the cost-effectiveness acceptability curve (CEAC) (Figure 2) shows that pegcetacoplan is 100% cost-effective at all willingness to pay thresholds.

Table 2: Mean PSA results

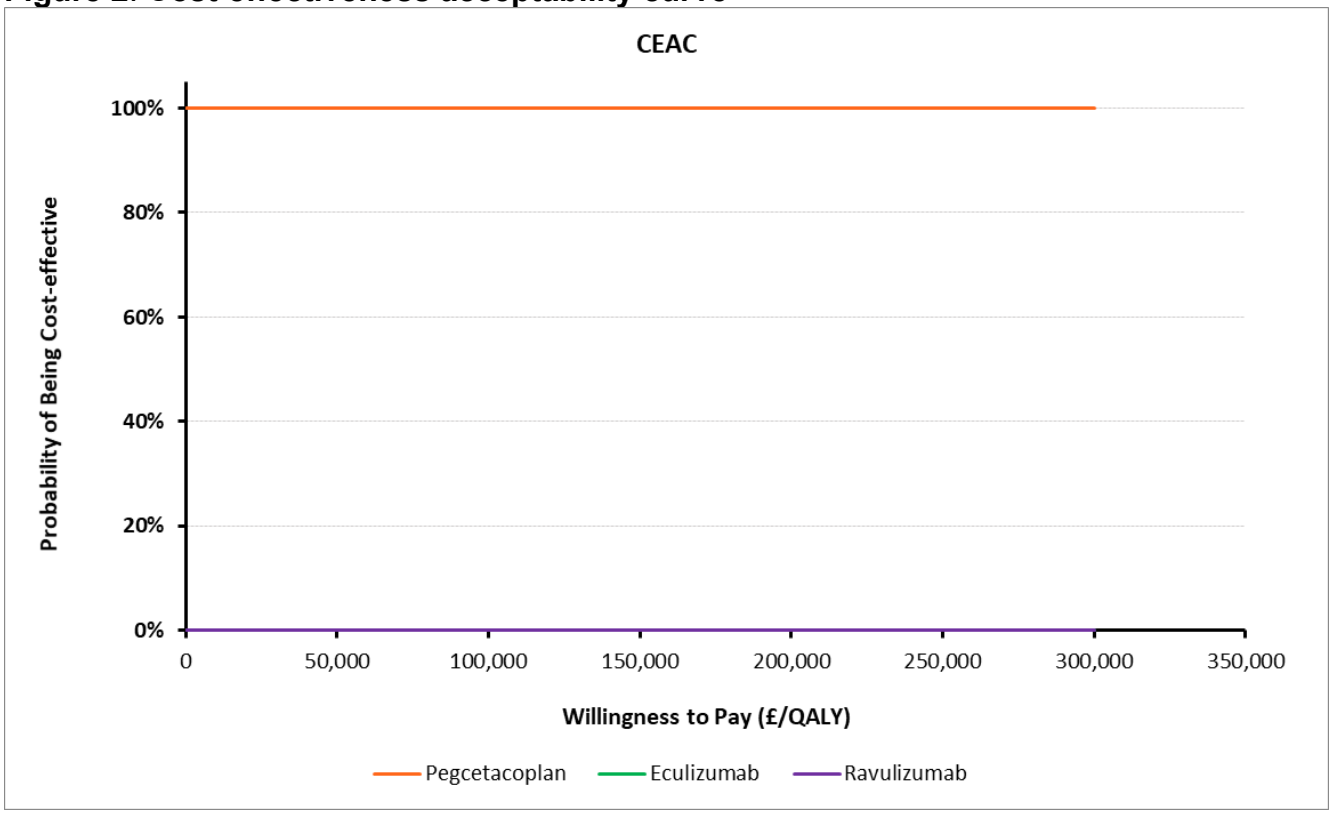
Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Eculizumab	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]	2,918,229	2,918,229
Pegcetacoplan	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Figure 1: **Incremental cost-effectiveness plane**

Abbreviations: QALY, quality-adjusted life year

Figure 2: **Cost-effectiveness acceptability curve**



Abbreviations: CEAC, cost-effectiveness acceptability curve; QALY, quality-adjusted life year

Deterministic sensitivity analysis

A OWSA tornado diagram presenting the top 10 most sensitive parameters for pegcetacoplan versus ravulizumab is presented in Figure 3. Table 3 presents the one-way sensitivity analysis (OWSA) results for these 10 parameters. The model was most sensitive to the mean weight of patients, utility values for no transfusion and Hb ≥10.5mg/dl health state and the cost of blood transfusion.

A OWSA tornado diagram presenting the top 10 most sensitive parameters for pegcetacoplan versus eculizumab is presented in Figure 3. Table 4 presents the OSWA results for these 10 parameters. The model was most sensitive to utility values for no transfusion and Hb ≥10.5mg/dl, the cost of blood transfusion and the mean units of blood per transfusion.

Figure 3 Tornado diagram for OWSA for pegcetacoplan versus ravulizumab

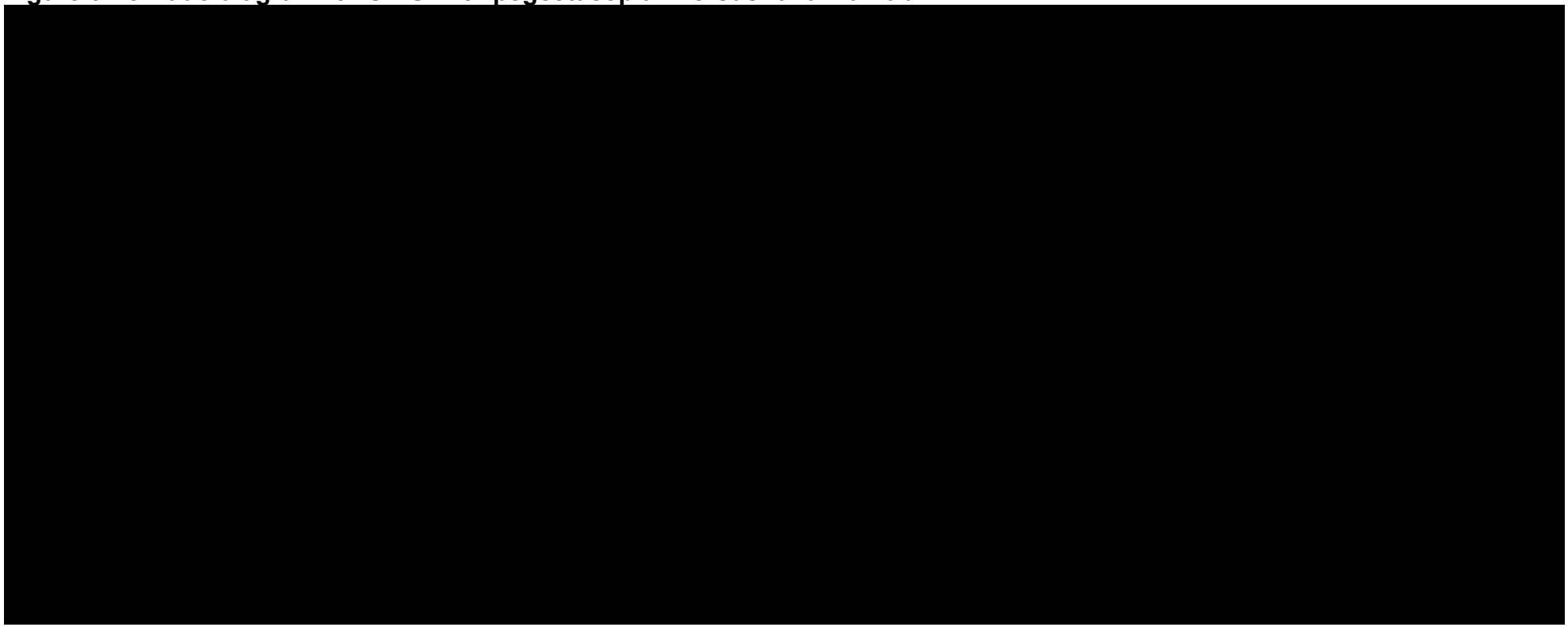


Figure 4 Tornado diagram for OWSA for pegcetacoplan versus eculizumab

Table 3: **OWSA results for the 10 parameters that contribute the largest difference to the NMB for pegcetacoplan versus ravulizumab**

Parameter	Base case NMB	Lower bound NMB	Upper bound NMB	Max Difference NMB
Mean weight (kg)	[redacted]	[redacted]	[redacted]	[redacted]
Utility: No transfusion and Hb≥10.5		[redacted]	[redacted]	[redacted]
Pack cost deferasirox		[redacted]	[redacted]	[redacted]
% on deferasirox		[redacted]	[redacted]	[redacted]
Cost of blood transfusion		[redacted]	[redacted]	[redacted]
Mean units of blood per transfusion		[redacted]	[redacted]	[redacted]
Female percentage		[redacted]	[redacted]	[redacted]
Utility: Transfusion Required		[redacted]	[redacted]	[redacted]
Utility: No transfusion and Hb<10.5		[redacted]	[redacted]	[redacted]
Cycle rate of patients receiving one-off dose of eculizumab		[redacted]	[redacted]	[redacted]

Abbreviations: NMB, net monetary benefit; OWSA, one-way sensitivity analysis

Table 4 OWSA results for the 10 parameters that contribute the largest difference to the NMB for pegcetacoplan versus eculizumab

Parameter	Base case NMB	Lower bound NMB	Upper bound NMB	Max Difference NMB
Utility: No transfusion and Hb≥10.5	[redacted]	[redacted]	[redacted]	[redacted]
Pack cost deferasirox		[redacted]	[redacted]	[redacted]
% on deferasirox		[redacted]	[redacted]	[redacted]
Cost of blood transfusion		[redacted]	[redacted]	[redacted]
Mean units of blood per transfusion		[redacted]	[redacted]	[redacted]
Mean weight (kg)		[redacted]	[redacted]	[redacted]
Utility: Transfusion Required		[redacted]	[redacted]	[redacted]
Female percentage		[redacted]	[redacted]	[redacted]
Utility: No transfusion and Hb<10.5		[redacted]	[redacted]	[redacted]
Cycle rate of patients receiving one-off dose of eculizumab		[redacted]	[redacted]	[redacted]

Abbreviations: NMB, net monetary benefit; OWSA, one-way sensitivity analysis

Scenario analysis

Table 5 details scenario analyses results for pegcetacoplan versus eculizumab and pegcetacoplan versus ravulizumab. Pegcetacoplan dominates eculizumab and ravulizumab in all scenarios.

Table 5: Scenario analysis results

Parameter	Base case	Scenario analysis	ICER (£/QALY) pegcetacoplan vs eculizumab	ICER (£/QALY) pegcetacoplan vs ravulizumab
Time horizon	Lifetime	10 years	Dominant	Dominant
		20 years	Dominant	Dominant
Discount rate (costs and QALYS)	3.5%	0%	Dominant	Dominant
		6%	Dominant	Dominant
Utility decrement of eculizumab vs. ravulizumab and pegcetacoplan	0.025	0.000	Dominant	Dominant
		0.057	Dominant	Dominant
Utility: general population age adjustment	Applied	Not applied	Dominant	Dominant
Iron overload disutility	-0.03	0.00	Dominant	Dominant
Transition probabilities	4-48 week data for all cycles	0-4 weeks per first cycle; 4-16 week data for subsequent cycles	Dominant	Dominant
Baseline distribution of patients	100% in no transfusion Hb <10.5	Distribution pre run-in	Dominant	Dominant
% of patients discontinuing pegcetacoplan	[redacted] at week 16	Assume all patients who initially discontinue remain discontinued (3 out of 41, 7.32%)	Dominant	Dominant

Abbreviations: Hb, Haemoglobin; ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year

NICE National Institute for Health and Care Excellence

Patient organisation submission

Pegcetacoplan for treating paroxysmal nocturnal haemoglobinuria [ID3746]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	
2. Name of organisation	PNH Support

3. Job title or position	
4a. Brief description of the organisation (including who funds it). How many members does it have?	PNH Support (www.pnhuk.org) is a Charitable Incorporated Organisation registered with the Charities Commission of England and Wales (no.1161518). The trustees operate within PNH Support's constitution dated 30 April 2015 amended on 16 May 2021. The Constitution is an 'Association' model and has 130 voting members other than its trustees. Membership is open to patients (and their families/carers) living with Paroxysmal Nocturnal Haemoglobinuria ("PNH") living in England, Wales and Northern Ireland. The objects of PNH Support (as set out in its Constitution) are as follows: 1) To promote, protect and preserve the physical and mental health of those diagnosed with PNH who reside in England, Wales and Northern Ireland (either permanently or temporarily) through the provision of support, education, advocacy and practical advice; 2) To advance the education of patients with PNH who reside in England, Wales and Northern Ireland, in particular but not exclusively, by the provision of advice and a point of contact for newly diagnosed PNH patients, in England, Wales and Northern Ireland. We moderate a closed Facebook group, send email updates to members, produce a 6 monthly newsletter, hold regional patient and family meetings (hosted on Zoom since the start of the pandemic), and hold a biennial patient and family conference. PNH Support is funded by donations together with honoraria and consultancy fees for the provision of advice relating to lived experience of PNH and has received grants from pharmaceutical companies.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.]If so, please state the name of manufacturer, amount, and purpose of funding.	Yes Apellis - £299.27 a project grant for a Zoom Pro licence for patient meetings during the pandemic Apellis - £927.50 - to assist with the development of a PNH burden of disease study
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients	We undertook an online survey (of primarily multi-choice questions) of 92 PNH patients and carers which was disseminated via: email and post to PNH Support members; closed Facebook groups of PNH Support and the Aplastic Anaemia Trust; email by the PNH National

and carers to include in your submission?	Service (Kings College Hospital, London) to patients for which they held email addresses; and email by the PNH National Service (St James's Hospital, Leeds) to patients treated with pegcetacoplan to invite them to take part in the survey. 76 patients and 16 carers provided completed survey responses. 91 responses were received from England: (75 patients) and (16 carers) and one patient from Northern Ireland responded. **Treatment:** Of the 76 patients who responded, 4 are being treated with pegcetacoplan and the rest are being treated with various other treatments or no treatment at all (see **Figure 1** in the Appendix). Of the 16 carers who responded, one is a carer of a patient being treated with pegcetacoplan and the rest care for patients being treated with various other treatments or no treatment at all (see **Figure 2** in the Appendix). **Gender:** Of the 76 patients surveyed, 63% (n=48) identified as female and 37% (n=28) identified as male. **Ethnicity:** The ethnicities of the 76 patients surveyed are set out in the Appendix at **Figure 3.** **Age:** the average age of patients who answered the survey was 54 years.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	**Patients** • There were 76 responses by **patients to what life is like with PNH** (where they could choose more than one answer - see **Figure 4** in the Appendix). • The majority (47) said that their PNH is managed well and (33) said living with PNH has a minimal impact on their life. • Equal number of responses (28) identified that: they needed to restrict daily activities because of PNH (with exercise and household chores needing to be restricted the most - see **Figure 5** in the Appendix); and that their veins are damaged from repeated cannulation from infusions. • Patients (25) said there is a lack of understanding of PNH and (23) had a fear of getting infections (which makes the condition worse) • Equal numbers of patients (22) said: PNH has a negative impact on their mental health (with feeling anxious and fearful of their PNH progressing being the most common - see **Figure 6** in the Appendix); and that PNH has a negative impact on family and social life (by limiting their social life, them not being able to contribute fully to family life, spend quality time with family or able to plan ahead being the main reasons - see **Figure 7** in the Appendix). • Equal numbers of patients (20) said they consider themselves to have a normal quality of life and that their PNH symptoms are unpredictable.

- Patients (15) said having 2 weekly infusions has a negative impact on their life (with the stress of accessing veins, the negative impact on veins of repeated cannulation and restricting full time work being the most common reasons - see **Figure 8** in the Appendix).
- When patients were asked whether their **employment status was affected by having PNH** (see **Figure 9** in the Appendix), the majority (29) said that it wasn't affected with 19 saying that they either worked part time or were unemployed because of PNH. In addition, 9 patients had changed the type of work they do because of PNH *"Yes, I don't have as senior a position anymore. Due to PNH I don't have the energy for all the responsibility anymore", "Yes, I can't work long hours as waitress or doing physical hard work* " 8 had retired early because of PNH and 3 were medically retired *"I was medically retired because of Aplastic Anaemia which then turned into PNH as well."*

Carers

- When carers were asked about their **experience when caring for someone with PNH** *(*where they could choose more than one answer - see **Figure 10** in the Appendix), the majority (10) said it had a negative impact on their family and social life (with not being able to plan ahead, limiting quality family time, the patient not being able to contribute fully to family life and limiting their social life being the main reasons). "*We plan family life around treatments*". Please see **Figure 11** in the Appendix.
- Equal numbers of carers' (6) said their loved one did not require care and that their own mental health was negatively impacted (by feeling anxious and fearful of the patient's PNH progressing - see **Figure 12** in the Appendix).
- 5 carers said they felt a burden to know a lot about PNH because many medical professionals knew little about it.
- Equal numbers of carers (4) said they didn't experience any impact on their life because of caring for someone with PNH and that PNH had a negative impact on their ability to work or study (with 2 having to work part time and 2 having to stop working because of PNH - see **Figure 13** in the Appendix).
- Of the 16 carers who said they carried out activities for a PNH patient (where they could choose more than one answer), the main activities chosen were attending medical appointments with the patient and providing moral/emotional support (see **Figure 14** in the Appendix).
- The average number of hours per week that carers carried out caregiving activities for a PNH patient was 11 hours with one carer saying it varied depending on how the patient was feeling.

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	**Current Treatments – Patients** • When patients were asked what they thought of the **current PNH treatments available on the NHS** (where they could choose more than one answer **- s**ee **Figure 15** in the Appendix), the majority (48) said they would like there to be more treatment options with different delivery methods e.g. injections, tablets etc. • Many (37) were satisfied with the currently available treatments, 34 said receiving treatment at home or work was an advantage and 32 said the opportunity to take part in clinical trials was an advantage. • Equal numbers (27) said eculizumab had positively impacted their quality of life and they would like there to be more treatment options which provide them with better quality of life (less symptoms etc). • 19 patients said ravulizumab had positively impacted their quality of life and 18 said the 2 weekly infusions of eculizumab are a burden. **Current Treatments – Carers** • When carers were asked what they thought of the **current PNH treatments available on the NHS** (where they could choose more than one answer - see **Figure 16** in the Appendix), the majority (11) said that the homecare service is a real advantage and that they would like there to be more treatment options with different delivery methods. • 10 carers said that eculizumab had positively impacted the PNH patient's quality of life. • Equal numbers of carers (9) said the 2 weekly infusions of eculizumab are a burden and they would like there to be more treatment options which provide the PNH patient with a better quality of life (e.g. improved symptom control). • 8 carers said that the **opportunities to take part in clinical trials is an advantage**. **Current Care - Patients** Care provided by the PNH National Service and care provided by the NHS (outside the PNH National Service) was asked about separately. • When patients were asked **what they thought of the current care available for PNH from the PNH National Service** (and the main reason for their answer,) 71% were very satisfied. Please see **Figure 17** in the Appendix. Reasons provided for this related to the PNH National Service centres at Leeds and Kings College Hospitals being readily available for advice or to answer questions. They offer support, opportunities for treatment, trials and specialisation is an asset. "*Leeds are only a phone call away and I get advice more or less straight away*", "*I feel very fortunate to be looked after by world leaders in this field*"

	• When patients were asked **what they thought of the current care available from the NHS for PNH outside the PNH National Service e.g. GPs, local haematologists (not part of the PNH National Service), other healthcare professionals** (and the main reason for their answer) 33% were very satisfied. Please see **Figure 18** in the Appendix. Reasons provided for this related to GPs and local haematologists being aware of, and responsive to, their PNH and liaising with the PNH National Service for advice. "*My Haematologist is very aware of PNH and referred me to Leeds when it was diagnosed he also includes LDH in my routine blood tests and liaises with Leeds on the outcome".* Those patients who chose "Neutral" (24%) provided reasons relating to there being little or no knowledge of PNH and therefore support and advice about PNH being limited. "*Due to PNH symptoms we don't always have the energy to insist on what we need and often the PNH National Service then has help us to convince the local professionals of what we need."* **Current Care - Carers** • When carers were asked what they thought of the **current care available for PNH from the PNH National Service** (and the main reason for their answer) 75% were very satisfied. Please see **Figure 19** in the Appendix. Reasons provided for this related to the responsiveness to queries and the knowledge of doctors and excellent support. One referred to the homecare service being "*amazing*". There was acknowledgement of access to new treatments. "*they really care about the patients*" • When carers were asked what they thought of the **current care available from the NHS for PNH outside the PNH National Service e.g. GPs, local haematologists (not part of the PNH National Service), other healthcare professionals** (and the main reason for their answer) 44% were very satisfied. Please see **Figure 20** in the Appendix. Reasons provided for this related to the sharing of correspondence between the PNH National Service and local healthcare providers and local healthcare providers being supportive, available and responsive. Those who were dissatisfied (31%) provided reasons relating to the lack of knowledge of PNH including by A&E staff. Two commented on the lack of joined up care including GPs not reading notes to see the diagnosis of PNH. *"There is not enough joined-up care for patients with multi-morbidities, the specialists don't get involved with care that does not cover their specialities leaving carers to be the 'middle man'"*
8. Is there an unmet need for patients with this condition?	• When **unmet need** was defined as "something that is not addressed by current NHS care or available treatments", 55% (n=42) said they did not have any **unmet needs**, 24% (n=18) said they didn't know, 16% (n=12) said they did have unmet needs, 4% (n=3) chose "Other" and listed their unmet need: "*Blood in urine*", "*Difficult to get general care from GP*", and "*Digestion issues and permanent low-level general inflammation*" (see **Figure 21** in the Appendix). • Of the 16% of patients who said they had an **unmet need** (where they could choose more than one answer - see **Figure 22** in the Appendix), the majority (11) chose PNH symptoms with fatigue, shortness of breath and cognitive problems being the main symptoms chosen (please see **Figure 23** in the Appendix). • Of the patients that said they had fatigue (11), the average rating of fatigue was 6 (with 1 being not fatigued at all and 10 being severely fatigued).

	• Of those reporting cognitive problems, 7 patients chose that they had all of: memory problems (long or short term); brain fog; problems concentrating; difficulty focusing on tasks; and word finding difficulties. • 8 patients said the need to address the psychological impact of PNH was an unmet need. • 7 patients said the negative side effects from treatment was an unmet need • 6 said the need for more treatment choices "*Treatment that is not restrictive to traveling*" was an unmet need
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	When the 4 patients treated with pegcetacoplan were asked what they thought the **advantages of the treatment were** (where they could choose more than one answer - see **Figure 24** in the Appendix): • all patients (4) said it had improved their PNH symptoms (including fatigue), had a positive impact on their family and social life and had a positive impact on their mental health • 3 patients all said it had: a **positive impact on their ability to work or undertake education** (with one being able to work full time, one being able to work part time and one saying it improved their quality of life - see **Figure 25** in the Appendix); they have the ability to travel with the medication; they have the ability to be flexible about the timing of their treatment; and that the reduced healthcare professional oversight is an advantage to them. • 2 patients said they preferred the delivery method of this treatment (i.e. sub-cutaneous injection (under the skin)) compared to their previous treatment method One patient commented "*I was lucky to be involved in the first phase of trials for eculizumab which was life changing for me and enabled me to live a full life and have four healthy children. However I continued to experience a degree of haemolysis which left me feeling constantly tired and I also required intermittent transfusions which tended to follow infections or periods of illness. I feel very lucky to have had the opportunity to participate on the trial for pegcetacoplan as this has had a huge impact on my life. I have not needed any blood transfusions since commencing the trial and my haemoglobin has been completely normal which has allowed me to live a normal life!*" Of all 4 patients who chose that their **PNH symptoms had improved** following treatment with pegcetacoplan (where they could choose more than one answer- see **Figure 26** in the Appendix): • All 4 patients said that their fatigue had improved • 3 patients all said that: shortness of breath; yellow pigmenting in eyes due to jaundice; dark urine (haemoglobinuria); and anaemia requiring red blood cell transfusions had all improved • 2 patients said regular headaches and breakthrough haemolysis (return of dark urine/return of my symptoms/anaemia) had improved • 1 patient said each of: abdominal pain, leg pain and difficulty with swallowing (dysphagia) had improved

	Of the 4 patients who said that being treated with pegcetacoplan has had a **positive impact on their social and family life,** (where they could choose more than one answer - see **Figure 27** in the Appendix): • 3 patients all said they can enjoy more quality time with my family • 2 patients said that they can contribute more fully to family life and are able to plan ahead • 1 patient said each of: they have a fuller social life and that their important relationships with people had been positively impacted Of the 4 patients who said being treated with pegcetacoplan has had a **positive impact on their mental health**, (where they could choose more than one answer - see **Figure 28** in the Appendix): • All 4 patients said that their mood had improved • 2 patients said they felt hopeful, more independent and less fearful (e.g. of their PNH progressing, getting infections). • 1 patient said each of: they felt less anxious and that their confidence had increased The one **carer** who responded to this question said all of the following were **advantages to them** of the treatment (see **Figure 29** in the Appendix): the improved PNH symptom control compared to the previous treatment , the way the treatment is delivered ie. Sub-cutaneous injection (under the skin), the logistics involved in the patient obtaining/administering the drug, the positive impact on their mental health (i.e. they feel hopeful and less fearful (e.g. of the PNH progressing, the patient getting infections), the positive impact on their family and social life (i.e. ability to plan ahead) and the ability for them to travel with the medication. • The carer commented: "*With Pegcetacoplan (APL2) the patient has not required a blood transfusion in over a year and even with an infection, the patient is able to recover quickly without any severe impact on the Hb level.* "
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	When the 4 patients treated with pegcetacoplan were asked what that thought the **disadvantages of the treatment** were (where they could choose more than one answer- see **Figure 30** in the Appendix), • 2 patients said the frequency of the pegcetacoplan injections and the lumps (or similar) under their skin at the injections sites is a disadvantage for them • 1 patient said each of: they experience less symptom control compared to before they were treated with pegcetacoplan; they are concerned about long term side effects; the reduced healthcare professional oversight is a disadvantage to them; and there are no disadvantages One patient commented *"I was lucky to be involved in the first phase of trials for eculizumab which was life changing for me and enabled me to live a full life and have four healthy children. However I continued to experience a degree of haemolysis which left me feeling*

	constantly tired and I also required intermittent transfusions which tended to follow infections or periods of illness. I feel very lucky to have had the opportunity to participate on the trial for pegcetacoplan as this has had a huge impact on my life. I have not needed any blood transfusions since commencing the trial and my haemoglobin has been completely normal which has allowed me to live a normal life!" **Carers -** The one carer said the disadvantage to them was: "I am concerned about unknown long term side effects of the treatment".
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	From the available data, patients who experience extravascular haemolysis and anaemia requiring blood transfusions whilst being treated with a C5 inhibitor will benefit in particular from this therapy.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	We are not aware of any equality issues.

Other issues	
13. Are there any other issues that you would like the committee to consider?	28% (21/76) of surveyed patients said they were either unemployed or worked part time because of PNH. It is therefore important that 50% (n=2/4) of surveyed patients treated with pegcetacoplan said they can now work part time or full time as a result of this treatment. As a result of this therapy improving patients' symptoms (in particular fatigue and anaemia requiring blood transfusions) and because of its sub-cutaneous administration, patients are enabled to work or work more hours (without interruptions from intravenous infusions and blood transfusions). This means that the patient can contribute more fully to society and can rely less on the State and their family leading to a positive impact on the mental health and quality of life of them and their families. The EQ 5D-5L asks patients about their ability to undertake "my usual activities (e.g. work, study, housework, family or leisure activities)". The way this question is worded won't necessarily capture patients who have not been working (as work would not be considered a usual activity for them) and have been able to start work or increase their hours as a result of treatment. This therapy presents a cost saving to the: • public purse for patients who are now able to work, or work more • NHS by reducing the need to manage, care for and treat patients whose anaemia has improved as a result of this therapy and no longer need blood transfusions. This is especially relevant in the current COVID 19 climate where patients have been shielding and therefore attending hospital for blood transfusions exposes them to an element of risk.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- Although the burden of PNH has been mitigated significantly in many patients by intravenous treatment with C5 inhibitors, some patients still remain affected by extravascular haemolysis and anaemia requiring blood transfusions. These patients have the potential to benefit significantly from pegcetacoplan in order for them (and their families) to experience an improved quality of life.
- Surveyed patients treated with pegcetacoplan identified its main advantages to be the improvement of PNH symptoms (especially fatigue and the need for blood transfusions as a result of anaemia), and the positive impact it has had on their: family and social life; mental health; and ability to work.
- Two surveyed patients (50% n=2/4) treated with pegcetacoplan are now able to work part time or full time as a result of this treatment. Employment means patients can contribute more fully to society and can rely less on the State and their families leading to increased independence and improvement of consequential factors including mental health and quality of life for both patients and their families.

- The improvement of anaemia (which requires blood transfusions) as a result of this therapy together with its self-administration means less oversight, care and treatment is required by the NHS.

- Surveyed PNH patients said they would like there to be more treatment options which provide them with better quality of life (less symptoms etc) and that PNH symptoms were their primary unmet need. Both PNH patients and their carers said they would like there to be more treatment options for PNH with different delivery methods (than the existing infusion methods).

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Appendix to PNH Support patient organisation submission re pegcetacoplan for treating PNH [ID 3746]

The question numbers and headings referred to below correspond to the NICE "Patient organisation submission" template document.

5. How did you gather information about the experiences of patients and carers to include in your submission?

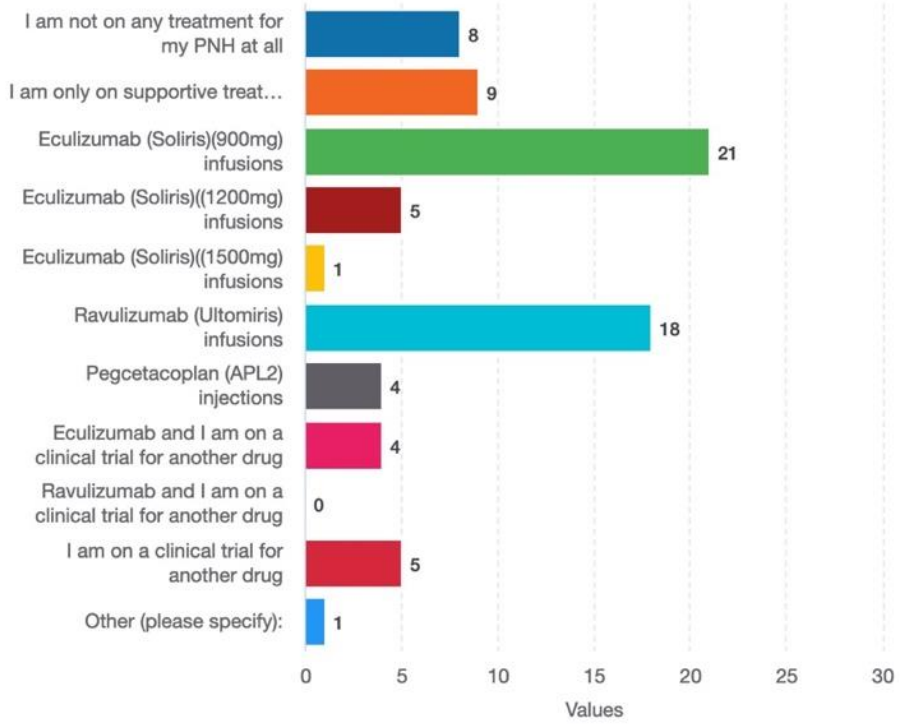

Figure 1: Patients' treatment who completed survey

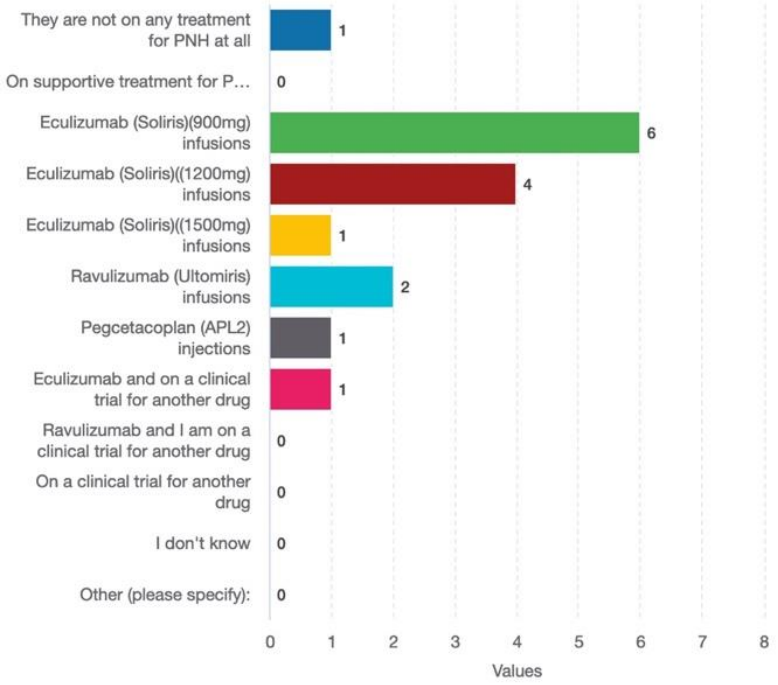

Figure 2: Carers' who completed survey (and what patient is treated with)

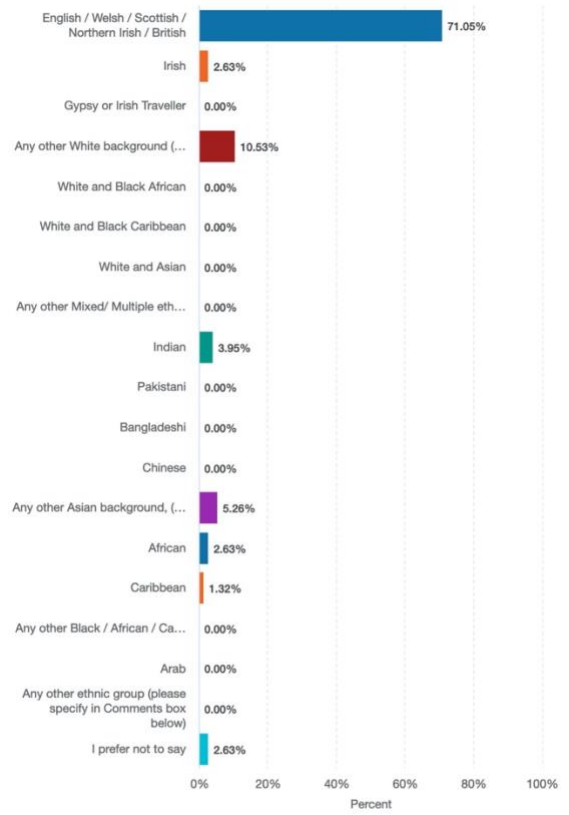

Figure 3: Ethnicities of the patients surveyed

6. What is it like to live with the condition?

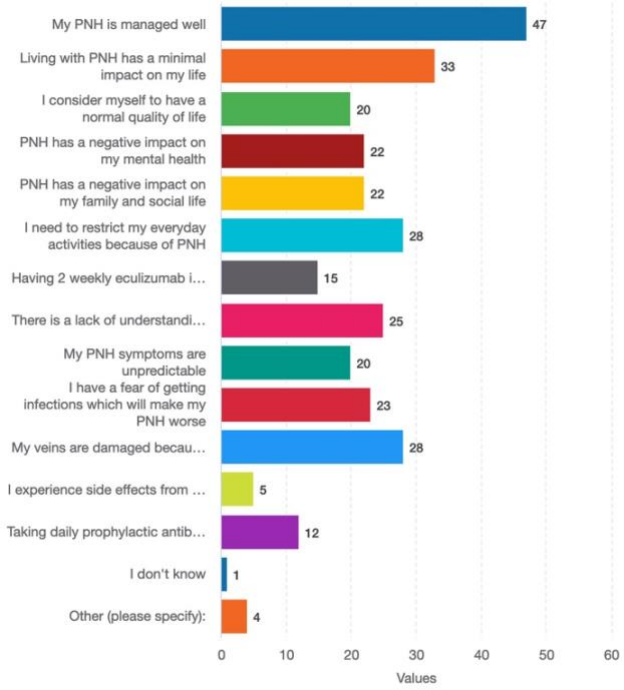

Figure 4: What is it like for a patient to live with PNH?

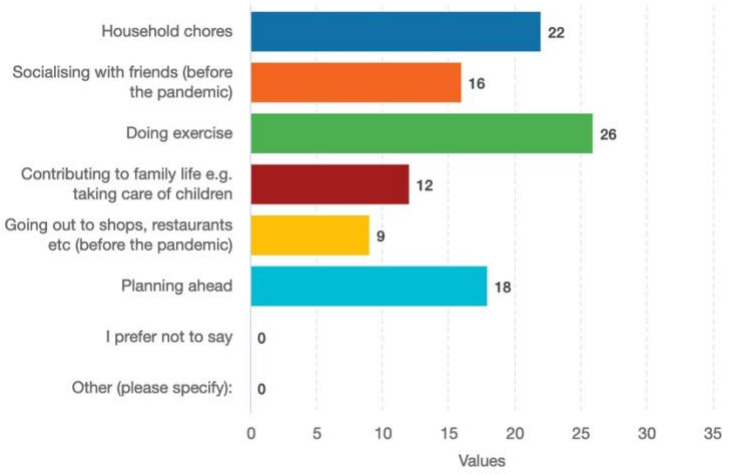

Figure 5: Restricted daily activities of patients

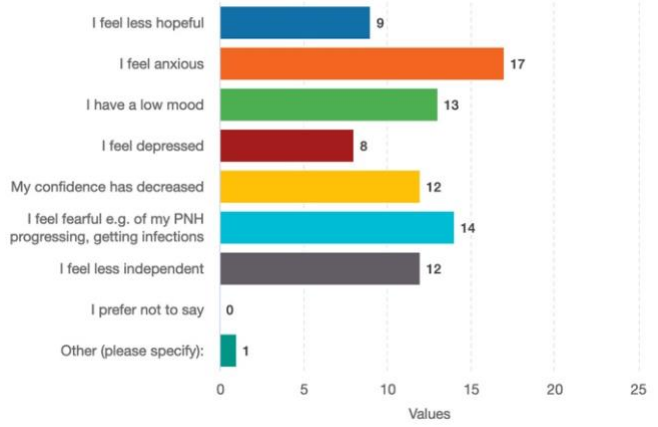

Figure 6: Negative impact on mental health of patients

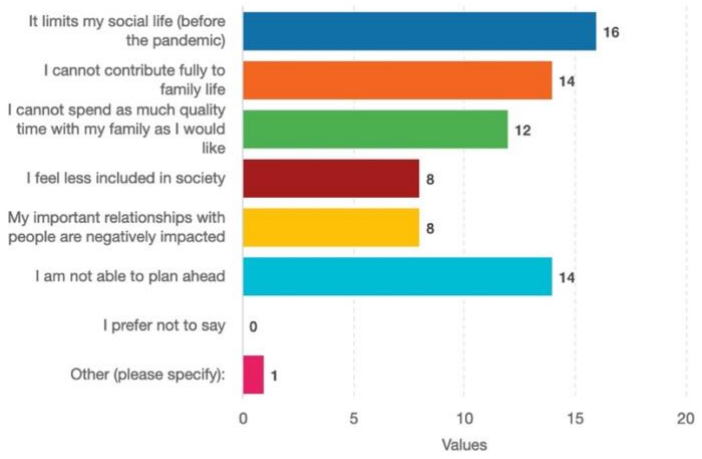

Figure 7: Negative impact on family and social life of patients

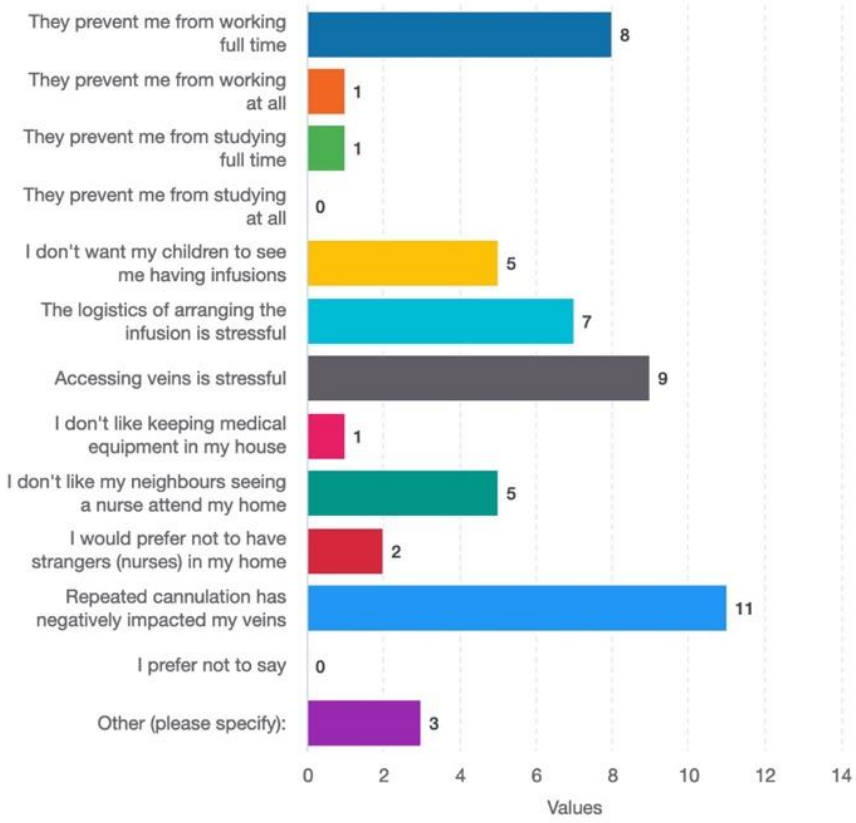

Figure 8: Negative impact of 2 weekly infusions on patients

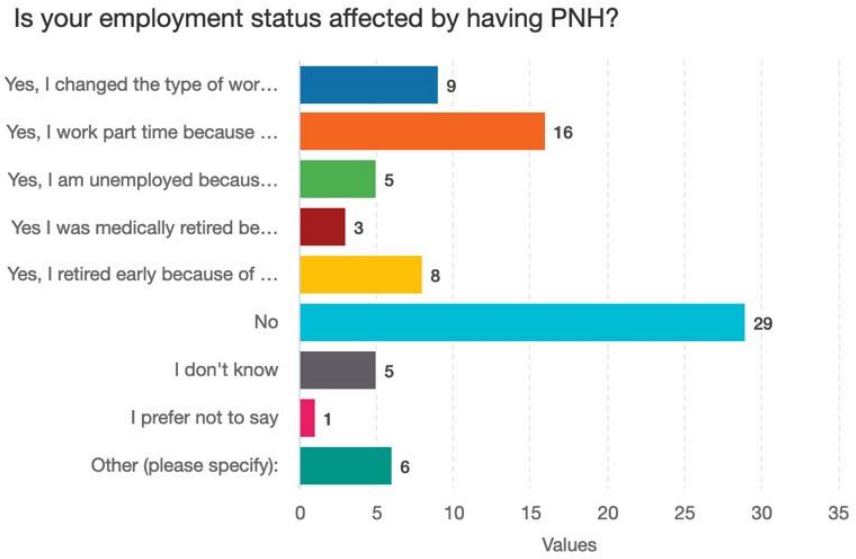

Figure 9: Impact of PNH on patients' employment status

6. What do carers experience when caring for someone with the condition?

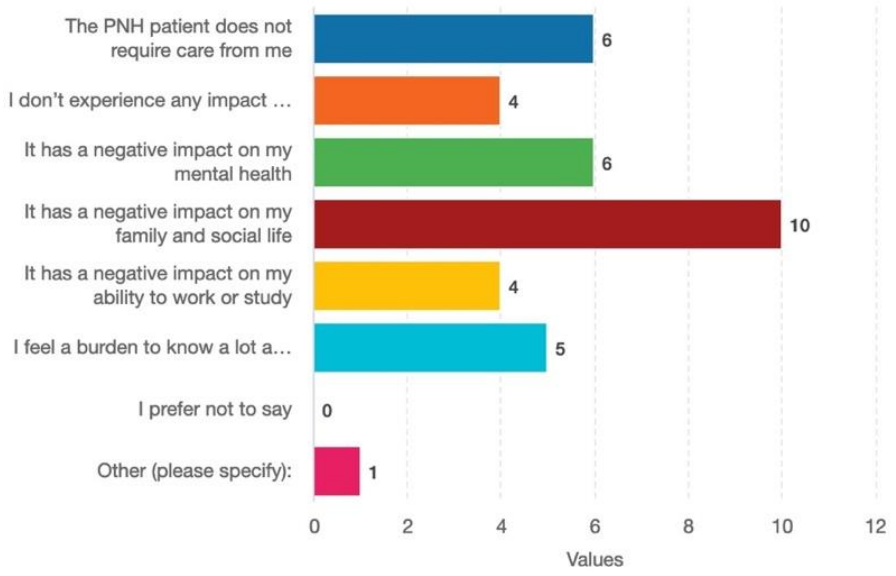

Figure 10: What do carers experience when caring for someone with the PNH?

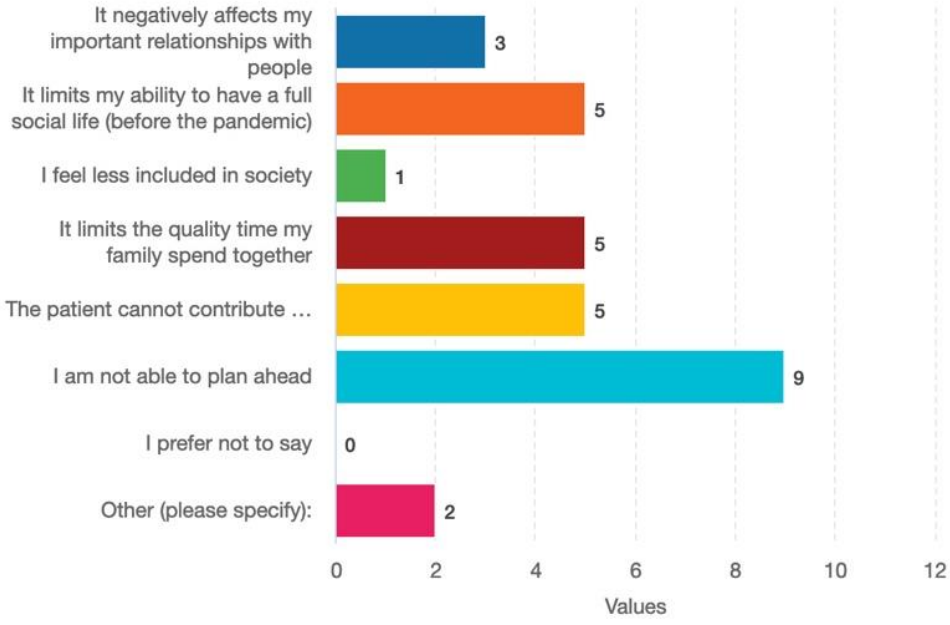

Figure 11: Negative impact on family and social life of carers

Figure 12: Negative impact on mental health of carers

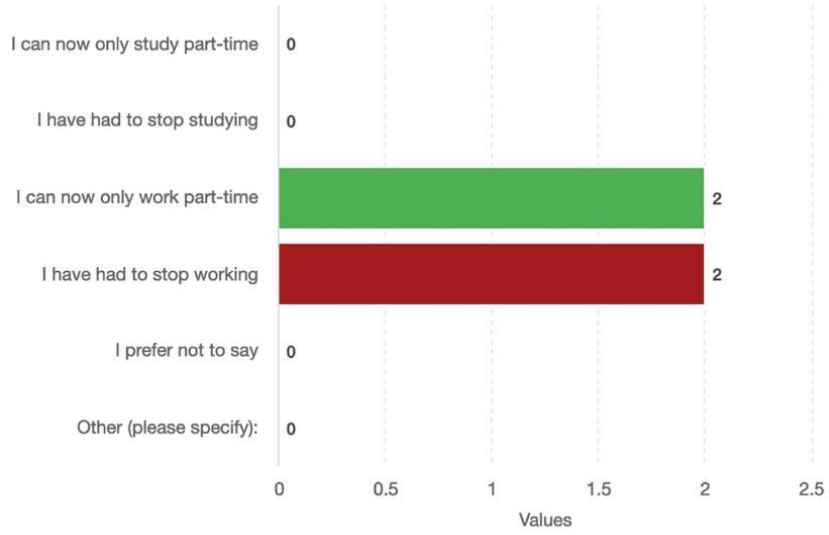

Figure 13: Negative impact on carers' ability to work or study

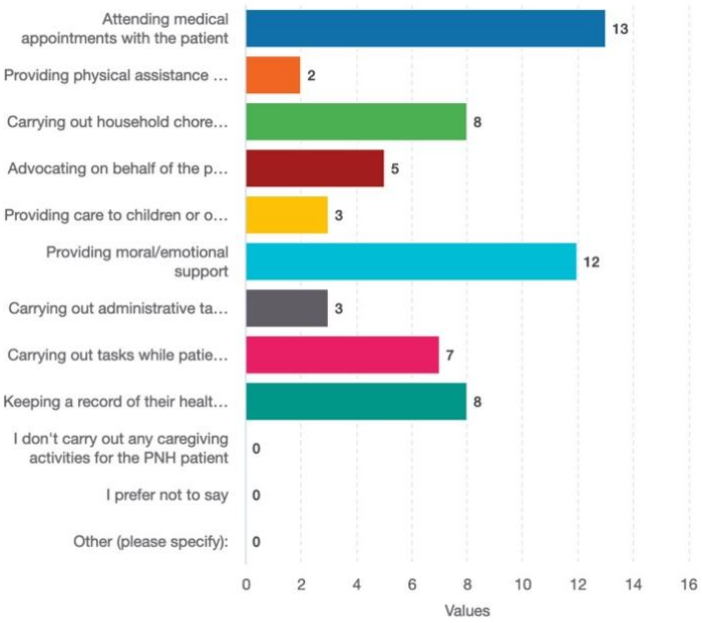

Figure 14: Activities carried out by carers for patients

7. What do patients or carers think of current treatments and care available on the NHS?

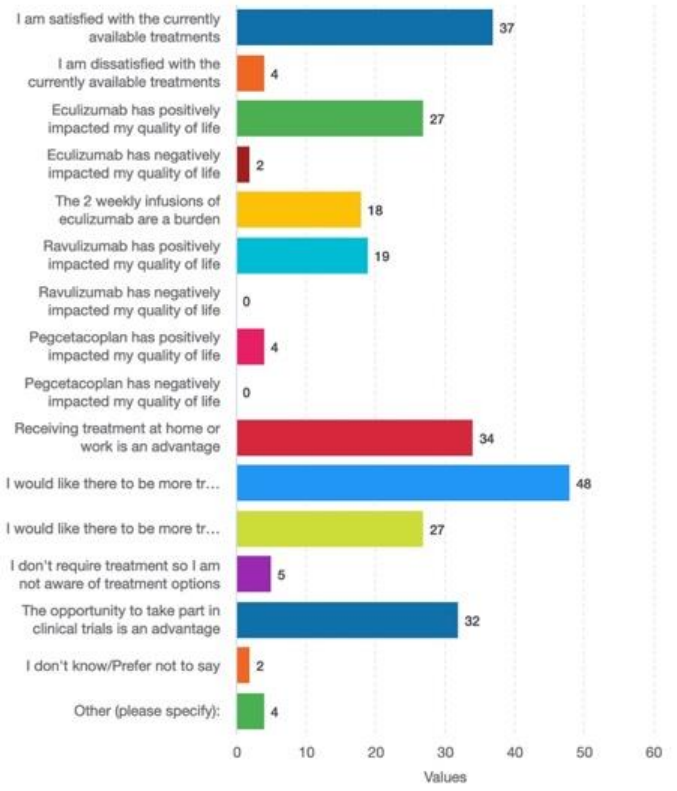

Figure 15: What do patients think of current treatments available on the NHS?

Figure 16: What do carers think of current treatments available on the NHS?

7. What do patients think of current care available on the NHS?

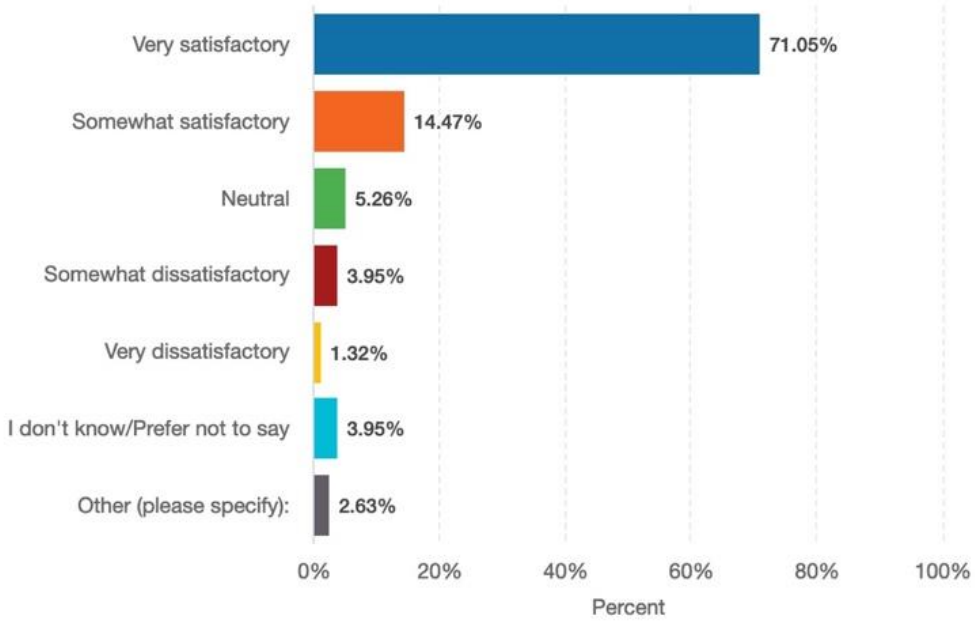

Figure 17: What do patients think of current care available from the PNH National Service?

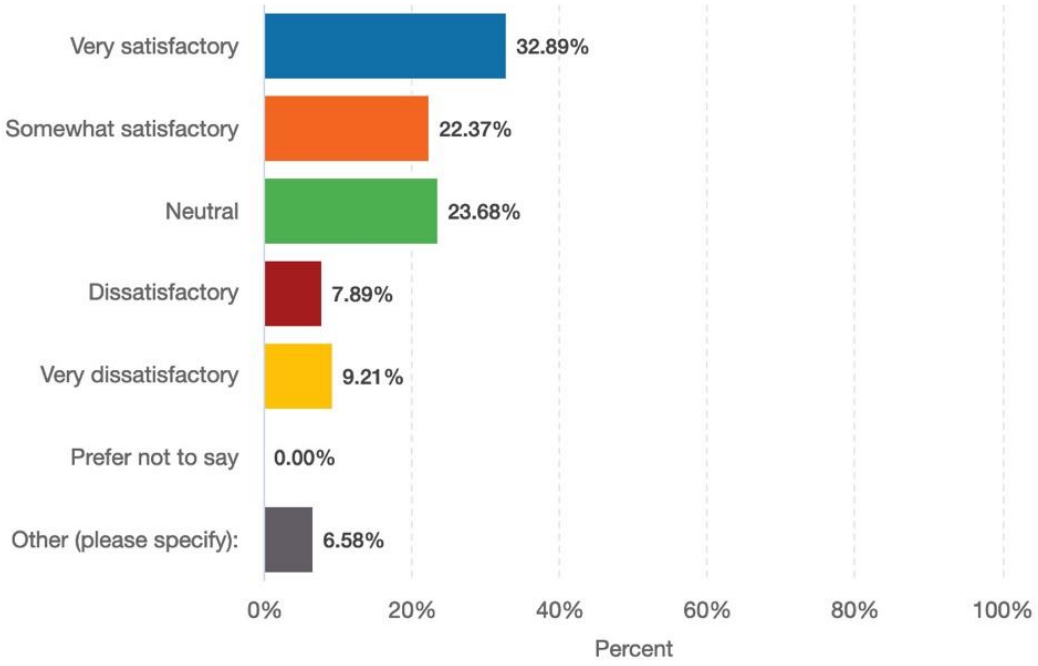

Figure 18: What do patients think of the current care available other than from than PNH National Service?

7. **What do carers think of current care available on the NHS?**

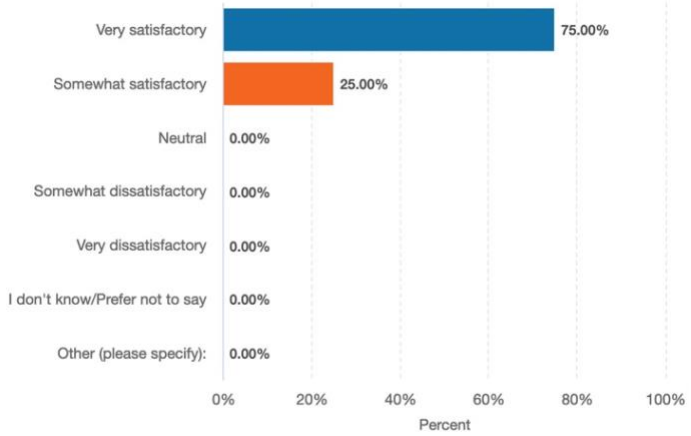

Figure 19: What do carers think of current care available from the PNH National Service?

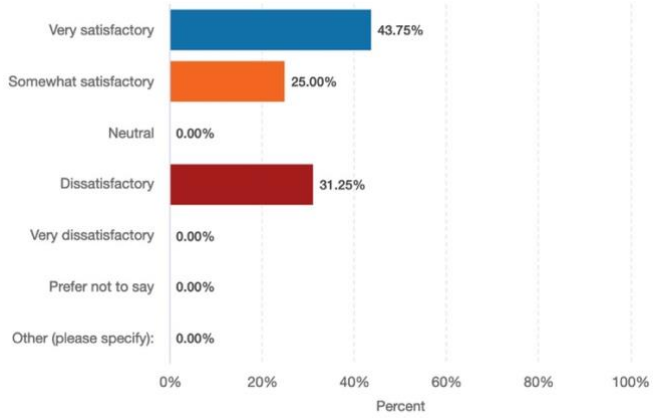

Figure 20: What do carers think of current care available other than from than PNH National Service?

8. Is there an unmet need for patients with this condition?

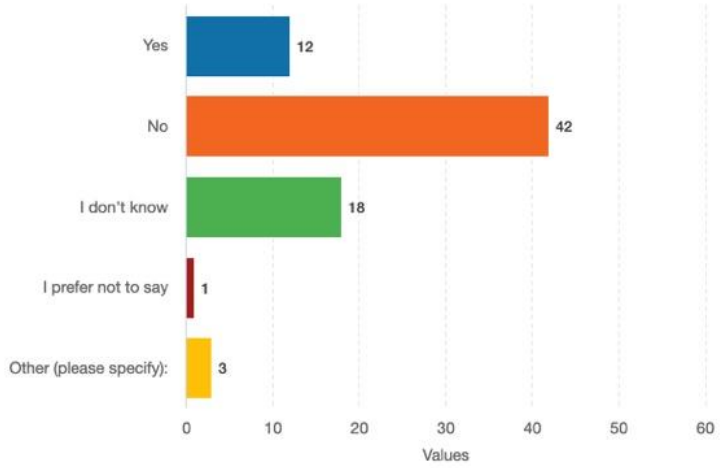

Figure 21: Is there an unmet need for patients with PNH?

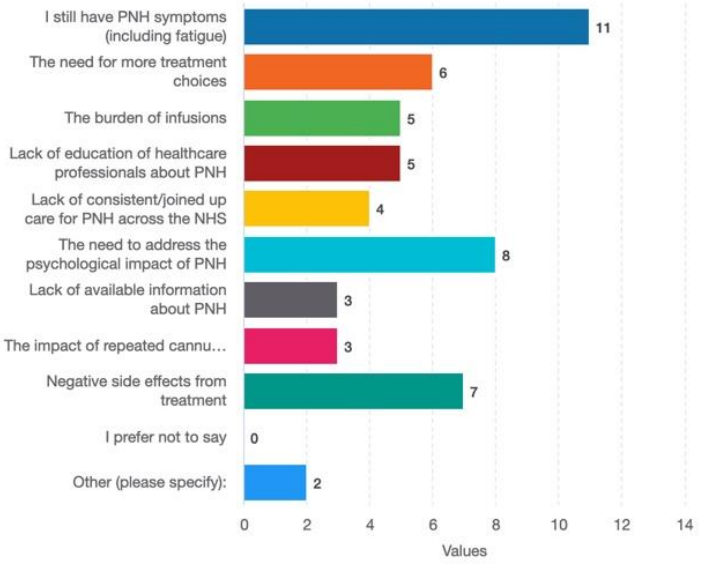

Figure 22: what do patients consider their unmet need to be?

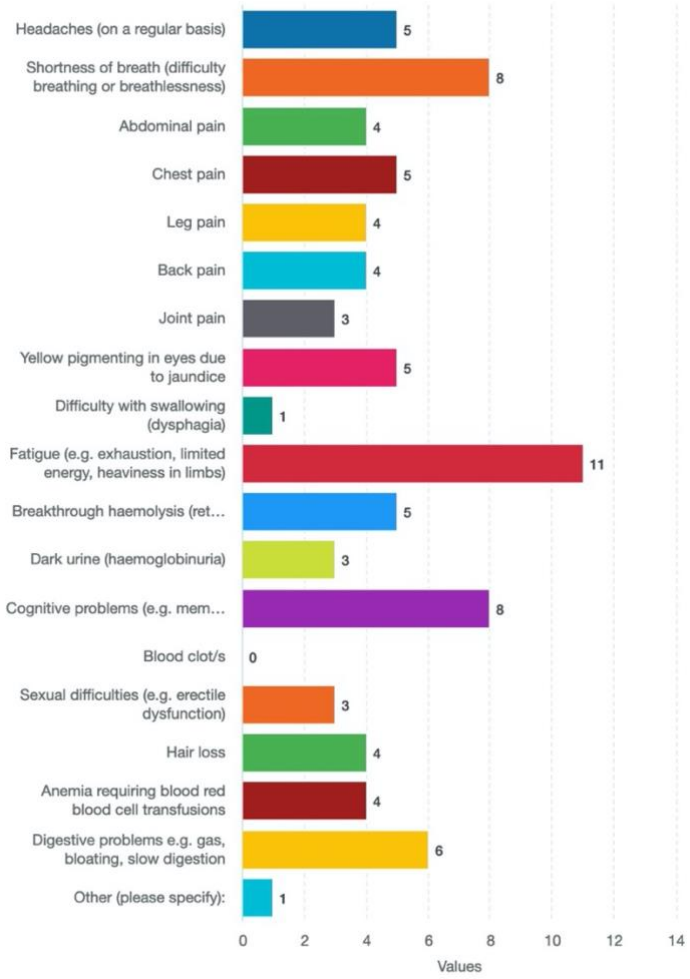

Figure 23: PNH symptoms identified as unmet need

9. What do patients or carers think are the advantages of the technology?

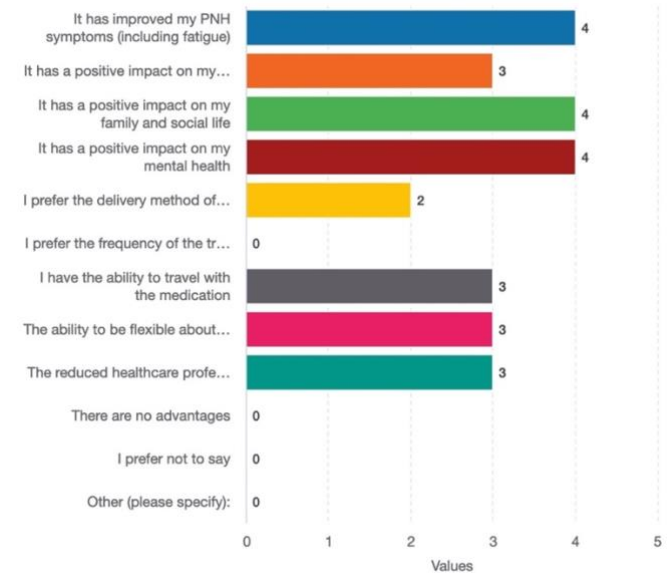

Figure 24: What do patients' think the advantages are of pegcetacoplan?

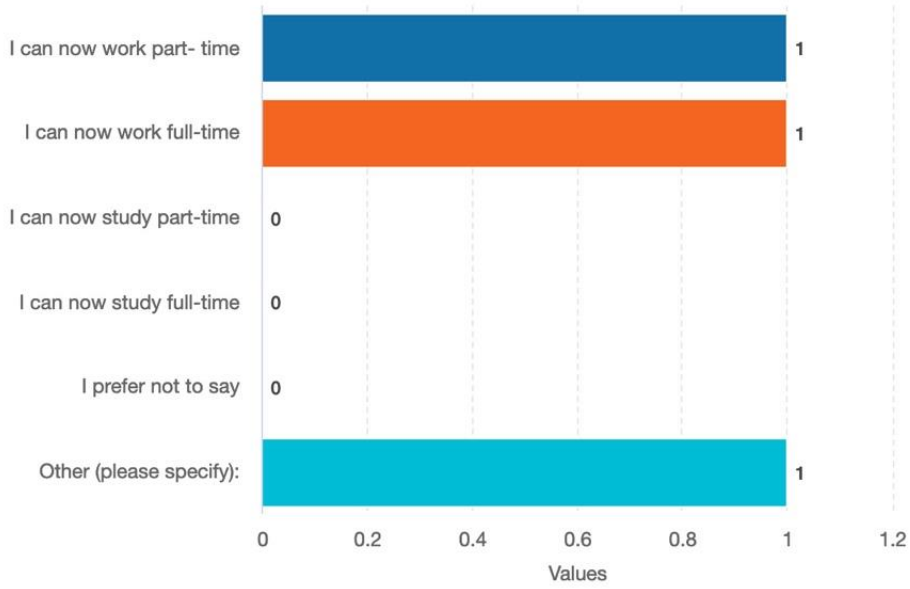

Figure 25: Positive impact of pegcetacoplan on patients' ability to work or undertake education

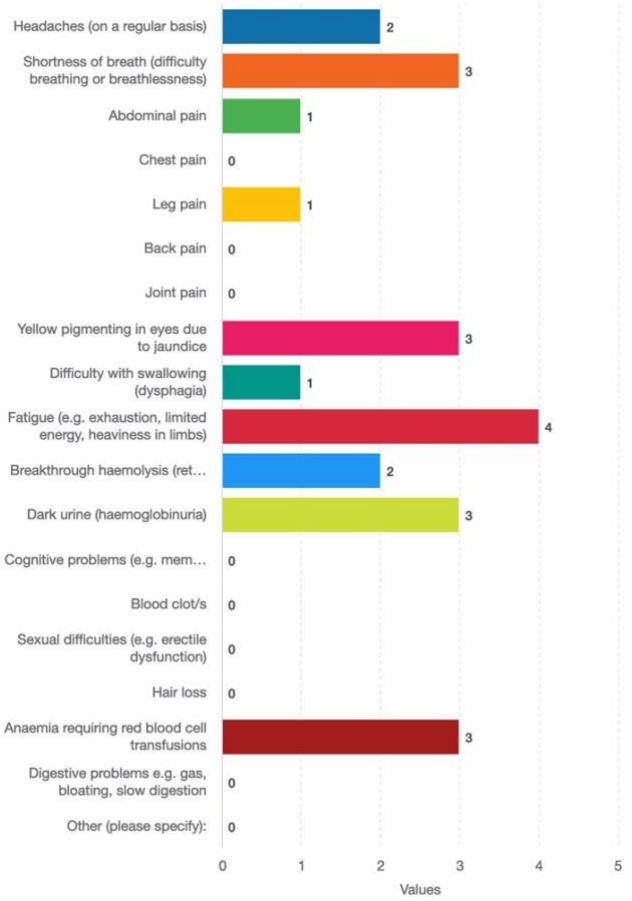

Figure 26: Positive impact of pegcetacoplan on patients' PNH symptoms

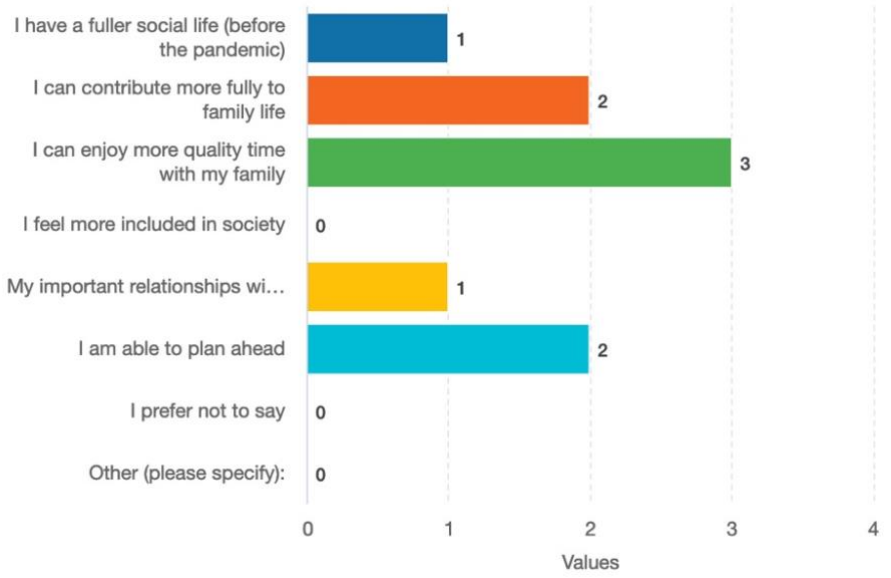

Figure 27: Positive impact of pegcetacoplan on patients' social and family life

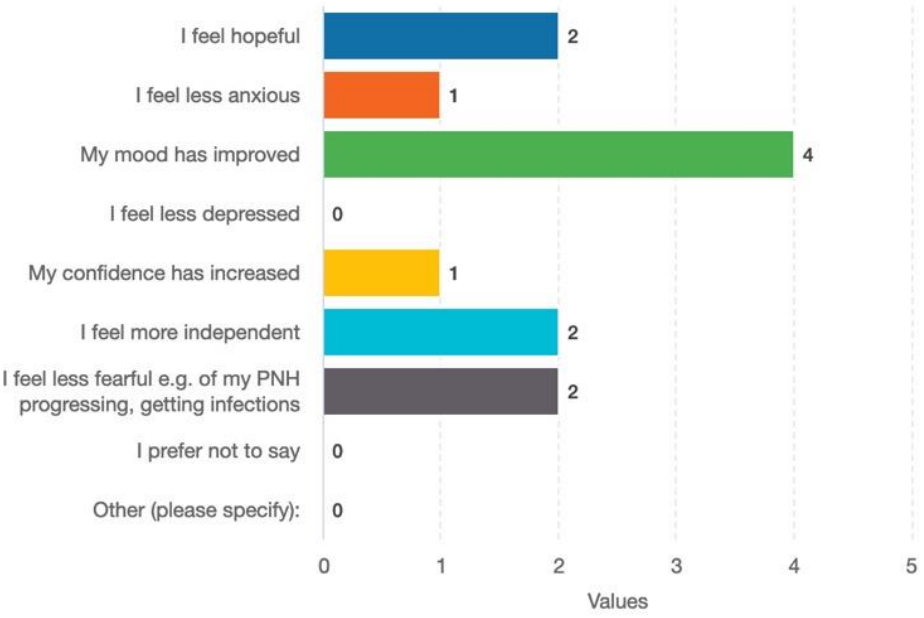

Figure 28: Positive impact of pegcetacoplan on patients' mental health

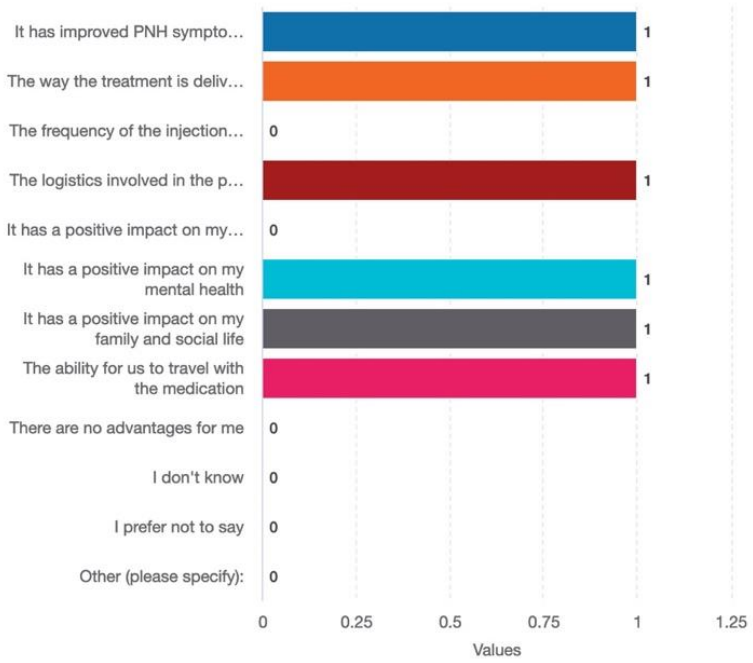

Figure 29: What do carers think the advantages are of pegcetacoplan?

10. What do patients or carers think are the disadvantages of the technology?

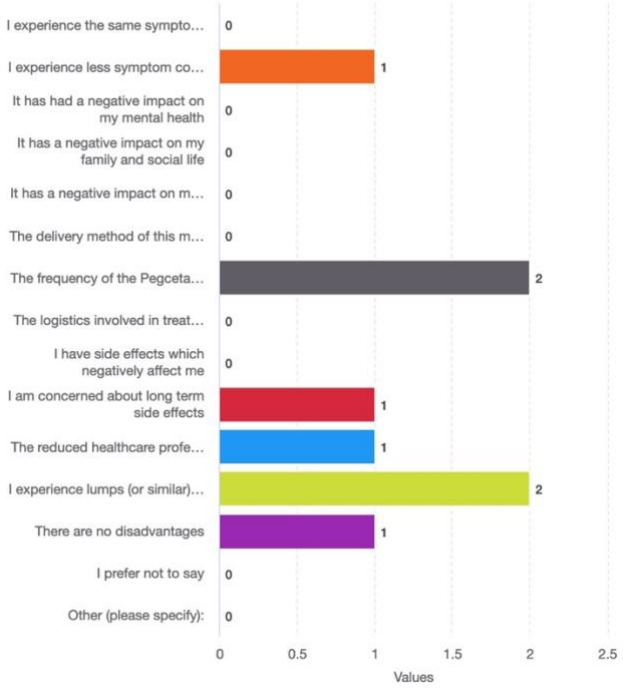

Figure 30: What do patients' think the disadvantages are of pegcetacoplan?

NICE National Institute for Health and Care Excellence

NHS organisation submission (CCG and NHS England)

Pegcetacoplan for treating paroxysmal nocturnal haemoglobinuria [ID3746]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	NHS ENGLAND

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☐ commissioning services for a CCG or NHS England in general? ☐ **x** commissioning services for a CCG or NHS England for the condition for which NICE is considering this technology? ☐ responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)? ☐ an expert in treating the condition for which NICE is considering this technology? ☐ an expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	NHS England leads the National Health Service (NHS) in England. We set the priorities and direction of the NHS and encourage and inform the national debate to improve health and care. NHS England shares out more than £100 billion in funds and holds organisations to account for spending this money effectively for patients and efficiently for the tax payer.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
Current treatment of the condition in the NHS	

6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are no NHSE clinical commissioning policies for paroxysmal nocturnal haemoglobinuria
7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care is well defined and there are no differences of opinion between professionals. There is a highly specialised service commissioned from two centres based in London and Leeds.
8. What impact would the technology have on the current pathway of care?	If the technology were approved it would be delivered through the existing pathway of care.
The use of the technology	
9. To what extent and in which population(s) is the technology being used in your local health economy?	This treatment is not currently commissioned by NHS England. Any patients accessing the drug will be doing so through clinical trials.

10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	If the technology were approved it would provide a therapeutic option for patients who have had a sub-optimal response to eculizumab and/or ravilizumab
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The use of the drug would be managed through the two centres in the highly specialised service and could eventually be delivered via homecare
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No additional investment required
• If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this	Not applicable

include any additional testing?	
11. What is the outcome of any evaluations or audits of the use of the technology?	To date, there have not been any evaluations or audits of the technology.
Equality	
12a. Are there any potential equality issues that should be taken into account when considering this treatment?	There are no specific equality issues or issues related to protected characteristics.
12b. Consider whether these issues are different from issues with current care and why.	Not applicable

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Pegcetacoplan for treating paroxysmal nocturnal haemoglobinuria [ID3746]

Thank you for agreeing to provide your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **Monday 11 October 2021.**

Completing this form

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send

a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with this condition and current treatment options	
About you	
1. Your name	**Dr Richard Kelly**
2. Name of organisation	**Leeds Teaching Hospitals NHS Trust**
3. Job title or position	**Haematology Consultant and Joint Lead for the English National PNH Service**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

nominating organisation's submission)	
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Not applicable.**
The aim of treatment for this condition	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Chronic intravascular haemolysis in Paroxysmal Nocturnal Haemoglobinuria (PNH) is due to uncontrolled activation of the complement pathway. This causes patients to experience extreme fatigue, thrombosis, renal impairment, difficulty swallowing (dysphagia), abdominal pain, erectile dysfunction, black urine (haemoglobinuria) and chest pain. As well as this increased morbidity, untreated patients have an increased mortality mainly due to thrombotic events. The aim of treatment for patients with PNH is to inhibit the complement pathway to stop intravascular haemolysis of PNH blood cells and thereby stop the symptoms caused by intravascular haemolysis.
9. What do you consider a clinically significant treatment	The same efficacy and a similar safety profile to current therapies, i.e. prevention of intravascular haemolysis and its consequences. Also, I expect improvement in haemoglobin levels, with reduced need for transfusions and an improvement in the degree of fatigue experienced as evidenced from the Pegasus trial (NEJM 2021;384:1028–37)

response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	using Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scores.
10. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes; currently approved therapies (eculizumab and ravulizumab) block complement at complement protein C5. Blocking at C5 stops intravascular haemolysis but ~70% patients on C5 inhibitors remain anaemic. This is largely due to extravascular haemolysis. Extravascular haemolysis occurs as a consequence of blocking at C5, with Complement protein C3 fragments marking the PNH red cells for destruction in the spleen. Pegcetacoplan instead inhibits the complement pathway at C3 stopping intravascular haemolysis whilst not causing extravascular haemolysis. The mode of administration is also important as pegcetacoplan is a subcutaneous therapy and the current treatments for PNH are intravenous requiring administration by a nurse.
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	Treatment for PNH is overseen by two centres of excellence, St. James's Hospital in Leeds and Kings College Hospital in London. Patients are managed in partnership between the PNH centres and the local haematology teams. Responsibility for treatment with anti-complement therapy is with the PNH centres. This includes treatment decisions, prescribing, administration and management of disease complications.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	No up-to-date published guidelines exist, but are in the process of development by the International PNH Interest Group (IPIG). There is agreed guidance between the PNH centres and NHS England as to who is eligible for anti-complement therapy. There are only seven clinicians who oversee PNH in England and they all work in the PNH centres.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals	Yes. The pathway is well defined and there are monthly multidisciplinary meetings between the two English PNH centres.

across the NHS? (Please state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	It would allow patients with evidence of extravascular haemolysis currently treated with C5 inhibitors to be treated with pegcetacoplan with likely improvements in their haemoglobin levels and their general functioning. It will also allow more choice for patients in terms of the route of administration of this treatment especially in those with poor venous access.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes, it will still need to be overseen by the PNH centres (decision on treatment, prescriptions, management of side effects etc).
• How does healthcare resource use differ between the technology and current care?	Pegcetacoplan is given subcutaneously two to three times per week and patients are taught how to administer it themselves, whereas eculizumab and ravulizumab require a nurse to administer treatment intravenously. Eculizumab is administered every two weeks after an initial loading period and ravulizumab every eight weeks. These therapies are given by a team of homecare nurses.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	It should be used only by specialists in PNH in the two English National PNH Centres.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No new investment is required to introduce this technology into practice.

13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. As outlined above it will be especially beneficial to those with evidence of extravascular haemolysis.
• Do you expect the technology to increase length of life more than current care?	No. Current care with anti-complement inhibitors prevent intravascular haemolysis and have been shown to improve life expectancy to nearly the same level as those without the illness (Blood. 2011;117:6786–92).
• Do you expect the technology to increase health-related quality of life more than current care?	Yes, the Pegasus trial (NEJM 2021;384:1028–37) evaluated the safety and efficacy of pegcetacoplan compared to eculizumab. Adult patients with PNH who had a haemoglobin level of <10.5 g/dL whilst receiving stable doses of eculizumab for at least three months were eligible for the study. The primary endpoint was achieved, with a mean increase in haemoglobin in the pegcetacoplan arm of 2.37 g/dL compared with a reduction in the eculizumab arm of 1.47 g/dL at 16 weeks. Significantly more patients were transfusion independent in the pegcetacoplan arm (35/41, 85%) when compared with the eculizumab arm (6/39, 15%) over the 16-week period. A clinically significant improvement in FACIT-F scores at week 16 was also observed in those receiving pegcetacoplan, with a 9.2 point increase compared with a 2.7 point decrease in those receiving eculizumab.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Pegcetacoplan should be available for use in patients with PNH who currently fulfil the criteria for anti-complement therapy in England. It will be of especial benefit in those with extravascular haemolysis on C5 inhibitors.
The use of the technology	

15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	In some ways pegcetacoplan will be easier for patients as it is a self-administered subcutaneous treatment rather than an intravenous one that has to be given by a nurse. However, it does need to be administered more frequently than current available options. Inhibiting complement causes a small but significant increase risk of meningococcal infection. All patients on complement inhibitors must receive vaccination against the meningococcal strains A, B,C,W and Y. As well as this, all patients receive prophylactic antibiotics to prevent this infection. As pegcetacoplan blocks complement earlier in the pathway than current therapies, it is recommended that vaccination against haemophilus influenza B and pneumococcus should also be administered.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The same rules as with current anti-complement therapy would be used in terms of starting pegcetacoplan, with two exceptions; it should be used in patients with evidence of extravascular haemolysis who are established on anti-C5 therapy, and it should not be used in pregnancy. Currently only eculizumab is recommended in pregnancy (NEJM 2015;373:1032–9). No additional testing is required.
17. Do you consider that the use of the technology will result in any substantial health-related benefits	No.

that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	It is innovative and will make a significant and positive impact on patients. Pegcetacoplan has been shown to block intravascular haemolysis without causing an increase in extravascular haemolysis. This will lead to fewer blood transfusions and increased functioning/wellbeing of patients.
• Is the technology a 'step-change' in the management of the condition?	Yes, it is a significant innovation in the treatment options available for patients.
• Does the use of the technology address any particular unmet need of the patient population?	Yes. It means anaemia due to extravascular haemolysis will not be an ongoing issue for patients and it allows for a different mode of administration.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	It is required to be administered subcutaneously two to three times per week. As with all complement inhibitors it increases the risk of meningococcal infection and patients need to contact their PNH centre (24 hour contact available) if they become unwell. Intravascular haemolysis whilst on anti-complement therapy (breakthrough haemolysis) can occur if a patient develops an infection/stressor. A strategy for managing this on pegcetacoplan is needed, whether this is the

	administration of an additional pegcetacoplan dose or a one-off dose of an anti-C5 inhibitor.
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	Yes. The Pegasus trial included patients from our centre.
• If not, how could the results be extrapolated to the UK setting?	N/A.
• What, in your view, are the most important outcomes, and were they measured in the trials?	The inhibition of terminal complement formation with prevention of the subsequent consequences of intravascular haemolysis. A similar side effect profile to current anti-C5 inhibitors. Improvements in haemoglobin levels and FACIT-F scores when compared with eculizumab in patients established on eculizumab but with a haemoglobin level of < 10.5g/dl. These outcomes were measured in the clinical trials.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A.

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
22. How do data on real-world experience compare with the trial data?	I have experience of treating patients with pegcetacoplan, in patients who were in the Pegasus study and in a selection of patients outwith trials with marked extravascular haemolysis on anti-C5 treatment. My experience mirrors that of the clinical trial data.
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	None perceived.
23b. Consider whether these issues are different from issues with current care and why.	N/A.

PART 2 - Key messages
24. In up to 5 sentences, please summarise the key messages of your statement: • Pegcetacoplan is a novel therapy for PNH that blocks intravascular haemolysis and the symptoms of the disease. • Pegcetacoplan has a similar efficacy and safety profile to current available anti-complement therapies. • It improves haemoglobin levels in patients with a haemoglobin of <10.5g/dl on anti-C5 therapy as it does not cause an increase in extravascular haemolysis. • In patients with a haemoglobin of <10.5g/dl on eculizumab therapy, pegcetacoplan has been shown to improve fatigue levels (using FACIT-F scoring). • Pegcetacoplan is self-administered as a subcutaneous therapy rather than needing to be given as an intravenous infusion.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

……

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NICE National Institute for Health and Care Excellence

Patient expert statement

Pegcetacoplan for treating paroxysmal nocturnal haemoglobinuria [ID3746]

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

About this Form
In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.
In **part 2** we are asking you to provide 5 summary sentences on the main points contained in this document.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please return this form by **5pm** on **Monday 11 October 2021.**

Completing this form
Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide.
You do not have to answer every question – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee. The text boxes will expand as you type.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 15 pages.

PART 1 – Living with or caring for a patient with this condition and current treatment options	
About you	
1.Your name	**Louise Katherine Pottinger**
2. Are you (please tick all that apply):	☒ a patient with this condition? ☒ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with this condition? ☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation.	PNH Support
4. Has your nominating organisation provided a submission? Please tick all options that apply.	☐ No, (please review all the questions below and provide answers where possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement

	☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience. ☐ I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience:
Living with the condition	
6. What is your experience of living with this condition? If you are a carer (for someone with this condition) please share your experience of caring for them.	I was diagnosed with PNH in 1997 at the age of sixteen. From that point I was transfusion dependent and required four units of blood every six to eight weeks in order to survive. The weeks between each transfusion were a repeating pattern of ups and downs. After a transfusion I felt great. I could see the colour instantly return to my face and my eyes looked bright and alive instead of yellow and dull. I loved to play sport and at school I was involved in many extra-curricular activities, but over the course of the six to eight weekly cycle, I noticed my urine getting gradually darker and I became increasing tired and anaemic. I found it really difficult to concentrate on school work and to retain information and I was frustrated by feeling too tired to participate in all of the activities that I wanted to. I suffered from stomach pain as well as pain in my legs and lower back and as the weeks passed towards each transfusion, I became breathless and physically exhausted. I was lucky enough to be referred to the PNH service in Leeds and in July 2002 I was one of the first patients to be involved in the clinical trial for Eculizumab. This treatment was completely life changing for me at that time. My need for blood transfusions massively decreased and instead of the constant pattern of peaks and troughs I felt much more stable. As time went on, I received Eculizumab at home once every two weeks. I successfully completed a degree, qualified as a Social

	Worker and most importantly for me, I went on to have four healthy children which I had never imagined possible. I have always tried to maintain a positive outlook in relation to my PNH. I didn't want to be defined by my condition and I have always tried to live as full and 'normal' a life as possible. However, Whilst Eculizumab did make a huge difference to my quality of life, I continued to experience extravascular haemolysis which meant that I maintained a haemoglobin of around 9-10 and continued to require transfusions from time to time, particularly after an infection or period of illness. Although I appreciated the reduction in blood transfusions and the more stable blood count that Eculizumab afforded me, I continued to feel tired, and to feel that day to day activities were a real effort at times. In April 2019 I started taking Pegcetacoplan and this drug has really been life changing for me. I think the best way of describing the change is to say that I now feel closest to my true self, or the closest I have felt to being myself without PNH. I have not had a single blood transfusion since starting treatment on Pegcetacoplan, (almost two and a half years). My haemoglobin has been between 12 and 14 and I have energy. My skin has colour and my eyes are clear, I look and feel well. When I first started taking Pegcetacoplan I was struck by a real sense of clarity in my head. It felt like a fog had lifted and everything felt clearer, sharper and brighter. Although I have had colds and felt unwell at times like anyone else, I have had no breakthrough haemolysis and I have not required any blood transfusions which is amazing to me! Due to the many years of frequent blood transfusions, I have iron overload. I was prescribed different medications to try and reduce my iron levels. However, these medicines made me feel unwell and I disliked taking them. Now, because my haemoglobin levels are so positive, I am having monthly venesections to reduce my iron levels. Even now I find this incredible and believe it is a really strong indicator of how far I've come.

	I have recently started working again for the first time in fourteen years. My new post is as a Healthcare Assistant in a busy Outpatients department. I believe that Pegcetacoplan has made this opportunity possible for me.
Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for this condition on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	I am very happy with the care I have received for my PNH. I was offered the opportunity to be involved in clinical trials for Eculizumab which was life changing for me and more recently I was offered the opportunity to be involved in the clinical trial for Pegcetacoplan which has had a huge impact on my wellbeing and quality of life. The PNH service at St James Hospital in Leeds has offered me incredible support over the years. They are my point of contact for anything PNH related and I fully trust and value the advice and support of the professionals in that service. I always prefer to contact the PNH service for any queries or advice instead of my local haematology services.
8. If there are disadvantages for patients of **current NHS treatments** for this condition (for example how the treatment is given or taken, side effects of treatment etc) please describe these	I can only speak of my own experience of being treated for many years with Eculizumab and the comparison of that with Pegcetacoplan which I am taking now. For me, the disadvantages of Eculizumab were that I continued to experience extravascular haemolysis so my haemoglobin tended to be between nine and ten. Although this was much better than before Eculizumab was available and I was completely dependent on blood transfusions, I still had periods of extreme tiredness, and never felt that I had the energy that I needed to fully participate in

	everything that I wanted to. When I was being treated with eculizumab I was anxious about catching viruses or being unwell as his often led to me requiring a transfusion. I found the dependence of nurse visits for Eculizumab restrictive as I had to be home for the nurse visit and any trips away had to be planned around my treatment dates. Also eculizumab was given intravenously I was concerned about the long term damage to my veins of frequent canulation. Iron overload was a growing concern when I was being treated with Eculizumab as I continued to require blood transfusions and found the medicines for collating iron difficult to tolerate.
Advantages of this treatment	
9a. If there are advantages of this treatment over current treatments on the NHS please describe these. For example, the impact on your Quality of Life your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does this treatment help to overcome/address any of the listed disadvantages of current treatment	9a. In my experience, Pegcetacoplan is a more effective drug for treating PNH than Eculizumab. It has allowed me to maintain a 'normal' haemoglobin and to be transfusion free. I feel well, I have energy and I am able to live an active life in which I can work and participate fully in family and social life. This has had a positive impact on my family as a whole as we are financially better off and there are less interruptions to 'normal' life such as nurse visits and hospital visits for blood transfusions which required my husband to take time off work to care for our four children. I am very grateful for the considerable improvement in how I have felt since taking Pegcetacoplan. I like the control that Pegcetacoplan allows me as I can decide the time of day to do my treatment that best suits my family and commitments. Previously, with Eculizumab, I had to organise my day around what time the nurse was visiting which might have been problematic had I been working. I also like the flexibility that I have now to travel as I can take my medication with me instead of basing my plans around my fortnightly nurse visits. I no longer require intravenous treatment, either for the Eculizumab or for blood transfusion and I see this as a great advantage of Pegcetacoplan as my veins are protected and I don't require any hospital visits other than for routine appointments.

that you have described in question 8? If so, please describe these.	The episodes of haemolysis that I experienced from time to time when I was taking Eculizumab made me feel very unwell and I struggled to do all of the tasks that I wanted to. I found it difficult to have the patience and energy necessary to be the parent that I wanted to be and my husband needed to take time off work to look after the children when I attended hospital for blood tests and treatment. 9b. For me the most important advantage of Pegcetacoplan is the change in my health and wellbeing. I haven't required a single blood transfusion since commencing treatment and my higher haemoglobin has had a huge impact on the way that I feel both physically and mentally, allowing me to participate more fully in life and allowing me to start work again with the confidence that my haemoglobin is stable. 9c. Pegcetacoplan has overcome the problem of extravascular haemolysis that I was experiencing with Eculizumab, it has addressed my anxieties around continued transfusions and periods of illness, as well as taking away the need for frequent canulation and nurse visits. Having a stable haemoglobin has given me the confidence to return to work and has removed the need for my husband to take time off work o care for our children during periods that I was unwell and needed to attend hodpital.
Disadvantages of this treatment	
10. If there are disadvantages of this treatment over current treatments on the NHS please describe these? For example, are there any risks with this treatment? If you are concerned about any potential	The only disadvantages I can see with this treatment are the frequency of injections. I would much prefer it if this medication were in tablet form. I like the freedom of being able to self -administer my medication at a time that suits me and my family but the twice weekly injections means that I need to take a cool bag and all of the equipment if we want to go away anywhere. The current requirement to store a number of weeks medication in the fridge is a little inconvenient in terms of space. Also, I find that I have some slight swelling to the area where I inject myself.

side affects you have heard about, please describe them and explain why.	I do feel that these are very minor inconveniences though compared to the huge benefits of Pecetacoplan.
Patient population	
11. Are there any groups of patients who might benefit more from this treatment or any who may benefit less? If so, please describe them and explain why. Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	I would assume that patients who continue to experience extravascular haemolysis would really benefit from Pegcetacoplan over Eculizumab. Patients who are frustrated by the nurse visits required for Eculizumab or those who have poor veins for cannulation would also be better suited to Pegcetacoplan.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.	

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-real and https://www.gov.uk/discrimination-your-rights.	
Other issues	
13. Are there any other issues that you would like the committee to consider?	

PART 3 - Key messages

14. In up to 5 sentences, please summarise the key messages of your statement:

- Pegcetacoplan has stopped my extravascular haemolysis so I now have a normal haemoglobin. I feel well and have energy, allowing me to participate fully in everything I wish to! I have also been able to return to work which has benefited us financially as a family.
- I no longer require blood transfusions which benefits both the NHS and me! I have been able to have venesection to address my iron overload because my haemoglobin is so stable at such a positive level.
- Pegcetacoplan allows me greater control over my own life. I can administer my medication when it best suits me and my family without the need for a nurse to visit my home.
- I no longer require frequent canulation which is better for my veins and also reduces anxieties around my health for my children who disliked seeing me being treated by the nurse within our home and were worried by my hospital visits for transfusions.
-

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient expert statement

Pegcetacoplan for treating paroxysmal nocturnal haemoglobinuria [ID3746]

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

About this Form
In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.
In **part 2** we are asking you to provide 5 summary sentences on the main points contained in this document.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please return this form by **5pm** on **Monday 11 October 2021.**

Completing this form
Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee. The text boxes will expand as you type.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable

- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 15 pages.

PART 1 – Living with or caring for a patient with this condition and current treatment options	
About you	
1.Your name	**Nelson Ekwedike**
2. Are you (please tick all that apply):	☒ a patient with this condition? ☐ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with this condition? ☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation.	PNH SUPPORT AND AA TRUST
4. Has your nominating organisation provided a submission? Please tick all options that apply.	☐ No, (please review all the questions below and provide answers where possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission

	☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience. ☐ I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience:
Living with the condition	
6. What is your experience of living with this condition? If you are a carer (for someone with this condition) please share your experience of caring for them.	Living with PNH can be daunting and sometimes feel like your life is dominated by the condition. The condition takes a central role in your life and you basically plan your life around the condition and the treatment necessary to keep you well. It was very difficult at the beginning when I was been treated with 2 weekly Eculizumab infusion but with APL2, the quality of life is much better.
Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for this condition on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	The current treatment available for PNH in NHS has huge advantages in terms of helping to manage symptoms in PNH patients. However, some patients like me still had symptoms uncontrolled due to extravascular haemolysis and so I was transfusion dependent throughout the period I was on Eculizumab from November 2015 – March 2019. Since commencing Pegcetacoplan in April 2019 under the Pegasus trial, my symptoms have improved, and I am no longer transfusion dependent.
8. If there are disadvantages for patients of **current NHS treatments** for this condition (for example how	The disadvantages of the current treatment which is Eculizumab include: the inconvenience of having a healthcare professional visit your house to give the

the treatment is given or taken, side effects of treatment etc) please describe these	intravenous injection. Another disadvantage of the current treatment is the issue of extravascular haemolysis with C5 inhibitors, which does occur in significant number of patients with PNH.
Advantages of this treatment	
9a. If there are advantages of this treatment over current treatments on the NHS please describe these. For example, the impact on your Quality of Life your ability to continue work, education, self-care, and care for others?	There is no extravascular haemolysis with Pegcetacoplan and so there is no transfusion dependence while on the treatment. Another advantage is the convenience of self-administration with Pegcetacoplan because it is given through the subcutaneous route and so no time is lost waiting for healthcare professional to provide care.
9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?	Extravascular haemolysis with the current therapy does not happen with Pegcetacoplan and so the symptom control is better with Pegcetacoplan.
9c. Does this treatment help to overcome/address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these.	It is convenient to have Pegcetacoplan because it is self-administered through the subcutaneous route while current treatment requires intravenous access, which can only be provided by health care professional. In addition, some patients on the current treatment do have extravascular haemolysis requiring regular transfusion but this does not happen with Pegcetacoplan.
Disadvantages of this treatment	
10. If there are disadvantages of this treatment over current treatments on the NHS please describe	NA

these? For example, are there any risks with this treatment? If you are concerned about any potential side affects you have heard about, please describe them and explain why.	
Patient population	
11. Are there any groups of patients who might benefit more from this treatment or any who may benefit less? If so, please describe them and explain why. Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Convenience of self-administration via subcutaneous route is an advantage for Pegcetacoplan, which the current therapy does not provide. Although the frequency of dosing makes Pegcetacoplan less appealing to some patients who will find it difficult to manage.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any	**NA**

groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-real and https://www.gov.uk/discrimination-your-rights.	
Other issues	
13. Are there any other issues that you would like the committee to consider?	NA

PART 3 - Key messages

14. In up to 5 sentences, please summarise the key messages of your statement:

- Pegcetacoplan is self-administered via the subcutaneous route and so makes it convenient for the patient.
- Patients on Pegcetacoplan do not experience extravascular haemolysis and so are not transfusion dependent unlike some patient on the current therapy.
- From my personal experience, symptoms like fatigue and low energy level are better controlled with Pegcetacoplan
- From my personal experience, my quality of life is better with Pegcetacoplan compared with when I was treated with Eculizumab.
- There is no one size fit all with this condition, so there should be options for different patients. Some patients are doing well with the current treatment, and some would require a different therapy.

Thank you for your time.

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ERG STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Pegcetacoplan for treating paroxysmal nocturnal haemoglobinuria [ID3746]

Confidential until published

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 133733

Completed 28th July 2021

CONTAINS [redacted] AND [redacted] DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Pegcetacoplan for treating paroxysmal nocturnal haemoglobinuria [ID3746]

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Contributions of authors

Rebecca Bresnahan	Project lead, critical appraisal of the clinical evidence and supervised the final report
Rachel Houten	Critical appraisal of the economic model
James Mahon	Critical appraisal of the economic model
Sophie Beale	Critical appraisal of the clinical and economic evidence, editorial input
Angela Boland	Critical appraisal of the clinical and economic evidence, editorial input
Sarah Nevitt	Critical appraisal of the statistical evidence
Janette Greenhalgh	Critical appraisal of the clinical evidence
Devarshi Bhattacharyya	Critical appraisal of the economic evidence
Yenal Dundar	Critical appraisal of the clinical evidence, including search strategies
Joanne McEntee	Critical appraisal of the company submission
Shreyans Gandhi	Clinical advice and critical appraisal of the clinical evidence

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AE	Adverse event
ARC	Absolute reticulocyte count
BNF	British National Formulary
BTH	Breakthrough haemolysis
CFB	Change from baseline
CI	Confidence interval
CRD	Centre for Reviews and Dissemination
CS	Company submission
CSR	Clinical Study Report
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EQ-5D-3L	EuroQol 5-dimensions 3-levels
ERG	Evidence Review Group
ESS	Effective sample size
EVBTH	Extravascular breakthrough haemolysis
EVH	Extravascular haemolysis
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy Fatigue Scale
g/dL	grammes per decilitre
GHS	Global health status
Hb	Haemoglobin
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost effectiveness ratio
IPD	Individual patient data
ISR	Injection site reactions
ITT	Intention-to-treat
IV	Intravenous
IVBTH	Intravascular breakthrough haemolysis
IVH	Intravascular haemolysis
kg	kilogramme
LASA	Linear Analog Scale Assessment
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
LR*i*G	Liverpool Reviews and Implementation Group
LS	Least Squares
MAIC	Matching-adjusted indirect comparison
mg	milligramme
MMRM	Mixed model repeated measures
NHS	National Health Service

NICE	National Institute for Health and Care Excellence
NMB	Net monetary benefit
NSCT	NHS England National Specialised Commissioning Team
OLP	Open-label period
OR	Odds ratio
OS	Overall survival
OWSA	One-way sensitivity analyses
PAS	Patient Access Scheme
PNH	Paroxysmal nocturnal haemoglobinuria
PRIMA	Preliminary Independent Model Advice
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality adjusted life year
QoL	Quality of life
RCP	Randomised controlled period
RCT	Randomised controlled trial
RD	Risk difference
SD	Standard deviation
SmPC	Summary of product characteristics
TEAE	Treatment-emergent adverse event
TRAE	Treatment-related adverse event
TSAP	Trial statistical analysis plan
U/L	Units per litre
ULN	Upper limit of normal
WTP	Willingness-to-pay

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the Evidence Review Group (ERG) as being potentially important for decision making. It also includes the ERG's preferred assumptions and resulting cost effectiveness results (presented as incremental cost effectiveness ratios [ICERs] per quality adjusted life year [QALY] gained).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of the model parameters and assumptions that have the greatest effects on cost effectiveness results. Sections 1.3 to 1.6 provide further information about the key issues identified by the ERG. A summary of the ERG's preferred assumptions and resulting ICERs per QALY gained are presented in Section 1.7. Background information on the condition, the technology and evidence and information on non-key issues are provided in the main body of the ERG report.

All the issues outlined in this report represent the views of the ERG and are not the opinion of NICE.

1.1 Overview of the ERG's key issues

Summary of key issues

ID3746	Summary of issue	Report sections
Issue 1	No ravulizumab clinical effectiveness evidence for the PEGASUS trial population	Section 2.6.4 and Section 3.6.1
Issue 2	Definition of uncontrolled anaemia	Section 2.6.2
Issue 3	Small PEGASUS trial population size and limited period of trial follow-up data	Section 2.6.5, Section 3.4, Section 3.5.4 and Section 6.5.2
Issue 4	Anchored MAIC results are subject to bias and should not be used to inform decision making	Section 2.6.4, Section 2.6.6 and Section 3.6
N/A	No economic or other issues	NA

MAIC=matching adjusted indirect comparison; NA=not applicable

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life. An ICER per QALY gained is the ratio of the extra cost for every QALY gained.

1.2.1 Company approach

Effect of the technology on incremental QALYs

Overall, treatment with pegcetacoplan is modelled by the company to increase incremental QALYs by avoiding more blood transfusions and increasing haemoglobin levels more than treatment with eculizumab or ravulizumab.

Effect of the technology on incremental costs

A comparison of the total costs of treatment, using the discounted Patient Access Scheme (PAS) prices for pegcetacoplan and ravulizumab (eculizumab is not available at a PAS price) shows that the total cost of treatment with pegcetacoplan is [redacted] than the total cost of treatment with eculizumab or ravulizumab.

Modelling assumptions that have the greatest effect on cost effectiveness results

The company carried out a wide range of one-way sensitivity and scenario analyses. For the comparison of pegcetacoplan versus eculizumab and for the comparison of pegcetacoplan versus ravulizumab, results from the 10 most sensitive parameters show that treatment with pegcetacoplan dominates eculizumab and that pegcetacoplan dominates ravulizumab.

1.2.2 ERG's preferred approach

The ERG preferred base case results incorporate two revisions to the company base case, (i) use of data from the Clinical Study Report to reflect the proportion of patients who, at baseline, were receiving chelation therapies and (ii) inclusion of AE costs. Results from the ERG preferred base case analyses demonstrate that pegcetacoplan dominates eculizumab and that pegcetacoplan dominates ravulizumab.

1.3 The decision problem: summary of the ERG's key issues

Issue 1 No ravulizumab clinical effectiveness evidence for the PEGASUS trial population

Report section	Section 2.6.4 and Section 3.6.1
Description of issue and why the ERG has identified it as important	There is no direct evidence to demonstrate the effectiveness of ravulizumab versus pegcetacoplan or ravulizumab versus eculizumab in the PEGASUS trial population. The NICE recommendation for ravulizumab is based on results from Study 302 (which showed that ravulizumab was non-inferior to eculizumab, with point estimates favouring ravulizumab for all primary and key secondary endpoints). However, Study 302 enrolled a population that was broader than the PEGASUS trial population. In addition, there are key differences between Study 302 and PEGASUS trial designs (CS, pp74-75).
What alternative approach has the ERG suggested?	None.
What is the expected effect on the cost-effectiveness estimates?	Unknown. The ERG was unable to test the consequences of removing the company assumption that ravulizumab and eculizumab were equally efficacious.
What additional evidence or analyses might help to resolve this key issue?	Clinical opinion could be elicited to inform discussions around the assumption that the efficacy of ravulizumab is equal to that of eculizumab in the PEGASUS trial population.

ERG=Evidence Review Group; NICE=National Institute for Health and Care Excellence

Issue 2 Definition of uncontrolled anaemia

Report section	Section 2.6.2
Description of issue and why the ERG has identified it as important	The population considered by the company matches the population described in the final scope issued by NICE, namely adults with PNH whose anaemia is not controlled after treatment with a C5 complement inhibitor (i.e., eculizumab or ravulizumab). However, the term 'not controlled' is not defined in the NICE scope. At baseline, patients enrolled in the PEGASUS trial had a Hb level <10.5g/dL and the company appears to have assumed, given clinical expert opinion and available literature, that having this Hb level means that these patients can be considered to have anaemia that is not controlled. Clinical advice to the ERG is that some PNH patients with Hb levels >10.5g/dL may also be considered to have anaemia that is not controlled.
What alternative approach has the ERG suggested?	None.
What is the expected effect on the cost-effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Clinical opinion could be elicited to inform discussions around whether a Hb level <10.5g/dL (PEGASUS trial entry criterion) is an appropriate cut-off level to determine whether PNH patients in NHS clinical practice have uncontrolled anaemia.

ERG=Evidence Review Group; Hb=haemoglobin; NHS=National Health Service; NICE=National Institute for Health and Care Excellence; PNH=paroxysmal nocturnal haemoglobinuria

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

Issue 3 Small PEGASUS trial population size and limited period of trial follow-up data

Report section	Section 2.6.5, Section 3.4, Section 3.5.4 and Section 6.5.2
Description of issue and why the ERG has identified it as important	PEGASUS trial results are available for patients randomised to pegcetacoplan (N=41) and for patients randomised to eculizumab (N=39) for Week 1 to Week 16, and then for patients from both arms of the trial ([redacted]) who were treated with pegcetacoplan during the open label extension period (Week 17 to Week 48). The small numbers of patients and the short follow-up period add uncertainty to trial results.
What alternative approach has the ERG suggested?	The ERG explored the impact of assuming that, after 1 year, the efficacy of pegcetacoplan was equal to the efficacy of eculizumab (and, therefore, also ravulizumab). Results from this scenario analysis showed that treatment with pegcetacoplan dominates eculizumab and that pegcetacoplan dominates ravulizumab.
What is the expected effect on the cost-effectiveness estimates?	The company and ERG one-way sensitivity analysis results are robust.
What additional evidence or analyses might help to resolve this key issue?	Clinical opinion could be elicited to inform discussions around whether the results demonstrated by the PEGASUS trial are likely to reflect the long-term experience of patients treated with pegcetacoplan and eculizumab (for example, AEs, discontinuation rates, number of blood transfusions and proportions of patients receiving chelation therapies).

AE=adverse event; ERG=Evidence Review Group

Issue 4 Anchored MAIC results are subject to bias and should not be used to inform decision making

Report section	Section 2.6.4, Section 2.6.6 and Section 3.6
Description of issue and why the ERG has identified it as important	The company provided indirect clinical effectiveness evidence for the comparison of pegcetacoplan versus ravulizumab from an anchored MAIC. The ERG agrees with the company conclusion (CS, p75) that the results of the anchored MAIC may be "subject to bias" due to differences between the two included trials (PEGASUS trial and Study 302) and because the impact of key effect modifiers could not be taken into account in the matching process and should not be used to inform decision making.
What alternative approach has the ERG suggested?	None (see above).
What is the expected effect on the cost-effectiveness estimates?	Unknown. The ERG was unable to test the consequences of removing the company assumption that ravulizumab and eculizumab were equally efficacious.
What additional evidence or analyses might help to resolve this key issue?	Clinical opinion could be elicited to inform discussions around the assumption that the efficacy of ravulizumab is equal to that of eculizumab in the PEGASUS trial population.

CS=company submission; ERG=Evidence Review Group; MAIC=matching adjusted indirect comparison

1.5 Summary of the ERG's key economic issues

If the efficacy of ravulizumab is equal to the efficacy of eculizumab for patients with PNH who have baseline Hb levels <10.5g/dL despite treatment with a stable dose of a C5 inhibitor for ≥3 months, the ERG is satisfied that the most plausible ICERs per QALY gained for the comparisons of pegcetacoplan versus eculizumab and pegcetacoplan versus ravulizumab are below £20,000. The ERG considers that there are no other critical issues relating to the economic evidence/model submitted by the company.

1.6 Other key issues: summary of the ERG's view

The ERG considers that the company, appropriately, has not put forward a case to demonstrate that pegcetacoplan meets the NICE End of Life criteria.

1.7 Summary of ERG's preferred assumptions and resulting ICERs

Using the PAS price for pegcetacoplan and the list prices for all other drugs, the results of the ERG exploratory cost effectiveness analyses are shown in Table A and Table B. As ravulizumab is available to the NHS at a confidential PAS price, the ERG has also provided a confidential appendix for the comparison of pegcetacoplan versus ravulizumab.

The ERG's critique of the company model is described in Section 6 of the ERG report. Details of the ERG's alternative approach to assessing cost effectiveness of pegcetacoplan versus C5 inhibitors (eculizumab and ravulizumab) are presented in Section 6.3 to Section 6.6 of the ERG report.

Table A ERG revisions to company model for the comparison of pegcetacoplan versus eculizumab (PAS price for pegcetacoplan, list price for eculizumab)

ERG revisions	Pegcetacoplan			Eculizumab			Incremental			ICER
	Cost	QALYs	Life Years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY gained
A. Company base case	[redacted]	[redacted]	19.706	[redacted]	[redacted]	19.706	[redacted]	[redacted]	0.000	**Pegcetacoplan dominates**
ERG revisions										
R1) Chelation therapy proportions from the CSR	[redacted]	[redacted]	19.706	[redacted]	[redacted]	19.706	[redacted]	[redacted]	0.000	**Pegcetacoplan dominates**
R2) Include AE costs	[redacted]	[redacted]	19.706	[redacted]	[redacted]	19.706	[redacted]	[redacted]	0.000	**Pegcetacoplan dominates**
B. ERG preferred base case (R1 & R2)	[redacted]	[redacted]	19.706	[redacted]	[redacted]	19.706	[redacted]	[redacted]	0.000	**Pegcetacoplan dominates**

AE=adverse event; CSR=clinical study report; ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year

Table B ERG revisions to company model for the comparison of pegcetacoplan versus ravulizumab (PAS price for pegcetacoplan, list price for ravulizumab)

ERG revisions	Pegcetacoplan			Ravulizumab			Incremental			ICER
	Cost	QALYs	Life Years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY gained
A. Company base case	[redacted]	[redacted]	19.706	[redacted]	[redacted]	19.706	[redacted]	[redacted]	0.000	**Pegcetacoplan dominates**
ERG revisions										
R1) Chelation therapy proportions from the CSR	[redacted]	[redacted]	19.706	[redacted]	[redacted]	19.706	[redacted]	[redacted]	0.000	**Pegcetacoplan dominates**
R2) Include AE costs	[redacted]	[redacted]	19.706	[redacted]	[redacted]	19.706	[redacted]	[redacted]	0.000	**Pegcetacoplan dominates**
B. ERG preferred base case (R1 & R2)	[redacted]	[redacted]	19.706	[redacted]	[redacted]	19.706	[redacted]	[redacted]	0.000	**Pegcetacoplan dominates**

AE=adverse event; CSR=clinical study report; ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

The focus of this appraisal is on pegcetacoplan as an option for treating paroxysmal nocturnal haemoglobinuria (PNH) in adults whose anaemia is not controlled after treatment with a C5 complement inhibitor. In this Evidence Review Group (ERG) report, references to the company submission (CS) are to the company's Document B, which is the company's full evidence submission.

2.2 Paroxysmal nocturnal haemoglobinuria

PNH is a rare, acquired, life-threatening chronic blood condition.[1] It is caused by a loss of function mutation in bone marrow stem cells which leads to production of abnormal red blood cells.[1] The abnormal red blood cells lack CD55 and CD59, two surface proteins that regulate the activity of the complement system (part of the immune system that consists of more than 30 proteins).[2] As a consequence, red blood cells become vulnerable to attack from the complement system (including the complement components C3 and C5).[2] This leads to the destruction of red blood cells (haemolysis) and formation of blood clots (thrombosis).[1]

Haemolysis can occur within the vasculature (intravascular haemolysis [IVH]) or in the liver, spleen, bone marrow, or lymph nodes (extravascular haemolysis [EVH]).[1] Treatment with a C5 inhibitor prevents IVH but does not prevent EVH.[3] A diagram showing how aspects of the complement system relate to PNH is provided in Figure 1.

Clinical symptoms associated with PNH include abdominal pain and bloating, kidney problems, fatigue, shortness of breath, bleeding and blood clots, dysphagia, erectile dysfunction and organ damage.[4] Clinical advice to the ERG is that prior to the introduction of treatment with C5 inhibitors, thrombosis was the most common cause of death for patients with PNH.

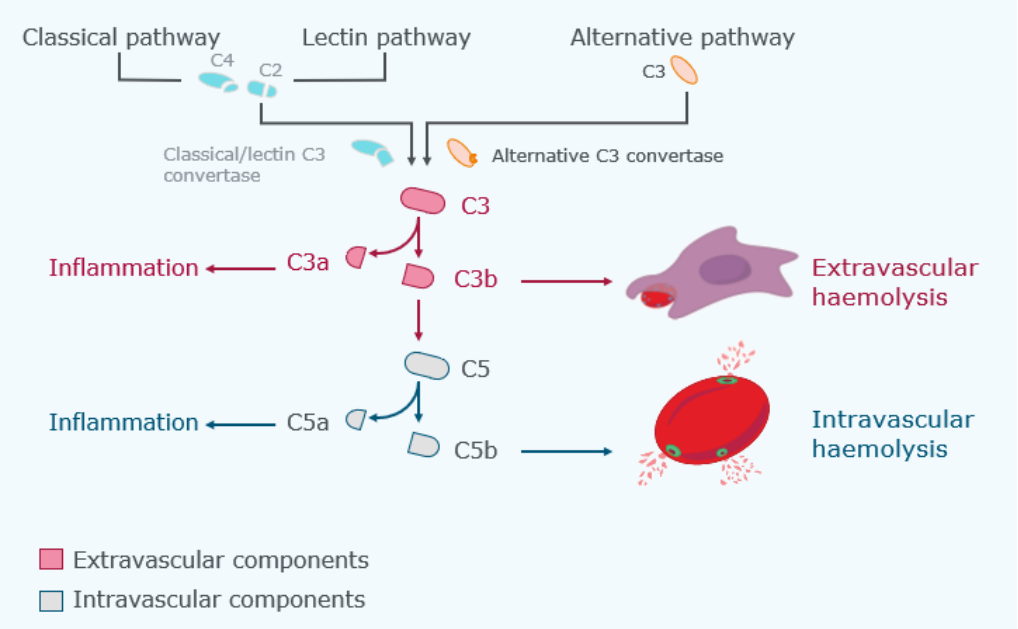

Figure 1 PNH and the complement system

C3=complement component C3; C5=complement component 5
Source: CS, Figure 1

PNH can be acquired at any age but is most frequently diagnosed in adults aged 30 to 40 years.[5] It is estimated that in the UK the incidence of PNH is 1 in 770,000 cases per year and the prevalence is 1 in 62,500 people; therefore, it is predicted that between 650 and 900 people in England have PNH.[6] Clinical advice to the ERG is that incidence rates are approximately the same for males and females. Approximately 15% of patients experience spontaneous remission, most commonly 10 to 20 years after diagnosis.[7]

For patients with PNH, the average time to diagnosis from symptom onset is <2 years. However, for approximately 25% of patients, the time from symptom onset to a correct diagnosis can be >5 years.[8] The diagnostic test for PNH is flow cytometric immunophenotyping. It is used to determine the clone size, i.e., the proportion of PNH-affected cells (those that do not express the CD55 and CD59 surface proteins) versus the proportion of normal cells within the total cell population.[9] Diagnostic testing using flow cytometric immunophenotyping is carried out in many UK centres.

2.3 Pegcetacoplan

Pegcetacoplan is an inhibitor of complement proteins C3 and C3b and prevents the complement system-mediated destruction of red blood cells. Pegcetacoplan targets the complement cascade earlier than the C5 inhibitors (i.e., eculizumab and ravulizumab) to

prevent EVH and IVH (Figure 1). Pegcetacoplan is a self-administered, twice weekly (1080mg subcutaneous [SC]) infusion.[10]

2.4 Company's overview of current service provision

2.4.1 Treatments in the pathway

In line with the final scope[11] issued by NICE, the company's proposed positioning of pegcetacoplan is as a treatment for adult patients with PNH whose anaemia is not sufficiently controlled after treatment with a C5 inhibitor (i.e., eculizumab and ravulizumab) for at least 3 months (Figure 2).

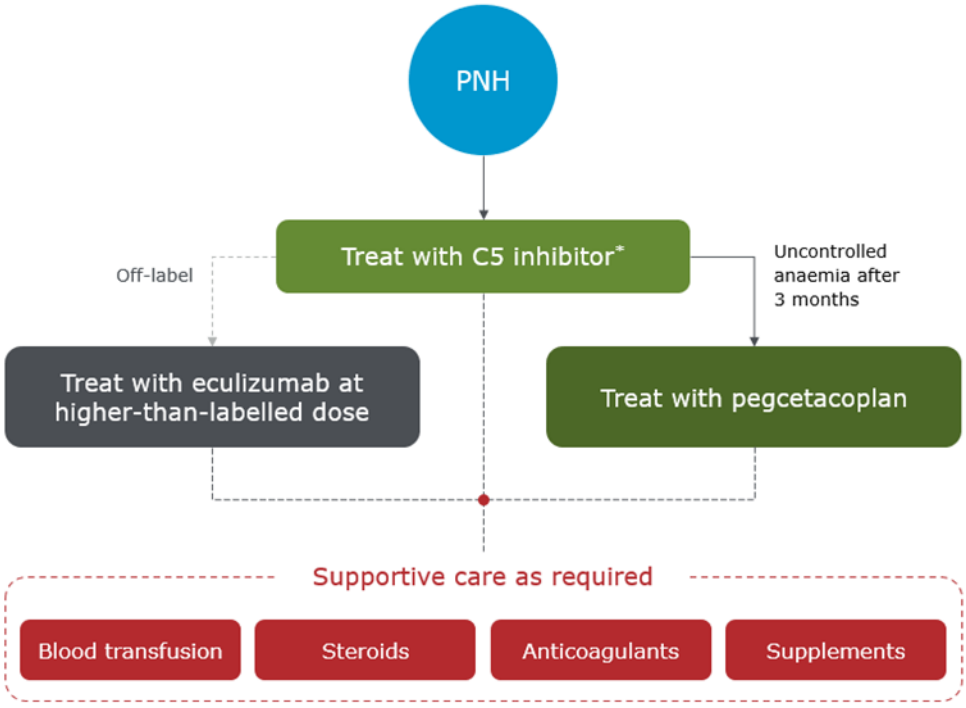

Figure 2 Proposed positioning of pegcetacoplan in the current treatment pathway for patients with PNH

C5=complement component 5; PNH=paroxysmal nocturnal haemoglobinuria
Source: CS, Figure 3

The International PNH Interest Group guidelines for the therapeutic treatment of PNH[12,13] are consistent with the care pathway described by the NHS England Specialised Commissioning Service.[4]

Bone marrow transplant is the only curative treatment for PNH. However, it is associated with significant risks and is only considered for patients with severe bone marrow failure, recurring life-threatening thromboembolic incidences, and refractory transfusion-dependent haemolytic anaemia.[14,15] For most patients, treatment is non-curative, the primary aim is to manage disease symptoms, improve health-related quality of life (HRQoL) and prevent life-threatening disease complications. Clinical management of PNH in the NHS includes treatment with C5 inhibitors and supportive care. Clinical advice to the ERG is that patients with PNH with a high clone load (>50%) who are symptomatic with haemolysis or any organ damage are treated with a C5 inhibitor and that patients with a low (<10%) to moderate clone load (10% to 50%) usually do not require treatment with a C5 inhibitor or supportive care. Clinical advice to the ERG is that approximately 50-60% of patients with PNH with a high clone load (i.e., >50%) are treated with a C5 inhibitor.

Eculizumab

Eculizumab is a C5 inhibitor. It has not been considered by NICE for the treatment of PNH; however, it is available to NHS patients and is funded by the NHS England National Specialised Commissioning Team (NSCT). Eculizumab is administered by intravenous (IV) infusion in the patient's home. Patients start treatment with eculizumab (600mg) weekly for 4 weeks and thereafter continue treatment with eculizumab (900mg) fortnightly. Clinical advice to the ERG is that, for patients with uncontrolled PNH after treatment with eculizumab (900mg), the dose can be increased to 1200mg fortnightly or 1500mg fortnightly (dose escalation is not described in the Summary of Product Characteristics [SmPC]).[16]

Ravulizumab

Ravulizumab is a C5 inhibitor and was recommended by NICE as an option for treating adults with PNH in May 2021.[17] It is derived from eculizumab and is over 99% homologous to eculizumab; however, it has a four times longer half-life than eculizumab and therefore provides sustained C5 inhibition, allowing for a longer dosing interval.[18] It is administered by IV infusion in the patient's home on an 8-weekly basis.[18] Patients with PNH start treatment with a loading dose of ravulizumab (2400mg to 3000mg) and then continue on a maintenance dose (3000mg to 3600mg); dose is dependent on body weight.[19]

Supportive care

Supportive care includes blood transfusions and treatment with steroids, erythropoietin stimulating agents, anti-coagulants and supplements (for example, folate and vitamin B12).

2.5 Number of patients eligible for treatment with pegcetacoplan

An estimate of the number of patients with PNH in England who would be eligible for treatment with pegcetacoplan (if recommended by NICE) was not presented in the CS. The number of patients treated with eculizumab in the UK in December 2018 was 239.[11] Clinical advice to the ERG is that approximately 20% of patients with PNH treated with eculizumab will have a suboptimal response, or their PNH will not be sufficiently controlled. The ERG, therefore, estimates that approximately 50 patients with PNH could be eligible for treatment with pegcetacoplan.

2.6 Critique of company's definition of decision problem

A summary of the decision problem outlined in the final scope[11] issued by NICE and addressed by the company is presented in Table 1. Each parameter is discussed in more detail in the text following Table 1 (Section 2.6.1 to Section 2.6.8).

Table 1 Summary of decision problem

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission	ERG comment
Population	Adults with PNH whose anaemia is not controlled after treatment with a C5 complement inhibitor	As per scope	As per scope
Intervention	Pegcetacoplan	As per scope	As per scope
Comparator (s)	Eculizumab Ravulizumab	As per scope	Direct evidence Direct evidence is available from the PEGASUS trial for the comparison of pegcetacoplan versus eculizumab Indirect evidence The company conducted an anchored MAIC to allow a comparison of the clinical effectiveness of pegcetacoplan versus ravulizumab The ERG agrees with the company that anchored MAIC results are unreliable due to differences in the designs of the PEGASUS trial and Study 302,[20] and because the impact of key effect modifiers could not be taken into account in the matching process In the company base case analysis, the company assumed that the efficacy of ravulizumab was the same as the efficacy of eculizumab

Outcomes	• OS • intravascular haemolysis • extravascular haemolysis • breakthrough haemolysis • transfusion avoidance • haemoglobin • thrombotic events • AEs • HRQoL	As per scope except that: OS and breakthrough haemolysis are not included as they were not endpoints in the PEGASUS study Post-hoc analyses of breakthrough haemolysis are considered where possible In addition, aligned with the population pegcetacoplan is indicated for, Hb normalisation and response are included	Direct evidence Direct evidence (from the PEGASUS trial) allows comparison of pegcetacoplan versus eculizumab for all outcomes except OS (clinical advice is that mortality hazards for treated patients are the same as those for the general population). Breakthrough haemolysis results were derived from a post-hoc analysis. Clinical advice to the ERG is that breakthrough haemolysis is an important outcome and that the 16-week RCP duration of the PEGASUS trial may not be sufficient to realise the full benefits of treatment or to identify any safety issues that might arise due to prolonged treatment Indirect evidence Indirect evidence for the comparison of pegcetacoplan versus ravulizumab has been provided for the following outcomes: intravascular haemolysis, transfusion avoidance, number of packs of red blood cells transfused, haemoglobin stabilisation and HRQoL. The company and ERG consider that anchored MAIC results are not robust and should not be used to inform decision making
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared	As NICE reference case	The company has provided cost effectiveness results in the form of ICERs per QALY gained for the comparisons of pegcetacoplan versus eculizumab and pegcetacoplan versus ravulizumab The time horizon considered is 51 years Costs are calculated from the perspective of the NHS and PSS The PAS price for pegcetacoplan and list prices for the comparator drugs are used in the company analyses

	Costs will be considered from an NHS and Personal Social Services perspective		
Subgroups	No subgroups specified		NA

AE=adverse event; CS=company submission; ERG=Evidence Review Group; Hb=haemoglobin; HRQoL=health-related quality of life; ICER=incremental cost effectiveness ratio; MAIC=matching-adjusted indirect comparison; NA=not applicable; OS=overall survival; PAS=Patient Access Scheme; PSS=Personal Social Services; QALY=quality adjusted life year; RCP=randomised controlled period

Source: Final scope[11] issued by NICE, and CS, Table 1

2.6.1 Source of direct clinical effectiveness data

The primary source of the evidence presented by the company is the PEGASUS[21,22] trial. This was a phase III, 48-week, multicentre, international, open-label, active-comparator, randomised controlled trial (RCT) that compared the clinical effectiveness of pegcetacoplan (N=41) versus eculizumab (N=39) in patients with PNH who had haemoglobin (Hb) levels <10.5 g/dL despite treatment with eculizumab. The trial was conducted in three phases (Table 2) and completed in August 2020.[23] The small numbers and short follow-up period add uncertainty to trial results. Whilst the PEGASUS trial sample size is small, PNH is a rare disease.

Table 2 Periods of the PEGASUS trial

Period	Intervention	Duration
Run-in	All patients received pegcetacoplan plus eculizumab at their current prescribed dose (baseline=Day -28)	4 weeks
RCP	Patients were randomised to receive pegcetacoplan monotherapy (N=41) or to stop pegcetacoplan and just receive their current prescribed dose of eculizumab (N=39)	16 weeks
OLP	All patients who completed the RCP ([redacted]) entered the OLP Patients randomised to pegcetacoplan monotherapy continued to receive pegcetacoplan monotherapy. Patients randomised to eculizumab were permitted to switch to pegcetacoplan monotherapy after completing another 4-week run-in period	32 weeks

RCP=randomised controlled period; OLP=open-label period
Source: CS, p29

PEGASUS trial results are available for all patients for Week 1 to Week 16 (N=80), and then for patients from both arms of the trial ([redacted]) who were treated with pegcetacoplan during the open label extension period (Week 17 to Week 48).

2.6.2 Population

In line with the final scope[11] issued by NICE, the company has presented clinical effectiveness evidence for patients with PNH who had uncontrolled anaemia after treatment with a C5 inhibitor for a period of at least 3 months. The term 'uncontrolled' is not defined in the NICE scope;[11] however, at baseline, patients enrolled in the PEGASUS trial had Hb levels <10.5g/dL and the company appears to have assumed that these patients can be considered to have anaemia that is not controlled. Clinical advice to the company was that quality of life, transfusion requirements and Hb level could potentially be used to define anaemia that is not controlled but noted that their relevance may vary between patients. The company considers Hb level to be the most appropriate way to define anaemia that is not controlled. The company acknowledges that this threshold is an imperfect measure but considers it to be the most

appropriate to define anaemia that is not controlled at a population level. Clinical advice to the ERG is that approximately 50% of patients with PNH have some underlying bone marrow failure (e.g., aplastic anaemia). In these patients, C5 and C3 inhibitors may lead to improvements in Hb levels. However, these patients may have additional anaemia that is not due to uncontrolled complement activity and is unlikely to respond to higher doses of C5 or C3 inhibitors. Clinical advice to the ERG is that in NHS clinical practice, some PNH patients with Hb levels ≥10.5g/dL may also be considered to have anaemia that is not controlled.

2.6.3 Intervention

In line with the final scope[11] issued by NICE, the intervention in the PEGASUS trial is pegcetacoplan. The company has provided the following information about pegcetacoplan (CS, Table 2):

- In the draft SmPC,[10] pegcetacoplan is indicated for the treatment of adult patients with PNH who are anaemic after treatment with a C5 inhibitor for at least 3 months.
- An application was submitted to the European Medicines Agency (EMA) in September 2020. Opinion from the EMA Committee for Medicinal Products for Human Use is expected in September 2021. [redacted] No conditional UK marketing authorisation is anticipated by the company.
- Pegcetacoplan (1080mg) is self-administered twice weekly via SC infusion with a syringe system infusion pump. The dose should be administered on day 1 and day 4 of each treatment week. It is recommended that treatment with pegcetacoplan continues for the patient's lifetime unless discontinuation is clinically indicated.[10]

The company has highlighted two points from the draft SmPC:[10]

i) For the first 4 weeks, pegcetacoplan should be given in addition to the patient's current dose of C5 inhibitor treatment (to minimise the risk of haemolysis with abrupt treatment discontinuation). After 4 weeks, pegcetacoplan should be given as a monotherapy. Clinical advice to the company is that the period of simultaneous administration may not happen in clinical practice, instead relying on the ongoing effect of C5 inhibition while initiating pegcetacoplan.

ii) [redacted]) In the event of a dose increase, LDH should be monitored twice weekly for at least 4 weeks. Clinical advice to the company and the ERG is that in NHS clinical practice, a single dose of eculizumab (900mg) would be administered to block IVH indicated by an increased LDH level.

Clinical effectiveness evidence for the use of pegcetacoplan is derived from the PEGASUS trial. This trial included a 4-week run-in period of dual therapy (eculizumab and pegcetacoplan). According to the draft SmPC,[10] patients should be treated with a C5 inhibitor

and pegcetacoplan for 4 weeks before switching to pegcetacoplan monotherapy; clinical advice to the ERG is that SmPC[10] guidance would be followed.

2.6.4 Comparators

The comparators listed in the final scope[11] issued by NICE are eculizumab and ravulizumab. The licensed indications for eculizumab, ravulizumab and pegcetacoplan are shown in Table 3.

Table 3 Licensed indications for eculizumab, ravulizumab and draft licensed indication for pegcetacoplan

Treatment	Licensed indication
Eculizumab	Adults and children for the treatment of PNH
Ravulizumab	Adult patients with PNH with haemolysis and clinical symptoms indicative of high disease activity and for adult patients who are clinically stable after having been treated with eculizumab for at least 6 months
Pegcetacoplan*	Adult patients with PNH who are anaemic after treatment with a C5 inhibitor for at least 3 months

* In the pegcetacoplan draft SmPC,[10] pegcetacoplan is indicated for the treatment of adult patients with PNH who are anaemic after treatment with a C5 inhibitor for at least 3 months
EMA=European Medicines Agency; PNH=paroxysmal nocturnal haemoglobinuria; SmPC=Summary of Product Characteristics
Source: EMA marketing authorisation for eculizumab,[24] ravulizumab[25] and CS, Table 2

Clinical advice to the ERG is that most patients currently treated with eculizumab are likely to switch to treatment with ravulizumab due to the reduced treatment burden and improved patient convenience associated with ravulizumab (infusions every 8 weeks rather than every 2 weeks).

The company has provided direct evidence, from the PEGASUS trial, for the comparison of the clinical effectiveness of pegcetacoplan versus eculizumab. An indirect treatment comparison, in the form of an anchored matching-adjusted indirect comparison (MAIC), has been carried out to provide evidence for the comparison of the clinical effectiveness of pegcetacoplan versus ravulizumab. The ERG agrees with the company that the anchored MAIC results are not robust (Section 3.6.3).

Alternative approach to anchored MAICs

Ravulizumab is a re-engineered form of eculizumab with an extended half-life. The longer half-life supports a dosing interval of 8 weeks for ravulizumab, compared to 2 weeks for eculizumab.

Ravulizumab was compared with eculizumab in Study 302[20] and treatment with ravulizumab was shown to be non-inferior to eculizumab, with point estimates favouring ravulizumab for all primary and key secondary endpoints. Based on these results, the NICE TA698 Appraisal

Committee[26] concluded that ravulizumab and eculizumab were similarly effective and that adverse events (AEs) experienced by patients treated with ravulizumab were likely to be similar to those experienced by patients treated with eculizumab.

The NICE recommendation for ravulizumab[17] is based on evidence from patients with PNH who had haemolysis with clinical symptom(s) indicative of high disease activity or whose disease was clinically stable after having been treated with eculizumab for at least 6 months. However, the PEGASUS trial population (patients with uncontrolled anaemia, defined as Hb level <10.5g/dL, after treatment with a C5 inhibitor for a period of at least 3 months) is not the same as the Study 302[20] population. In addition, as the company explains (CS, pp74-75), there are key differences in the design of the two trials.[20]

In the company base case cost effectiveness analysis, the company has assumed that the efficacy of ravulizumab is equal to the efficacy of eculizumab. However, the ERG considers that it is not possible to be certain from the available clinical trial evidence that, in the PEGASUS trial population, the efficacy of ravulizumab would be the same as the efficacy of eculizumab.

2.6.5 Outcomes

The outcomes listed in the final scope[11] issued by NICE are overall survival (OS), IVH, EVH, breakthrough haemolysis (BTH), transfusion avoidance, Hb level, thrombotic events, adverse events (AEs) and HRQoL. Clinical advice to the ERG is that these outcomes, except for OS, are the most relevant outcomes for patients with PNH.

The PEGASUS trial primary outcome was change from baseline (CFB) in Hb level at Week 16. Clinical advice to the ERG is that Hb normalisation in the absence of transfusion is the most clinically relevant outcome but that it should be considered in conjunction with Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-Fatigue) score.

Clinical advice to the ERG is that the PEGASUS trial 16-week RCP is sufficient to demonstrate most of the benefit that patients would accrue from treatment with eculizumab or pegcetacoplan; however, a longer term follow-up period would be needed to fully assess clinical effectiveness and long-term safety.

Clinical advice to the ERG is that BTH is a key clinical outcome. BTH was not a pre-specified outcome in the PEGASUS trial; however, the company generated results via post-hoc analyses. The company defined BTH as one or more new or worsening symptom(s) or sign(s) of IVH (fatigue, haemoglobinuria, abdominal pain, dyspnoea, Hb <10g/dL, major adverse

vascular events, including thrombosis, dysphagia, or erectile dysfunction) in the presence of elevated LDH ≥2×ULN after prior LDH reduction to <1.5×ULN on therapy (CS, p106).

The company provided indirect evidence (via an anchored MAIC) for the comparison of pegcetacoplan versus ravulizumab was provided for the following outcomes: IVH, transfusion avoidance, number of packs of red blood cells transfused, haemoglobin stabilisation and HRQoL.

2.6.6 Economic analysis

The company has carried out cost effectiveness analyses for the comparison of pegcetacoplan versus eculizumab and versus ravulizumab. Company cost effectiveness results are expressed in terms of incremental cost per quality adjusted life years (QALYs) gained. These results were generated using the Patient Access Scheme (PAS) price for pegcetacoplan and list prices for eculizumab and ravulizumab. Outcomes were assessed over a lifetime horizon (considered to be 51 years) and costs were reported to have been considered from an NHS and Personal Social Services (PSS) perspective.

The ERG highlights that anchored MAIC results were not used in the company model.

2.6.7 Subgroups

No patient subgroups are specified in the final scope[11] issued by NICE.

2.6.8 Other considerations

The company, appropriately, did not consider that treatment with pegcetacoplan meets the NICE End of Life criteria.[27] The company has not identified any inequity or equality issues. Pegcetacoplan and ravulizumab are available to the NHS at PAS discounted prices.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

Full details of the methods used by the company to identify and select relevant evidence to demonstrate the clinical effectiveness of pegcetacoplan for patients with PNH whose anaemia is not controlled after treatment with a C5 inhibitor are presented in the CS (Appendix D). The ERG searched for, but did not find, any relevant studies in addition to those identified by the company. An assessment of the extent that the company review was conducted in accordance with the LR*i*G in-house systematic review checklist is provided in Table 4. The ERG considers the methods used by the company to conduct a systematic review of the clinical effectiveness evidence were appropriate.

Table 4 ERG appraisal of the company's systematic review methods

Review process	ERG response	ERG comment
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes	CS, Appendix D, Table 1
Were appropriate sources searched?	Yes	CS, Appendix D, page 2
Was the timespan of the searches appropriate?	Yes	Databases were searched from inception to March 2021. Conference proceedings published from July 2020 to March 2021 were hand searched
Were appropriate search terms used?	Yes	CS, Appendix D, Table 2, Table 3, Table 4, Table 5 and Table 6
Were the eligibility criteria appropriate to the decision problem?	Yes	CS, Appendix D, Table 1
Was study selection applied by two or more reviewers independently?	Yes	Two reviewers independently screened titles and abstracts and full texts
Was data extracted by two or more reviewers independently?	Yes	One reviewer extracted data and the data were then checked by a second (independent) reviewer. The ERG considers that this is standard practice
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes	The company quality assessed the trials using the minimum criteria set out in the NICE company evidence submission template[28]
Was the quality assessment conducted by two or more reviewers independently?	Yes	Assessment was made by one researcher and checked by a second researcher. The ERG considers that this is standard practice
Were attempts to synthesise evidence appropriate?	Yes	Section 3.2.5 and Section 3.6.2 include a description of the company's methods and the ERG's critique of the syntheses of direct and indirect evidence

CS=company submission; ERG=Evidence Review Group
Source: LR*i*G in-house checklist

3.2 ERG summary and critique of clinical effectiveness evidence

3.2.1 Included trials

The company identified one relevant trial, the PEGASUS trial (NCT03500549) that provided clinical effectiveness evidence of pegcetacoplan (versus eculizumab) for patients with PNH whose anaemia is not controlled after treatment with a C5 inhibitor.

3.2.2 Characteristics of the PEGASUS trial

The PEGASUS trial was a phase III, 48-week, multicentre, international, open-label, active-comparator, RCT of pegcetacoplan versus eculizumab for patients with PNH whose anaemia is not controlled after treatment with a C5 inhibitor. The PEGASUS trial was conducted in 11 countries. The key characteristics of the PEGASUS trial are presented in Table 5.

Table 5 Key characteristics of the PEGASUS trial

Trial parameter	The PEGASUS trial
Design	• Phase III, 48-week, multicentre, international, open-label, active-comparator, RCT • 44 sites across 11 countries (Australia, Belgium, Canada, France, Germany, Japan, Republic of Korea, Russian Federation, Spain, UK and US) • Screening; 4-week run-in period; 16-week RCP; 32-week open-label follow-up
Patient population	• Patients (≥18 years old) with PNH who continued to have Hb levels <10.5g/dL despite treatment with eculizumab • Dosage of eculizumab stable for ≥3 months prior to screening • ARC>1xULN, platelet count>50,000mm^3 and absolute neutrophil count >500mm^3 at screening visit • Vaccination against *N. meningitidis* types A, C, W, Y, and B; *S. pneumoniae* and *Hib*. • Negative pregnancy test for females • Willing and able to self-administer pegcetacoplan (administration by caregiver was allowed) • BMI <35.0kg/m^3
Intervention	• 1080mg self-administered SC pegcetacoplan twice weekly or every 3 days (N=41)
Comparator	• Current prescribed dosage (stable for ≥3 months) IV infusion eculizumab (N=39)
Primary outcome	• CFB in Hb level at Week 16
Secondary outcomes	• Transfusion avoidance • CFB in ARC at Week 16 • CFB in LDH level at Week 16 • CFB in FACIT-Fatigue Scale score v4 at Week 16
Additional secondary endpoints	• Hb response in the absence of transfusions (CFB ≥1g/dL at Week 16) • Hb normalisation in the absence of transfusions (Hb level >gender-specific LLN range [>12g/dL for females; >13.6g/dL for males]) • ARC normalisation in the absence of transfusions (ARC <226U/L [ULN] at Week 16) • CFB in indirect bilirubin level at Week 16 • CFR in LASA scores at Week 16 • CFB in EORTC-QLQ-C30 at Week 16
Safety outcomes	• TEAEs (any AE that occurred after dosing on Day-28 or worsened in severity) • Incidence of thromboembolic events • CFB laboratory parameters (Hb, neutrophil and platelet levels) • CFB in ECG parameters

AE=adverse event; ARC=absolute reticulocyte count; BMI=body mass index; CFB=change from baseline; g/dL=gram per deciltre; ECG=electrocardiogram; EORTC-QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; FACIT-Fatigue= Functional Assessment of Chronic Illness Therapy; Hb=haemoglobin; Hib=H. influenzae Type B; IV=intravenous; LASA=Linear Analog Assessment Scale; LDH=lactate dehydrogenase; LLN=lower limit of normal; PNH=paroxysmal nocturnal haemoglobinuria; RCP=randomised controlled period; RCT=randomised controlled trial; TEAE=treatment-emergent adverse event; SC=subcutaneous; U/L=unit per litre; ULN=upper limit of normal
Source: CS, Table 3, Table 4 and pp35-36 and supplementary appendix to the PEGASUS trial publication[29]

3.2.3 Characteristics of patients in the PEGASUS trial

The baseline characteristics of patients in the PEGASUS trial are provided in Table 6. The ERG agrees with the company (CS, p37) that the characteristics of patients participating in the PEGASUS trial were well-balanced across the treatment arms. The mean LDH level was higher for the eculizumab arm (308.64U/L) compared to the pegcetacoplan arm (257.48U/L). However, clinical advice to the ERG is that this difference is not clinically important because the mean baseline LDH level is well-controlled (<1.5xULN) [<339U/L]) in both treatment arms.

Clinical advice to the ERG is that approximately 20% of patients in NHS clinical practice have a suboptimal response (i.e., no change to transfusion requirements) to eculizumab and that the patients in the PEGASUS trial are representative of this population.

Table 6 PEGASUS trial baseline patient characteristics (ITT population)

Characteristics	Pegcetacoplan (N=41)	Eculizumab (N=39)	Total (N=80)
Age, years			
Mean (SD)	50.2 (16.29)	47.3 (15.81)	48.8 (16.02)
Sex, n (%)			
Female	27 (65.9)	22 (56.4)	49 (61.3)
Race, n (%)			
Asian	5 (12.2)	7 (17.9)	12 (15.0)
Black or African American	2 (4.9)	0	2 (2.5)
White	24 (58.5)	25 (64.1)	49 (61.3)
Other or not reported	10 (24.4)	7 (18.0)	17 (21.3)
Weight, (kg)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Region, n (%)			
Asia-Pacific	[redacted]	[redacted]	[redacted]
Europe	[redacted]	[redacted]	[redacted]
North America	[redacted]	[redacted]	[redacted]
Time since diagnosis of PNH (years) to Day 28			
Mean (SD)	[redacted]	[redacted]	[redacted]
Duration (days) of treatment with eculizumab prior to Day 28			
Mean (SD)	[redacted]	[redacted]	[redacted]
Current eculizumab dosing level and dosing regimen, n (%)			
Every 2 weeks IV 900mg	26 (63.4)	30 (76.9)	56 (70.0)
Every 11 days IV 900mg	[redacted]	[redacted]	[redacted]
Every 2 weeks IV 1200mg	12 (29.3)	9 (23.1)	21 (26.3)
Every 2 weeks IV 1500mg	2 (4.9)	0	2 (2.5)
Number of transfusions in the last 12 months prior to Day 28			
Mean (SD)	6.1 (7.26)	6.9 (7.72)	6.5 (7.45)
Platelet count at screening ($x10^{-9}$/L)			
Mean (SD)	166.6 (98.28)	146.9 (68.81)	157.0 (85.24)
Hb level (g/dL)			
Mean (SD)	8.69 (1.075)	8.68 (0.886)	8.69 (0.982)
ARC (10^9 cells/mL)			
Mean (SD)	217.52 (74.96)	216.15 (69.14)	216.85 (71.73)
LDH level (U/L)			
Mean (SD)	257.48 (97.65)	308.64 (284.84)	282.42 (210.99)
Indirect bilirubin level (µmol/L)			
Mean (SD)	34.65 (28.49)	32.89 (22.97)	33.80 (25.80)
Total FACIT-Fatigue score			
N	41	38	79
Mean (SD)	32.16 (11.38)	31.55 (12.51)	31.87 (11.87)

ARC=absolute reticulocyte count; BMI=body mass index; g/dL=gram per decilitre; FACIT-Fatigue=Functional Assessment of Chronic Illness Therapy; Hb=haemoglobin; IV=intravenous; LDH=lactate dehydrogenase; SD=standard deviation; U/L=unit per litre; ULN=upper limit of normal
Source: CS, Table 5

3.2.4 Quality assessment of the PEGASUS trial

The company conducted a quality assessment of the PEGASUS trial using the quality assessment checklist for clinical trials devised by the Centre for Reviews and Dissemination (CRD) at the University of York.[30] The company's assessments and ERG comments are presented in Table 7. The ERG considers that the PEGASUS trial was well-designed and well-conducted.

Table 7 Quality assessment for the PEGASUS trial

Study questions	Company assessment	ERG assessment	ERG comment
Was randomisation carried out appropriately?	Yes (1:1 randomisation to pegcetacoplan and eculizumab treatment cohorts)	Yes	Randomisation conducted by IRT
Was the concealment of treatment allocation adequate?	No (This was an open-label study)	Yes	Randomisation by IRT concealed allocation
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes (Reported baseline characteristics were largely similar between the arms, with lactate dehydrogenase levels appearing higher in the eculizumab group than in the pegcetacoplan group.	Yes	
Were the care providers, participants and outcome assessors blind to treatment allocation?	No (This was an open-label study)	No	
Were there any unexpected imbalances in drop-outs between groups?	No (3 patients on pegcetacoplan discontinued due to breakthrough haemolysis, [redacted] of which re-entered the study during the follow-up period)	No	
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No (All measurements listed in the methods were reported)	No	
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes (Analyses were performed on the intention-to-treat population. Data from patients who withdrew from the study were handled in the same manner as for patients who received transfusions)	Yes	

ERG=Evidence Review Group; IRT=interactive response technology; ITT=intention-to-treat
Source: CS, Section B.2.3.1 and Appendix D, Table 13

3.2.5 Statistical approach adopted for the analysis of the PEGASUS trial data

Information about the statistical approach used by the company to analyse PEGASUS trial data has been extracted from the Clinical Study Report (CSR) (which is based on the 24th December 2019 database lock),[22] the trial protocol (Amendment 4, version 1.0, dated 16th August 2019) and the trial statistical analysis plan (TSAP, version 2.0, dated 5th December 2019), available as supplementary materials to the PEGASUS trial publication[21] and the CS. A summary of the ERG checks of the company's pre-planned statistical approach is provided in Table 8; the ERG considers that the company's pre-planned statistical approach was pre-specified and is appropriate.

Table 8 ERG assessment of statistical approaches used in the PEGASUS trial

Item	ERG assessment	Statistical approach	ERG comments
Were all analysis populations clearly defined and pre-specified?	Yes	ITT population clinical effectiveness results are presented in the CS (Section B.2.6). The ITT population was defined as all randomised patients analysed within their randomised treatment group (CS, Section B.2.4).	The ERG is satisfied that the PEGASUS trial analysis population were clearly defined and pre-specified (TSAP, Section 4).
Were all protocol amendments made prior to analysis?	Yes	A summary of changes from the original protocol (version 1.0) are provided in the latest version (Amendment 4, version 1.0, 16th August 2019) of the PEGASUS trial protocol. All amendments were minor and were clarifications of trial procedures, eligibility criteria and outcome definitions.	The ERG is satisfied that all protocol amendments were appropriate and were made prior to the latest database lock (24 December 2019).
Were all primary and secondary efficacy outcomes pre-defined and analysed appropriately?	Yes	The PEGASUS trial primary outcome was CFB to Week 16 in Hb level (CS, Section B.2.3.1, p35). Key secondary outcomes were transfusion avoidance (defined as the proportion of patients who do not require a transfusion during the 16-week RCP) and CFB to Week 16 in ARC, LDH level and the FACIT-Fatigue scale score. Additional secondary outcomes are described in the CS (Section B.3.2.1, p35). Analysis approaches for primary, key secondary and additional secondary outcomes are described in the CS (Table 6).	The ERG is satisfied that primary, key secondary and additional secondary efficacy outcomes were clearly defined and pre-specified (TSAP, Section 2.2) and that the analysis approaches were appropriate and pre-specified (TSAP, Section 6.2 to 6.4).
Was an appropriate trial design and sample size calculation pre-specified?	Yes	The PEGASUS trial sample size calculation is outlined in the CS (Table 6). Key secondary outcomes were firstly tested for non-inferiority in a hierarchical manner (in order, transfusion avoidance, CFB to Week 16 in ARC, LDH level and FACIT-Fatigue scale) after statistical significance (superiority at a 5% significance level) was reached for the primary outcome. The company clarified the basis of the non-inferiority margins for each outcome in response to question A1 of the clarification letter. If non-inferiority was established for key secondary outcomes, superiority would be assessed for key secondary outcomes.	The ERG is satisfied that the sample size calculation and hierarchical testing procedure to test key secondary outcomes for non-inferiority then for superiority were appropriate and pre-specified (TSAP, Section 3.3, Section 6.5).

Item	ERG assessment	Statistical approach	ERG comments
Was the analysis approach for PROs appropriate and pre-specified?	Yes	PROs were CFB to Week 16 in the FACIT-Fatigue score and the EORTC-QLQ-C30 score in the ITT population. Analysis approaches for PROs are described in the CS (Table 6).	The ERG is satisfied that the PRO outcome definitions and analysis approaches were pre-specified (TSAP, Section 2.2, Section 6.2 and Section 6.3) and were appropriate.
Was the analysis approach for AEs appropriate and pre-specified?	Yes	TEAEs during the run-in period or the RCP were coded in accordance with MedDRA® version 20.0 within the 'safety population,' defined as patients who received at least one dose of the study drug analysed according to the actual treatment received (TSAP, Section 4). AEs are presented as numbers and percentages of patients experiencing events. No formal statistical analyses of AEs were conducted. All TEAEs, related TEAEs, TEAEs by severity, TEAEs leading to study drug discontinuation, serious TEAEs and specific TEAES in ≥5% of patients in either treatment group during the RCP are presented in the CS (Table 37 and Table 38). Incidence of thromboembolic events was also pre-specified as a safety outcome (Protocol, Section 9.2.6). No thromboembolic events were reported in the PEGASUS trial (CS, Section B.2.10.1).	The ERG is satisfied that the analysis approach for AEs was pre-specified (Protocol, Section 15; TSAP, Section 7) and is appropriate. Additional summary tables of TEAEs are provided in the CSR (Section 12.2 and 12.3, pp201-239).
Were all subgroup and sensitivity analyses pre-specified?	Yes	Subgroup analyses by number of PRBC transfusions within the 12 months prior to baseline (<4 or ≥4), platelet count at screening (<100,000/mm^3 or ≥100,000/mm^3), sex, race (Asian, Black or African American, White, Other or Unknown) and age (≤65 years or >65 years) are presented for primary and key secondary outcomes (CS, Section B.2.7 and Appendix E). Sensitivity analyses of the primary outcome were performed to examine lack of treatment benefits following a patient's discontinuation from study treatment using a CBPI method and a delta-adjusted stress testing (Tipping Point) method and a supportive analysis of the primary outcome was performed using data uncensored for transfusion and a nonparametric randomisation based ANCOVA in the ITT population (CS, Section 2.6.2).	The ERG is satisfied that all of the subgroup (TSAP, Section 6.6), sensitivity (TSAP, Section 6.2.2) and supportive analyses (TSAP, Section 6.2.3) of the primary outcome were pre-specified. Supportive analyses of key secondary outcomes using data uncensored for transfusion in the ITT population were pre-specified (TSAP, Section 6.3.4) and results are provided in the CSR (Section 11.2.4.2).

Item	ERG assessment	Statistical approach	ERG comments
Was a suitable approach employed for handling missing data?	Yes	Clinical effectiveness outcomes measured as CFB were 'censored for transfusion' (i.e., subsequent outcome measurements set to missing following a transfusion) and analysed using an MMRM approach. The validity of the MMRM approach relies on the assumption that missing data are missing at random (MAR), which may not be a valid assumption for missing data due to censoring following transfusion or following discontinuation from study treatment. The company conducted a sensitivity analysis for the primary outcome using a CBPI method with a missingness not at random mechanism and conducted a supportive analysis for primary and key efficacy outcomes using all available data (i.e., without censoring for transfusion). Methods for handling other missing data, including missing and partially missing dates, are described in the TSAP (Section 13.8).	The ERG is satisfied that methods for handling missing data were appropriate and were pre-specified (TSAP, Section 6.2.2 and Section 6.2.3).

AE=adverse event; ANCOVA=analysis of covariance; CBPI=control based pattern imputation; CFB=change from baseline; CSR=clinical study report; EORTC-QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core30; ERG=Evidence Review Group; FACIT=Functional Assessment of Chronic Illness Therapy; MedDRA=Medical Dictionary for Regulatory Activities; MMRM=mixed-effect model for repeated measures; PRO=patient reported outcome; RCP=randomised controlled period; SAE=serious adverse event; TEAE=treatment emergent adverse event; TSAP=trial statistical analysis plan

Source: CS, CSR,[22] the most recent version of the trial protocol and TSAP,[21] company's response to the clarification letter, and ERG comment

3.3 Efficacy results from the PEGASUS trial

Efficacy results presented in this section are based on RCP data from the 24th December 2019 database lock.

In response to question A3 of the clarification letter, the company provided the observed values and CFB without censoring for transfusion for Hb level, ARC, ARC normalisation, LDH level and indirect bilirubin level for the 16-week RCP. The ERG considers that the uncensored values are consistent with the censored values.

In response to question A7 of the clarification letter, the company provided the observed values and CFB without censoring for the 32-week open-label period (OLP) from Week 17 to Week 48 for all reported outcomes. At Week 48 of the PEGASUS trial, [redacted]/41 patients from the pegcetacoplan arm and [redacted]/39 patients from the eculizumab arm after switching to pegcetacoplan discontinued treatment with pegcetacoplan due to AEs with [redacted] discontinuations due to haemolysis.

3.3.1 Haemoglobin outcomes

Change from baseline in haemoglobin level at Week 16

Summary results for CFB in Hb level at Week 16 are provided in Table 9.

Table 9 Summary of PEGASUS trial CFB in Hb level at Week 16 results: ITT population

	Pegcetacoplan	Eculizumab
MMRM model, censored for transfusion		
N	41	39
LS Mean (SE) g/dL	2.37 (0.363)	-1.47 (0.666)
LS Mean difference (95% CI)	3.84 (2.33 to 5.34)	
p-value	<0.0001	
All available data, uncensored for transfusion		
N	[redacted]	[redacted]
Mean (SD) g/dL	[redacted]	[redacted]

CFB=change from baseline; CI=confidence interval; ITT=intention-to-treat; LS=least squares; MMRM=mixed model repeated measures; SE=standard error
Source: CS, Table 7 and company response to question A3 of the clarification letter, Table 1

CFB in Hb level was the PEGASUS trial primary outcome. In all randomised patients, CFB in Hb level at Week 16 was statistically significantly higher in the pegcetacoplan arm compared to the eculizumab arm (least squares [LS] mean difference=3.84, 95% confidence interval [CI]: 2.33 to 5.34, p<0.0001).

The observed Hb level values were higher in the pegcetacoplan arm compared to the eculizumab arm at all time points when data were censored (CS, Table 8) and uncensored (company response to question A3 of the clarification letter, Table 1) for transfusion. The ERG notes that when data were censored for transfusion, observed data up to Week 16 were only available from [redacted]/39 patients in the eculizumab arm compared to [redacted]/41 patients in the pegcetacoplan arm.

The observed values and CFB in Hb level (uncensored for transfusion) at Week 16 (company response to question A3 of the clarification letter, Table 1) were maintained at Week 48 (company response to question A7 of the clarification letter, Table 11) for patients originally randomised to the pegcetacoplan arm.

Haemoglobin response in absence of transfusion

In the PEGASUS trial, Hb response in the absence of transfusion was defined as an increase of ≥1g/dL from baseline Hb level at Week 16 without transfusion (CS, p35). At Week 16, [redacted]/41 patients ([redacted]) in the pegcetacoplan arm met the definition for Hb response compared to [redacted]/39 patients ([redacted]) in the eculizumab arm (CS, Table 19). At Week 48, [redacted]/41 patients ([redacted]) originally randomised to the pegcetacoplan arm met the definition for Hb response (company response to question A7 of the clarification letter, Table 17).

Haemoglobin normalisation in absence of transfusion

In the PEGASUS trial, Hb normalisation in the absence of transfusion was defined as patients who achieved a Hb level at or above the gender-specific lower limit of normal (LLN) range (female LLN=12g/dL; male LLN=13.6g/dL) at Week 16 without transfusion.[29] In the pegcetacoplan arm, 14/41 patients (34.1%) achieved Hb normalisation without transfusion compared to 0/39 patients (0%) in the eculizumab arm (CS, Table 20). At Week 48, [redacted]/41 patients ([redacted]) originally randomised to the pegcetacoplan arm achieved Hb normalisation without transfusion (company response to question A7 of the clarification letter, Table 18).

3.3.2 Transfusion avoidance

Summary results for transfusion avoidance at Week 16 are provided in Table 10.

Table 10 Summary of PEGASUS trial transfusion avoidance at Week 16 results: ITT population

Transfusion avoidance	Pegcetacoplan (N=41)	Eculizumab (N=39)
Yes (patient did not receive a transfusion)		
n (%)	35 (85.4)	6 (15.4)
No (patient did receive a transfusion)		
n (%)	6 (14.6)	33 (84.6)
Difference in percentage		
Risk difference (95% CI)	0.6253 (0.4830 to 0.7677)	
Nominal p-value	<0.0001	

CI=confidence interval; ITT=intention-to-treat
Source: CS, Table 13

In all randomised patients, transfusion avoidance during the RCP was statistically significantly higher in the pegcetacoplan arm compared to the eculizumab arm (risk difference [RD]=0.63, 95% CI: 0.48 to 0.77, p<0.0001). Non-inferiority was demonstrated (as the lower bound of the 95% CI exceeded the pre-defined non-inferiority margin of -20%) for pegcetacoplan versus eculizumab for transfusion avoidance (CS, Figure 7). At Week 48, [redacted]/41 patients ([redacted]) originally randomised to the pegcetacoplan arm did not require a transfusion; [redacted]/41 patients ([redacted]) required a transfusion and [redacted]/41 patients ([redacted]) withdrew from treatment with pegcetacoplan without having had a transfusion (company response to question A7 of the clarification letter).

3.3.3 Absolute reticulocyte count outcomes

Change from baseline in absolute reticulocyte count at Week 16

Summary results for CFB in absolute reticulocyte count (ARC) at Week 16 are provided in Table 11.

Table 11 Summary of PEGASUS trial CFB in ARC at Week 16 results: ITT population

	Pegcetacoplan	Eculizumab
MMRM model, censored for transfusion		
N	41	39
LS Mean (SE) 10^9 cells/L	−135.82 (6.54)	27.79 (11.86)
LS Mean difference (95% CI) 10^9 cells/L	-163.61 (−189.91 to −137.30)	
p-value	<0.0001	
All available data, uncensored for transfusion		
N	[redacted]	[redacted]
Mean (SD) 10^9 cells/L	[redacted]	[redacted]

CFB=change from baseline; CI=confidence interval; ITT=intention-to-treat; LS=least squares; MMRM=mixed model repeated measures; SD=standard deviation; SE=standard error
Source: CS, p53 and Figure 8, CSR, Table 30 and company response to question A3 of the clarification letter, Table 2

ARC is an indicator of EVH. Reduced ARC indicates reduced EVH. In all randomised patients, when data were analysed using the mixed model repeated measures (MMRM) approach and were censored for transfusion, compared to baseline values, ARC was statistically significantly reduced in the pegcetacoplan arm compared to the eculizumab arm at Week 16 (LS mean difference=-163.61x10^9 cells/L, 95% CI: -189.91 to -137.30, p<0.0001). Non-inferiority was demonstrated (as the upper bound of the 95% CI was less than the pre-defined non-inferiority margin of 10 10^9 cells/L) for pegcetacoplan versus eculizumab for CFB in ARC at Week 16 (CS, Figure 9). The observed values for ARC were lower in the pegcetacoplan arm compared to the eculizumab arm at all time points during the RCP (company response to question A3 of the clarification letter, Table 2).

The observed values and CFB in ARC (uncensored for transfusion) at Week 16 (company response to question A3 of the clarification letter, Table 2) were maintained at Week 48 (company response to question A7 of the clarification letter, Table 13) for patients originally randomised to the pegcetacoplan arm.

Absolute reticulocyte count normalisation

In the PEGASUS trial, ARC normalisation in the absence of transfusion was defined as patients who achieved an ARC below the upper limit of normal (ULN; 120x10^9 cells/L) at Week 16 without transfusion.[29] In the pegcetacoplan arm, 32/41 patients (78.0%) achieved ARC normalisation compared to 1/39 patient (2.6%) in the eculizumab arm (CS, Table 21; odds ratio [OR]=[redacted], 95% CI: [redacted] to [redacted]). At Week 48, [redacted]/41 patients ([redacted]) originally randomised to the pegcetacoplan arm achieved ARC normalisation without transfusion (company response to question A7 of the clarification letter, Table 19).

When data were not censored for transfusion, [redacted]/41 patients ([redacted]) in the pegcetacoplan arm achieved ARC normalisation at Week 16 compared to [redacted]/39 patients ([redacted]) in the eculizumab

arm (company response to question A3 of the clarification letter, Table 5, OR=[redacted], 95% CI: [redacted] to [redacted]).

3.3.4 Lactate dehydrogenase outcomes

Change from baseline in lactate dehydrogenase level at Week 16

Summary results for CFB in LDH level at Week 16 are provided in Table 12.

Table 12 Summary of PEGASUS trial CFB in LDH level at Week 16 results: ITT population

	Pegcetacoplan	Eculizumab
MMRM model, censored for transfusion		
N	41	39
LS Mean (SE) U/L	−14.76 (42.71)	−10.12 (71.03)
LS Mean difference (95% CI) U/L	−4.63 (−181.30 to 172.04)	
p-value	0.9557	
All available data, uncensored for transfusion		
N	[redacted]	[redacted]
Mean (SD) U/L	[redacted]	[redacted]

CFB=change from baseline; CI=confidence interval; ITT=intention-to-treat; LS=least squares; MMRM=mixed model repeated measures; SD=standard deviation; SE=standard error
Source: CS, Table 14 and p54 and company response to question A3 of the clarification letter, Table 3

In all randomised patients (MMRM model, data censored for transfusion), CFB in LDH level at Week 16 was similar in the pegcetacoplan (−14.76U/L) and eculizumab (-10.12U/L) arms (LS mean difference=-4.63U/L, 95% CI: -181.30 to 172.04, p=0.9557). The observed values for LDH level were lower in the pegcetacoplan arm compared to the eculizumab arm from Week 2 to Week 6 when data were censored for transfusion (CS, Table 15) and at all time points when data were uncensored for transfusion (company response to question A3 of the clarification letter, Table 3). The mean LDH level for the pegcetacoplan arm was within the normal range from Week 2 to Week 16 (CS, Table 15). Clinical advice to the ERG supports the company conclusion that LDH levels in the pegcetacoplan and eculizumab arms were well-controlled at baseline and remained well-controlled at Week 16. Pegcetacoplan did not demonstrate non-inferiority for CFB in LDH level versus eculizumab (CS, Figure 11) as the upper bound of the 95% CI was not less than the pre-defined non-inferiority margin of 20U/L.

At Week 48, the mean LDH level remained within the normal range for patients originally randomised to the pegcetacoplan arm (company response to question A7 of the clarification letter, Table 14). Although the observed values (uncensored for transfusion) and CFB in LDH level fluctuated from Week 16 to Week 48, the observed mean LDH level remained below 1.5xULN (company response to question A3 of the clarification letter, Table 3 and company response to question A7 of the clarification letter, Table 14).

Lactate dehydrogenase normalisation

In the PEGASUS trial, LDH normalisation in the absence of transfusion was defined as patients who achieved an LDH level below the upper limit of normal (ULN; 226U/L) at Week 16 without transfusion.[29] In the pegcetacoplan arm, 29/41 patients (70.7%) achieved LDH normalisation compared to 6/39 patients (15.4%) in the eculizumab arm (CS, Table 16; OR=20.71, 95% CI: 5.35 to 80.17). At Week 48, [redacted]/41 patients ([redacted]) originally randomised to the pegcetacoplan arm achieved LDH normalisation (company response to question A7 of the clarification letter, Table 15).

3.3.5 Change from baseline in indirect bilirubin level at Week 16

Summary results for CFB in indirect bilirubin level at Week 16 are provided in Table 13

Table 13 Summary of PEGASUS trial CFB in indirect bilirubin level at Week 16 results: ITT population

	Pegcetacoplan	Eculizumab
MMRM model, censored for transfusion[a]		
N	41	39
LS Mean (SE) µmol/L	[redacted]	[redacted]
LS Mean difference (95% CI) µmol/L	[redacted]	
ITT population, all available data, uncensored for transfusion		
N	[redacted]	[redacted]
Mean (SD) µmol/L	[redacted]	[redacted]

CFB=change from baseline; CI=confidence interval; ITT=intention-to-treat; LS=least squares; MMRM=mixed model repeated measures; SD=standard deviation; SE=standard error
[a] The company did not report a p-value for this outcome
Source: CS, Table 22 and clarification response, Table 6

In all randomised patients (MMRM model, data censored for transfusion), the pegcetacoplan arm showed a [redacted] from baseline at Week 16 in indirect bilirubin level compared to the eculizumab arm (LS mean difference=[redacted]µmol/L, 95% CI: [redacted] to [redacted]). The pegcetacoplan arm had [redacted] indirect bilirubin level compared to baseline at all time points during the RCP. The eculizumab arm had [redacted] indirect bilirubin level compared to baseline at all time points during the RCP, except at Week 12 (CS, p62). The observed indirect bilirubin levels (uncensored for transfusion) were lower in the pegcetacoplan arm compared to the eculizumab arm at all time points (company response to question A3 of the clarification letter, Table 6). The observed values and CFB in indirect bilirubin level (uncensored for transfusion) at Week 16 (company response to question A3 of the clarification letter, Table 6) were maintained at Week 48 (company response to question A7 of the clarification letter, Table 20) for patients originally randomised to the pegcetacoplan arm.

3.4 Patient reported outcomes from the PEGASUS trial

HRQoL data were collected as part of the PEGASUS trial using three instruments:

- the EORTC QLQ-C30 questionnaire (v0)
- the FACIT-Fatigue scale (v4)
- Linear Analog Scale Assessment (LASA)

Clinical advice to the ERG is that EORTC QLQ-C30 questionnaire, FACIT-Fatigue scale and LASA are standard methods of collecting HRQoL data from patients with PNH. The FACIT-Fatigue scale was the only HRQoL outcome included in the PEGASUS trial hierarchical testing strategy (Table 8).

HRQoL was assessed in Week -2 and Week -4 of the run-in period and in Weeks 1, 2, 4, 6, 8, 12 and 16 of the RCP. Data collection was also scheduled during the 32-week OLP and twice post-study.

In response to question A3 of the clarification letter, the company provided the observed values and CFB without censoring for the 16-week RCP. The observed values without censoring for transfusion for global health status (GHS)/quality of life (QoL) score of the EORTC QLQ-C30 (CSR, Table 14.2.10.1.2), FACIT-Fatigue (company response to question A3 of the clarification letter, Table 4) and LASA (company response to question A3 of the clarification letter, Table 7) show that the scores at baseline for the two trial arms were [redacted].

In response to question A7 of the clarification letter, the company provided the observed values and CFB without censoring for the 32-week OLP from Week 17 to Week 48 for all HRQoL outcomes. HRQoL data are only available from the PEGASUS trial for 48 weeks. The ERG considers that long-term conclusions about the effect of pegcetacoplan on the HRQoL of patients with PNH are unknown.

The PEGASUS trial uncensored HRQoL data were mapped from the EORTC QLQ-C30 to the EuroQoL 5-dimension 3-level (EQ-5D-3L) scores and were used to generate the utility values used in the company model (Section 4.3.8).

3.4.1 Summary of EORTC QLQ-C30 data

The EORTC QLQ-C30 questionnaire CFB to Week 16 results, calculated using the MMRM approach are presented in the CS (Table 25). The company reported that the GHS/QoL score in the pegcetacoplan arm [redacted] (standard error [SE]: [redacted]) (a 10 point increase is generally considered to be clinically meaningful).[31] The ERG notes that patients in the eculizumab arm had a mean [redacted] ([redacted]; [redacted]) in GHS/QoL score. The company highlighted that patients in the pegcetacoplan arm experienced improvements on all functional

scales. Further, the GHS/QoL scores during the RCP of patients in the pegcetacoplan arm [redacted], whilst scores for patients in the eculizumab arm [redacted] from baseline to Week 6, [redacted] from Week 7 to Week 16 but [redacted] (CS, Figure 17). The improvement in GHS/QoL score was maintained at Week 48 for patients originally randomised to the pegcetacoplan arm (company response to question A7 of the clarification letter, Table 22).

On the individual symptoms scale, patients in the pegcetacoplan arm reported numerically greater improvements on several items compared with patients in the eculizumab arm, notably, fatigue, dyspnoea, appetite loss and financial difficulties. Patients in the eculizumab arm reported lower scores for pain, constipation and diarrhoea compared with patients in the pegcetacoplan arm.

3.4.2 Summary of FACIT-Fatigue data

Due to the PEGASUS trial pre-specified hierarchical testing rules, the company was unable to formally test the FACIT-Fatigue results for non-inferiority between pegcetacoplan and eculizumab (CS, p59).

The baseline scores for FACIT-Fatigue were similar in both arms of the trial (CS, Table 18).

The CFB results for FACIT-Fatigue during the RCP, calculated using the MMRM approach, are shown in the CS (Table 17). The company highlighted that at Week 16, a LS mean numerical difference of 11.87 (95% CI: 5.49 to 18.25) was observed (an increase of 3 points is accepted as clinically meaningful).[32]

The company reported (CS, p60) that from Week 2 onwards, the observed (censored for transfusion) mean score for FACIT-Fatigue of patients in the pegcetacoplan arm was comparable to scores derived from the general population (43.38 and 43.60, respectively). FACIT-Fatigue score ([redacted]) remained clinically improved for patients originally randomised to the pegcetacoplan arm at Week 48 of the OLP (company response to question A7 of the clarification letter, Table 16). The ERG notes that when data were censored for transfusion, the observed values for patients in the eculizumab arm remained largely unchanged from baseline (CS, Table 18).

3.4.3 Summary of LASA data

The results for CFB in LASA during the 16-week RCP, calculated using the MMRM approach are presented in the CS (Table 23). The company stated (CS, p64) that, throughout the 16-week RCP, patients in the pegcetacoplan arm recorded statistically significantly [redacted] CFB LS

mean scores compared with patients in the eculizumab arm. At Week 16, the difference between the two groups was [redacted] ([redacted]) in favour of pegcetacoplan. The company also stated (CS, p64) that the minimally clinically important difference for scores on the LASA is 30 to 60 points.[33]

When data were censored for transfusion, the observed values for mean LASA score at baseline were similar for both treatment arms (CS, Table 24). The company highlighted that the observed, uncensored values for CFB in LASA are similar to the values of the MMRM analysis. The company also highlighted that the trend across time in CFB (CS, Figure 16) showed that patients in the pegcetacoplan arm [redacted], whilst scores for patients in the eculizumab arm [redacted]. The improvement in LASA scores was maintained at Week 48 for patients originally randomised to the pegcetacoplan arm (company response to question A7 of the clarification letter, Table 21).

3.5 Safety and tolerability results from the PEGASUS trial

Safety and tolerability data from the PEGASUS trial are presented in the CS (Section B.2.10). Safety data were presented using the run-in and safety analysis populations (Table 8). AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA, version 20.0).[34]

The company defined a treatment-emergent adverse event (TEAE) as any AE that started or increased in severity on or after the first dose of study drug (or any AE that started before the date of the first dose but increased in severity on or after the first dose), and no later than 30 days after the last dose (CS, Table 6).

3.5.1 Exposure to study treatment

During the run-in period (28 days), the mean treatment duration was [redacted] days for the pegcetacoplan arm and [redacted] days for the eculizumab arm. Nearly all ([redacted]/80; [redacted]) patients treated with eculizumab+pegcetacoplan completed treatment without dosing interruption, with a mean of [redacted] pegcetacoplan infusions per patient.

During the 16-week RCP, the mean treatment duration was [redacted] days for the pegcetacoplan arm and [redacted] days for the eculizumab arm. [redacted]/41 ([redacted]) patients in the pegcetacoplan arm completed all infusions (mean=[redacted] infusions). [redacted] of 41 patients ([redacted]) had a total of [redacted] interrupted pegcetacoplan infusions.

Treatment exposure data for the safety population during RCP are summarised in the CS (Table 36).

3.5.2 Treatment-emergent adverse events

A summary of safety population treatment emergent adverse events (TEAEs) is provided in Table 14.

Table 14 Summary of safety population TEAEs (RCP)

	Pegcetacoplan (N=41) n (%)	Eculizumab (N=39) n (%)
Any TEAEs	36 (87.8)	34 (87.2)
Total events	[redacted]	[redacted]
Unique events	[redacted]	[redacted]
Treatment-related TEAEs, related to pegcetacoplan	[redacted]	[redacted]
Treatment-related TEAEs, related to eculizumab	[redacted]	[redacted]
Treatment-related TEAEs, related to infusion	[redacted]	[redacted]
Serious TEAEs	7 (17.1)	6 (15.4)
Serious TEAEs, related to pegcetacoplan	[redacted]	[redacted]
Serious TEAEs, related to eculizumab	[redacted]	[redacted]
Serious TEAEs, related to infusion	[redacted]	[redacted]
Mild	[redacted]	[redacted]
Moderate	[redacted]	[redacted]
Severe	[redacted]	[redacted]
Injection site reaction	[redacted]	[redacted]
TEAEs leading to study drug discontinuation	3 (7.3)	0
TEAEs leading to death	0	0

[a] TEAEs that occurred after randomisation date but before the first monotherapy are summarised under the pegcetacoplan+ eculizumab group
AE=adverse event; NA=not applicable; RCP=randomised controlled period; TEAE=treatment-emergent adverse event
Source: Primary CSR, Table 99[22]

During the run-in period, there was [redacted] SAE ([redacted]), attributed to both pegcetacoplan and eculizumab, which resolved by Day -15. During the run-in period, there were no TEAEs reported leading to study or treatment discontinuation, or death.

During the RCP, similar proportions of patients in the pegcetacoplan and eculizumab arms experienced at least one TEAE (87.8% and 87.2%, respectively). A higher proportion of patients ([redacted]/41 patients; [redacted]) in the pegcetacoplan arm experienced treatment-related AEs (TRAEs) than patients ([redacted]/39 patients; [redacted]) in the eculizumab arm. The most common TRAEs ([redacted]/41 patients; [redacted]) in the pegcetacoplan arm were injection site reactions (ISRs). However, none of the ISRs reported by patients in the pegcetacoplan arm were considered as serious, severe, or led to treatment discontinuation.

During the RCP, 7/41 patients in the pegcetacoplan arm and 6/39 patients in the eculizumab arm experienced serious TEAEs; of these, [redacted] in each arm experienced a TRAE. There were no deaths reported in either treatment arm.

During the RCP, [redacted]/39 patients ([redacted]%) in the eculizumab arm experienced haemolytic events compared to 4/41 patients (9.8%) in the pegcetacoplan arm. From post-hoc analysis, 4/41 patients (9.8%; five events) in the pegcetacoplan arm and 9/39 patients (23.1%) in the eculizumab arm were considered to have experienced BTH (CS, p90). In the pegcetacoplan arm, 3/41 patients discontinued treatment due to BTH; of these, [redacted] withdrew from the study and [redacted] were able to re-enter the study during the follow-up period.

3.5.3 Common treatment-emergent adverse events

A summary of specific TEAEs reported by ≥5% patients in the safety population is provided in Table 15.

Table 15 TEAEs reported by ≥5% patients during the 16-week RCP (safety population)

System organ class/ preferred term	Pegcetacoplan (N=41) n (%)	Eculizumab (N=39) n (%)
Any TEAEs	36 (87.8)	34 (87.2)
General disorders and administration site conditions	[redacted]	[redacted]
Injection site erythema	7 (17.1)	0
Injection site reaction	5 (12.2)	0
Injection site swelling	4 (9.8)	0
Asthenia	3 (7.3)	3 (7.7)
Injection site induration	3 (7.3)	0
Fatigue	2 (4.9)	6 (15.4)
Pyrexia	2 (4.9)	2 (5.1)
Vaccination site pain	0	2 (5.1)
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]
Back pain	3 (7.3)	4 (10.3)
Pain in extremity	3 (7.3)	1 (2.6)
Gastrointestinal disorders	[redacted]	[redacted]
Diarrhoea	9 (22.0)	1 (2.6)
Abdominal pain	5 (12.2)	4 (10.3)
Nausea	2 (4.9)	2 (5.1)
Vomiting	0	3 (7.7)
Infections and infestations	[redacted]	[redacted]
Viral upper respiratory tract infection	2 (4.9)	2 (5.1)
Urinary tract infection	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]
Haemolysis	4 (9.8)	9 (23.1)
Anaemia	0	5 (12.8)
Nervous system disorders	[redacted]	[redacted]
Headache	3 (7.3)	9 (23.1)
Dizziness	1 (2.4)	4 (10.3)
Vascular disorders	[redacted]	[redacted]
Hypertension	3 (7.3)	1 (2.6)
Metabolism and nutrition disorders	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]
Dyspnoea	1 (2.4)	2 (5.1)
Oropharyngeal pain	0	2 (5.1)
Hepatobiliary disorders	[redacted]	[redacted]
Hyperbilirubinaemia	0	2 (5.1)
Psychiatric disorders	[redacted]	[redacted]
Anxiety	1 (2.4)	2 (5.1)
Insomnia	0	2 (5.1)

Cardiac disorders	[redacted]	[redacted]
Palpitations	0	2 (5.1)
Renal and urinary disorders	[redacted]	[redacted]
Chromaturia	0	2 (5.1)

[a] TEAEs that occurred after randomisation date but before the first monotherapy are summarised under the pegcetacoplan+ eculizumab group
RCP=randomised controlled period; TEAE=treatment-emergent adverse event
Source: Primary CSR, Table 100[22]

Run-in period

During the run-in period, [redacted]/80 patients experienced TEAEs that were attributed to pegcetacoplan. Of the [redacted]/80 patients ([redacted]) who experienced general disorders and administration site conditions during the run-in period, injection site erythema was the most common TEAE and occurred in [redacted]/80 patients ([redacted]), followed by injection site pruritus and injection site swelling ([redacted]/80 patients; [redacted]), ISR ([redacted]/80 patients; [redacted]), injection site induration ([redacted]/80 patients; [redacted]) and injection site pain ([redacted]/80 patients; [redacted]). [redacted]/80 patients ([redacted]) experienced nervous system disorders, with [redacted]/80 patients ([redacted]) reporting headache.

Eculizumab-related TEAEs were reported by [redacted]/80 patients ([redacted]) and included increased alanine aminotransferase (ALT), sepsis, decreased platelet count, neutropenia, and jaw pain.

Of the [redacted]/80 patients ([redacted]) who experienced at least one TEAE, most frequently reported events (reported by ≥5% of patients) included injection site erythema ([redacted]/80 patients; [redacted]), injection site pruritus ([redacted]/80 patients; [redacted]), injection site swelling ([redacted]/80 patients; [redacted]), ISR ([redacted]/80 patients; [redacted]), injection site induration ([redacted]/80 patients; [redacted]) and injection site pain ([redacted]/80 patients; [redacted]).

Randomised controlled period

The company reports (CS, p88) that during the RCP, system organ class of TEAEs were reported by [redacted]/41 patients ([redacted]) in the pegcetacoplan arm and [redacted]/39 patients ([redacted]) as shown in Table 15.

3.5.4 Summary of safety results

The company considers that pegcetacoplan is well-tolerated and has a manageable toxicity profile. Of the TEAEs that were possibly related to pegcetacoplan, the majority were related to the injection site. No thromboembolic events or deaths were reported.

Clinical advice to the ERG is that although there are no unexpected safety concerns associated with pegcetacoplan, long-term follow-up data are required to ensure that there are no AEs associated with prolonged treatment with pegcetacoplan.

3.6 ERG critique of the indirect evidence

In the absence of head-to-head data comparing the efficacy and safety of pegcetacoplan with ravulizumab, the company conducted an anchored MAIC using PEGASUS trial and Study 302[20] data. The company concluded that the results of the anchored MAIC may be biased due to the heterogeneity between the patient populations enrolled in these two trials[20,21] and did not use results in their economic model (CS, Section B.3.2). The ERG has, therefore, only provided a brief description and critique of the indirect evidence and the company anchored MAIC. Full details of the company approach to the anchored MAIC, trial and participant characteristics and the company's quality assessments of the two trials[20,21] can be found in the CS (Section 2.9 and Appendix D).

3.6.1 Trials identified and included in the anchored MAIC

The company anchored MAIC included the PEGASUS trial and Study 302.[20] Study 302[20] is a randomised, open-label, multicentre, phase III non-inferiority study which compared the clinical efficacy of ravulizumab versus eculizumab among adult patients with PNH who had previously been treated with eculizumab. The company adjusted individual patient data (IPD) from the PEGASUS trial (CS, Table 31) to match the aggregate baseline characteristics of Study 302[20] and the indirect comparison of pegcetacoplan and ravulizumab was anchored by the common eculizumab control arm of the two trials.

Trial designs and populations

The company identified key differences in the designs of the two trials[20,21] which could not be adjusted to make them comparable using anchored MAIC methods (or any other adjusted indirect comparison method). These differences include treatment phases, lengths of treatment periods, routes of administration and the treatment administration schedules of pegcetacoplan and ravulizumab, as well as the dose of eculizumab.

The company also identified important differences in eligibility criteria. The PEGASUS trial population enrolled adults with PNH who had Hb levels lower than 10.5 g/dL despite treatment with eculizumab, while Study 302[20] enrolled adults with PNH who were clinically stable after having been treated with eculizumab for at least 6 months (i.e., all patients were eligible regardless of Hb levels). This difference means that the Study 302[20] population is wider than the PEGASUS trial population in terms of Hb levels. It is, therefore not possible to accurately match the Hb levels of PEGASUS trial patients to the Hb levels of the Study 302[20] population.

Outcomes measured in the trials

The clinical, haematological, fatigue and HRQoL outcome data reported in both trials[20,21] that were considered in the company anchored MAIC are listed in the CS (Table 33). Definitions of the outcomes measured in both trials were similar, although outcomes were measured up to Week 16 in the PEGASUS trial and up to Week 26 in Study 302.[20] CFB in Hb level, the primary outcome of the PEGASUS trial, was not measured in Study 302.[20]

3.6.2 Methodological approach to the indirect comparisons

The company conducted an anchored MAIC following the methods described in the NICE DSU Technical Support Document 18.[35]

The baseline characteristics considered in the anchored MAIC are described in the CS (Table 32) and the company used a propensity score model (logistic regression approach) to match characteristics of patients in the PEGASUS trial to the characteristics of patients in Study 302.[20] The weights estimated from the propensity score model were used to calculate an effective sample size (ESS) for the anchored MAIC. An ESS which is approximately equal to the sample size of the PEGASUS trial data prior to matching indicates sufficient overlap in the two trial populations for an anchored MAIC to be appropriate. However, following matching and exclusion of some baseline characteristics from the matching process (i.e., the ones that were very different between the trials) (CS, Table 32), the estimated ESS for pegcetacoplan and the estimated ESS for eculizumab were smaller than the PEGASUS trial arms prior to matching that were included within the anchored MAIC (CS, Table 34 and Table 35), which indicates a lack of overlap in the trial populations following matching.

The company and the ERG agree with the authors of the NICE DSU TSD 18 report,[35] that exclusion of important effect modifiers from the matching process (in this case, Hb level and history of transfusions) means that anchored MAIC results will be biased.

3.6.3 Anchored MAIC results and conclusions

Statistically significant advantages for pegcetacoplan over ravulizumab were shown for all outcomes considered in the anchored MAIC. However, it was not possible to adjust for differences in trial designs and populations and this is likely to have introduced bias into the anchored MAIC. The ERG, therefore, agrees with the company conclusion that anchored MAIC results are not robust and should not be used to inform decision making.

3.7 Conclusions of the clinical effectiveness section

Results from the PEGASUS trial demonstrated that treatment with pegcetacoplan was superior to eculizumab in improving clinical and haematologic outcomes in patients with PNH. The key area of concern is the absence of direct evidence (and only biased indirect evidence) to demonstrate the effectiveness of pegcetacoplan versus ravulizumab in the PEGASUS trial population. The NICE recommendation for ravulizumab[17] is based on results from Study 302[20] (which showed that ravulizumab was non-inferior to eculizumab, with point estimates favouring ravulizumab for all primary and key secondary endpoints). However, Study 302[20] enrolled a population that was broader than the PEGASUS trial population. In addition, there are key differences between the Study 302[20] and PEGASUS trial designs (CS, pp74-75).

It is unclear whether the Hb cut-off level of <10.5g/dL (a PEGASUS trial entry criterion) is relevant to PNH patients treated in NHS clinical practice.

4 COST EFFECTIVENESS EVIDENCE

The CS includes cost effectiveness evidence to support the use of pegcetacoplan as a treatment for PNH. The two key components of the economic evidence presented in the CS are (i) a systematic review to identify relevant economic evidence and (ii) a report of the company's de novo economic evaluation. The company has also provided an electronic copy of their economic model, which was developed in Microsoft Excel.

4.1 ERG critique of the company systematic review methods

The company searched relevant databases (MEDLINE, MEDLINE In-Process, Embase, BioScience Information Service of Biological Abstracts, EconLit and Cochrane Library comprising the Database of Abstracts of Reviews of Effectiveness, National Health Service's Economic Evaluation Database and Health Technology Assessment [HTA] database) to find economic evaluations, HRQoL, cost and resource use linked to PNH; see CS, Appendix G for full details. The searches were conducted on 30 July 2020 and updated on 11 March 2021. In addition, the company carried out the following grey literature searches:

- a search of the European Hematology Association's website to identify conference abstracts not yet indexed in Embase
- a search of the Cost-Effectiveness Analysis Registry to identify relevant utility weights
- searches to identify relevant HTA documents from the International Network of Agencies for Health Technology Assessment (INAHTA), National Institute for Health and Care Excellence (NICE), the Scottish Medicines Consortium (SMC), the Canadian Agency for Drugs and Technologies in Health (CADTH), and the Pharmaceutical Benefits Advisory Committee (PBAC).

The searches identified 10 unique economic evaluations of PNH treatments (12 publications). All these evaluations considered eculizumab, except for one HTA report[18] that focussed on ravulizumab. No economic evaluations of pegcetacoplan were identified by the company.

An assessment of the extent to which the company's economic literature review was conducted in accordance with the LR*i*G in-house systematic review checklist is summarised in Table 16.

Table 16 ERG comments on company review methods

Review process	ERG response
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes
Were appropriate sources searched?	Yes
Was the timespan of the searches appropriate?	Yes
Were appropriate search terms used?	Yes
Were the eligibility criteria appropriate to the decision problem?	Yes
Was study selection applied by two or more reviewers independently?	Yes
Was data extracted by two or more reviewers independently?	Yes
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes
Was the quality assessment conducted by two or more reviewers independently?	Yes
Were attempts to synthesise evidence appropriate?	Yes

ERG=Evidence Review Group
Source: LR*i*G in-house checklist

4.2 ERG conclusions regarding company systematic review methods

The ERG considers that the methods used by the company to identify economic studies were appropriate. The ERG re-ran the company searches on 28 June 2021 and is satisfied that no relevant economic evaluations of pegcetacoplan have been published that include patients with PNH.

4.3 ERG summary of the company's submitted economic evaluation

The information summarised in this section has been sourced from the CS, the updated company economic model (12 July 2021) and the company response to the clarification letter.

4.3.1 NICE Reference Case and Drummond checklists

Table 17 NICE Reference Case checklist

Element of health technology assessment	Reference case	ERG comment on the company's economic evaluation
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	Partly. Focus is on NHS costs
Type of economic evaluation	Cost utility analysis with fully incremental analysis	Partly. Company presented pairwise cost effectiveness results
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes
Synthesis of evidence on health effects	Based on systematic review	No. A synthesis of evidence was not possible. Based on clinical opinion and results from Study 302,[20] the company assumed that the efficacy of ravulizumab was the same as the efficacy of eculizumab
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults	Yes
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes

EORTC QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core30; EQ-5D=EuroQol-5 dimensions; ERG=Evidence Review Group; PSS=Personal Social Services; QALY=quality adjusted life years
Source: NICE Guide to the Methods of Technology Appraisal[36] and ERG comment

Table 18 Critical appraisal checklist for the economic analysis completed by the ERG

Question	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Partly	PEGASUS trial data were used to calculate transition probabilities for pegcetacoplan (48-week data) and eculizumab (16-week data). The ERG considers that it is not possible to be certain from the available clinical trial evidence that, for the PEGASUS trial population, the efficacy of ravulizumab is the same as the efficacy of eculizumab.
Were all the important and relevant costs and consequences for each alternative identified?	Yes	
Were costs and consequences measured accurately in appropriate physical units?	Yes	
Were the cost and consequences valued credibly?	Yes	
Were costs and consequences adjusted for differential timing?	Yes	
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	
Did the presentation and discussion of study results include all issues of concern to users?	Yes	

ERG=Evidence Review Group
Source: Drummond and Jefferson 1996[37] and ERG comment

4.3.2 Population

The company describe the modelled population as adults with PNH whose anaemia is not sufficiently controlled after treatment with a C5 complement inhibitor for at least 3 months. Baseline characteristics of the modelled population were obtained from the PEGASUS trial (mean age=48.8 years old; mean body weighed=[redacted]kg; proportion female=61.3%; average time since diagnosis=[redacted] years).

4.3.3 Model structure

The company's de novo cost utility model was developed in Microsoft Excel. The model is a cohort-based Markov model comprising four mutually exclusive health states: No Transfusion (in previous 4 weeks) and Hb <10.5g/dL, No Transfusion (in previous 4 weeks) and Hb ≥10.5g/dL, Transfusion Required (in previous 4 weeks) and Death (Figure 3). The company stated (CS, Section B.3.2) that the model structure reflects both the nature of PNH and the evidence that is available from the PEGASUS trial. The Hb cut-off (10.5g/dL) used in the model is consistent with a PEGASUS trial inclusion criterion. The company has assumed that the frequency of spontaneous remissions do not vary by treatment arm.

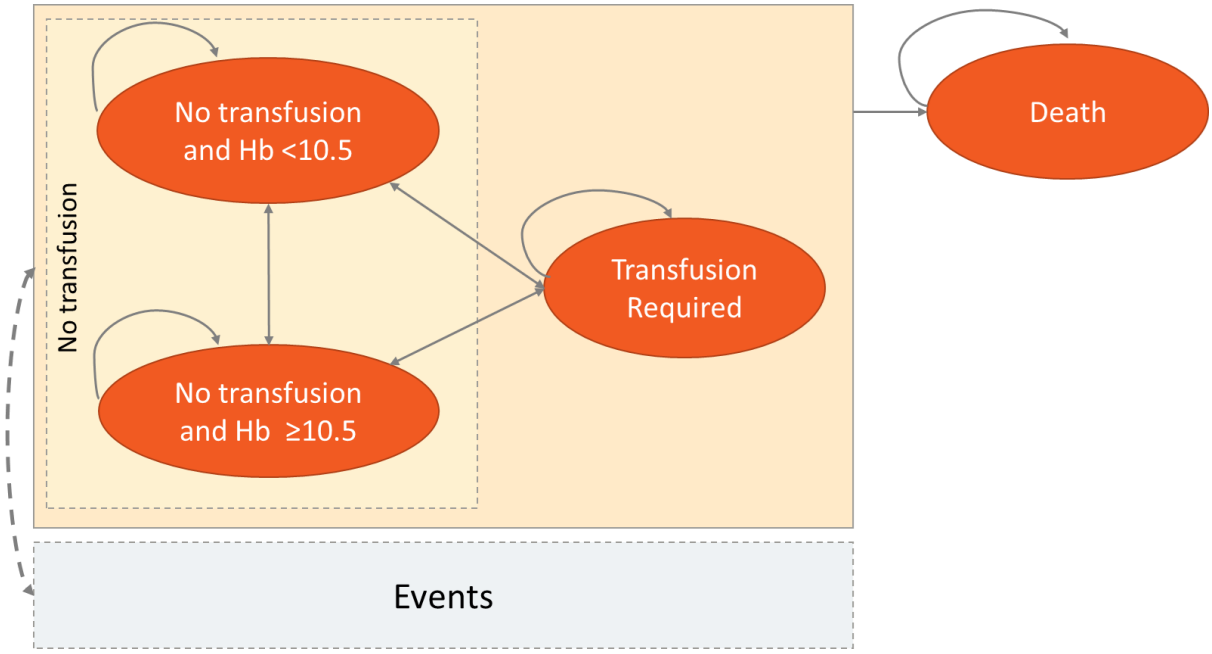

Figure 3 Structure of the company model

Hb=haemoglobin
Source: CS, Figure 18

The model starts with all patients being in the No Transfusion and Hb <10.5g/dL health state. At the end of each cycle, patients can remain in their current health state or move to any other health state. Death is an absorbing state from which no transition is permitted.

4.3.4 Interventions and comparators

The modelled intervention is pegcetacoplan and the comparators are eculizumab and ravulizumab. The intervention and comparators match those listed in the final scope[11] issued by NICE.

4.3.5 Perspective, time horizon and discounting

The company stated that, in line with the NICE Reference Case,[36] the model perspective is the NHS and PSS. The model cycle length is 4 weeks, and a half-cycle correction is applied.

The model time horizon is 51 years, and costs and outcomes are discounted at 3.5% per annum.

4.3.6 Treatment effectiveness and extrapolation

The key clinical effectiveness parameter used in the company model is CFB to Week 16 Hb level (PEGASUS trial primary outcome).

Modelling transition probabilities

Patient level data from the PEGASUS trial were used by the company to estimate transition probabilities for patients receiving pegcetacoplan and eculizumab. The efficacy of ravulizumab was assumed to be equal to that of eculizumab. A multinomial logistic regression model with the current health state as the outcome variable and age, visits, treatment and health as covariates, was used to calculate transition probabilities. The base case transition probabilities were derived from PEGASUS trial data (pegcetacoplan: baseline to Week 48; eculizumab: baseline to Week 16). The transition probabilities used in the model are shown in Table 19.

Table 19 Company model base case transition probabilities

From	To		
	No Transfusion and Hb <10.5g/dL	**No Transfusion and Hb ≥10.5g/dL**	**Transfusion Required**
Pegcetacoplan			
No transfusion and Hb <10.5g/dL	[redacted]	[redacted]	[redacted]
No transfusion and Hb ≥10.5g/dL	[redacted]	[redacted]	[redacted]
Transfusion required	[redacted]	[redacted]	[redacted]
Eculizumab/ravulizumab			
No transfusion and Hb <10.5g/dL	[redacted]	[redacted]	[redacted]
No transfusion and Hb ≥10.5g/dL	[redacted]	[redacted]	[redacted]
Transfusion required	[redacted]	[redacted]	[redacted]

Hb=haemoglobin
Source: Updated company model (12 July 2021)

Breakthrough haemolysis

Expert advice to the company was that the decrease in Hb levels and blood transfusions resulting from extravascular breakthrough haemolysis (EVBTH) were captured in the model health states and, therefore, it was not necessary to explicitly model EVBTH.

Pegcetacoplan

At the time of the PEGASUS trial, there was no established approach to treating intravascular breakthrough haemolysis (IVBTH) for patients treated with pegcetacoplan; however, expert advice to the company was that patients treated with pegcetacoplan who experienced IVBTH would be prescribed a one-off dose of eculizumab (900mg). Based on [redacted]/41 patients in the PEGASUS trial experiencing IVBTH, an IVBTH per cycle (month) rate of [redacted]% was used in the base case. In the company model, following a one-off treatment with eculizumab, patients return to treatment with pegcetacoplan.

Eculizumab and ravulizumab

IVBTH was not modelled for patients receiving eculizumab or ravulizumab; the company has assumed that for patients treated with these drugs, IVBTH would be managed using dose adjustments.

Discontinuation of treatment with pegcetacoplan

The company highlighted that, of the 41 patients in the pegcetacoplan arm of the PEGASUS trial, [redacted] ([redacted]) discontinued treatment with pegcetacoplan over the 16 Week RCP and was prescribed eculizumab. In the pegcetacoplan arm of the company model, at Week 16, [redacted] of patients were modelled to switch from treatment with pegcetacoplan to treatment with eculizumab.

Iron overload

It is stated in the CS (p23) that patients treated with pegcetacoplan do not need chelation therapy as their Hb levels can be managed by phlebotomy. Clinical advice to the company is that the majority of transfusion dependent patients with EVH will be on life-long chelation therapy for iron overload (CS, p 123).

Mortality

In the model, it has been assumed that mortality is not affected by treatment. Probabilities of death used in the model are estimated based on age- and sex-matched general population mortality data.[38]

4.3.7 Adverse events

AE costs were not included in the company base case analysis. The costs associated with serious TEAEs occurring in ≥2% of the PEGASUS trial population (CS, Table 51) were included a scenario analysis.

4.3.8 Health-related quality of life

The company literature searches did not identify any published data reporting EQ-5D responses for patients with PNH.

The company utilised PEGASUS trial EORTC QLQ-C30 data as the basis for calculating utility values (EQ-5D data were not collected as part of the PEGASUS trial). In line with the NICE Reference Case,[36] the company mapped PEGASUS trial EORTC QLQ-C30 data to EQ-5D-3L values using the Longworth 2014[39] mapping algorithm. The resulting utility values were then age-adjusted using the Ara and Brazier[40] 2011 algorithm. The model also includes a disutility to account for the effect of chelation therapy (-0.03) and a disutility to model the effect of frequent regular eculizumab infusion (-0.025) (TA698).[18] The base case utility values used in the company model are presented in Table 20.

Table 20 Base case utilities used in the model

Utilities/disutilities	Value	Source
Health state utilities		
No transfusion and Hb <10.5g/dL	0.738	PEGASUS trial EORTC QLQ-C30 mapped to EQ-5D-3L values
No transfusion and Hb ≥10.5g/dL	0.809	
Transfusion required	0.695	
Disutilities		
Chelation therapy (iron overload)	-0.03	Cherry 2012[41]
Eculizumab IV infusions	-0.025	Assumption based on NICE TA698[18]

EORTC QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core30; EQ-5D=EuroQol-5 dimensions; Hb=haemoglobin; IV=intravenous; NICE=National Institute for Health and Care Excellence; TA=technology appraisal
Source: CS, Table 53

4.3.9 Resource use and costs

The costs included in the company model are considered under three categories:

- intervention and comparator costs
- AE costs
- other costs.

Intervention and comparator treatment acquisition and administration costs

Pegcetacoplan is available to the NHS at a discounted confidential PAS price. This price is used in the company model. The unit costs of eculizumab and ravulizumab were obtained from the British National Formulary (BNF)[42] and TA698[18] respectively. In the base case, the company has assumed no vial wastage and has calculated the doses of pegcetacoplan and eculizumab per administration based on the PEGASUS trial data.

Pegcetacoplan dosing schedule

In the company model, only the cost of pegcetacoplan at the maintenance dose of SC pegcetacoplan 1080mg twice weekly is included (i.e., treatment with eculizumab for the initial 4-week period is not included). The first dose of pegcetacoplan was administered in a clinic whilst subsequent doses were administered by the patient at home (the second and third doses were administered under the supervision of a community nurse).

Eculizumab dosing schedule

IV eculizumab (900mg) was administered to patients every 14 days. This dose could be escalated to 900mg every 11 days or to between 1200mg and 1500mg every 14 days. Based on the trial data, 70% patients received the licensed dose of IV 900mg every 2 weeks. Dose escalation (every 11 days) was: IV 900mg ([redacted]% of patients), 1200mg ([redacted]% of patients) and 1500mg ([redacted]% of patients). The model did not include any administration costs for eculizumab and ravulizumab as the company assumed that the manufacturer of these drugs would cover these costs.

Ravulizumab dosing schedule

Weight-based IV infusion of ravulizumab is with one loading dose (2400mg for body weight 40-59kg, 2700mg for body weight 60-99kg, 3000mg for body weight 100kg and above) followed, after 2 weeks, by a maintenance dose varying from 3000mg to 3600mg administered every 8 weeks. The drug acquisition (list) prices and drug administration costs used in the company model are presented in Table 21.

Table 21 Drug acquisition and administration costs

Drug	Dosing	List price per vial	Cost per admin (no vial wastage)	Source
Pegcetacoplan	1080mg SC twice weekly Dosing escalation: 1080mg SC every 3 days	[redacted] (for 1080mg vial size)	£49 (1st dose); £29.67 (2nd/3rd dose)	PSSRU[43]
Eculizumab	IV 600mg loading dose infused over 30 minutes and given weekly for 4 doses, then IV 900mg maintenance dose infused over 35 minutes every 2 wks Dosing escalation: IV 900mg every 11 days or IV 1200mg/1500mg every 2 wks	£3,150 (for 300mg vial size)	£0	BNF[42] PSSRU[43]
Ravulizumab	IV 2400mg loading dose for one dose infused over at least 114 minutes and IV 3000mg maintenance dose (40-59kgs) infused over at least 140 minutes every 8 wks Dosing escalation: None recommended	£4,533 (for 300mg vial size)	£0	TA698[18] PSSRU[43]
	IV 2700mg loading dose for one dose infused over at ≥102 minutes and IV 3300mg maintenance dose (60-99kgs) infused over ≥120 minutes every 8 wks Dosing escalation: None recommended			
	IV 3000mg loading dose for one dose infused over at least 108 minutes and IV 3600mg maintenance dose (>100kgs) infused over 132 minutes every 8 wks Dosing escalation: None recommended			

admin=administration; BNF=British National Formulary; PSSRU=Personal Social Services Research Unit; SC=subcutaneous; IV=intravenous; wks=weeks
CS, Table 56, Table 57, updated company model (12 July 2021)

Other costs

- BTH: as highlighted in the CS (Section 4.2.6), the company assumed that BTH only affects patients treated with pegcetacoplan; the effect was modelled as a one-off cost (£392.86).
- Iron overload: in the PEGASUS trial, at baseline, [redacted]% of patients were receiving desferrioxamine mesilate and [redacted]% of patients were receiving deferasirox, indicating that [redacted]% of patients were experiencing iron overload (Table 22 legend). The company estimated the treatment costs associated with iron overload based on PEGASUS trial baseline concomitant medication data as shown in Table 22.

Table 22 Iron overload costs per patient per cycle

Procedure/ Drugs	Assumptions	Average cost per patient per cycle cost
Haemochromatosis for patients receiving pegcetacoplan		
Phlebotomy	Half an hour of specialist nurse time[43]	£44.61
Chelation therapy for patients receiving eculizumab or ravulizumab		
Deferasirox	[redacted]% of patients were assumed to be receiving deferasirox* Dosage was assumed to be 21mg/kg once daily using film-coated tablets/granules	£594.68
Desferrioxamine mesilate	[redacted]% patients were assumed to be receiving desferrioxamine mesilate* Dosage was assumed to be 35mg/kg once daily	£147.31
Total cost per cycle of iron overload for patient receiving eculizumab or ravulizumab		**£741.99**

*Based on PEGASUS trial data as reported in the CS. The ERG highlights the possibility of a transcription error when compared to the CSR data (Section 6.4.1 for details)
Source: CS Table 63, updated company model (12 July 2021)

Adverse event costs

The company base case analysis did not include AE costs. However, the company presented results from a scenario analysis that included AE costs. In this scenario analysis, the estimated AE management costs per cycle were: £48.49 for patients receiving pegcetacoplan, £46.49 for patients receiving eculizumab and £46.49 for patients receiving ravulizumab.

5 COST EFFECTIVENESS RESULTS

5.1 Deterministic base case cost effectiveness results

The company's pairwise base case ICERs per QALY gained are shown in Table 23. Results were generated using the discounted PAS price for pegcetacoplan and list prices for eculizumab and ravulizumab.

Table 23 Deterministic base case pairwise cost effectiveness results for pegcetacoplan versus eculizumab and versus ravulizumab (pegcetacoplan PAS price)

Treatment	Total costs	Total LYG	Total QALYs	Incremental			Incremental cost per QALY gained
				Costs	LYG	QALYs	
Pegcetacoplan	[redacted]	19.706	[redacted]				
Eculizumab	[redacted]	19.706	[redacted]	[redacted]	0.000	[redacted]	Pegcetacoplan dominates
Ravulizumab	[redacted]	19.706	[redacted]	[redacted]	0.000	[redacted]	Pegcetacoplan dominates

LYG=life years gained; PAS=Patient Access Scheme; QALY=quality adjusted life year
Source: Updated company model (12 July 2021)

5.2 Probabilistic sensitivity analysis

The company carried out probabilistic sensitivity analyses (PSAs). Results (means from 1000 iterations) using the discounted PAS price for pegcetacoplan are provided in Table 24. The probabilistic results are similar to the deterministic results. The company estimated that the probability of pegcetacoplan being a cost effective treatment option compared with eculizumab at all willingness-to-pay (WTP) thresholds was 100%. The probabilistic results showed that pegcetacoplan was similarly (100%) cost effective versus ravulizumab.

Table 24 Probabilistic case pairwise cost effectiveness results for pegcetacoplan versus eculizumab and ravulizumab (pegcetacoplan PAS price)

Treatment	Total cost	Total QALYs	Incremental cost per QALY gained
Pegcetacoplan	[redacted]	[redacted]	-
Eculizumab	[redacted]	[redacted]	Pegcetacoplan dominates
Ravulizumab	[redacted]	[redacted]	Pegcetacoplan dominates

PAS=Patient Access Scheme; QALY=quality adjusted life year
Source: Updated company model (12 July 2021)

5.3 Deterministic sensitivity analyses

Using the discounted PAS price for pegcetacoplan, the company carried out deterministic one-way sensitivity analyses (OWSA) using net monetary benefit (NMB) at a WTP threshold of £10,000 per QALY gained. Results from the company's OWSAs for the comparison of treatment with pegcetacoplan versus eculizumab showed that the three analyses that had the

biggest effect on cost effectiveness results were the pack cost of deferasirox, the percentage of patients on deferasirox and the cost of blood transfusion (Figure 4).

Figure 4 Deterministic sensitivity analysis results for pegcetacoplan versus eculizumab, generated using the discounted price (PAS) of pegcetacoplan

Hb=haemoglobin; NMB=net monetary benefit; PAS=Patient Access Scheme
Source: Updated company model (12 July 2021)

For the comparison of treatment with pegcetacoplan versus ravulizumab, the three analyses that had the biggest effect on cost effectiveness results were the mean weight of patients, the pack cost of deferasirox and the percentage of patients on deferasirox (Figure 5).

Figure 5 Deterministic sensitivity analysis results for pegcetacoplan versus ravulizumab, generated using the discounted price (PAS) of pegcetacoplan

Hb=haemoglobin; NMB=net monetary benefit; PAS=Patient Access Scheme
Source: Updated company model (12 July 2021)

5.4 Scenario analyses

Using the discounted PAS price of pegcetacoplan, the company explored several areas of uncertainty. Treatment with pegcetacoplan dominated eculizumab and ravulizumab for all the explored scenarios (Table 25).

Table 25 Scenario analysis results generated using the PAS price of pegcetacoplan

Parameter	Value	Pegcetacoplan versus eculizumab (ICER/QALY gained)	Pegcetacoplan versus ravulizumab (ICER/QALY gained)
Time horizon (years)	10	Dominant	Dominant
	20	Dominant	Dominant
Discount rate – costs and QALYs	0%	Dominant	Dominant
	6%	Dominant	Dominant
Utility decrement of eculizumab versus ravulizumab and pegcetacoplan	0.000	Dominant	Dominant
	0.057	Dominant	Dominant
Utility: general population age adjustment	Not applied	Dominant	Dominant
Iron overload disutility	0.00	Dominant	Dominant
Transition probabilities	0-4 weeks per first cycle; 4-16-week data for subsequent cycles	Dominant	Dominant
Baseline distribution of patients	Distribution pre-run-in	Dominant	Dominant
% Of patients discontinuing pegcetacoplan	7.32% (all 3 out of 41 patients who initially discontinue)	Dominant	Dominant

Hb=haemoglobin; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year
Source: Updated company model (12 July 2021)

5.5 Model validation and face validity

The company stated that six UK clinical experts reviewed the model assumptions during an advisory board meeting.[44] The company also utilised insights from the ravulizumab NICE appraisal[18] during model development. The company stated (CS, p171) that they conducted a Preliminary Independent Model Advice (PRIMA) check to ensure that the model was theoretically sound. In addition, the model was validated by external health economists.

6 ERG CRITIQUE OF COMPANY ECONOMIC MODEL

6.1 Introduction

The company model was constructed in MS Excel and has been used to compare the cost effectiveness of pegcetacoplan versus eculizumab, and pegcetacoplan versus ravulizumab in a population of patients with PNH who had baseline Hb levels <10.5g/dL despite treatment with a stable dose of a C5 inhibitor for ≥3 months. Clinical advice to the ERG is that eculizumab and ravulizumab are the most appropriate comparators for this population.

6.2 Model validation

To date, the company has submitted three economic models. In addition to the company model submitted as part of the original CS (dated 25 May 2021), the company submitted an updated model as part of their clarification response (dated 6 July 2021) and a further updated, model (dated 12 July 2021). All references to the company model in this ERG report relate to the model submitted by the company that is dated 12 July 2021.

The ERG has validated the company model by:

- checking that parameter values in the CS matched those in the company model
- testing the effect of using extreme values of key model parameters on cost effectiveness results
- tracing algorithms from results back to model parameters
- checking PSA parameter values are reasonable and re-running the PSA.

Full results from the ERG validation performed using the TECH-VER checklist[45] are provided in Section 8.1, Appendix 1. The ERG has no major concerns about the company model.

6.3 Summary of model aspects identified by the ERG

A summary of the most relevant model aspects considered by the ERG is provided in Table 26.

Table 26 Summary of relevant model aspects considered by the ERG

Aspects	ERG comment	Section of ERG report
Model revisions included in the ERG preferred base case analysis		
Proportion of patients in the eculizumab arm who were receiving chelation therapy at baseline	Correction of data transcription error in company base case.	6.4.1
Adverse events	Addition of AE costs to company base case.	6.4.2
Other model aspects		
Assumption of equal efficacy of eculizumab and ravulizumab	The ERG considers that it is not possible to be certain from the available clinical trial evidence that, in the PEGASUS trial population, the efficacy of ravulizumab is the same as the efficacy of eculizumab.	6.5.1
Limited clinical effectiveness data	The only data available to demonstrate the effects (in terms of efficacy or AEs) of treatment with pegcetacoplan (48 weeks) or treatment with eculizumab (16 weeks) are derived from the PEGASUS trial.	6.5.2
Impact of pegcetacoplan treatment discontinuations	The ERG explored the impact of a range of pegcetacoplan treatment discontinuation rates in the company base case.	6.5.3
Position of ravulizumab in the treatment pathway	Clinical advice to the ERG is that ravulizumab is likely to replace eculizumab as the first-line treatment option for patients with PNH.	6.5.4
Half-cycle correction	The company applied half-cycle corrections from cycle zero (i.e., by averaging cycle zero and cycle one values), instead of starting at cycle one. The ERG has not corrected this error as doing so would have made a negligible difference to cost effectiveness results.	NA
Utility values	EORTC-QLQ-C30 data were collected as part of the PEGASUS trial. The company mapped these data to EQ-5D-3L scores and generated health state utility values. The ERG has no concerns relating to this approach.	NA

AE=adverse event; EQ-5D-3L=EuroQol-5 Dimensions-3 Levels; ERG=Evidence Review Group; NA=not applicable; PNH=paroxysmal nocturnal haemoglobinuria

6.4 ERG company model revisions

6.4.1 Proportion of patients treated with chelation therapy

The company states that during the PEGASUS trial run-in period, a period when all patients were receiving eculizumab, [redacted]% of patients were treated with desferrioxamine mesilate or deferasirox (CS, p123). Data presented in the PEGASUS trial CSR[22] (Table 14.1.7.1.1) show that prior medications included deferasirox ([redacted]) and desferrioxamine mesilate ([redacted]). This suggests that during the run-in period a maximum of [redacted] of patients were receiving chelation therapy. The ERG has amended the company model inputs to reflect the CSR data. The results from these analyses show that treatment with pegcetacoplan dominates eculizumab and ravulizumab (Table 27 and Table 28).

However, the ERG considers that the proportion of patients receiving chelation therapy during the PEGASUS trial run-in period is a poor proxy for the proportion of patients who would require chelation therapy over the whole model time horizon. It has been reported that chronic blood transfusion therapy inevitably leads to secondary iron overload and that, generally, chelation therapy with deferoxamine is started after 2 to 3 years of transfusions (or when ferritin exceeds 1,000ng/mL).[46] Thus, the company assumption of limiting the proportion of patients requiring chelation therapy to the proportion who were receiving it during the run-in period may underestimate the costs and overestimate the utilities associated with treatment with eculizumab and ravulizumab meaning that the cost effectiveness of pegcetacoplan has been underestimated in the company base case.

6.4.2 Adverse events

Adverse event costs are not included in the company base case analysis. The company and the ERG consider that the impact of AEs on utilities will have been captured by the EORTC-QLQ-30 data (which were mapped to EQ-5D scores to generate health state utility values) and, therefore, adding AE-related disutilities represents double counting. The ERG has run a scenario that includes AE costs estimated by the company; the results from these analyses show that treatment with pegcetacoplan dominates eculizumab and ravulizumab (Table 27 and Table 28).

6.5 Other model aspects

6.5.1 Assumption of equal efficacy of ravulizumab and eculizumab

The ERG considers that it is not possible to be certain from the available evidence that, in the PEGASUS trial population, the efficacy of ravulizumab is the same as the efficacy of eculizumab. If the assumption that ravulizumab and eculizumab are equally efficacious does not hold for the PEGASUS trial population, then this will have implications for the cost effectiveness of pegcetacoplan versus ravulizumab. The ERG was unable to test the consequences of varying this assumption in the company model.

6.5.2 Clinical effectiveness data are only available for a limited time period

The only data available to demonstrate the effects (in terms of efficacy or AEs) of treatment with pegcetacoplan (48 weeks) or treatment with eculizumab (16 weeks) are derived from the PEGASUS trial. The ERG is concerned that short-term data from a small population (N=80) have been used to generate the transition probabilities that control movement between the model health states over the 51-year model time horizon. The ERG explored the impact of assuming that, after 1 year, the efficacy of pegcetacoplan was equal to the efficacy of eculizumab. Results from this scenario analysis showed that treatment with pegcetacoplan dominates eculizumab and ravulizumab.

6.5.3 Impact of pegcetacoplan treatment discontinuations

PEGASUS trial data presented in the company response to the ERG clarification letter (Question A6, Figure 2) show that, in the pegcetacoplan arm, during the RCP, three patients discontinued treatment (although the company states that [redacted] of these patients would not have discontinued treatment in clinical practice) and during the OLP, an additional [redacted] patients discontinued treatment. In the company base case analysis, it is assumed that [redacted] treated with pegcetacoplan discontinues treatment during Year 1.

In the PEGASUS trial, of the patients originally randomised to the eculizumab arm, [redacted] patients discontinued treatment with pegcetacoplan during the OLP. The company considered that it was not appropriate to model the discontinuation experience of this patient group due to the complex treatment history of these patients.

The ERG has explored the effect on cost effectiveness results of assuming that [redacted]/80 ([redacted]) patients discontinue treatment with pegcetacoplan during Year 1. The implementation of this change has no effect on cost effectiveness conclusions; treatment with pegcetacoplan dominates eculizumab and ravulizumab.

6.5.4 Position of ravulizumab in the treatment pathway

Clinical advice to the ERG is that, over time, ravulizumab is likely to become the first-line treatment for most patients with PNH. This is likely to mean that patients who have an IVBTH and permanently discontinue treatment with pegcetacoplan would return to their original ravulizumab treatment rather than switch to treatment with eculizumab, as occurs in the company model. The ERG has not explored the impact of this change on cost effectiveness results but highlights that, if ravulizumab costs more (or less) than eculizumab, this change will increase (or decrease) the total costs associated with BTH treatment and the consequence of this will be to increase (or decrease) the base case ICER per QALY gained for the comparison of pegcetacoplan versus ravulizumab.

6.6 ERG cost effectiveness analyses results

The ERG has only implemented two revisions to the company base case analysis:

- proportions of patients treated with eculizumab who were receiving chelation therapies at baseline according to the CSR (R1)
- addition of AE costs (R2)

The results of the ERG exploratory cost effectiveness analyses, generated using the PAS price for pegcetacoplan and list prices for eculizumab and ravulizumab, are shown in Table 27 and Table 28. The (individual and combined) results of these analysis show that treatment with pegcetacoplan dominates eculizumab and ravulizumab.

Ravulizumab is available to the NHS at a confidential discounted PAS price. The ERG has provided a confidential appendix for the comparison of pegcetacoplan versus ravulizumab.

Details of the Microsoft Excel revisions carried out by the ERG to the company model are provided in Section 8.2, Appendix 2.

Table 27 ERG revisions to company model for the comparison of pegcetacoplan versus eculizumab (PAS price for pegcetacoplan, list price for eculizumab)

ERG revisions	Pegcetacoplan			Eculizumab			Incremental			ICER
	Cost	QALYs	Life Years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY gained
A. Company base case	[redacted]	[redacted]	19.706	[redacted]	[redacted]	19.706	[redacted]	[redacted]	0.000	**Pegcetacoplan dominates**
ERG revisions										
R1) Chelation therapy proportions from the CSR	[redacted]	[redacted]	19.706	[redacted]	[redacted]	19.706	[redacted]	[redacted]	0.000	**Pegcetacoplan dominates**
R2) Include AE costs	[redacted]	[redacted]	19.706	[redacted]	[redacted]	19.706	[redacted]	[redacted]	0.000	**Pegcetacoplan dominates**
B. ERG preferred base case (R1 & R2)	[redacted]	[redacted]	19.706	[redacted]	[redacted]	19.706	[redacted]	[redacted]	0.000	**Pegcetacoplan dominates**

AE=adverse event; CSR=clinical study report; ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality

Table 28 ERG revisions to company model for the comparison of pegcetacoplan versus ravulizumab (PAS price for pegcetacoplan, list price for ravulizumab)

ERG revisions	Pegcetacoplan			Ravulizumab			Incremental			ICER
	Cost	QALYs	Life Years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY gained
A. Company base case	[redacted]	[redacted]	19.706	[redacted]	[redacted]	19.706	[redacted]	[redacted]	0.000	**Pegcetacoplan dominates**
ERG revisions										
R1) Chelation therapy proportions from the CSR	[redacted]	[redacted]	19.706	[redacted]	[redacted]	19.71	[redacted]	[redacted]	0.000	**Pegcetacoplan dominates**
R2) Include AE costs	[redacted]	[redacted]	19.706	[redacted]	[redacted]	19.706	[redacted]	[redacted]	0.000	**Pegcetacoplan dominates**
B. ERG preferred base case (R1 & R2)	[redacted]	[redacted]	19.706	[redacted]	[redacted]	19.71	[redacted]	[redacted]	0.000	**Pegcetacoplan dominates**

AE=adverse event; CSR=clinical study report; ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year

6.7 Conclusions of the cost effectiveness section

If the efficacy of ravulizumab is equal to the efficacy of eculizumab for patients with PNH who have baseline Hb levels <10.5g/dL despite treatment with a stable dose of a C5 inhibitor for ≥3 months, the ERG is satisfied that the most plausible ICERs per QALY gained for the comparisons of pegcetacoplan versus eculizumab and pegcetacoplan versus ravulizumab are below £20,000. The ERG considers there are no other critical issues relating to the economic model submitted by the company.

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8 APPENDICES

8.1 Appendix 1: TECH-VER Checklist

Table 29 ERG validation performed using the TECH-VER checklist

Test description (Please document how the test is conducted, as well)	Expected result of the test	Results of Pegcetacoplan Model
Pre-analysis calculations		
Does the technology (drug/device, etc.) acquisition costs increase with higher prices?	Yes	Yes
Does the drug acquisition cost increase for higher weight or body surface area?	Yes	Yes
Does the probability of an event, derived from an odds ratio (OR)/ relative risk (RR) / hazard ratio (HR) and baseline probability, increases with higher OR/RR/HR?	Yes	Yes
If survival parametric distributions are used in the extrapolations, can the formulae used for the Weibull (generalized gamma) distribution generate the values obtained from the exponential (the Weibull or Gamma) distribution(s) under some parameter transformations?	Yes	N/A
In a partitioned survival model, does the progression free survival curve or the time on treatment curve crosses the overall survival curve?	No	N/A
If survival parametric distributions are used in the extrapolations or time-to-event calculations, can the formulae used for the Weibull (generalized gamma) distribution generate the values obtained from the exponential (the Weibull or Gamma) distribution(s) after replacing/transforming some of the parameters?	Yes	N/A
Is hazard ratio calculated from Cox proportional hazards model applied on top of the parametric distribution extrapolation found from the survival regression?	No, it is better if the treatment effect that is applied to the extrapolation comes from the same survival regression in which the extrapolation parameters are estimated.	N/A
For the treatment effect inputs, if the model uses outputs from WINBUGs, are the OR, HR and RR values all within plausible ranges? (should be all non-negative and the average of these WINBUGs outputs should give the mean treatment effect)	Yes	N/A
Event-state calculations		
Calculate the sum of the number of patients at each health state	Should add up to the cohort size	Adds up to cohort size
Check if all probabilities and number of patients in a state are greater than or equal to zero	Yes	Yes
Check if all probabilities are smaller than or equal to one	Yes	Yes

Compare the number of dead (or any absorbing state) patients in a period with the number of dead (or any absorbing state) patients in the previous periods?	Should be larger	Larger
In case of lifetime horizon, check if all patients are dead at the end of the time horizon	Yes	Yes
Discrete event simulation specific: sample one of the "time to event" types used in the simulation from the specified distribution. Plot the samples and compare the mean and the variance from the sample	Sample mean and variance & the simulation outputs should reflect the distribution it is sampled from.	N/A
Set all utilities to one Set all utilities to zero	The QALYs accumulated at a given time would be the same as the life years accumulated at that time No utilities will be accumulated in the model	Life Years= QALYs (age adjustment kept off) No QALYs accumulated in the model
Decrease all state utilities simultaneously (but keep event based utility decrements constant)	Lower utilities will be accumulated each time	Correctly implemented
Set all costs to zero	No costs will be accumulated in the model at any time	Correctly implemented
Put mortality rates to 0	Patients never die	Yes
Put mortality rate extremely high	Patients die in the first few cycles	Yes
Set the effectiveness, utility and safety related model inputs for all treatment options equal	Same life years and QALYs should be accumulated for all treatment at any time	Yes
In addition to the inputs above, set cost related model inputs for all treatment options equal	Same costs, life years and QALYs should be accumulated for all treatment at any time	Yes
Change around the effectiveness, utility and safety related model inputs between two treatment options	Accumulated life years and QALYs in the model at any time should be also reversed	Yes

Check if the number of alive patients estimate at any cycle is in line with general population life table statistics	At any given age, the % alive should be lower or equal in comparison to the general population estimate	Yes
Check if the QALY estimate at any cycle is in line with general population utility estimates	At any given age, the utility assigned in the model should be lower or equal in comparison to the general population estimate	Yes
Set the inflation rate of the previous year higher	The costs (which are based on a reference from previous years) assigned at each time will be higher	Yes
Calculate the sum of all ingoing and outgoing transition probabilities	Both should be one	Yes
Calculate the number of patients entering and leaving a tunnel state throughout the time horizon	Numbers entering = Numbers leaving	Yes
Check if the time conversions for probabilities were conducted correctly.	Yes	
Decision tree specific: calculate the sum of the expected probabilities of the terminal nodes	Should sum up to one	N/A
Patient-level model specific: check if common random numbers are maintained for sampling for the treatment arms?	Yes	N/A
Patient-level model specific: check if correlation in patient characteristics is taken into account when determining starting population?	Yes	N/A
Increase the treatment acquisition cost	Costs accumulated at a given time will increase during the period when the treatment is administered	Yes
Population model specific: set the mortality and incidence rates to zero	Prevalence should be constant in time	Yes
Result calculations		
Check the incremental life years and QALYs gained results. Are they in line with the comparative clinical effectiveness evidence of the treatments involved?	If a treatment is more effective, it generally results	Correct

	in positive incremental LYs and QALYs in comparison with the less effective treatments	
Check the incremental cost results. Are they in line with the treatment costs?	If a treatment is more expensive, and if it does not have much effect on other costs, it generally results in positive incremental costs.	Correctly implemented
Total life years > total quality adjusted life years	Yes	Yes
Undiscounted results > discounted results	Yes	Yes
Divide undiscounted total QALYs by undiscounted life years.	This value should be within the outer ranges (maximum and minimum) of the all utility value inputs.	Within range
Subgroup analysis results: How do the outcomes change if the characteristics of the baseline change?	Better outcomes for better baseline health conditions and worse outcomes for worse health conditions are expected.	Yes
Could you generate all the results in the report from the model (including the uncertainty analysis results)?	Yes	Yes
Does the total life years, QALYs and costs decrease if a shorter time horizon is selected?	Yes	Yes, although costs do not reduce much.
Is the reporting and contextualization of the incremental results correct?	The use of the terms such as: “dominant”/ “dominated”/ “extendedly dominated”/ “cost-effective” etc. should be in line with the results. In the incremental analysis table involving multiple treatments, ICERs should be calculated	Correctly implemented

	against the next non-dominated treatment.	
Are the reported ICERs in the fully incremental analysis non-decreasing?	Yes	Yes
If disentangled results are presented, do they sum up to the total results? (e.g. different cost types sum up to the total costs estimate)	Yes	Yes
Check if half cycle correction is implemented correctly (total life years with half cycle correction should be lower than without)	The half cycle correction implementation should be error free. Also check if it should be applied for all costs, for instance if a treatment is administered at the start of a cycle, half cycle correction might be unnecessary.	Not correctly implemented
Check the discounted value of costs/QALYs after 2 years	Discounted value=undiscounted/$(1+r)^2$	Yes
Set discount rates to zero	The discounted and undiscounted results should be the same	Yes
Set mortality rate to zero	The undiscounted total life years per patient should be equal to the length of the time horizon	Yes
Put the consequence of adverse event/discontinuation to zero. (zero costs and zero mortality/utility decrements)	The results would be the same as the results when AE rate is set to zero.	Yes
Divide total undiscounted treatment acquisition costs by the average duration on treatment.	This should be similar to treatment related unit acquisition costs	Yes
Set discount rates to a higher value	Total discounted results should decrease	Yes
Set discount rates of costs/effects to an extremely high value	Total discounted results should be more or less the same as the	Yes

	discounted results accrued in the first cycles	
Put adverse event/discontinuation rates to zero and then to extremely high level.	Less costs higher QALYS/LYs when adverse event rates are 0, higher costs and lower QALYS/LYs when AE rates are extreme	Yes
Double the difference in efficacy and safety between new intervention and comparator and report the incremental results.	Approximately twice of the incremental effect results of the base case. If this is not the case : report and explain the underlying reason/ mechanism	Yes
Do the same for a scenario in which the difference in efficacy and safety is halved.	Approximately halve of the incremental effect results of the base case. If this is not the case : report and explain the underlying reason/ mechanism	Yes
Uncertainty analysis calculations		
Are all parameters subject to uncertainty included in the one-way sensitivity analysis (OWSA)? Check if the OWSA includes any parameters associated with joint uncertainty (e.g. parts of a utility regression equation, survival curves with multiple parameters).	Yes	No
Are the upper and lower bounds used in the one-way sensitivity analysis used confidence intervals based on the statistical distribution assumed for that parameter? Are the resulting ICER, incremental costs/QALYs with upper and lower bound of a parameter plausible and in line with a priori expectations?	Yes Yes	Yes Yes
Check that all parameters used in the sensitivity analysis have an appropriate associated distributions - upper and lower bounds should surround the deterministic value (i.e. Upper bound ≥ mean ≥ Lower bound) - standard error and not standard deviation used in sampling - Lognormal / gamma distribution for hazard ratios and costs/ resource use	Yes	Yes

- Beta for utilities and proportions/probabilities - Dirichlet for multinomial - Multivariate normal for correlated inputs (e.g. survival curve or regression parameters) - Normal for other variables as long as samples don't violate requirement to remain positive when appropriate		
Check PSA output mean costs, QALYs and ICER compared to the deterministic results. Is there a large discrepancy?	No (in general)	No
If you take new PSA runs from the excel model do you get similar results?	Yes	Yes
Is(are) the CEAC line(s) in line with the CE scatter plots and the efficient frontier?	Yes	Yes
Does the PSA cloud demonstrate an unexpected behavior or has an unusual shape?	No	No
Is the sum of all CEAC lines equal to 1 for all WTP values?	Yes	Yes
Are the explored scenario analyses provide a balanced view on the structural uncertainty? (i.e. not always looking at more optimistic scenarios)	Yes	Yes
Are the scenario analysis results plausible and in line with a priori expectations?	Yes	Yes
Check the correlation between 2 PSA results (i.e. costs/QALYs under the SoC and costs/QALYs under the comparator)	Should be very low (very high) if different (same) random streams are used for different arms	
If a certain seed is used for random number generation (or previously generated random numbers are used), check if they are they scattered evenly between 0-1 when they are plotted?	Yes	
Compare the mean of the parameter samples generated by the model against the point estimate for that parameter, use graphical methods to examine distributions, functions	The sample means and the point estimates will overlap, the graphs will be similar to the corresponding distribution functions (e.g. Normal, Gamma, etc.)	Yes
Check if sensitivity analyses include any parameters associated with methodological/ structural uncertainty (e.g. annual discount rates, time horizon).	No	No
Value of information analysis if applicable: Was this implemented correctly? Which types of analysis? Were aggregated parameters used? Which parameters are grouped together? Does it match the write-up's suggestions? Is EVPI larger than all individual EVPPI? Is EVPPI for a (group of) parameters larger than the EVSI of that (group) of parameter(s)?	Yes	Not available

Are the results from EVPPI in line with OWSA or other parameter importance analysis (e.g. ANCOVA)?		
Did the electronic model pass the black-box tests of the previous verification stages in all PSA iterations and in all scenario analysis settings? (additional macro can be embedded to PSA code, which stops the PSA when an error such as negative transition probability, is detected)	Yes	Yes
Check the correlation between 2 PSA results (i.e. costs/QALYs under the SoC and costs/QALYs under the comparator)	Should be very low (very high) if different (same) random streams are used for different arms	Correct

OWSA=one-way sensitivity analysis; ICER=incremental cost-effectiveness ratio; PSA=probabilistic sensitivity analysis; WTP=willingness-to-pay; CE=cost-effectiveness; CEAC=cost-effectiveness acceptability curve; LY=life years; QALYs=Quality adjusted life years; OR=odds ratio; RR= relative risk; HR=hazard ratio
Source: TECH-VER checklist[45] and ERG comment

8.2 Appendix 2: Microsoft Excel revisions made by the ERG to the company model

Table 30 Microsoft Excel revisions made by the ERG to the company model

ERG revision number	Sheet(s)	Cells	Modified formulae
Naming the cells	"3.1 CE Results_Switch"	R111	Name the cell as ERG_ModA and put value as 1 or 0
		R112	Name the cell as ERG_ModB and put value as 1 or 0
R1	"4.1 Country-Specific Data"	D93	=IF(ERG_ModA=1,[redacted]
		D94	=IF(ERG_ModA=1,[redacted]
	"2.4 Utilities"	D29	=IF(ERG_ModA=1,'4.1 Country-Specific Data'!D93+'4.1 Country-Specific Data'!D94,[redacted]
		D30	=IF(ERG_ModA,LV_IOrate_Ecu,[redacted]
R2	"2.6 Other costs"	D115	= IF(ERG_ModB=1,SUMPRODUCT('2.7 SA Inputs_Switch'!$R$160:$R$170,'2.7 SA Inputs_Switch'!R127:R137),IF(switch_AE_disutility=1,0,SUMPRODUCT('2.7 SA Inputs_Switch'!$R$160:$R$170,'2.7 SA Inputs_Switch'!R127:R137)))
		D117	= IF(ERG_ModB=1,SUMPRODUCT('2.7 SA Inputs_Switch'!$R$160:$R$170,'2.7 SA Inputs_Switch'!R138:R148),IF(switch_AE_disutility=1,0,SUMPRODUCT('2.7 SA Inputs_Switch'!$R$160:$R$170,'2.7 SA Inputs_Switch'!R138:R148)))
		D119	= IF(ERG_ModB=1,SUMPRODUCT('2.7 SA Inputs_Switch'!$R$160:$R$170,'2.7 SA Inputs_Switch'!R149:R159),IF(switch_AE_disutility=1,0,SUMPRODUCT('2.7 SA Inputs_Switch'!$R$160:$R$170,'2.7 SA Inputs_Switch'!R149:R159)))

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Pegcetacoplan for treating paroxysmal nocturnal haemoglobinuria [ID3746]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Friday 6 August 2021** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Effect of the technology on incremental QALYs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Paragraph 2, page 10: *"…treatment with pegcetacoplan is modelled by the company to increase incremental QALYs by avoiding more blood transfusions than treatment with eculizumab or ravulizumab".* The ERG has stated that QALY increase is driven by blood transfusion avoidance. Blood transfusion avoidance is not the sole driver of QALY improvement, as health states are comprised of both transfusion avoidance and haemoglobin levels.	The Company ask for the following text to be added: *"…treatment with pegcetacoplan is modelled by the company to increase incremental QALYs by avoiding more blood transfusions* ***and increasing haemoglobin levels more than*** *treatment with eculizumab or ravulizumab".*	Health states within the cost-effectiveness model, and thus drivers of QALY improvement, are comprised of both blood transfusion avoidance and increases in haemoglobin levels.	Thank you. The report has been amended as suggested.

Issue 2 Assessing anaemia that is not controlled

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG believes that the Company assumed that Hb level of <10.5g/dL was the only method considered for selecting patients with anaemia that is not controlled, despite treatment with C5 inhibition. Issue 2, page 11:	The Company ask for text to be modified to ensure that the text is balanced as follows: Issue 2, page 11: *"The population considered by the company matches the population described in the final scope issued by NICE, namely adults with PNH whose anaemia is not controlled after treatment with a C5 complement inhibitor (i.e.,*	The Company acknowledges that some patients with Hb >10.5 g/dL may also be considered to have anaemia that is not controlled. Defining anaemia that is not controlled is challenging and multifaceted. For this reason, the Company arranged for an advisory board with	Thank you. The report has been changed to: Issue 2, p11: *"The population considered by the company matches the population described in the final scope issued by NICE, namely adults with PNH whose*

"The population considered by the company matches the population described in the final scope issued by NICE, namely adults with PNH whose anaemia is not controlled after treatment with a C5 complement inhibitor (i.e., eculizumab or ravulizumab). However, the term 'not controlled' is not defined in the NICE scope. At baseline, patients enrolled in the PEGASUS trial had a Hb level <10.5g/dL and the company appears to have assumed that having this Hb level means that these patients can be considered to have anaemia that is not controlled. Clinical advice to the ERG is that some PNH patients with Hb levels >10.5g/dL may also be considered to have anaemia that is not controlled." Paragraph 3, page 24: *"The term 'uncontrolled' is not defined in the NICE scope;[11] however, at baseline, patients enrolled in the PEGASUS trial had Hb levels <10.5g/dL and the company appears to have assumed that these patients can be considered to have anaemia that is not controlled."*	*eculizumab or ravulizumab). However, the term 'not controlled' is not defined in the NICE scope. At baseline, patients enrolled in the PEGASUS trial had a Hb level <10.5g/dL.* ***The company sought guidance from clinical experts, who considered quality of life, transfusion requirements and Hb level as potential definers, but noted that their impact would vary patient by patient. Given the available literature and precedent for Hb level, the company considers this to be the most appropriate way to define anaemia that is not controlled at a population-wide level.*** *Clinical advice to the ERG is that some PNH patients with Hb levels >10.5g/dL may also be considered to have anaemia that is not controlled."* Paragraph 3, page 23: *"The term 'uncontrolled' is not defined in the NICE scope;[11] however, at baseline, patients enrolled in the PEGASUS trial had Hb levels <10.5g/dL.* ***The company acknowledges that this threshold is an imperfect measure, but considers it to be the most appropriate to define anaemia that is not controlled at a population level.****"*	key PNH experts from the UK, to help assess how it might be defined. Clinicians noted that anaemia or non-/insufficient control would vary on a patient-by-patient basis, and that in addition to Hb levels, quality of life and transfusion requirements should be considered (1). While quality of life is an important consideration, and a potential scale, the FACIT-Fatigue, was mentioned, clinicians could not provide a threshold under which a patient might be considered to have anaemia that is not controlled. High transfusion requirements could also indicate anaemia that is not controlled, however clinicians were not able to provide a number that would be considered as a threshold. Clinicians also noted that transfusion requirements would change over time, and patients could be regularly transfusion dependent or intermittently transfusion dependent. Transfusion may also be driven by an acute event, e.g. a drop in Hb following massive activation of the complement pathway during an infection, or by chronic, compounding conditions, e.g. bone marrow failure.	*anaemia is not controlled after treatment with a C5 complement inhibitor (i.e., eculizumab or ravulizumab). However, the term 'not controlled' is not defined in the NICE scope. At baseline, patients enrolled in the PEGASUS trial had a Hb level <10.5g/dL and the company appears to have assumed,* ***given clinical expert opinion and available literature,*** *that having this Hb level means that these patients can be considered to have anaemia that is not controlled. Clinical advice to the ERG is that some PNH patients with Hb levels >10.5g/dL may also be considered to have anaemia that is not controlled."* Paragraph 2, p24: Thank you. The report has been changed to: *"The term 'uncontrolled' is not defined in the NICE scope; however, at baseline, patients enrolled in the PEGASUS trial had Hb levels <10.5g/dL and the company appears to have assumed that these patients*

		Defining patient response to eculizumab by Hb level has precedent in literature and in previous clinical trial design (2) (3). Additionally, RWE from an international registry and an analysis of the UK National PNH Service showed a median Hb level of 10.6 g/dL and 10.9 g/dL, suggesting that 10.5 g/dL is an appropriate method of defining response (4) (5). The Company believe that when assessing anaemia that is not controlled *at a population-wide level*, Hb level is the most appropriate criterion. The Company utilised an analysis of registry data defining response to eculizumab as the basis for their assessment. The Company would like to highlight that in this analysis of registry data, the seven patients who required a transfusion in the last year all had an Hb of <10.5g/dl (2). This threshold is also supported by the inclusion criteria of the PEGASUS trial (6).	*can be considered to have anaemia that is not controlled.* ***Clinical advice to the company was that quality of life, transfusion requirements and Hb level could potentially be used to define anaemia that is not controlled but noted that their relevance may vary between patients. The company considers Hb level to be the most appropriate way to define anaemia that is not controlled. The company acknowledges that this threshold is an imperfect measure but considers it to be the most appropriate to define anaemia that is not controlled at a population level."***

Issue 3 Eligible population

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG states that no estimate of eligible population was provided in the company submission. Paragraph 1, page 20: *"An estimate of the number of patients with PNH in England who would be eligible for treatment with pegcetacoplan (if recommended by NICE) was not presented in the CS. The number of patients treated with eculizumab in the UK in December 2018 was 239.[11] Clinical advice to the ERG is that approximately 20% of patients with PNH treated with eculizumab will have a suboptimal response, or their PNH will not be sufficiently controlled."*	The Company ask for text to be modified to ensure that the text is balanced as follows: *"**The company estimated the total number of patients who would be eligible for treatment with pegcetacoplan (if recommended by NICE) would be 129 in 2022, rising to 140 in 2024 (BIA template, page 15).** Clinical advice to the ERG is that approximately 20% of patients with PNH treated with eculizumab will have a suboptimal response, or their PNH will not be sufficiently controlled. **This is in line with the clinical advice received by the company and provided in the advisory board report, which stated that [redacted]% of patients treated with C5 inhibition would benefit from treatment with pegcetacoplan.** The number of patients treated with eculizumab in the UK in December 2018 was 239.[11] The ERG, therefore, estimates that approximately 50 patients with PNH would be treated with pegcetacoplan**, broadly in line with the company's estimate of [redacted] patients in the first year, rising to [redacted] in year 3."**	As noted by the ERG, the definition of anaemia that is 'not controlled' was not defined in the NICE scope. Through clinician engagement the Company confirmed that, defining an eligible patient population (i.e. patients treated with C5 inhibition who are 'not controlled') is challenging and multifaceted.. Using the approach outlined in the submission, and in Issue 2 above, the Company identified a potential eligible population. This eligible population is presented on page 15 of the BIA summary. During an advisory board of key PNH experts from the UK, clinicians stated that patient eligibility should considered on a patient-by-patient basis. The Company asked them to estimate how many patients they would treat with pegcetacoplan. Clinical opinion was that approximately 15-30% of patients currently treated with C5 inhibition would benefit from, and be moved to, treatment with pegcetacoplan (1). The Company would like to highlight that this is in line with the clinical advice provided to the ERG. The	No change required. At the time of writing the ERG report, the BIA was not available to the ERG. The ERG is therefore unable to cross-reference to this document.

		number of patients expected to be treated with pegcetacoplan is provided in Table 7 of the BIA summary.	

Issue 4 Run-in period

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Paragraph 6, page 25: *"The company has highlighted two points from the draft SmPC:[10]* *i) For the first 4 weeks, pegcetacoplan should be given in addition to the patient's current dose of C5 inhibitor treatment (to minimise the risk of haemolysis with abrupt treatment discontinuation). After 4 weeks, pegcetacoplan should be given as a monotherapy."* Paragraph 8, page 25: *"According to the draft SmPC,[10] patients should be treated with a C5 inhibitor and pegcetacoplan for 4 weeks before switching to pegcetacoplan monotherapy; clinical advice to the ERG is that SmPC[10] guidance would be followed."* Paragraph 3, page 64:	The Company ask for the following text to be added: Paragraph 6, page 25: *"The company has highlighted two points from the draft SmPC:[10]* *i) For the first 4 weeks, pegcetacoplan should be given in addition to the patient's current dose of C5 inhibitor treatment (to minimise the risk of haemolysis with abrupt treatment discontinuation). After 4 weeks, pegcetacoplan should be given as a monotherapy.* ***Clinical advice to date suggests that this period of simultaneous administration may not happen in clinical practice, relying on the ongoing effect of C5 inhibition while initiating pegcetacoplan.****"* Paragraph 8, page 25: *"According to the draft SmPC,[10] patients should be treated with a C5 inhibitor and pegcetacoplan for 4 weeks before switching to pegcetacoplan monotherapy; clinical advice to the ERG is that SmPC[10] guidance would be followed.* ***Clinical advice to date suggests***	The Company asks the ERG to add additional text to highlight clinical expert advice that the period of simultaneous administration of pegcetacoplan and a C5 inhibitor is unlikely to be required in clinical practice (1). The Company would like to highlight that the wording surrounding the run-in period within the draft SmPC is based on the design of the PEGASUS clinical trial (6). However, clinicians have since advised that a 4-week period of simultaneous administration may not be required in UK clinical practice (1). This is because when patients switch from eculizumab to pegcetacoplan, an ongoing effect of C5 inhibition will persist and hence simultaneous administration is not required. It is also unlikely that a run-in period will be required for patients switching from ravulizumab to	Thank you. The report has been changed to: Paragraph 6, page 25: *"The company has highlighted two points from the draft SmPC:[10]* *i) For the first 4 weeks, pegcetacoplan should be given in addition to the patient's current dose of C5 inhibitor treatment (to minimise the risk of haemolysis with abrupt treatment discontinuation). After 4 weeks, pegcetacoplan should be given as a monotherapy.* ***Clinical advice to the company is that the period of simultaneous administration may not happen in clinical practice, instead relying on the ongoing effect of C5***

"For the initial 4 weeks, SC pegcetacoplan (1080mg) was administered twice weekly along with the patient's current dose of eculizumab."	***that this period of simultaneous administration may not happen in clinical practice, relying on the ongoing effect of C5 inhibition while initiating pegcetacoplan."*** The Company ask the for the following text to be removed which indicates an initial 4-week period of simultaneous administration of pegcetacoplan and eculizumab in the economic model: Paragraph 3, page 64:***~~"For the initial 4 weeks, SC pegcetacoplan (1080mg) was administered twice weekly along with the patient's current dose of eculizumab."~~***	pegcetacoplan in clinical practice, given that the dosing interval for ravulizumab is 8 weeks. The Company would like to highlight that given this clinical advice; the run-in period was not modelled. The economic model excluded costs associated with the run-in period and utilised transition probabilities calculated from Week 4 to Week 48 only. The company would also like to clarify that the draft SmPC is not yet finalised, hence this wording could still be subject to change.	***inhibition while initiating pegcetacoplan.*** Paragraph 8, page 25: No change required. Thank you. The suggested text in Paragraph 3, page 64 was deleted and subsequent content replaced with: **In the company model only the cost of pegcetacoplan at the maintenance dose of SC pegcetacoplan 1080mg twice weekly is included (i.e., treatment with eculizumab for the initial 4-week period is not included).**

Issue 5 Treatment pathway of ravulizumab

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Paragraph 1, page 75: *"…patients who have a BTH and discontinue treatment with pegcetacoplan would return to their original ravulizumab treatment rather than switch to*	The Company ask for text to be modified as follows: *"…patients who have **an IVBTH would pause** treatment with pegcetacoplan **and be treated with a one-off dose of 900 mg eculizumab. These patients then continue with***	The company would like to clarify that patients who experience intravascular breakthrough haemolysis (IVBTH) on pegcetacoplan would be unlikely discontinue from treatment in clinical practice. Rather they would	Thank you. The report has been changed to: Paragraph 1, page 75: *…patients who have a**n** **IV**BTH and **permanently***

treatment with eculizumab, as occurs in the company model."	***pegcetacoplan treatment after BTH has been resolved."***	pause treatment and be treated with a one-off dose of eculizumab before returning back to treatment with pegcetacoplan (1). At the time of the PEGASUS trial there was no established way of treating IVBTH for patients on pegcetacoplan and as such the safest treatment decision was for patients to switch back to eculizumab. Clinicians at an advisory board confirmed that they would treat IVBTH for patients on pegcetacoplan with a one-off 900 mg dose of eculizumab. In this situation, clinicians noted that eculizumab is preferred over ravulizumab for this one-off off label dose due to the shorter half-life (1).	*discontinue treatment with pegcetacoplan would return to their original ravulizumab treatment rather than switch to treatment with eculizumab, as occurs in the company model.*

Issue 6 Comparability of the populations of PEGASUS and Study 302

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Paragraph 5, page 26-27: *"However, the PEGASUS trial population (patients with uncontrolled anaemia, defined as Hb level <10.5g/dL, after treatment with a C5 inhibitor for a period of at least 3 months) is a*	The company ask for this statement to be removed:. ***~~"However, the PEGASUS trial population (patients with uncontrolled anaemia, defined as Hb level <10.5g/dL, after treatment with a C5 inhibitor for a period of at least 3 months) is a subset of the Study 302[20] population."~~***	The Company would like to highlight that there are differences in the populations investigated by Study 302 and PEGASUS, which mean that the PEGASUS population cannot be considered a subset of the Study 302 population. Study 302 included adults with PNH who were clinically stable after	Thank you. The report has been changed to: *However, the PEGASUS trial population (patients with uncontrolled anaemia, defined as Hb level <10.5g/dL, after treatment with a C5 inhibitor for a period of at least 3*

subset of the Study 302[20] population."		having been treated with eculizumab for at least 6 months; hence, all patients were eligible regardless of Hb levels. On the other hand, PEGASUS considered only patients with Hb levels lower than 10.5g/dL (7). Furthermore, Study 302 also required the following two additional inclusion criteria, which were not required in PEGASUS: 1. LDH level ≤1.5x the ULN at screening visit 2. No major adverse vascular events (MAVE) in 6 months prior to treatment. Additionally, 30% of patients enrolled in PEGASUS were treated with a higher-than-labelled dose of eculizumab (8). Hence, these patients cannot be considered to have optimised control of their disease, as in Study 302. The Company would like to emphasise that Study 302 aimed to identify a population who responded well to C5 inhibition and thus those who may safely switch from eculizumab to ravulizumab. On the contrary, PEGASUS identified patients who were not sufficiently controlled, despite treatment with a C5 inhibitor (6). Hence, PEGASUS	*months) is* ***not the same as the Study 302[20] population.***

		patients cannot be considered a subset of the Study 302 population.	

Issue 7 Efficacy in PNH patients with underlying bone barrow failure

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Paragraph 3, page 24: *"Clinical advice to the ERG is that approximately 50% of patients with PNH have some underlying bone marrow failure (e.g., aplastic anaemia). In these patients, the anaemia is not due to uncontrolled complement activity and is unlikely to respond to higher doses of C5 or C3 inhibitors."*	The company ask for this text to be modified as follows: *"Clinical advice to the ERG is that approximately 50% of patients with PNH have some underlying bone marrow failure (e.g., aplastic anaemia).* ***In these patients, compliment inhibition will still lead to improvements in Hb levels. However, there may be some additional anaemia due to the underlying bone marrow failure that does not respond to C5 or C3 inhibitors.****"*	Clinical experts stated that there is likely to be no difference in the efficacy of pegcetacoplan between patients with classic PNH, and those with PNH associated with bone marrow failure (1). The Company would therefore like to clarify that there will still be improvements in Hb levels with pegcetacoplan treatment in patients with PNH and underlying bone marrow failure, since the PNH will still be targeted by C5 or C3 inhibitors. However, there may be some additional anaemia which can be attributed directly to the bone marrow failure.	Thank you. The report has been changed to: *Clinical advice to the ERG is that approximately 50% of patients with PNH have some underlying bone marrow failure (e.g., aplastic anaemia). In these patients,* ***C5 and C3 inhibitors may lead to improvements in Hb levels. However, these patients may have additional*** *anaemia* ***that*** *is not due to uncontrolled complement activity and is unlikely to respond to higher doses of C5 or C3 inhibitors.*

Issue 8 Assumption of equal efficacy between ravulizumab and eculizumab

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Issue 1, page 11:	The company ask for this text to be modified as follows: Issue 1, page 11:	The company believes that from the evidence available, there is no reason to suggest that the efficacy	Thank you for your comment. This is not a factual inaccuracy. No change required.

"...the company assumption that ravulizumab and eculizumab were equally efficacious." Issue 1, page 11 and Issue 4, page 12: *"Clinical opinion could be elicited to inform discussions around the assumption that the efficacy of ravulizumab is equal to that of eculizumab in the PEGASUS trial population."* Paragraph 2, page 27: "*In the company base case cost effectiveness analysis, the company has assumed that the efficacy of ravulizumab is equal to the efficacy of eculizumab. However, the ERG considers that it is not possible to be certain from the available clinical trial evidence that, in the PEGASUS trial population, the efficacy of ravulizumab would be the same as the efficacy of eculizumab."* Paragraph 3, page 61: *"The efficacy of ravulizumab was assumed to be equal to that of eculizumab."* Table 26, page 72: *"The ERG considers that it is not possible to be certain from the*	*"...the company assumption, **as supported by clinical trial evidence and clinical opinion,** that ravulizumab and eculizumab were equally efficacious."* Issue 1, page 11 and Issue 4, page 12: *"**Though clinical opinion has already been elicited** to inform the discussions around the assumption that the efficacy of ravulizumab is equal to that of eculizumab in the PEGASUS trial population, **further validation is required**".* Paragraph 2, page 29: *"In the company base case cost effectiveness analysis, the company has assumed that the efficacy of ravulizumab is equal to the efficacy of eculizumab. **Though available clinical trial evidence and clinical opinion suggest that in** the PEGASUS trial population the efficacy of ravulizumab would be the same as the efficacy of eculizumab, the ERG do not consider it possible to be certain of this equal efficacy assumption"* Paragraph 3, page 61: ***"In light of clinical evidence and current clinical opinion, t**he efficacy of ravulizumab was assumed to be equal to that of eculizumab."* Table 26, page 72 and paragraph 1, page 74: ***"Despite currently available clinical evidence,** the ERG considers that it is not possible to be certain from the available*	of eculizumab and ravulizumab are not equivalent. Study 302 assessed noninferiority of ravulizumab to eculizumab in clinically stable PNH patients during previous eculizumab therapy (7). A non-inferiority trial refers to a study in which the primary objective is to evaluate whether the new treatment is not inferior to or as effective (equal efficacy) as the standard therapy (9). Study 302 concluded that ravulizumab met its primary endpoint (percentage change in LDH from baseline to day 183) and all key secondary endpoints (BTH, FACIT-Fatigue score, transfusion avoidance, and stabilised Hb rate), showing noninferiority to bi-weekly treatment with 900 mg eculizumab, although none of the results from the trial demonstrated superiority (7). Additionally, the NICE committee has recently accepted equal efficacy between ravulizumab and eculizumab as published in the TA698 guidance document. NICE have published that "ravulizumab is as effective and costs less than eculizumab" in their recommendation for ravulizumab (10). Furthermore, this was validated by clinicians in the ravulizumab technical engagement	

available clinical trial evidence that, in the PEGASUS trial population, the efficacy of ravulizumab is the same as the efficacy of eculizumab."	*clinical trial evidence that, in the PEGASUS trial population, the efficacy of ravulizumab is the same as the efficacy of eculizumab."*	call. A clinical expert noted that "eculizumab and ravulizumab are essentially the 'same' drug (they share 99% homology and the same mode of action) and the difference seen with regard to BTH is not so much driven by difference in efficacy but reflects the extended bioavailability of ravulizumab" (11). Clinical experts at a recent advisory board of key PNH experts also noted that eculizumab and ravulizumab are essentially the same, the only difference is convenience for the patient (1). Switching from eculizumab to ravulizumab would not be based on efficacy and any EVH experienced by eculizumab patients would still be experienced by patients once they switched to ravulizumab (1). The Company also note that Study 302 assessed ravulizumab in comparison with a 900mg dose of eculizumab. The Company believes it is conservative to assume that ravulizumab would be equally efficacious as higher-than-labelled dosages of eculizumab, which made up 30% of the patients in PEGASUS (6). The Company see no reason to assume that ravulizumab would be more effective than higher-than-labelled doses of eculizumab in patients	

		who are not sufficiently controlled despite C5 inhibitor treatment. Given the above, the Company considers it reasonable to assume that ravulizumab and eculizumab are equally efficacious. It should be noted that ravulizumab is yet to become routine standard of care in the UK. Therefore, any arguments regarding the efficacy of ravulizumab are currently arguably of limited relevance to UK clinical practice.	

Issue 9 Scenario analysis exploring the impact of assuming equal efficacy

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Issue 3, page 12: *"The ERG explored the impact of assuming that, after 1 year, the efficacy of pegcetacoplan was equal to the efficacy of eculizumab (and, therefore, also ravulizumab). Results from this scenario analysis showed that treatment with pegcetacoplan dominates eculizumab and that pegcetacoplan dominates ravulizumab."* Paragraph 2, page 74: *"The ERG explored the impact of assuming that, after 1 year, the*	The Company ask for these statements to be removed: Issue 3, page 12: *"**~~The ERG explored the impact of assuming that, after 1 year, the efficacy of pegcetacoplan was equal to the efficacy of eculizumab (and, therefore, also ravulizumab). Results from this scenario analysis showed that treatment with pegcetacoplan dominates eculizumab and that pegcetacoplan dominates ravulizumab.~~**"* Paragraph 2, page 74:	The Company acknowledges that there will always be uncertainty in extrapolating clinical trial data for use in long-term economic modelling. However, the Company notes that the efficacy of pegcetacoplan has not been shown to wane over time, and that results at Week 48 of PEGASUS are in line with those at Week 16. The ERG does not propose a plausible mechanism of action or effect to suggest why the efficacy of pegcetacoplan would be expected to reduce over time.	Thank you. This is not a factual inaccuracy, no change required. The ERG agrees with the company that there will always be uncertainty in extrapolating clinical trial data. The ERG considers that the results from an extreme scenario may be informative.

efficacy of pegcetacoplan was equal to the efficacy of eculizumab. Results from this scenario analysis showed that treatment with pegcetacoplan dominates eculizumab and ravulizumab."	*"**~~The ERG explored the impact of assuming that, after 1 year, the efficacy of pegcetacoplan was equal to the efficacy of eculizumab. Results from this scenario analysis showed that treatment with pegcetacoplan dominates eculizumab and ravulizumab.~~**"*	During a recent advisory board of key experts in PNH, clinicians confirmed that C5 inhibitors, such as eculizumab, only disrupt IVH, unlike pegcetacoplan which disrupts both IVH and EVH. Clinicians believed that this disruption, earlier in the complement cascade, is the driver of the improved Hb levels demonstrated in PEGASUS when patients move to pegcetacoplan. During this advisory board, the Company also validated the transition probabilities used in the model with the same key PNH clinical experts (1). Suggesting that eculizumab and pegcetacoplan may have equal efficacy ignores their differing modes of action and is contrary to clinical opinion.	

Issue 10 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Paragraph 4, page 10: *"For the comparison of pegcetacoplan versus eculizumab and for the comparison of pegcetacoplan*	Please amend the text as follows: *"For the comparison of pegcetacoplan versus eculizumab and for the comparison of pegcetacoplan versus ravulizumab, results from the 10 most sensitive parameters show that*	Typographical error	Thank you. The report has been corrected as suggested.

versus ravulizumab, results from the 10 most sensitive parameters show that treatment with pegcetacoplan dominates eculizumab and that pecetacoplan dominates ravulizumab."	*treatment with pegcetacoplan dominates eculizumab and that **pegcetacoplan** dominates ravulizumab."*		
Table 6, row 10, page 33: *"7 (17.9)"*	Please amend the text as follows: *"7 (18.0)"*	Typographical error	
Table 6, row 35, page 33: *"282.42 (210.9)"*	Please amend the text as follows: *"282.42 (210.99)"*	Typographical error	
Table 23, row 3, page 67: *"2.080"*	*Eculizumab* | [redacted] | *19.706* | [redacted] | [redacted] | *0.000* | [redacted] | *Pegcetacoplan dominates*	Typographical error	
Paragraph 2, page 73: *"Thus, the company assumption of limiting the proportion of patients requiring chelation therapy to the proportion who were receiving it during the run-in period may underestimate of the costs and an overestimate of the utilities associated with treatment with eculizumab and ravulizumab and that the cost effectiveness of pegcetacoplan has been underestimated in the company base case."*	Please amend the text as follows: *"Thus, the company assumption of limiting the proportion of patients requiring chelation therapy to the proportion who were receiving it during the run-in period may underestimate ~~**of**~~ the costs and ~~**an**~~ overestimate ~~**of**~~ the utilities associated with treatment with eculizumab and ravulizumab **meaning ~~and~~** that the cost effectiveness of pegcetacoplan has been underestimated in the company base case."*	Typographical error	

Paragraph 3, page 74: *"In the company base case analysis, it is assumed that [redacted] patients treated with pegcetacoplan discontinue treatment during Year 1."*	Please amend the text as follows: *"In the company base case analysis, it is assumed that [redacted] treated with pegcetacoplan discontinue treatment during Year 1."*	Typographical error	

Issue 11 Mark-up errors

Location of incorrect marking	Description of incorrect marking	Amended marking	ERG response
Issue 3, page 12 and Paragraph 2, page 24	Trial data to be marked as academic in confidence (AiC)	[redacted]	Thank you. The report has been corrected as suggested.
Table 7, row 6, page 35	AiC mark up to be removed	No (3 patients on pegcetacoplan discontinued due to breakthrough haemolysis, [redacted] of which re-entered the study during the follow-up period)	
Table 8, row 8, page 38	AiC mark up to be removed	Sensitivity analyses of the primary outcome were performed to examine lack of treatment benefits following a patient's discontinuation from study treatment using a CBPI method and a delta-adjusted stress testing (Tipping Point) method and a supportive analysis of the primary outcome was performed using data uncensored for transfusion and a nonparametric randomisation based ANCOVA in the ITT population (CS, Section 2.6.2).	

<table>
<tr><td>Table 8, row 9, page 39</td><td>AiC mark up to be removed</td><td>The company conducted a sensitivity analysis for the primary outcome using a CBPI method with a missingness not at random mechanism and conducted a supportive analysis for primary and key efficacy outcomes using all available data (i.e., without censoring for transfusion).</td><td></td></tr>
<tr><td>Table 9, row 9, page 40</td><td>Trial data to be marked as AiC</td><td><table><tr><td colspan="3">All available data, uncensored for transfusion</td></tr><tr><td>N</td><td>37</td><td>38</td></tr><tr><td>Mean (SD) g/dL</td><td>[redacted]</td><td>[redacted]</td></tr></table></td><td></td></tr>
<tr><td>Paragraph 4, page 41</td><td>AiC mark up to be removed</td><td>In the pegcetacoplan arm, 14/41 patients (34.1%) achieved Hb normalisation without transfusion compared to 0/39 patients (0%) in the eculizumab arm (CS, Table 20).</td><td></td></tr>
<tr><td>Table 14, row 16, page 49</td><td>AiC mark up to be removed</td><td><table><tr><td>TEAEs leading to study drug discontinuation</td><td>3 (7.3)</td><td>0</td></tr></table></td><td></td></tr>
<tr><td>Paragraph 1, page 50</td><td>Trial data to be marked as AiC</td><td>During the RCP, 7/41 patients in the pegcetacoplan arm and 6/39 patients in the eculizumab arm experienced serious TEAEs; of these, [redacted] in each arm experienced a TRAE. There were no deaths reported in either treatment arm.</td><td></td></tr>
<tr><td>Paragraph 2, page 50</td><td>AiC mark up to be removed</td><td>During the RCP, [redacted]/39 patients ([redacted]%) in the eculizumab arm experienced haemolytic events compared to 4/41 patients (9.8%) in the pegcetacoplan arm. From post-hoc analysis, 4/41 patients (9.8%; five events) in the pegcetacoplan arm and 9/39 patients (23.1%) in the eculizumab arm were considered to have</td><td></td></tr>
</table>

		experienced BTH (CS, p90). In the pegcetacoplan arm, 3/41 patients discontinued treatment due to BTH; of these, [redacted] withdrew from the study and [redacted] were able to re-enter the study during the follow-up period.	
Paragraph 2, page 50	Trial data to be marked as AiC	In the pegcetacoplan arm, 3/41 patients discontinued treatment due to BTH; of these, [redacted] withdrew from the study and [redacted] were able to re-enter the study during the follow-up period.	
Paragraph 1, page 52	AiC mark up to be underlined	Of the [redacted]/80 patients ([redacted]) who experienced general disorders and administration site conditions during the run-in period, injection site erythema was the most common TEAE and occurred in [redacted]/80 patients ([redacted]), followed by injection site pruritus and injection site swelling ([redacted]/80 patients; [redacted]), ISR ([redacted]/80 patients; [redacted]), injection site induration ([redacted]/80 patients; [redacted]) and injection site pain ([redacted]/80 patients; [redacted]). [redacted]/80 patients ([redacted]) experienced nervous system disorders, with [redacted]/80 patients ([redacted]) reporting headache.	
Paragraph 1, page 59	AiC mark up to be removed	Baseline characteristics of the modelled population were obtained from the PEGASUS trial (mean age=48.8 years old; mean body weighed=75.3kg; proportion female=[redacted]; average time since diagnosis=[redacted] years).	

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