ERG STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Pegcetacoplan for treating paroxysmal nocturnal haemoglobinuria [ID3746]

Confidential until published

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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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LIST OF ABBREVIATIONS

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.

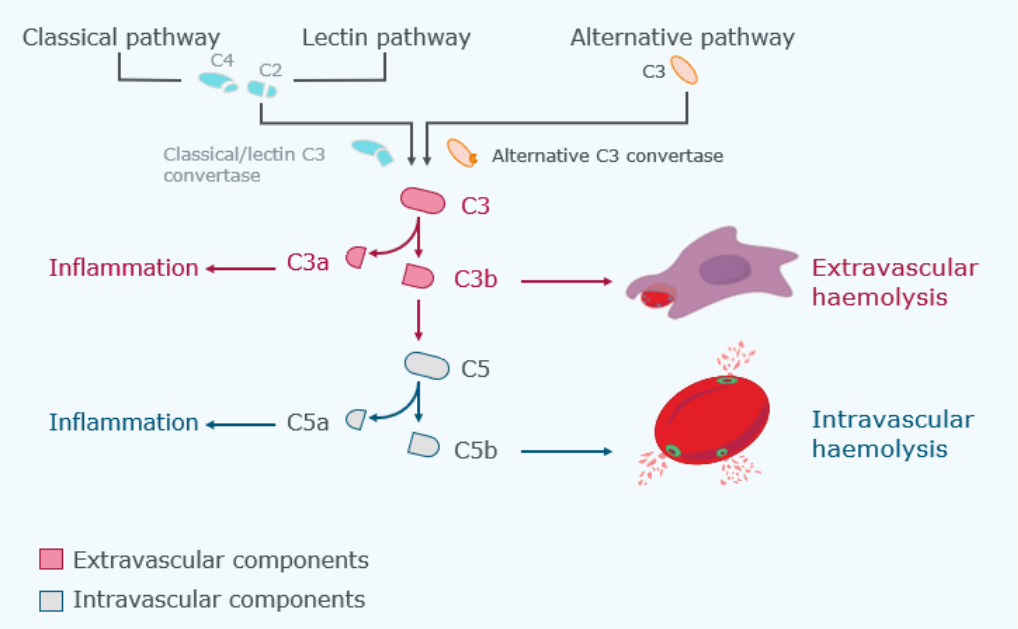

Figure 1 PNH and the complement system

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).

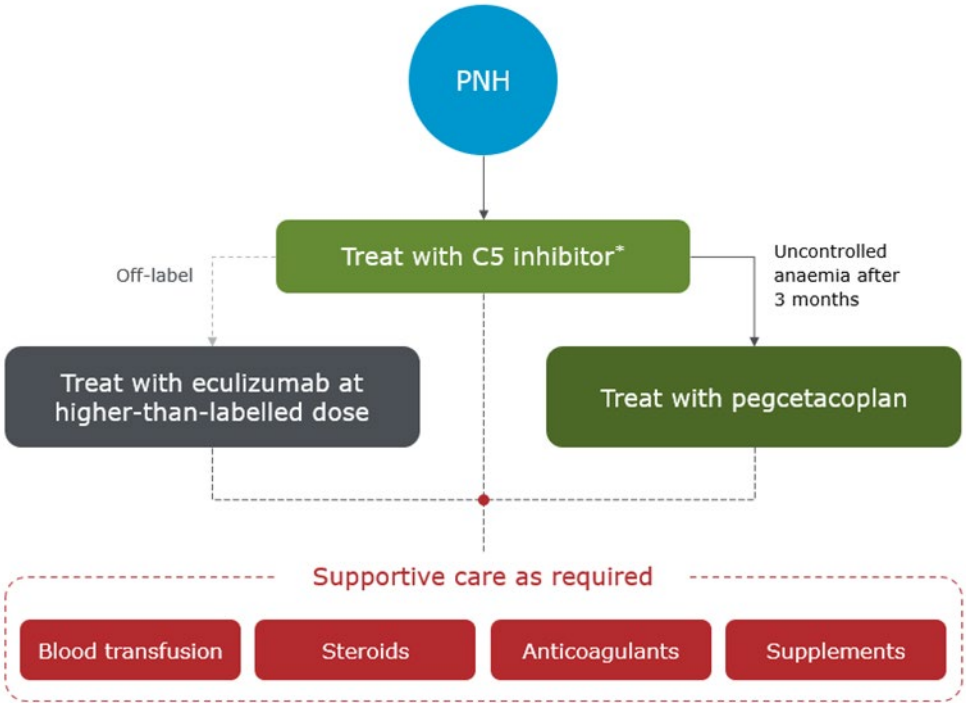

Figure 2 Proposed positioning of pegcetacoplan in the current treatment pathway for patients with PNH

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.

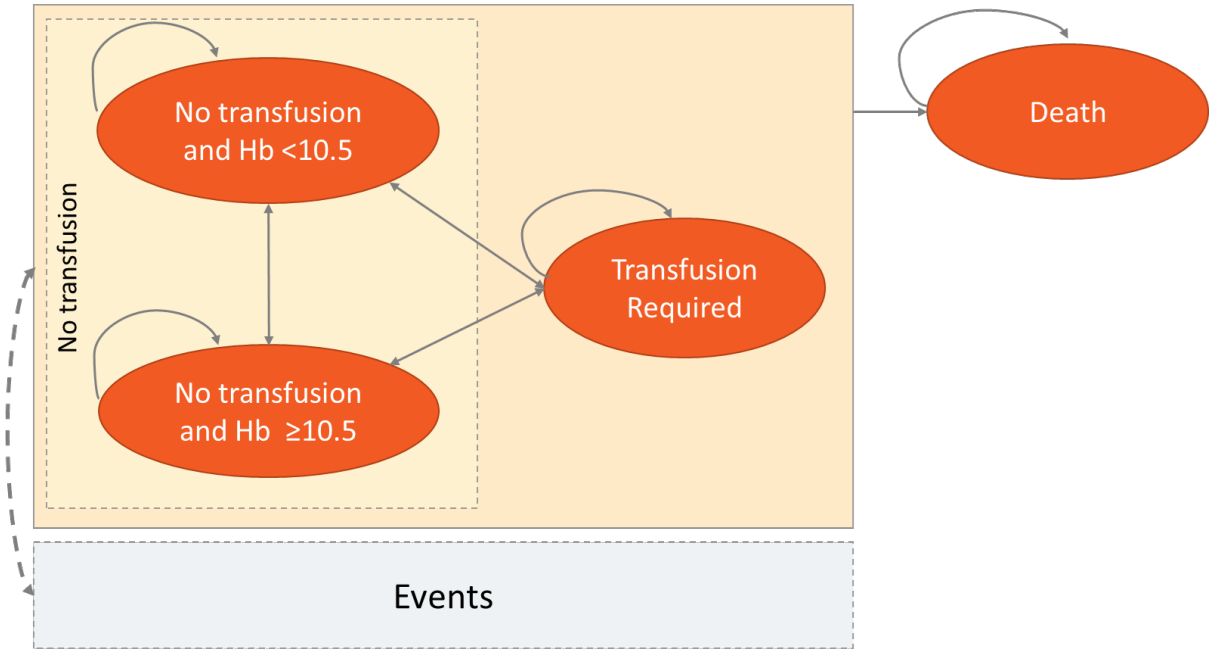

Figure 3 Structure of the company model

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.

7 REFERENCES

1. Hill A, DeZern AE, Kinoshita T, Brodsky RA. Paroxysmal nocturnal haemoglobinuria. Nat Rev Dis Primers. 2017; 3:17028.
2. Brodsky RA. Complement in hemolytic anemia. Blood. 2015; 126:2459-65.
3. Debureaux P-E, Cacace F, Silva BGP, Barone F, Calado RT, Sicre de Fontbrune F*, et al.* Hematological response to eculizumab in paroxysmal nocturnal hemoglobinuria: Application of a novel classification to identify unmet clinical needs and future clinical goals. Blood. 2019; 134:3517.
4. NHS Commissioning Board. 2013/2014 NHS standard contract for paroxysmal nocturnal haemoglobinuria service (adults and adolescents). Published 2013; Available from: www.england.nhs.uk/wp-content/uploads/2013/06/b05-parox-haem-serv.pdf. Accessed 9 June 2021.
5. Al-Ani F, Chin-Yee I, Lazo-Langner A. Eculizumab in the management of paroxysmal nocturnal hemoglobinuria: patient selection and special considerations. Ther Clin Risk Manag. 2016; 12:1161-70.
6. Orphanet. Paroxysmal nocturnal haemoglobinuria. Published October 2017; Available from: https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=447. Accessed 9 June 2021.
7. Hillmen P, Lewis SM, Bessler M, Luzzatto L, Dacie JV. Natural history of paroxysmal nocturnal hemoglobinuria. N Engl J Med. 1995; 333(19):1253-8.
8. Shammo JM, Mitchell RL, Ogborn K, Salkeld E, Chisolm S. Path to diagnosis of paroxysmal nocturnal hemoglobinuria: The results of an exploratory study conducted by the aplastic anemia and myelodysplastic syndrome international foundation and the national organization for rare disorders utilizing an internet-based survey. Blood. 2015; 126:3264.
9. European Society for Blood and Marrow Transplantation. A practical guide for nurses and allied healthcare professionals: Understanding PNH. Published October 2015; Available from: www.ebmt.org/sites/default/files/migration_legacy_files/document/EBMT%20Practical%20Guides%20for%20Nurses_Paroxysmal%20Nocturnal%20Haemaglobinuria%20%28PNH%29_UK.pdf. Accessed 10 June 2021.
10. Apellis Pharmaceuticals. Data on file. Annex I Summary of product characteristics (Pegcetacoplan 1080 mg).
11. National Institute of Health and Care Excellence. Pegcetacoplan for treating paroxysmal nocturnal haemoglobinuria [ID3746]: Final scope. Published 12 March 2021; Available from: www.nice.org.uk/guidance/gid-ta10651/documents/final-scope. Accessed 7 June 2021.
12. Parker CJ. Update on the diagnosis and management of paroxysmal nocturnal hemoglobinuria. ASH. 2016; 2016(1):208-16.
13. Parker C, Omine M, Richards S, Nishimura J, Bessler M, Ware R*, et al.* Diagnosis and management of paroxysmal nocturnal hemoglobinuria. Blood. 2005; 106:3699-709.
14. Young NS, Meyers G, Schrezenmeier H, Hillmen P, Hill A. The management of paroxysmal nocturnal hemoglobinuria: Recent advances in diagnosis and treatment and new hope for patients. Semin Hematol. 2009; 46:S1-S16.
15. Sahin F, Akay OM, Ayer M, Dal MS, Ertop S, Ilhan O*, et al.* PESG PNH diagnosis, follow-up and treatment guidelines. Am J Blood Res. 2016; 6:19-27.
16. Alexion Europe SAS. Annex I Summary of product characteristics (Soliris 300 mg). Published 29 June 2020; Available from: www.ema.europa.eu/en/documents/product-information/soliris-epar-product-information_en.pdf. Accessed 12 July 2021.
17. National Institute for Health and Care Excellence. Ravulizumab for treating paroxysmal nocturnal haemoglobinuria: 1 Recommendations. Published 19 May

2021; Available from: www.nice.org.uk/guidance/ta698/chapter/1-Recommendations. Accessed 11 June 2021.
18. National Institute of Health and Care Excellence. Ravulizumab for treating paroxysmal nocturnal haemoglobinuria [TA698]: Committee papers. Published 15 April 2021; Available from: www.nice.org.uk/guidance/ta698/documents/committee-papers. Accessed 11 June 2021.
19. Alexion Europe SAS. Annex I Summary of product characteristics (Ultomiris 300 mg/30 mL). Published 2 July 2021; Available from: www.medicines.org.uk/emc/product/10457/smpc#gref. Accessed 5 July 2021.
20. Kulasekararaj AG, Hill A, Rottinghaus ST, Langemeijer S, Wells R, Gonzalez-Fernandez FA, *et al.* Ravulizumab (ALXN1210) vs eculizumab in C5-inhibitor-experienced adult patients with PNH: The 302 study. Blood. 2019; 133:540-9.
21. Hillmen P, Szer J, Weitz I, Roth A, Hochsmann B, Panse J, *et al.* Pegcetacoplan versus eculizumab in paroxysmal nocturnal hemoglobinuria. N Engl J Med. 2021; 384:1028-37.
22. Apellis Pharmaceuticals. Data on file. Pegcetacoplan. Protocol number APL2-302: A phase 3, randomized, multicenter, open-label, active-comparator controlled study to evaluate the efficacy and safety of pegcetacoplan in patients with paroxysmal nocturnal hemoglobinuria (PNH) Week 16 analysis. May 2020.
23. ClinicalTrials.gov. NCT03500549. Study to evaluate the efficacy and safety of APL-2 in patients with paroxysmal nocturnal hemoglobinuria (PNH). Published 8 December 2020; Available from: www.clinicaltrials.gov/ct2/show/NCT03500549. Accessed 10 June 2020.
24. European Medicines Agency. Soliris (eculizumab). Published 7 July 2021; Available from: www.ema.europa.eu/en/medicines/human/EPAR/soliris#product-information-section. Accessed 12 July 2021.
25. European Medicines Agency. Ultomiris (ravulizumab). Published 9 April 2021; Available from: www.ema.europa.eu/en/medicines/human/EPAR/ultomiris#authorisation-details-section. Accessed 30 June 2021.
26. National Institute for Health and Care Excellence. Final appraisal document: Ravulizumab for treating paroxysmal nocturnal haemoglobinuria. Published 15 April 2021; Available from: www.nice.org.uk/guidance/ta698/documents/final-appraisal-determination-document. Accessed 14 July 2021.
27. National Institute for Health and Care Excellence. Appraising life-extending, end of life treatments. Published July 2009; Available from: www.nice.org.uk/guidance/gid-tag387/documents/appraising-life-extending-end-of-life-treatments-paper2. Accessed 10 June 2021.
28. National Institute of Health and Care Excellence. Single technology appraisal: User guide for company evidence submission template. 2.5 Quality assessment of the relevant clinical effectiveness evidence. Published 1 April 2017; Available from: www.nice.org.uk/process/pmg24/chapter/clinical-effectiveness#quality-assessment-of-the-relevant-clinical-effectiveness-evidence. Accessed 14 June 2021.
29. Hillmen P, Szer J, Weitz I, Roth A, Hochsmann B, Panse J, *et al.* Pegcetacoplan versus eculizumab in paroxysmal nocturnal hemoglobinuria. Supplementary Appendix. N Engl J Med. 2021; 384:1028-37.
30. Centre for Reviews and Dissemination. Systematic Reviews: CRD's guidance for undertaking reviews in health care. York: University of York; 2008.
31. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol. 1998; 16(1):139-44.
32. Cella D, Eton DT, Lai J-S, Peterman AH, Merkel DE. Combining anchor and distribution-based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy (FACT) Anemia and Fatigue scales. J Pain Symptom Manage. 2002; 24(6):547-61.

33. Leaf DE, Goldfarb DS. Interpretation and review of health-related quality of life data in CKD patients receiving treatment for anemia. Kidney Int. 2009; 75:15-24.
34. MedDRA. MedDra term selection: Points to consider. Published 1 March 2017; Available from: www.meddra.org/how-to-use/support-documentation/english. Accessed 14 June 2021.
35. National Institute for Health and Care Excellence Decision Support Unit. NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submissions to NICE. Published December 2016; Available from: www.nicedsu.org.uk/wp-content/uploads/2017/05/Population-adjustment-TSD-FINAL.pdf. Accessed 15 June 2021.
36. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013: Process and methods [PMG9] Published 4 April 2013; Available from: www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781. Accessed 22 June 2021.
37. Drummond M, Jefferson T. Guidelines for authors and peer reviewers of economic submissions to the BMJ. BMJ. 1996; 313(7052):275-83.
38. Office for National Statistics. Population estimates for the UK, England and Wales, Scotland and Northern Ireland Published 24 June 2020; Available from: www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/annualmidyearpopulationestimates/mid2019estimates. Accessed 15 June 2021.
39. Longworth L, Yang Y, Young T, Mulhern B, Hernandez Alava M, Mukuria C*, et al.* Use of generic and condition-specific measures of health-related quality of life in NICE decision-making: A systematic review, statistical modelling and survey. Health Technol Assess. 2014; 18(9):1-224.
40. Ara R, Brazier JE. Using health state utility values from the general population to approximate baselines in decision analytic models when condition-specific data are not available. Value Health. 2011; 14:539-45.
41. Cherry MG, Greenhalgh J, Osipenko L, Venkatachalam M, Boland A, Dundar Y*, et al.* The clinical effectiveness and cost-effectiveness of primary stroke prevention in children with sickle cell disease: A systematic review and economic evaluation. Health Technol Assess. 2012; 16(43):1-129.
42. National Institute for Health and Care Excellence. British National Formulary. Eculizumab: Indications and doses. Published 5 August 2014; Available from: www.bnf.nice.org.uk/drug/eculizumab.html#indicationsAndDoses. Accessed 22 June 2021.
43. Curtis L, Burns A. Unit Costs of Health and Social Care 2020. Published 17 December 2020: Personal Social Services Research Unit, University of Kent. Available from: www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2020/.
44. FIECON. Data on file. Pegcetacoplan in paroxsymal nocturnal haemoglobinuria (PNH): Uniited Kingdom health technology assessment virtual advisory board. June 2021.
45. Büyükkaramikli NC, Rutten-van Mölken M, Severens JL, Al M. TECH-VER: A verification checklist to reduce errors in models and improve their credibility. Pharmacoeconomics. 2019; 37(11):1391-408.
46. Poggiali E, Cassinerio E, Zanaboni L, Cappellini MD. An update on iron chelation therapy. Blood Transfus. 2012; 10:411-22.

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)))